Received: 11 August 2017 | Revised: 7 December 2017 | Accepted: 12 December 2017

DOI: 10.1111/ajt.14631

ORIGINAL ARTICLE

AJT

Inferior long-term allograft and patient outcomes among recipients of offspring living donor kidneys

J. B. Cohen[1,2] | **L. Owei**[2] | **D. L. Sawinski**[1,2] | **P. M. Porrett**[2,3]

[1]Renal-Electrolyte and Hypertension Division, Department of Medicine, University of Pennsylvania, Philadelphia, PA, USA

[2]Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

[3]Division of Transplant Surgery, Department of Surgery, Hospital of the University of Pennsylvania, Philadelphia, PA, USA

Correspondence
Jordana B. Cohen
Email: jco@pennmedicine.upenn.edu

Funding information
National Heart, Lung, and Blood Institute, Grant/Award Number: K23-HL133843; National Institutes of Health, Grant/Award Number: K23-HL133843

While offspring-to-parent living donor kidney transplantations may represent an ideal donor–recipient combination to optimize long-term transplantation outcomes, the sex-specific long-term success of these transplantations remains unclear. We hypothesize that allograft and recipient survivals in offspring-to-parent living donor kidney transplantation differ between men and women due to donor-specific alloimmunization during pregnancy. We retrospectively analyzed long-term allograft and patient survival among men and women who received an offspring living donor kidney compared with those who received other haplotype-matched living donor kidneys. Based on multivariable Cox proportional hazards modeling of Organ Procurement and Transplantation Network data from 2001 to 2015, we found that both men and women who received offspring living donor kidneys had significantly increased mortality compared with recipients who received nonoffspring living donor kidneys. While male recipients of any living donor kidney had greater risk of mortality and allograft failure than female recipients, there was no significant difference in all-cause allograft failure or mortality in male versus female recipients of offspring living donor kidney transplantations. Our analysis demonstrated no significant interaction between recipient sex and donor offspring status. We conclude that nonoffspring living donors should be considered whenever feasible for both men and women with multiple donor options.

KEYWORDS
clinical research/practice, epidemiology, gender, graft survival, kidney transplantation/nephrology, kidney transplantation: living donor, pregnancy

1 | INTRODUCTION

Living donor (LD) kidney transplantation provides the greatest opportunity to maximize long-term patient and graft survival.[1-4] Although multiple factors contribute to prolonged graft survival for LDKT recipients, HLA matching remains an important determinant of long-term outcome.[5-8] First-degree genetic relatives (ie, siblings, parents, offspring), therefore, represent a prevalent and accessible pool of well-matched kidneys[1,9] that may optimize long-term allograft outcomes. Among these donor types, offspring ostensibly represent the ideal donor group given the combined benefit of haplotype matching and younger donor age.

Although most LDKT recipients would benefit from transplantation with offspring donor kidneys, women with a history of pregnancy may be poorly served by this approach. Given that pregnancy is an immune-sensitizing event, long-lived immune memory cells with specificity for offspring HLA may increase the risk of acute or chronic rejection and negate long-term benefit. While the use of offspring donors for female candidates was limited in the past by fears surrounding the potential harm posed by pregnancy-induced memory T and B cells,[10] offspring living donors (LDs) have been associated with excellent

Abbreviations: aHR, adjusted hazard ratio; BMI, body mass index; CI, confidence interval; CMV, cytomegalovirus; HR, hazard ratio; LDKT, living donor kidney transplantation; LD, living donor; OPTN, Organ Procurement and Transplantation Network; OR, odds ratio.

short-term outcomes.[11] However, there is limited contemporary evidence evaluating longitudinal allograft and patient survival among maternal recipients of offspring LDKTs. Further, existing data do not thoroughly assess whether these kidneys perform as expected given their high degree of HLA matching and overall quality. Most studies that report on outcomes of LDKTs directly compare the performance of kidneys in female recipients with the performance of kidneys in male recipients.[11-13] In light of a number of studies demonstrating inferior transplant outcomes in male recipients of LDKTs,[14-16] it is unclear whether men represent an appropriate control group for comparison of outcomes. The question, therefore, remains whether long-term outcomes meet expectations for female recipients of an offspring kidney.

Recent innovations in LD kidney transplantation and an improving understanding of the immunology of pregnancy prompt reconsideration of the potential risks and long-term benefits associated with offspring-to-parent LD kidney transplantation. First, paired exchange programs are now extremely well established.[17-20] These programs provide the option of finding an alternative and potentially more desirable LD for any given LDKT candidate. Second, animal studies of maternal immune responses to the fetus during pregnancy suggest that graft-destructive memory T cells may not necessarily predominate the postpartum repertoire. Instead, emerging data suggest that the maternal repertoire consists of both regulatory and "dysfunctional" antigen-experienced populations that may permit the long-term survival of an allograft.[21,22] While comparable studies in humans have yet to be performed, these animal data suggest that the postpartum repertoire may promote long-term graft survival instead of graft loss. However, there is little epidemiologic evidence to support either immunologic model, as most studies that compare offspring-to-parent recipient outcomes were performed in earlier eras of immunosuppression therapy and have not sufficiently addressed important confounders such as PRA, degree of HLA matching, or relevant donor and recipient characteristics.[11,12,23,24]

In this study, we aimed to determine whether offspring LDKTs were associated with optimal long-term outcomes, especially among female recipients with prior donor-specific alloimmunization during pregnancy. To this end, we compared outcomes of recipients of offspring LDKTs with nonoffspring LDKTs after taking sex, degree of detectable sensitization, and HLA matching into careful consideration. The primary objective of this work was to determine whether offspring-to-parent transplants should be embraced or avoided in kidney transplantation.

2 | METHODS

2.1 | Data source

We performed a retrospective analysis of national registry data collected by the Organ Procurement and Transplantation Network (OPTN). The OPTN data system includes data on all donor, waitlisted candidates, and transplant recipients in the United States, submitted by the members of the OPTN. The Health Resources and Services Administration, US Department of Health and Human Services provides oversight to the activities of the OPTN contractor. The study was determined to be exempt category 4 status by the institutional review board at the University of Pennsylvania (protocol No. 823223).

2.2 | Subjects

The cohort was restricted to patients who receive a transplant between January 1, 2001, and March 31, 2015. Patient follow-up was through June 1, 2015. Only patients who were recipients of LDKTs and aged 36 years or older (the youngest age of a recipient of an offspring LD kidney) were included in the study. The primary cohort was restricted to LD recipients with exactly 3 HLA matches with his or her donor (to represent the expected number of matches between a mother and her offspring) and with a maximal PRA of 0%. A secondary, modified cohort included recipients with a minimum of 3 HLA matches, as opposed to exactly 3 HLA matches. The modified cohort did not require a maximal PRA of 0% for inclusion.

Se was assessed as an effect modifier for offspring donor status with regard to recipient outcomes. However, given differences in alloimmunization during pregnancy and concerns that men are not appropriate controls for women in this context, we were particularly interested, a priori, in determining se-specific associations between offspring LDKTs and longitudinal outcomes, even if sex was not a significant effect modifier. As such, our primary analysis compared female recipients of offspring LDKTs with female recipients of nonoffspring LDKTs. Sensitivity analyses in both cohorts evaluated outcomes among (1) all recipients of offspring LDKTs versus all recipients of nonoffspring LDKTs, (2) all male recipients of LDKTs versus all female recipients of LDKTs, (3) male recipients of offspring LDKTs versus female recipients of offspring LDKTs, and (4) male recipients of offspring LDKTs versus male recipients of nonoffspring LDKTs.

2.3 | Outcomes and covariates

The primary outcomes in the study were acute rejection at 1 year, all-cause allograft failure (a composite of allograft failure and mortality), and all-cause mortality. Death-censored allograft failure and allograft failure with death as a competing risk were also evaluated (see Supplemental Materials). Recipient characteristics included in the primary models were recipient age, African American race, dialysis vintage time (reported in years), diabetes, previous sensitization events, and body mass index (BMI). Locally weighted scatterplot smoothing was performed to determine a cut-point for recipient age with regard to mortality and allograft failure.[25,26] Previous sensitization events included previous transplants or blood transfusions; previous pregnancy was not reliably documented in the data set and was not able to be included. Donor characteristics included age, African American race, sex, BMI, and cold ischemia time. Immunologic factors included ABO compatibility (identical, compatible, or incompatible), induction type (lymphocyte-depleting agents such as antithymocyte globulin or alemtuzumab vs nondepleting agents such as daclizumab or basiliximab vs no induction), calcineurin inhibitor therapy (tacrolimus, cyclosporine, or neither), and cytomegalovirus (CMV) risk status (both recipient and

donor negative, recipient positive, or recipient negative with positive donor). All analyses were also adjusted by year of transplantation. To account for dependence among observations within the same transplant center (given center-specific differences in recipient and donor selection), all analyses were clustered by transplant center using a robust sandwich estimator for calculation of the standard error.

2.4 | Statistical analyses

Statistical analyses were performed by using STATA version 13.0 (StataCorp LP, College Station, TX) with 2-sided hypothesis testing and *P*-value of <.05 as the criteria for statistical significance. Descriptive statistics (median and proportion) were used to describe baseline donor and recipient clinical and demographic characteristics. Rank-sum test was used to compare continuous variables, and χ^2 test was used to compare categorical and binary variables.

Multivariable logistic regression models were performed to assess the outcome of acute rejection at 1 year. Multivariable Cox proportional hazards models were performed to assess the outcomes of allograft failure and mortality. The Cox models were subsequently stratified by recipient factors that are known to have an important impact on the outcomes, including diabetes,[26] African American race, and age.[27]

We generated Kaplan–Meier curves with log rank testing to assess for equality of survival distributions.[28] For the multivariable regressions, we selected variables a priori that were known to be risk factors

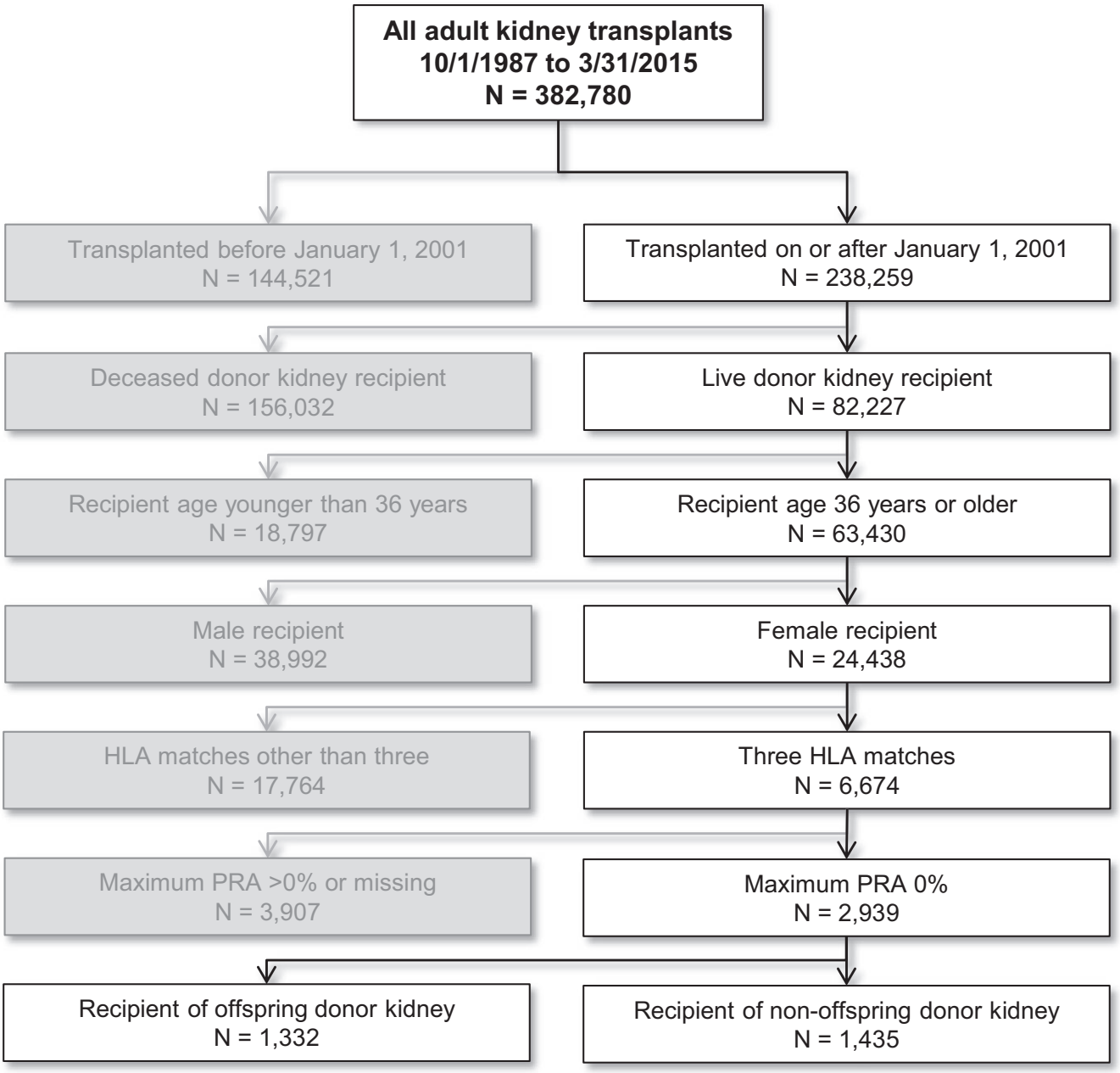

FIGURE 1 Primary cohort selection for evaluation of outcomes of recipients of offspring live donors

for the outcomes based on clinical judgment and previously published literature.[29,30] The proportional hazards assumption was assessed via weighted versions of Kaplan–Meier curves by using statistical testing and graphical displays based on the Schoenfeld and scaled Schoenfeld residuals.[31]

2.5 | Handling of covariate missingness

Most covariates included in the multivariate models were <5% incomplete. Donor hypertension was highly missing (>20%) and was omitted; understanding current policies with regard to live kidney donation,[32] we anticipated that donor hypertension would have a very low prevalence among LDs (among those donors in whom it was reported, a diagnosis of hypertension was present in <2%). We performed complete case analysis to address any other missing data.[33]

3 | RESULTS

3.1 | Recipient and donor characteristics

There were 2767 women who met inclusion criteria for the primary analyses (see Figure 1), of whom 1332 were recipients of offspring LDKTs and 1435 were recipients of nonoffspring LDKTs. Recipients of offspring LDKTs were significantly older (median age 59 vs 49 years, $P < .001$), more likely to be African American race (28% vs 11%, $P < .001$), and more likely to be diabetic (40% vs 27%, $P < .001$) compared with recipients of nonoffspring LDKTs (see Table 1). Recipients of offspring kidneys were less likely to be CMV high risk (recipient negative, donor positive) than do recipients of nonoffspring kidneys (7% vs 10%, $P < .001$); other immunologic characteristics, including ABO compatibility, induction immunosuppression, and calcineurin inhibitor immunosuppression, were similar across the 2 groups. Recipients of offspring kidneys had a similar prevalence of total pretransplantation sensitization events as did recipients of nonoffspring kidneys (23% vs 25%, $P = .286$) but a significantly lower prevalence of previous kidney transplantation (4% vs 9%, $P < .001$). While recipients of offspring LDKTs had a higher BMI than recipients of nonoffspring LDKTs, the difference in donor and recipient BMI was the same across the 2 groups (0.5 vs 0.5, $P = .897$). Offspring donors were significantly younger than nonoffspring donors (median age 34 vs 46 years, $P < .001$) and were more likely to be male (40% vs 34%, $P < .001$).

In analyses comparing the 1332 female recipients of offspring LDKTs with the 2245 male recipients of offspring LDKTs (see Table S1), the women were closer in age to the men (59 vs 61 years, $P < .001$), more likely to be African American race (28% vs 16%, $P < .001$), and less likely to be diabetic (40% vs 50%, $P < .001$) and had a lower BMI (27.9 vs 28.2 kg/m^2, $P = .007$). Male recipients had a significantly greater donor-recipient BMI differential (1.6 vs 0.5 kg/m^2, $P < .001$), lower prevalence of sensitization events (23% vs 20%, $P = .020$), and the same prevalence of previous kidney transplantation (4%) compared with female recipients.

3.2 | Multivariable regression models

Multivariable logistic regression modeling showed that female recipients of offspring LDKTs had no difference in acute rejection at 1 year compared with female recipients of nonoffspring kidneys (adjusted odds ratio [OR] 1.01, 95% confidence interval [CI] 0.68-1.51; see Table 2). In multivariable Cox proportional hazards models, female recipients of offspring kidneys had a significantly greater hazard of all-cause allograft failure (adjusted hazard ratio [aHR] 1.65, 95% CI 1.11-2.44; see Table 2 and Figure 2A) and mortality (aHR 1.37, 95% CI 1.02-1.86; see Table 2 and Figure 2B) compared with female recipients of nonoffspring kidneys.

Multivariable Cox models for death-censored allograft failure and mortality as a competing risk demonstrated a trend toward increased risk among female recipients of offspring kidneys but were underpowered to assess for a significant difference (see Table S2). Secondary analyses using a modified, expanded cohort (comparing female recipients of offspring LDKTs with female recipients of nonoffspring LDKTs with a *minimum* of 3 HLA matches and adjusting for PRA) demonstrated a significantly increased risk of death-censored allograft failure (aHR 1.27, 95% CI 1.04-1.56; see Table S3) and allograft failure treating mortality as a competing risk (sub-aHR 1.24, 95% CI 1.01-1.53) among female recipients of offspring LDKTs.

In multivariable Cox proportional hazards models using the primary cohort inclusion criteria (recipient age ≥36, exactly 3 HLA matches, and maximum PRA 0%) and adjusting for sex instead of restricting to female recipients, recipients of offspring LDKTs had a significantly greater risk of all-cause allograft failure (aHR 1.35, 95% CI 1.08-1.68) and mortality (1.30, 95% CI 1.10-1.54) compared with recipients of nonoffspring LDKTs (see Table 3). Male recipients of any LDKT, adjusting for offspring relationship status, had significantly greater hazard of all-cause allograft failure (aHR 1.23, 95% CI 1.08-1.39) and mortality (aHR 1.17, 95% CI 1.04-1.31) compared with female recipients of LDKTs. Male recipients of offspring LDKTs had no significant difference in all-cause allograft failure (aHR 1.19, 95% CI 0.99-1.44) but did have a significantly higher risk of mortality (aHR 1.25, 95% CI 1.07-1.47) compared with female recipients of offspring LDKTs. Similarly, compared with male recipients of nonoffspring LDKTs, male recipients of offspring LDKTs had no significant difference in all-cause allograft failure (aHR 1.28, 95% CI 0.99-1.65) but showed a significantly higher risk of mortality (aHR 1.25, 95% CI 1.03-1.52).

The results were similar in the modified cohort (with inclusion criteria expanded to include recipients with a *minimum* of 3 HLA matches, adjusting for number of HLA matches and PRA), except male recipients of offspring LDKTs had a significantly increased hazard of all-cause allograft failure (aHR 1.14, 95% CI 1.03-1.26) and mortality (aHR 1.21, 95% CI 1.14-1.29) compared with female recipients of offspring LDKTs. Also, male recipients of offspring LDKTs had a significantly higher risk of mortality (aHR 1.50, 95% CI 1.36-1.66) but not all-cause allograft failure (aHR 1.20, 95% CI 1.00-1.45) compared with male recipients of nonoffspring LDKTs. There was no statistically significant interaction between recipient sex and offspring status with regard to allograft failure or mortality.

TABLE 1 Recipient and donor characteristics comparing female live donor recipients by donor relationship

	Offspring donor n = 1332	Nonoffspring donor n = 1435	*P*-value
Recipient characteristics			
Median age, y (IQR)	59 (53-65)	49 (42-57)	<.001
African American race, n (%)	369 (28)	154 (11)	<.001
Median dialysis vintage, d (IQR)	322 (0-714)	168 (0-538)	<.001
Diabetic, n (%)	524 (40)	378 (27)	<.001
Cause of end-stage renal disease, n (%)			<.001
Diabetes	385 (29)	285 (20)	
Hypertension	369 (28)	209 (15)	
Glomerular disease	184 (14)	319 (22)	
Cystic disease	110 (8)	248 (17)	
Other cause	195 (15)	286 (20)	
Missing	88 (6)	87 (6)	
Any pretransplantation sensitization events, n (%)	275 (23)	324 (25)	.286
Previous kidney transplant, n (%)	58 (4)	123 (9)	<.001
Median body mass index, kg/m^2 (IQR)	27.9 (24.2-32.1)	26.7 (22.7-31.6)	<.001
Donor characteristics			
Median age, y (IQR)	34 (28-40)	46 (38-53)	<.001
African American race, n (%)	376 (28)	143 (10)	<.001
Male sex, n (%)	527 (40)	493 (34)	<.001
Median cold ischemia time, h (IQR)	1 (1-2)	1 (1-2)	.738
Median body mass index, kg/m^2 (IQR)	27.1 (24.3-30.7)	26.2 (23.5-29.5)	<.001
Median recipient minus donor body mass index (IQR)	0.5 (-3.7-4.9)	0.5 (-4.0-5.0)	.897
Immunologic characteristics			
ABO blood type match level, n (%)			.631
Identical	1053 (79)	1117 (78)	
Compatible	262 (20)	302 (21)	
Incompatible	17 (1)	16 (1)	
CMV risk status, n (%)			<.001
Recipient positive	910 (75)	765 (62)	
Donor and recipient negative	217 (18)	264 (21)	
Recipient negative, donor positive	85 (7)	208 (17)	
Induction immunosuppression, n (%)			.799
Depleting	630 (47)	662 (46)	
Nondepleting	372 (28)	415 (29)	
None	330 (25)	358 (25)	
Calcineurin inhibitor immunosuppression, n (%)			.078
Tacrolimus	1072 (81)	1199 (84)	
Cyclosporine	179 (13)	148 (10)	
Both	3 (0)	2 (0)	
Neither	78 (6)	86 (6)	

CMV, cytomegalovirus.

3.3 | Stratified analyses

Stratified Cox proportional hazards analyses evaluating all-cause allograft failure and mortality were performed by using the modified cohort (comparing female recipients of offspring LDKTs with female recipients of nonoffspring LDKTs with a *minimum* of 3 HLA matches) due to insufficient power in the primary cohort. The analyses demonstrated similar results across strata and compared with

TABLE 2 Multivariable logistic regression model for acute rejection at 1 year and multivariable Cox proportional hazards models for all-cause allograft failure and mortality comparing female recipients of offspring live donors vs female recipients of nonoffspring live donors, clustered by transplant center

	Acute rejection		Allograft failure		Mortality	
	OR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Offspring donor	1.01 (0.68-1.51)	.949	1.65 (1.11-2.44)	.012	1.37 (1.02-1.86)	.040
Recipient age category, y						
<40	REF		REF		REF	
40-54	1.08 (0.58-2.02)	.805	0.89 (0.53-1.48)	.645	1.08 (0.73-1.59)	.706
≥55	0.88 (0.47-1.64)	.692	1.08 (0.61-1.91)	.787	1.92 (1.21-3.03)	.005
Recipient African American race	1.24 (0.75-2.05)	.394	1.12 (0.42-3.02)	.823	0.95 (0.44-2.06)	.904
Dialysis vintage, y	1.02 (0.94-1.10)	.689	1.11 (1.08-1.15)	<.001	1.13 (1.08-1.18)	<.001
Recipient diabetes			1.68 (1.30-2.18)	<.001	1.94 (1.57-2.39)	<.001
Any previous sensitization event	1.09 (0.66-1.79)	.734	1.16 (0.87-1.56)	.320		
Recipient body mass index			0.99 (0.97-1.02)	.578		
Donor age			1.03 (1.01-1.04)	.005	1.02 (1.01-1.04)	.001
Donor African American			1.25 (0.42-3.67)	.689	1.17 (0.52-2.65)	.706
ABO compatibility						
Identical	REF		REF			
Compatible	0.87 (0.50-1.50)	.614	1.02 (0.75-1.38)	.904		
Incompatible	2.55 (0.91-7.13)	.075	1.10 (0.45-2.66)	.841		
Donor male sex			1.00 (0.81-1.25)	.982	1.08 (0.90-1.30)	.425
Induction type						
None	REF		REF			
Depleting	2.08 (1.05-4.11)	.035	1.09 (0.78-1.52)	.613		
Nondepleting	1.09 (0.56-2.13)	.792	1.16 (0.83-1.60)	.383		
Calcineurin Inhibitor						
Neither	REF		REF			
Tacrolimus	0.92 (0.40-2.10)	.846	0.44 (0.25-0.77)	.004		
Cyclosporine	1.18 (0.49-2.85)	.709	0.49 (0.27-0.89)	.018		
CMV risk status						
Both negative			REF			
Recipient positive			0.95 (0.70-1.28)	.745		
Recipient negative, donor positive			0.57 (0.34-0.94)	.029		
Donor body mass index			1.00 (0.98-1.02)	.755		
Cold ischemia time			0.99 (0.95-1.03)	.625		
Transplant year	0.92 (0.87-0.98)	.005	0.94 (0.90-0.98)	.002	0.95 (0.92-0.99)	.013

OR odds ratio; CI, confidence interval; REF, reference; CMV, cytomegalovirus.

the primary analyses after stratifying by recipient diabetes status, recipient and donor African American race, recipient and donor age, cause of end-stage renal disease, donor sex, and recipient–donor BMI mismatch. There was significant interaction between older donor age (≥40 years) and offspring status with regard to allograft failure and mortality (ie, older donor age was associated with greater risk of allograft failure [HR 1.82, 95% CI 1.64-2.01] and mortality [HR 2.52, 95% CI 2.25-2.82] compared with younger donor age among recipients of offspring donors). There was no significant interaction between the other stratifying variables and donor offspring status with regard to all-cause allograft failure and mortality (see Tables 4 and S4).

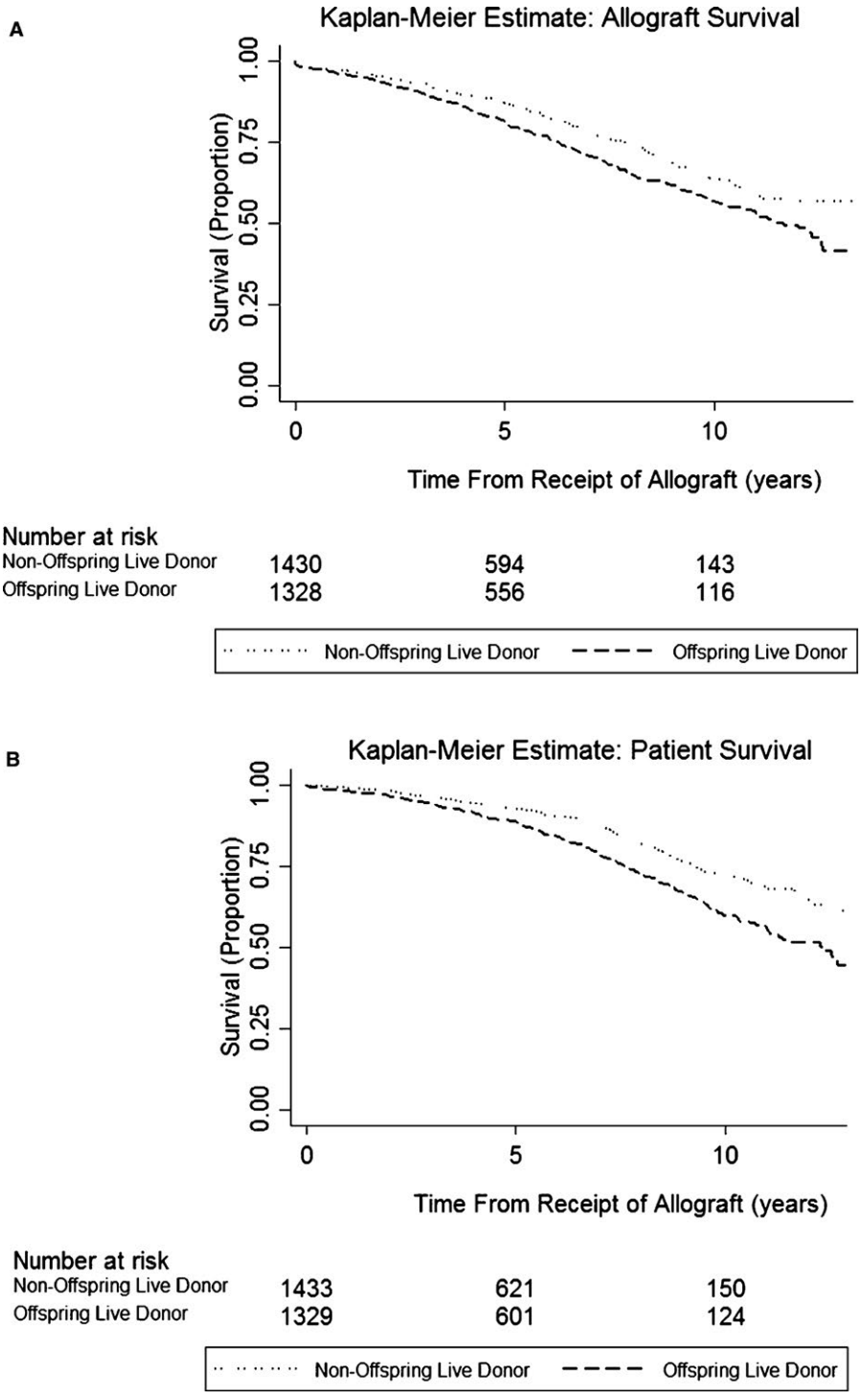

FIGURE 2 A. Kaplan–Meier curve evaluating allograft survival in female recipients of offspring donor kidneys vs female recipients of nonoffspring live donor kidneys. B. Kaplan–Meier curve evaluating patient survival in female recipients of offspring donor kidneys vs female recipients of nonoffspring live donor kidneys

4 | DISCUSSION

Adult offspring remain a prevalent source of potential LDs for kidney transplant candidates.[1,9] Although the use of offspring LDs has diminished in recent years in the United States (see Figure S1), these donors may nevertheless represent the optimal choice to maximize long-term benefit in LDKT. However, it is unclear whether these donors are really the best option for women, who may have developed an immunologic memory response to the donor during exposure in prior pregnancy that ultimately threatens graft outcomes. Given that LDKT candidates at many centers have access to alternative donors through the pipeline of paired exchange, we asked whether parents achieve the expected benefits of offspring LDs or should potentially be offered paired exchange as an alternative to optimize long-term outcomes. The primary goal of this study was to determine whether offspring donors perform up to expectations in individuals who have been previously exposed to the donor through the unique route of pregnancy.

TABLE 3 Multivariable Cox proportional hazards models for all-cause allograft failure and mortality, clustered by transplant center: sensitivity analyses

	Allograft failure[a]		Mortality[b]	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Primary cohort[c]				
A. Recipients of offspring donors vs recipients of nonoffspring live donors	1.35 (1.08-1.68)	.007	1.30 (1.10-1.54)	.003
B. Female recipients of offspring donors vs female recipients of nonoffspring live donors (primary analysis)	1.65 (1.11-2.44)	.012	1.37 (1.02-1.86)	.040
C. Male recipients of live donors vs female recipients of live donors	1.23 (1.08-1.39)	.002	1.17 (1.04-1.31)	.010
D. Male recipients of offspring donors vs female recipients of offspring donors	1.19 (0.99-1.44)	.070	1.25 (1.07-1.47)	.006
E. Male recipients of offspring donors vs male recipients of nonoffspring live donors	1.28 (0.99-1.65)	.062	1.25 (1.03-1.52)	.023
Modified cohort[d]				
A. Recipients of offspring donors vs recipients of nonoffspring live donors	1.21 (1.07-1.37)	.002	1.55 (1.42-1.68)	<.001
B. Female recipients of offspring donors vs female recipients of nonoffspring live donors	1.66 (1.12-2.46)	.012	1.61 (1.42-1.84)	<.001
C. Male recipients of live donors vs female recipients of live donors	1.10 (1.03-1.16)	.002	1.13 (1.07-1.18)	<.001
D. Male recipients of offspring donors vs female recipients of offspring donors	1.14 (1.03-1.26)	.014	1.21 (1.14-1.29)	<.001
E. Male recipients of offspring donors vs male recipients of nonoffspring live donors	1.20 (1.00-1.45)	.056	1.50 (1.36-1.66)	<.001

HR, hazard ratio; CI, confidence interval.

[a]Allograft failure models adjusted for recipient age, recipient race, dialysis vintage time, recipient diabetes status, prior sensitization events, recipient body mass index, donor age, donor race, donor sex, donor body mass index, cold ischemia time, ABO compatibility, induction immunosuppression, calcineurin inhibitor treatment, and cytomegalovirus risk status.

[b]Mortality models adjusted for recipient age, recipient race, dialysis vintage time, recipient diabetes status, donor age, donor race, and donor sex.

[c]Primary cohort inclusion criteria: recipient age ≥36 y, transplanted on or after 2001, exactly 3 HLA matches, maximal PRA 0%.

[d]Modified cohort inclusion criteria: recipient age ≥36 y, transplanted on or after 2001, minimum of 3 HLA matches (adjusted for number of HLA mismatches and PRA).

In this study, we used a series of analytic strategies to compare the observed long-term outcomes of offspring-to-mother LDKTs against the expected outcomes among patient cohorts who were not immunologically exposed to the donor during pregnancy. In our primary analysis, female recipients who received a 3-antigen–matched kidney in the absence of pregnancy immunization against their LDs defined the expected long-term patient and graft survival. We found that the risk of graft loss was significantly higher in women who received an offspring LD kidney (ie, mothers) compared with women who received a nonoffspring kidney. This difference in graft survival expanded over 15 years of follow-up and was greater among recipients of kidneys from older donors (age ≥40 years). Analysis of the modified cohort suggested that the difference in graft survival was not entirely attributable to differences in overall patient survival, as inferior graft survival persisted when we examined death-censored graft survival or when death was treated as a competing risk (Table S3).

Taken in isolation, these results suggest that pregnancy immunization against the donor is detrimental to long-term graft survival. However, our analyses of offspring and nonoffspring graft survival in men suggest an alternative interpretation. As noted in Table 3, all recipients of offspring LDs fared worse than did recipients of nonoffspring donors after adjusting for sex. Moreover, graft and patient survivals were similar between mothers and fathers in both the primary and modified cohorts. Our analyses, therefore, collectively suggest that kidney transplants from offspring LDs do not provide the greatest long-term benefit to their recipients compared with recipients who receive comparably well-matched kidneys. Nonetheless, male recipients had worse overall outcomes than female recipients across multiple sensitivity analyses, which has been demonstrated previously.[14-16,34,35] Although there was no significant interaction between recipient sex and offspring status, these findings suggest that male recipients may not be an ideal control for female recipients and further support that female recipients of offspring LDKTs had worse outcomes than expected compared with more-fitting female controls. Furthermore, due to important sex-based differences in previous immunologic exposures,[36,37] immune responses,[38] and other unmeasured risk factors,[34,39,40] men broadly make a poor control group when evaluating outcomes of kidney transplantation in women.

TABLE 4 Cox proportional hazards models for all-cause allograft failure and mortality in stratified analyses comparing female recipients of offspring donors vs female recipients of nonoffspring donors in the modified cohort,[a] clustered by transplant center

	n	Allograft failure		Mortality	
		HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Recipient characteristics					
Diabetics	4209	1.35 (1.20-1.53)	<.001	1.41 (1.24-1.61)	<.001
Nondiabetics	9405	1.38 (1.27-1.50)	<.001	1.84 (1.64-2.05)	<.001
African American	2472	1.26 (1.09-1.46)	.002	1.77 (1.43-2.20)	<.001
Non–African American	11 344	1.40 (1.30-1.51)	<.001	1.70 (1.55-1.86)	<.001
Age <55 y	7525	1.31 (1.16-1.48)	<.001	1.43 (1.23-1.65)	<.001
Age ≥55 y	6291	1.19 (1.07-1.33)	.002	1.20 (1.07-1.35)	.003
Recurrent cause of ESRD (diabetes or glomerular disease)	5828	1.52 (1.36-1.69)	<.001	2.11 (1.78-2.51)	<.001
Nonrecurrent cause of ESRD (hypertension or cystic disease)	4132	1.61 (1.41-1.85)	<.001	1.76 (1.54-2.00)	<.001
Transplanted before 2008	7621	1.46 (1.35-1.58)	<.001	1.75 (1.60-1.92)	<.001
Transplanted during or after 2008	6195	1.24 (1.07-1.44)	.005	1.56 (1.31-1.85)	<.001
Donor characteristics					
Age <40 y[b]	6729	1.41 (1.26-1.57)	<.001	1.71 (1.48-1.97)	<.001
Age ≥40 y[b]	7087	1.82 (1.64-2.01)	<.001	2.52 (2.25-2.82)	<.001
Male	5281	1.45 (1.30-1.61)	<.001	1.72 (1.51-1.96)	<.001
Female	8535	1.43 (1.30-1.57)	<.001	1.75 (1.57-1.94)	<.001
African American	2432	1.39 (1.29-1.50)	<.001	1.83 (1.45-2.32)	<.001
Non–African American	11 384	1.30 (1.11-1.52)	.001	1.69 (1.55-1.85)	<.001
Recipient with larger BMI than donor	6509	1.34 (1.20-1.48)	<.001	1.59 (1.42-1.79)	<.001
Recipient with the same or smaller BMI than donor	6278	1.53 (1.38-1.70)	<.001	1.87 (1.65-2.13)	<.001

HR, hazard ratio; CI, confidence interval; ESRD, end-stage renal disease; BMI, body mass index.
[a]Modified cohort inclusion criteria: recipient age ≥36, transplanted on or after 2001, minimum of 3 HLA matches.
[b]Indicates significant interaction between the covariate and offspring status with regard to allograft failure and mortality.

Given the premise of the study, we were surprised to find that recipients of any offspring donor fared worse regardless of the sex of the recipient. We currently speculate that either genetic or shared environmental factors between donor and recipient dictate the inferior outcome of these grafts. This hypothesis is indirectly supported by the findings of other investigators who note higher rates of adverse allograft outcomes among recipients of kidneys from LDs who themselves go on to develop end-stage renal disease.[41] Indirect support for this hypothesis may also be provided from within our data set, given the interaction between older donor age and offspring status, as well. However, while we had hoped that stratification by disease etiology would provide particularly useful insight into the biologic factors that contribute to inferior graft survival of offspring kidneys, we could find no interaction between disease etiology and offspring status. These epidemiologic, observational data, therefore, do not provide a biologic mechanism that explains why graft and patient survivals are inferior among recipients of offspring LDKTs. Additional insights about the biologic process that diminishes offspring-to-parent outcomes may be gained through the study of paired exchange recipient outcomes, particularly the outcomes of

recipients who received a haplotype-matched kidney originally intended for a parent.

The principal strengths of our study include (1) long duration of follow-up, (2) use of a large-scale, population-based, contemporary transplant cohort, (3) use of multiple sensitivity analyses to validate our interpretation of the data set, and (4) use of a highly detailed national registry database, allowing for appropriate statistical control of multiple variables known to affect graft and patient survival. Our study particularly highlights the significant impact of donor and recipient se, age, race, and HLA matching on long-term graft survival among LDKT recipients, which previous studies in this area have not thoroughly explored. We also took into careful account body size mismatch between the recipient and donor, which is emerging as an important factor in outcomes for recipients of deceased donor kidneys.[42,43] Additionally, understanding that substantial center-specific variability exists with regard to donor and recipient selection criteria and the concerns related to the relationship between the donor and recipient, we used statistical techniques to account for clustering by transplant center.

Despite these strengths, our study also has a number of important limitations. As with any retrospective study, the analyses were susceptible to unmeasured confounding. Unmeasured confounders that we identified included previous number of pregnancies, which were not adequately captured in the data set; donor hypertension, which was highly missing; and information on donor-specific antibody and cardiovascular comorbidities. Regarding the absence of previous number of pregnancies in the data set, we attempted to overcome this limitation by carefully controlling for sensitization in multiple other ways, including PRA (with our primary cohort being restricted only to patients with a maximal PRA of 0%), previous transfusion exposure, and prior transplant. We do not suspect that missing donor hypertension status influenced the results meaningfully, given that transplant centers generally have strict guidelines regarding LDKTs from LDs with hypertension and the kidneys that are used tend to have no signs of end organ effects that would influence allograft outcomes.[44] Regrettably, the lack of information on donor-specific antibody in the data set limits our ability to understand the degree to which any immunologic mechanisms contributed to long-term graft loss. Similarly, insufficient data on cardiovascular comorbidities limit our ability to adequately adjust our outcome models. Furthermore, given that the OPTN database is a registry that relies on input from transplant centers and organ procurement organizations, it is prone to the possibility of inaccuracies, which, in a cohort as select as this, could feasibly contribute considerable misinformation bias. Additionally, while we controlled for a multitude of critical confounders and covariates related to the relationship between donor type and recipient outcomes, we were inadequately powered to use more-robust matching techniques to account for such issues as confounding by indication and selection bias.

In conclusion, we report that kidney transplants from offspring LDs appear to underperform transplants from comparably HLA-matched LDs, particularly among female recipients and recipients of kidneys from older donors. Altogether, our data suggest that offspring-to-parent transplantations represent an unfavorable pairing independent of recipient sex or prior immunologic exposure through pregnancy. While the decision to transplant any individual with any particular donor must take into account overall donor access and transplantation urgency, our results encourage the escalating use of paired kidney exchange whenever possible to avoid less-favorable pairings such as offspring-to-parent transplantation while maintaining or improving HLA matching between donors and recipients. While this data sset was unable to delineate the biologic factors that contribute to diminished outcomes in recipients of offspring kidneys, our study nevertheless provides important information that will help guide selection of the optimal LD for patients with multiple donor options. Additional work that helps define the long-term impact of donor relationship on recipient outcome will provide much-needed information to help optimize LD–recipient matching through any available vehicle.

ACKNOWLEDGMENTS

This research was supported in part by the National Institutes of Health grant K23-HL133843 (National Heart, Lung, and Blood Institute, PI: Cohen). The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy of or interpretation by the National Institutes of Health.

DISCLAIMER

The data reported here have been supplied by the United Network of Organ Sharing as the contractor for the OPTN. The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy of or interpretation by the OPTN or the US government.

DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Cohen JB, Owei L, Sawinski DL, Porrett PM. Inferior long-term allograft and patient outcomes among recipients of offspring living donor kidneys. *Am J Transplant*. 2018;18:1699–1709. https://doi.org/10.1111/ajt.14631