KI REPORTS
KIReports.org

A Multi-Institutional Report of Intermediate-Term Kidney Outcomes in Uterus Transplant Recipients

Liza Johannesson[1,2,11], Deirdre Sawinski[3,11], David M. Vock[4], Jakub Kristek[5,6], Jiri Fronek[5,6,7], Elliott G. Richards[8], Kathleen E. O'Neill[9], Uma Perni[8], Paige M. Porrett[10,12] and Giuliano Testa[2,12]

[1]Division of Obstetrics and Gynecology, Baylor University Medical Center, Dallas, Texas, USA; [2]Annette C. and Harold C. Simmons Transplant Institute, Baylor University Medical Center, Dallas, Texas, USA; [3]Division of Nephrology and Transplantation, Weill Cornell Medical College, New York, New York, USA; [4]Division of Biostatistics, School of Public Health, University of Minnesota, Minneapolis, Minnesota, USA; [5]Department of Transplantation Surgery, Institute for Clinical and Experimental Medicine, Prague, Czech Republic; [6]Department of Anatomy, Second Faculty of Medicine, Charles University, Prague, Czech Republic; [7]First Faculty of Medicine, Charles University, Prague, Czech Republic; [8]Obstetrics and Gynecology and Women's Health Institute, Cleveland Clinic, Cleveland, Ohio, USA; [9]University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania, USA; and [10]Comprehensive Transplant Institute, University of Alabama at Birmingham, Birmingham Alabama, USA

Correspondence: Deirdre Sawinski, Division of Nephrology and Transplantation, Weill Cornell Medical College, New York, New York 10065, USA. E-mail: dls7001@med.cornell.edu

[11]LJ and DS are co-first authors.

[12]PMP and GT are co-senior authors.

Received 15 May 2023; revised 25 July 2023; accepted 31 July 2023; published online 5 August 2023

Kidney Int Rep (2023) **8,** 2156–2159; https://doi.org/10.1016/j.ekir.2023.07.036
KEYWORDS: kidney function; uterus transplant

INTRODUCTION

Uterus transplant (UTx) is a treatment for uterine factor infertility. Globally, the number of UTx recipients is increasing.[1–3] Many recipients have Mayer-Rokitansky-Kuster-Hauser syndrome, which may include unilateral kidney agenesis in addition to a congenitally absent uterus and vaginal aplasia.[4] Therefore, kidney dysfunction is a potential complication of UTx.

We have previously demonstrated that UTx recipients experience a decrease in estimated glomerular filtration rate (eGFR) early posttransplant,[5] that persists into the early postpartum period. We have also demonstrated that the incidence of acute kidney injury (AKI) and preeclampsia (28%) are increased.[5] However, UTx is a unique transplant paradigm; after childbearing is complete, a graft hysterectomy is performed and immunosuppression is discontinued. The cumulative effect of pregnancy, AKI episodes, preeclampsia, and temporary calcineurin inhibitor (CNI) exposure on longer-term kidney function remains undefined. We undertook this study in a cohort representing most of the United States UTx population and selected participants from Europe to elucidate intermediate-term kidney outcomes among UTx recipients.

RESULTS

Twenty-two women who received UTx from September 2016 to February 2020 across 4 institutions were included in the study (Table 1; Supplementary Methods/Supplementary References [S1-S13]; Supplementary Table S1). All the women have had at least 1 successful pregnancy; 5 have delivered 2 children. At last follow-up, 20 have had a hysterectomy and discontinued immunosuppression; 2 recipients have retained their uteri for an additional pregnancy. Most had Mayer-Rokitansky-Kuster-Hauser syndrome as etiology of uterine factor infertility (95.5%) and only 1 had radiological evidence of a solitary kidney. Mean pretransplant serum creatinine in the cohort overall was 0.76 mg/dl (±0.08 mg/dl) and the mean pretransplant eGFR was 106.5 ml/min per 1.73 m^2 (±11.4 ml/min per 1.73 m^2). Median follow-up since UTx was 3.01 years (interquartile range 2.23–3.43 years) and the median exposure to immunosuppression was 2 years

Table 1. Demographics of the uterus transplant recipients included in this cohort

Characteristic	UTx recipients $N = 22$
Mean age at transplant in yrs (±SD)	31 (±4.9)
Race	
Black	1 (4.5%)
Middle Eastern	1 (4.5%)
White	20 (90.9%)
Etiology of uterine factor infertility	
MRKH	21 (95.5%)
Hysterectomy	1 (4.5%)
Solitary kidney	1 (4.5%)
Transplant type	
Living	14 (63.6%)
Deceased	8 (36.4%)
Mean pretransplant creatinine, mg/dl (±SD)	0.76 (±0.08)
Mean pretransplant eGFR, ml/min/1.73 m^2 (±SD)	106.5 (±11.4)
On immunosuppression at last follow-up	2 (9.1%)
AKI at any time during pregnancy	10 (45.5%)
Pre-eclampsia	5 (22.7%)

AKI, acute kidney injury; eGFR, estimated glomerular filtration rate; MRKH, Mayer-Rokitansky-Kuster-Hauser syndrome; UTx, uterus transplant.

(interquartile range 1.2–3.1 years). Mean eGFR at last follow-up (92.1 ml/min per 1.73 m^2 ± 18.4 ml/min per 1.73 m^2) was significantly lower than the pretransplant eGFR (pre-eGFR 106.4 ml/min per 1.73 m^2 ± 11.8 ml/min per 1.73 m^2, $P = 0.001$) (Supplementary Figure S1).

The eGFR slope is depicted in Figure 1a to c. Using linear mixed effect models, we estimated the postpartum eGFR while on immunosuppression was 25.7 ml/min per 1.73 m^2 lower (95% confidence interval [CI]: 18.7–32.7 ml/min per 1.73 m^2) than pretransplant values. eGFR rebounds after immunosuppression discontinuation by an average 11.6 ml/min per 1.73 m^2 (95% CI: 6.1–17.1 ml/min per 1.73 m^2); however, eGFR off immunosuppression was still 14.1 ml/min per 1.73 m^2 lower (95% CI: 8.5–19.8 ml/min per 1.73 m^2) than pretransplant. Rebound in eGFR was smallest early after immunosuppression discontinuation (rebound of 8.0 ml/min per 1.73 m^2, 95% CI: 1.9–14.1 and 9.9 ml/min per 1.73 m^2, 95% CI: 3.7–16.0 at 1 and 3 months after stopping, respectively) but increased at later timepoints (15.0 ml/min per 1.73 m^2, 95% CI: 8.8–21.2 at 6 months). The eGFR slope at 12 months postpartum was −10.2 ml/min per 1.73 m^2 lower than the pretransplant eGFR (Figure 1a).

We examined factors hypothesized to moderate eGFR change. Participants experiencing AKI during pregnancy (6.3 ml/min per 1.73 m^2 greater decline, 95% CI: −4.8 to 17.3 ml/min per 1.73 m^2) and preeclampsia (7.3 ml/min per 1.73 m^2 greater decline, 95% CI: −5.4 to 20.0 ml/min per 1.73 m^2) had greater declines in eGFR from baseline but differences were not statistically significant. The effect of immunosuppression duration was small (0.1 ml/min per 1.73 m^2 difference in eGFR per 100 days of additional immunosuppression, 95% CI: −1.1 to 1.4 ml/min per 1.73 m^2). For every 10 ml/min/m^2 decline in eGFR from pre-UTx to embryo transfer, we observed an estimated 5.2 ml/min/m^2 (95% CI: 3.4–7.0 ml/min/m^2) greater decline in postpartum eGFR slope.

DISCUSSION

We demonstrate that during a median of 3 years follow-up, UTx recipients are at risk for ongoing kidney dysfunction, manifested as a persistent reduction in eGFR of 10.2 ml/min per 1.73 m^2, despite hysterectomy and immunosuppression withdrawal. We observed a trend toward lower eGFR among UTx recipients who experienced AKI or preeclampsia during pregnancy.

This study, with more participants and longer follow-up, extends our previous observations[5] of a numerically lower eGFR in the postpartum period. We demonstrate a significant difference in both pretransplant versus 12 months postpartum eGFR and in estimates of eGFR slope. This result has important implications for the long-term health of UTx recipients. An annual decline in eGFR of −3 ml/min per 1.73 m^2 per year confers a 31% increase in all-cause mortality.[6,7] The rate of eGFR decline we observed exceeds typical eGFR loss rates of −0.3 to 1 ml/min per 1.73 m^2 per year expected in individuals without significant comorbidities or proteinuria.[8] Discontinuation of immunosuppression did not completely restore kidney function, despite UTx recipients being healthy, rigorously prescreened for systemic illnesses and having normal pretransplant kidney function (in contrast to other solid organ transplant recipients who often have comorbidities including preexisting kidney disease). UTx recipients are young women with normal life expectancies; therefore, an early loss of kidney function is particularly concerning. Chronic kidney disease, where stage I is defined as an eGFR ≤90 ml/min per 1.73 m^2, has negative implications for overall health, increasing the risk of mortality, cardiovascular disease, AKI, and end-stage kidney disease.[8] UTx is not a lifesaving procedure and the risks must be weighed against the benefits. Longer follow-up of UTx recipients is needed to determine if their eGFR slope stabilizes over several years or if glomerular filtration rate decline continues.

In the general population, preeclampsia and AKI episodes have been associated with an increased risk of future chronic kidney disease.[9,S8] We also observed a trend toward lower eGFR slope among UTx recipients

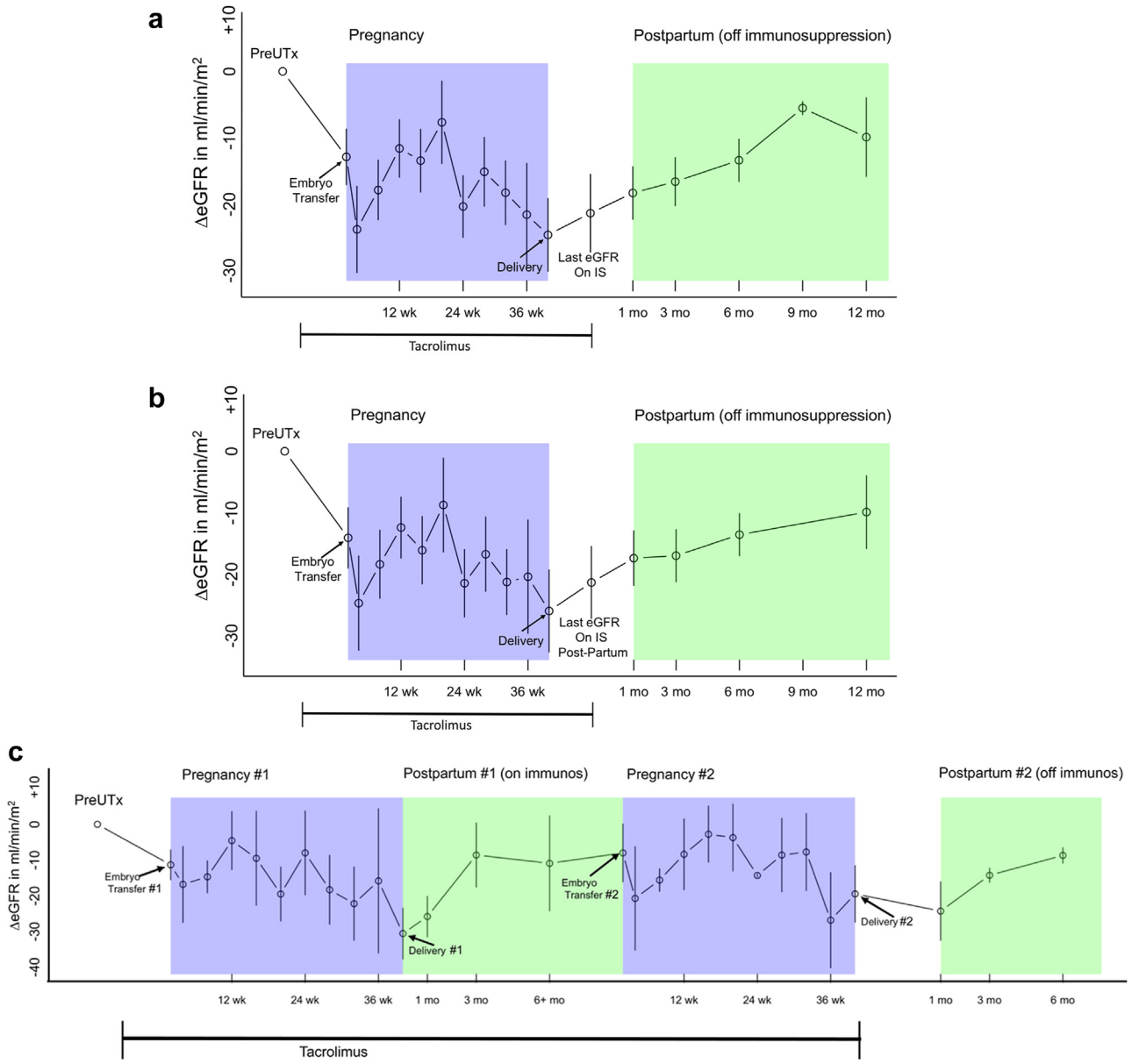

Figure 1. eGFR trajectory pretransplant, during pregnancy and in the postpartum period off immunosuppression. (a) Entire cohort ($N = 22$). Among women with 2 pregnancies, only data from the second pregnancy are included. (b) Women with only 1 pregnancy ($n = 17$). (c) Women with 2 pregnancies ($n = 5$). The circles plot average delta eGFR with 1 standard error bars. Starting delta eGFR at time of uterus transplant is zero; subsequent eGFR negative values indicate a relative loss (decline) in eGFR from the baseline established prior to transplant. eGFR, estimated glomerular filtration rate.

who experienced AKI or preeclampsia in our cohort. This observation is useful when counseling UTx recipients considering a second pregnancy, because AKI or preeclampsia during a first pregnancy could increase their future chronic kidney disease risk.

Our findings highlight the need for mitigation strategies. Effective options to prevent preeclampsia are limited. All UTx recipients are maintained on low-dose aspirin, the standard intervention in the general population.[S9] AKI episodes during pregnancy are infrequent but more common among those with pre-existing chronic kidney disease or transplants[S10]; fluctuations and inaccuracies in whole blood CNI measurements during pregnancy may contribute to this risk among transplant recipients.[S11] Although the effect of immunosuppression duration on eGFR among UTx recipients was minimal, efforts to reduce CNI exposure, such as reducing the time interval between transplant and embryo transfer and withdrawing immunosuppression immediately after hysterectomy, are warranted. Dedicated studies to determine the ideal CNI trough levels among UTx recipients and optimize CNI dosing during pregnancy would be beneficial. CNIs have well-described nephrotoxicity. Alternatives, such as belatacept, exist but have not been extensively studied in pregnancy[S12] and there

are theoretical concerns regarding fetal toxicity.[S13] Our study highlights the need for prospective study of targeted interventions, such as CNI-free immunosuppressive regimens, that could mitigate some of the deleterious effects of UTx on kidney function.

Our study has notable strengths. Our cohort represents a large, multicenter and international group of UTx recipients with serial kidney function measurements. We used linear mixed effects models to examine trends in eGFR. Linear mixed effects models naturally handle missing data and are enhanced by multiple observations across different timepoints. We were able to account for the impact of AKI and preeclampsia. There are limitations to our work: a lack of consistent proteinuria assessments, variation in candidate evaluation and follow-up, and center-level variation in immunosuppression protocols. Compared to typical studies of eGFR slope trajectory, the overall size of our cohort is small; however, this should bias our findings toward the null.

UTx is an established treatment for uterine factor infertility and moving into general clinical care; however, kidney risks persist beyond the period in which recipients are on immunosuppression. Reduction in eGFR has negative implications for long-term health outcomes. It will be important to clarify the contribution of Mayer-Rokitansky-Kuster-Hauser syndrome versus aspects of the transplant procedure or immunosuppression. Further study is required to delineate these risks and provided optimal informed consent to UTx candidates.

DISCLOSURE

The authors declare no competing interests.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods.

Supplementary References.

Figure S1. Mean eGFR with standard deviation from preuterus transplant through delivery and last follow-up among (a) women with only one pregnancy and (b) women with 2 pregnancies.

Table S1. Mean tacrolimus levels with standard deviation among UTx recipients at different time points during the study.

REFERENCES

1. Brannstrom M, Tulius SG, Brucker S, et al. Registry of the International Society of uterus transplantation. *Transplantation*. 2023;107:10–17.
2. Johannesson L, Testa G, Putman JM, et al. Twelve live births after uterus transplantation in the Dallas UtErus transplant study. *Obstet Gynecol*. 2021;137:241–249. https://doi.org/10.1097/AOG.0000000000004244
3. Vali S, Jones BP, Saso S, Yazbek J, Quiroga I, Smith JR. Uterus transplantation: a 50-year journey. *Clin Obstet Gynaecol*. 2022;65:92–100. https://doi.org/10.1097/GRF.0000000000000679
4. Chen N, Pan H, Luo G, et al. Clinical characteristics of 1,055 Chinese patients with Mayer-Rokitansky-Kuster-Hauser syndrome: a nationwide multicentric study. *Fertil Steril*. 2021;116:558–565. https://doi.org/10.1016/j.fertnstert.2021.02.033
5. Sawinski D, Johannesson L, Kristek J, et al. A multi-institutional study of renal outcomes and renal-related pregnancy outcomes in uterus transplant recipients. *Am J Transplant*. 2022;22:3101–3110. https://doi.org/10.1111/ajt.17149
6. Turin TC, Coresh J, Tonelli M, et al. Change in the estimated glomerular filtration rate over time and risk of all-cause mortality. *Kidney Int*. 2013;83:684–691. https://doi.org/10.1038/ki.2012.443
7. Rifkin DE, Shlipak MG, Katz R, et al. Rapid kidney function decline and mortality risk in older adults. *Arch Intern Med*. 2008;168:2212–2218. https://doi.org/10.1001/archinte.168.20.2212
8. Kidney Disease: Improving Global Outcomes CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl*. 2013;3:1–150.
9. Kristensen JH, Basit S, Wohlfahrt J, Damholt MB, Boyd HA. Pre-eclampsia and risk of later kidney disease: nationwide cohort study. *BMJ*. 2019;365:1516. https://doi.org/10.1136/bmj.l1516