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Pregnancy after Kidney Transplantation

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Abstract

Pregnancy is not contraindicated in renal transplant recipients with stable renal function, and a successful and healthy obstetric outcome can be expected in 95% of several cases. The incidence of maternal and fetal complications is related to the degree of graft dysfunction and/or hypertension prior to pregnancy. Poorer prognosis is connected with poor renal function. If complications occur before 28 weeks, then successful obstetric outcome is minimized by 20%. More information is needed about the intrauterine effects and neonatal consequences of maternal immunosuppression, which shows harmless at maintenance levels. From the data that was available it seems that pregnancy does not compromise long-term transplant prognosis. Non-existence of prospective controlled studies transplant pregnancy registries are the only viable means of providing clinicians with timely and relevant guidance on pregnancy outcomes on which to base management guidelines.

Keywords: Natural dye; Color; Cotton fabric; Opium dyel; Mor dents; Optical density; Dyeing; Dye; Liquor; Dye bath; Mordent

Introduction

Kidney Transplantation (KT) is the treatment of choice for End-Stage Renal Disease (ESRD) patients. It improves survival and quality of life. In women in childbearing age, it also restores the fertility, and this can be within the first few months after the kidney transplantation.

The pregnancy during the lifetime of KT is considered to be safe for the mother and the child when a functional graft is present, however, an increased incidence of preeclampsia, surgical delivery, and prematurity. However, the effect of pregnancy on graft function and loss is less clear [1-4].

In light of the limited evidence in graft outcomes, especially in developing countries were the pregnancy occurs in quite different circumstances than in developed countries, we aimed to investigate the effect of pregnancy in allograft function and rejections, as well as obstetrics complication associated with pre and post-transplant characteristics [5] .

Materials and Methods

Patients

We performed a retrospective cohort of women with pregnancies after at least one year of their KT, who was treated at the Nephrology Department from the hospital general Regional 46 of the Instituto Mexicano del Seguro Social. Our institution has a nominal census of 1200 KT recipients with more than one year, of which, approximately 35% to 40% are female on childbearing age. From January 1994 to January 2017, there were 41 pregnancies on 34 patients with a kidney allograft and were included to the study. As control group for the primary outcome, 66 women that received a kidney allograft during childbearing age without a history of pregnancy were included [6-8].

Outcomes: The primary outcome was the time to occurrence of Chronic Allograft Dysfunction (CAD), defined as a composite of persistently elevated Serum Creatinine (SCr) >1.5 mg/dL, estimated Glomerular Filtration Rate (eGFR) calculated using the CKD-EPI equation <40 ml/min/1.73 m^2, and 24-hour urine protein collection >500 mg/day or urine Protein/Creatinine Ratio (PCR)>0.5 g/g [9].

Secondary outcomes included frequency of allograft related complications: sCr>1.5 mg/dL, eGFR<40 ml/min/1.73 m2, persistent proteinuria (>500 mg/day), need for allograft biopsy and biopsy proven rejections. Obstetrics complications as preeclampsia, abortion, surgical delivery, preterm delivery were also considered secondary outcomes.

Statistical analysis: Categorical variables presented as frequencies and proportions were compared using chi-square tests or Fisher exact test. Parametric continuous variables expressed as mean values ± Standard Deviations (SDs) and were compared using the Student unpaired t test. Nonparametric continuous variables expressed as median values and Inter Quartile Ranges (IQR) was compared using Mann-Whitney U tests [10].

Kaplan-Meier survival analysis estimated for the primary outcome with comparisons using the log-rank test was used, as well as Cox proportional hazard ratios with time varying covariate for multivariate analysis. All analyses were performed with SPSS software.

Results

Baseline characteristics

A total of 100 women were included with a median follow-up of 97.2 months (IQR 47.4-136.2). The age at the moment of KT in our cohort was 22.3 years (IQR 17.3-25.1). Briefly, the age at diagnosis of CKD was 18 years (IQR 14.2-22), the more frequent etiology was unknown in 84 (84%) of the women, follow by glomerulopathies in seven (7%) cases, three (3%) due to preeclampsia, one (1%) case attributed to hypertension and three (3%) associated to ureterovesical reflux. For RRT, 20 (20%) women received Intermittent Hemodialysis (HD), 25 (25%) Peritoneal Dialysis (PD), seven (7%) had both therapies, and 28 (28%) received a preemptive Kidney Transplantation (KT) (Figure 1).

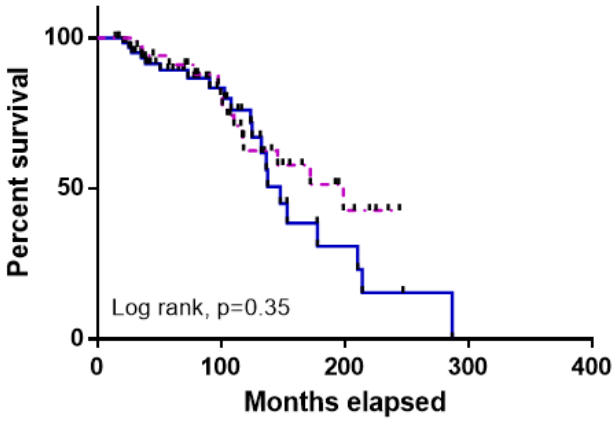

Figure 1: Univariate Kaplan-Meier survival analysis for CAD between pregnancy women and control women. Note: Pregnancy group Control group.

Kidney transplantation characteristics: The main donor type was alive in 92 (92%) women, of whom 75 were relatives (i.e. parents, siblings) and 17 were not, the average age of the donor was 35.7 years ± 10.6 years. Six women included in the study were carries of a second kidney graft. Information about induction therapy was available in 50 (50%) women, of which, thymoglobulin was used in 22 (22%), basiliximab in 26 (26%), and daclizumab in two (2%) patients. The infectious risk for CMV was low in three (3%) women, intermediate in 36 (36%), high in 18 (18%) and unknown in 41 (41%) patients. The baseline sCr (lowest level immediately after KT) was 0.9 mg/dL (IQR 0.8-1.0) (Figure 2) [11].

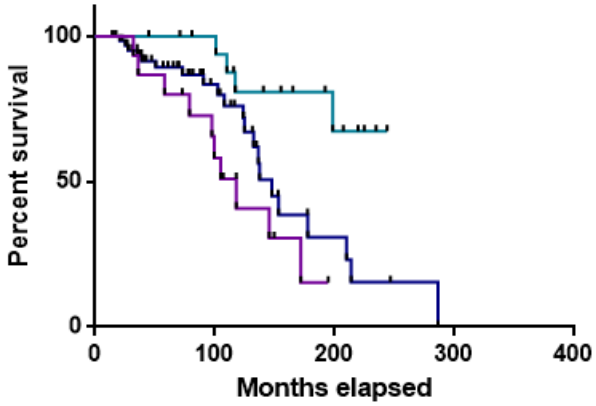

Figure 2: Univariate Kaplan-Meier survival analysis for CAD between pregnancy women and control women. Note: Preeclampsia Pregnancy without preeclamps Controls.

As expected, the number of biopsies was associated with CAD (p<0.01), proteinuria (p=0.03), and persistent sCr elevation (p=0.01). And the number of biopsies were not associated to donor type, CMV risk nor induction therapy (p=0.12, 0.16, 0.82) (Table 1).

	Mean survival (months)	CI 95%	p[a]
Pregnancy group	173.1	145.8-200.4	0.35
Control group	158.7	128.7-188.8	
Note: a=Long range test			

Table 1: Patients with unplanned pregnancies the initial treatment included Mycophelonate Mofetil (MMF) and subsequently changed.

Pregnancy related outcomes: Thirty-four women got pregnant during the study, the mean age at pregnancy was 25.8 years ± 5.2 years, with a transplantation-pregnancy interval of 6.3 years ± 3.3 years. The sCr previous to the pregnancy was 0.8 mg/dL (IQR 0.7-1.1), and there were not patients with sCr>1.5 mg/dL. The proteinuria was 200 mg/day (IQR 107.5-307.5), without patients with >500 mg/day prior pregnancy. The immune suppressive treatment during pregnancy was CNI/azathioprine/prednisone in 25 (73%) women, where the CNI more frequently used was tacrolimus; azathioprine/prednisone without CNI were used in five (14.7%) patients, and in four (11.8%) patients with unplanned pregnancies the initial treatment included Mycophelonate Mofetil (MMF) and subsequently changed (Table 2).

	Total	Pregnancy	Control	P
	N=100	n=34	n=66	
Weight (kg)	60.2 (54-70)	60 (58-70)	61 (52-70)	0.52
Height (m)	1.58 (1.53-1.60)	1.57 (1.52-1.6)	1.58 (1.53-1.61)	0.45
BMI (kg/m2)	24.5 (22.1-27.8)	25.1 (22.7-27.7)	24.2 (21.6-28.3)	0.35
Age at CKD diagnosis (years)	18 (14.2-22)	17 (13-20)	20 (16-23)	0.02
CKD etiology				
Unknown	84 (84.8)	30 (88.2)	54 (83.1)	
Primary GNa	7 (7)	1 (2.9)	6 (9.3)	0.37
Otherb	8 (8.1)	3 (8.8)	5 (7.7)	
RRT				
PD	25 (31.3)	0 (0)	25 (53.2)	

HD	20 (25%)	7 (21.2)	13 (27.7)	<0.01
Preemptive KT	28 (35)	24 (72.7)	4 (8.5)	
Dialysis vintage (years)	1.9 (1-3)	1 (1-2)	2 (2-3)	<0.03
Hypertension	22 (22)	9 (26.5)	13 (19.7)	0.44
Diabetes	2 (2)	1 (2.9)	1 (1.5)	0.64
Age at KT (years)	22.3 (17.3-25)	18.8 (15.4-23)	23.2 (19.3-26.6)	<0.01
Second graft	6 (6)	4 (11.8)	2 (3.0)	0.18
Donor type				
Alive	92 (92)	34 (100)	58 (88)	0.08
Donor age (years)	35.7 ± 10.6	34.3 ± 10.2	37.3 ± 10.9	0.25
Baseline sCr (mg/dL)	0.9 (0.8-1.0)	0.8 (0.7-0.9)	1 (0.8-1.1)	<0.01
Induction therapy				
Thymoglobulin	22 (22)	2 (6.1)	20 (30.3)	
Basiliximab	26 (26.3)	9 (27.3)	17 (25.8)	0.01
Daclizumab	2 (2)	2 (6.1)	0 (0)	
Unknown	49 (45.5)	20 (60.6)	29 (43.9)	
CMV risk				
Low	3 (3.1)	1 (3.0)	2 (3.1)	
Intermediate	36 (36.7)	14 (42.4)	22 (33.8)	0.05
High	18 (18.4)	1 (3.0)	17 (26.2)	
Unknown	41 (41.8)	17 (51.5)	24 (36.9)	

Table 2: Baseline characteristics.

During pregnancy, were two (5.9%) cases of diabetes, three (8.8%) women had anemia, fifteen (44.1%) suffered preeclampsia, one (2.9%) had HELLP syndrome, and 13 (38.2%) had a Urinary Tract Infection (UTI).

There were 27 (79.4) alive newborns, four (11.8%) cases of abortion, and three (8.8%) stillbirths. The median gestational age was 37 weeks (IQR 34.5-40.5), and nine (26.5%) of the products were preterm. There were six (17.6%) vaginal deliveries, nine (26.5%) elective surgical deliveries, 15 (44.1%) emergent surgical deliveries associated with the development of preeclampsia. The patients that developed preeclampsia had less time in dialysis (p=0.01), higher baseline sCr (p<0.01), as expected, had higher sCr at the second trimester of pregnancy (p<0.01) and higher proteinuria but only at the third trimester (p<0.01). No other pre-transplantation and transplantation characteristic was associated to the development of preeclampsia. Also, the presence of preeclampsia was strongly associated with adverse obstetrical outcomes as stillbirth, preterm delivery, and need for emergent surgical delivery (Table 3).

	Coefficient	P	HR	CI 95%
PD	-1.45	0.25	0.23	0.02-2.8
Dialysis vintage	-0.18	0.43	0.83	0.53-1.30
Age at KT	0.01	0.77	1.01	0.92-1.11
Baseline sCr	1.9	0.02	6.7	1.3-34.9
Intermediate CMV risk	1.84	<0.01	6.32	1.6-25.2
High CMV risk	0.25	0.84	1.29	0.11-15.2
Pregnancy	0.73	0.45	2.07	0.30-14.1

Table 3: Cox proportional hazard ratio model for CAD.

At the end of pregnancy, patients who had preeclampsia remained with higher sCr and proteinuria (p=0.04 and 0.03 respectively), but it was not associated with the need for a kidney biopsy after the pregnancy or presence of rejections (p=0.06, 0.22 respectively) (Table 4).

Total N=100	Pregnancy N=34	Control N=66	P	
Chronic allograft dysfunction	35 (35)	14 (41.2)	21 (31.8)	0.38
sCr >1.5 mg/dL (%)	25 (25)	10 (29.4)	15 (22.7)	0.48
eGFR<40 ml/min/1.73 m2 (%)	18 (18)	8 (23.5)	10 (15.2)	0.3
Proteinuria>500 mg/day (%)	24 (24)	12 (35.3)	12 (18.2)	0.06
Number of biopsies	1 (0-2)	1 (1-2)	1 (0-2)	0.63
Histological diagnosis				
Normal	29 (22.7)	8 (19)	21 (24)	
TCMR	25 (19.5)	13 (32)	12 (13)	
Acute ABMRb	7 (5.5)	2 (5)	5 (5)	<0.01
Chronic ABMR	4 (3.1)	2 (5)	2 (2)	
CNI toxicity	35 (27.3)	11 (27)	24 (29)	
Othera	28 (21.9)	5 (12)	23 (27)	

Table 4: Graft related outcomes. Note: a= reported 128-allograft biopsies, b=Other diagnosis included three *de novo* FSGS, two IgAN, one MN, 18 unknown or improper sample, and four cases of non-specific IFTA.

Finally, we decide to analyze if patients with preeclampsia had an increased risk for the primary outcome compared to patients with pregnancy without preeclampsia and women without pregnancies (Table 5) [12].

	At pregnancy n=34	After pregnancy n=34	P
Antimetabolites			
Mycophelonate	4 (11.8)	21 (61.8)	<0.01
Azathioprine	30 (88.2)	8 (23.5)	
CNI and mTORi			
Tacrolimus	21 (61.8)	18 (52.9)	0.57
Ciclosporine	5 (14.7)	3 (8.8)	
Sirolimus	3 (8.8)	4 (11.8)	
CNI free regimen	5 (14.7)	9 (26.5)	

Table 5: Immunosuppressive therapy during and after pregnancy. Also, the patients who suffered from preeclampsia had higher prevalence of CAD, persistent sCr elevation, eGFR<40 ml/min/1.73 m2, and proteinuria at the end of follow-up (p<0.01, 0.04, and <0.01 respectively) (Table 6).

	Total N=34	Preeclampsia n=15	Without preeclampsia n=19	P
Age at diagnosis of CKD (years)	-	16.6 ± 4.2	16.6 ± 6.2	0.99
Dialysis vintage (years)	1.1 (0.9-2)	1 (1-1)	2 (1-3)	0.01
Age at KT (years)	-	18.9 ± 4.4	19.3 ± 6.7	0.88
Donor type				
Relative	29 (85.3)	16 (84.2)	13 (86.7)	0.84
No relative	5 (14.7)	2 (13.3)	3 (15.8)	
CMV risk				

Low	1 (3)	0 (0)	1 (5.6)	
Intermediate	14 (42.4)	5 (33.3)	9 (50)	0.4
High	1 (3)	1 (6.7)	0 (0)	
Unknown	17 (51.5)	9 (60)	8 (44.4)	
Baseline sCr (mg/dL)	0.8 (0.7-0.9)	0.8 (0.8-1.0)	0.8 (0.7-0.8)	<0.01
sCr prior pregnancy (mg/dL)	0.81 (0.7-1.1)	0.9 (0.8-1.5)	0.72 (0.7-0.9)	<0.01
Proteinuria prior pregnancy (mg/day)	220.1±134.4	205.2±100.8	233.2±160.4	0.57
Unplanned pregnancy	14 (41.2)	8 (53.3)	6 (31.6)	0.2
Product outcome				
Alive	27 (79.4)	12 (80)	15 (78.9)	
Abortion	4 (11.8)	0 (0)	4 (21.1)	0.03
Stillbirth	3 (8.8)	3 (20)	0 (0)	
Delivery				
Vaginal	6 (17.6)	5 (33.3)	1 (5.3)	
Elective surgical	9 (26.5)	0 (0)	9 (47.4)	<0.01
Emergent surgical	15 (44.1)	10 (66.7)	5 (26.3)	
Preterm delivery	9 (26.5)	5 (33.3)	4 (21.1)	0.05
sCr after delivery (mg/dL)	0.8 (0.7-1.1)	0.95 (0.8-1.25)	0.72 (0.7-1.0)	0.03
Proteinuria after delivery (mg/day)	400 (285-700)	650 (350-1630)	300 (250-450)	0.01

Table 6: Factors associated with preeclampsia.

The histological results of all the biopsies were grouped in normal, acute TCMR, acute and chronic ABMR, CNI toxicity, and other pathologies. Patients with pregnancy had more TCMR and chronic ABMR than the controls (p=0.01) (Table 7) [13-15].

	Cox regression			Logistic regression				
	Coefficient	p	HR	CI 95%	Coefficient	p	OR	CI 95%
Preeclampsia	0.6	0.13	1.82	0.84-3.95	1.45	0.02	4.29	1.3-14.1
Pregnancy without preeclampsia	0.02	0.02	0.28	0.09-0.82	-0.56	0.37	0.57	0.17-1.9

Table 7: Risk for CAD in patients with preeclampsia.

Discussion

In a logistic regression model, the history of preeclampsia had an increased risk for the development of CAD (OR 4.8, CI 95% 1.5-15.5, p<0.01), value that remain significant after adjusting for CMV risk, baseline sCr, age at KT and dialysis vintage (HR 3.6 CI95% 1.33-9.6, p=0.01) (Table 8).

	Mean survival (months)	CI 95%	p[a]
Preeclampsia	119.1	90.9-147.3	
Pregnancy without preeclampsia	212.2	185.0-239-4	<0.01
Controls	158.7	128.7-188.8	

Table 8: Log rank test.

Conclusion

The pregnancy after transplantations is safe, but is associated with an increased risk for maternal complications as surgical delivery,

prematurity and the develop of preeclampsia, that can have a long lasting effect on the graft and is associated with worse renal outcomes, independently of rejections.The maternofetal outcomes in patients with kidney transplantation are comparable with those of nontransplanted CKD patients with similar levels of kidney function impairment and progressive and/or immunologic kidney disease. Our data were in agreement with the literature confirming that pregnancy after kidney transplant though possible carries elevated risks

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