Long-Term Effects of Pregnancy on Renal Graft Function in Women After Kidney Transplantation Compared With Matched Controls

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ABSTRACT

Background. An important benefit associated with kidney transplantation in women of child-bearing age is increased fertility. We retrospectively evaluated the maternal and fetal complications and evolution of graft function associated with 22 pregnancies post–kidney and kidney-pancreas transplantation, compared with controls without pregnancy post-transplantation, who were matched for gender, year of transplantation, type of donor, age at transplantation, number of transplants, type of transplant (kidney vs kidney-pancreas), and cause of native kidney failure, as well as for renal parameters including serum creatinine and urine protein excretion 1 year before delivery.

Results. The mean age at time of transplantation was 22.32 (range, 19.45–33.1) years. The mean interval between transplantation and delivery was 75.7 (range, 34–147.8) months. Main maternal complications were pre-eclampsia in 27.3%. The main fetal complications included delayed intrauterine growth (18.2%), preterm deliveries (89.4%), and one death at 3 days postdelivery. The mean serum creatinine level pre-pregnancy was 1.17 (range, 0.7–3.1) mg/dL. Graft failure was higher in the pregnancy group (6 vs 3) but did not differ statistically from the control group, and was associated with creatinine pre-pregnancy (odds ratio [OR], 1.71; 95% confidence interval [CI], 1.15–3.45; $P = .04$), age at transplantation (1.13 [1.03–1.21]; $P = .032$), and time of follow-up (2.14 [1.27–2.98]; $P = .026$). Delta serum creatinine was not different in both groups: 1.05 ± 0.51 versus 0.99 ± 0.92 mg/dL, study versus control group, respectively ($P = .17$).

Conclusion. Pregnancy after kidney transplantation is associated with serious maternal and fetal complications. We did not observe a significantly increased risk of graft loss or reduced graft function in comparison with recipients with similar clinical characteristics.

IN ADDITION to its other beneficial effects, renal transplantation improves the fertility of women of child-bearing age [1]. Studies have been published examining the obstetric and renal outcomes of the resultant pregnancies. Although these pregnancies clearly have better outcomes than those that occur during dialysis treatment, they are still fraught with complications [2].

Studies have shown more maternal complications, with a higher rate of pre-eclampsia and delivery by cesarean section, and more adverse fetal outcomes, including intrauterine growth restriction, preterm delivery, and low birth weight, resulting in increased neonatal morbidity and mortality [3,4]. In addition, the prognosis of the infants born is affected regardless of prematurity because they experience a higher risk of severe infections in the first year of life due to intrauterine exposure to immunosuppressant drugs [5].

While most studies have not found an overall negative effect of pregnancy on graft function and survival, they have found an association between graft function at the time of conception and subsequent deterioration of function and graft loss. The parameters that were found to be related to

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Table 1. Baseline Population Characteristics of Study (Pregnancy) Group and Matched Controls (Mean [SD], Unless Otherwise Stated)

Parameter	Study Group n = 22	Matched Controls n = 22	*P*
Ethnicity (white), n (%)	22 (100)	22 (100)	1
Age at transplantation (y)	22.32 (5.9)	23.1 (7.1)	.74
Number of transplantations, n (%)			1
First	18 (81.8)	18 (81.8)	
Second	4 (18.2)	4 (18.2)	
Organs, n (%):			1
Kidney	20 (90.9)	20 (90.9)	
Kidney-pancreas	2 (9.1)	2 (9.1)	
Donor, n (%):			.77
Living related	9 (40.9)	7 (31.8)	
Living unrelated	7 (31.8)	9 (40.9)	
Deceased	6 (27.3)	6 (27.3)	
Reason for ESRD, n (%):			1
Diabetes	3 (13.6)	3 (13.6)	
Glomerular	15 (68.2)	15 (68.2)	
Urologic	4 (18.2)	4 (18.2)	
Pre-emptive transplantation, n (%):	15 (68.2)	12 (54.5)	.535
Induction (Thymoglobulin) n (%):	16 (72.7)	18 (81.8)	.72
Maintenance immunosuppression (CNIs, prednisone, MMF), n (%):	20 (90.9)	20 (90.9)	1
Serum creatinine pre-pregnancy (mg/dL):	1.17 (0.57)	1.09 (0.66)	.43
Serum creatinine >1.5 mg/dL, pre-pregnancy, n (%):	3 (13.6)	3 (13.6)	1
eGFR pre-pregnancy (mL/min/1.73 m^2)	78.1 (8.4)	80.4 (7.9)	.59
Urine protein pre-pregnancy (mg/24 h)	127 (53)	149 (76)	.69
Chronic hypertension, n (%):	8 (36.3)	11 (50)	.54
New-onset diabetes post-transplantation, n (%):	2 (9)	1 (4.5)	1
Biopsy-proven rejection pre-pregnancy, n (%):	1 (4.5)	2 (9.09)	1
Live birth pretransplantation, n (%):	5 (22.7)	2 (9.1)	.412
Time of delivery post-transplantation (mo)	75.7 (31.8)	N/A	
Mean follow-up time (y)	12.4 (4.78)	12.7 (5.01)	.81

Abbreviations: CNI, calcineurin inhibitors; ESRD, end-stage renal disease; MMF, mycophenolate mofetil; N/A, not applicable.

decreased graft function and loss after pregnancy were time between transplantation and pregnancy, estimated glomerular filtration rate (GFR) and level of urinary protein pre-pregnancy, and hypertension [6–8]. Studies have also shown an increase in graft loss during and after pregnancy among sensitized patients [9,10] and higher risk of graft failure due to rejection in pregnancies occurring in the first and second year post-transplantation [11].

Most of these observations were found in studies using controls of nonpregnant recipients, but most did not match the study group in several critical clinical parameters, such as the gender of the controls, the creatinine level pre-pregnancy, or the cause of native kidney failure [8,12–15].

The aim of our study was to investigate the long-term effects of pregnancy on graft function in women treated in our transplantation unit who experienced a pregnancy ending in live birth after kidney or simultaneous kidney and pancreas transplantation. Our control group was carefully selected to match our study group in gender, year of transplantation, type of donor, age at transplantation, number of transplants, type of transplant (kidney or kidney and pancreas), and cause of native kidney failure, as well as for renal parameters including serum creatinine level and urine protein excretion 1 year before delivery, to make the comparison as accurate as possible.

METHODS

The study group consisted of 22 consecutive pregnancies ending in live birth, in 18 kidney and simultaneous kidney and pancreas (SPK) recipients that occurred between the years of 2001 and 2017. All women from the study group underwent transplantation between the years 1996 and 2016 in the Renal Transplantation unit of Tel Aviv Sourasky Medical Center, and were in routine follow-up post-transplantation in our unit. No recipient from the study group was lost to follow-up.

The control group included kidney and SPK recipients from our center who did not conceive post-transplantation and were in follow-up in our unit at least until the last day of follow up (LDFU) of the matched study participant, or until graft loss. The controls were matched 1:1 for the following parameters: gender, year of transplantation (±1 years), type of donor (deceased vs living donor), age at transplantation (±2 years), number of transplants, type of transplant (kidney vs SPK), and cause of native kidney failure, which we divided into three groups: urological causes, glomerular disease, and diabetes. The controls were also matched for renal parameters that included the following: serum creatinine level (±0.2 mg/dL) 1 year before the date of delivery and urine protein excretion (±50 mg/24 h) 1 year before the date of delivery.

GFR was estimated (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation, a four-variable formula [16] adjusted for Body Surface Area (Mosteller calculation). Graft loss was defined as return to dialysis or new