

RENAL AND OBSTETRIC OUTCOMES AFTER KIDNEY TRANSPLANTATION IN PREGNANCY: A SINGLE CENTER EXPERIENCE

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INTRODUCTION

In uremic women, inhibition of releasing of gonadotropin releasing hormone (GnRH) results hypothalamic-pituitary dysfunction, and leads to anovulation, abnormal menstrual cycle, amenorrhea and infertility. Furthermore, the drugs cause fatigue, weight loss, depression and loss of sexual drive (1-3). After kidney transplantation, in 2-5% of women of childbearing age, recovery of normal menstrual function occurs in 1-20 months (4). Those who wish to become pregnant, are recommended to wait at least 2 years after transplantation. A stable trend in renal function (serum creatinine <1.5 mg/dL) is one of the most important factors affecting becoming pregnant. Controlling blood pressure, keeping immunosuppressive drugs in optimal levels, using azathioprine (AZA) instead of mycophenolate (MMF) and keeping urinary protein excretion under 500 mg/day are other suggestions. During and after pregnancy, both patient and fetus should be monitored closely for maternal complications such as hypertension (HT), preeclampsia, gestational diabetes, proteinuria, rejection, drug side effects, and infections and fetal complications such as intrauterine growth retardation (IUGR), low birth weight, premature birth, low Apgar score, and need for intensive care unit (5-9). In present study, outcomes of pregnancy after kidney transplantation were evaluated retrospectively.

SUBJECTS AND METHODS

In the study, 140 women of reproductive age (15-49 year-old) who had kidney transplantation between January 1st, 2009 and June 30th, 2015, were included. The patients wishing to conceive were allowed after post-transplant two-year stable trend in renal functions (serum creatinine <1.5 mg/dL). AZA was substituted for MMF. Other risky medications were changed or stopped. Low dose prednisolone and calcineurin inhibitor were continued. Clinical and laboratory data of the patients were obtained from electronic files. Demographic data, primary disease, duration of dialysis prior to transplantation, donor age, type of transplantation, time after transplantation, immunosuppressive therapy, history of rejection and urinary tract infection were recorded. Patients were divided into two groups based on pregnancy: pregnant and non-pregnant control. Serum creatinine, hemoglobin, amount of urinary protein excretion, age of pregnant women at birth, TTB, weeks at pregnancy termination, hypertension rate, history of preeclampsia, mode of delivery, birth weight, IUGR, Apgar scores and need for intensive care unit were evaluated and compared in both groups.

Statistical Analysis

Continuous variables and categorical variables were expressed by median (minimum-maximum) values and corresponding percentage values, respectively. Wilcoxon test was used for comparison of intra-group; Mann-Whitney, Fisher's exact test and Fisher-Freeman-Halton tests were used for comparison of inter-group. Independent risk factors for pregnancy were assessed by logistic regression analysis and forward method was used to select variables. In all analysis, p<0.05 was accepted as significance level. Data was statistically processed by IBM SPSS version 21 software (IBM Acquires SPSS Inc., Somers, NY, USA).

RESULTS

Twenty-four patients conceived (17.1%). In pregnant group, median age was significantly lower than in non-pregnant group (p=0.014). Median age of pregnant group at the time of transplantation was also significantly lower than non-pregnant patients (p<0.001). 66.7% of pregnant patients were in 18-25 year age group (p=0.008). Rate of urinary tract infection in non-pregnant group was higher than pregnant group (p=0.03). Most of pregnant women took medication including tacrolimus, azathioprine and prednisolone. Median age of pregnant patients at birth was 29 (23-39) years and median time from transplantation to birth (TTB) was 52.5 (20-178) months (Table 1 and 2). The mode of delivery was cesarean section in 70.8% and 54.2% of births occurred over 37 weeks. Live births rate was 83.3 and 45.8% of those had birth weight higher than 2500 grams. Increased level of daily urinary proteinuria and the time from diagnosis of renal failure to transplantation had significant effect on pregnancy (OR=13.81; %95 CI: 2.06 to 92.45; p=0.007 and OR=3.25; %95 CI: 1.11 to 9.48; p=0.031, respectively). Low serum creatinine level had significant protective effect (OR=0.001; %95 CI: 0 to 0.30, p=0.018). The patients in 18-25 age group were 48.39 times more eligible for pregnancy compared to those in >35 age group (OR=48.39; %95 CI: 1.26 to 1860.72; p=0.037). Rejection episodes were observed in 1 of pregnant women and 11 of non-pregnant women (p>0.05) (Table 3 and 4).

DISCUSSION

Despite all complications and side effects of the drugs, pregnancy in kidney transplant can end successfully. Risk factors associated with successful pregnancies after renal transplantation were identified in European Best Practice Guidelines (EBPG). The risks of proteinuria, infection, anemia, arterial hypertension, acute rejection episode for pregnant and premature birth and low birth weight for fetus were increased in pregnancy. Therefore, pregnancy should be monitored more closely in especially third trimester (9). In nearly 50 studies conducted in 25 countries, 4706 pregnancies have been reported in 3570 recipients of kidney transplants. In that report, rates of pre-eclampsia, live births, preterm birth and cesarean delivery were 27%, 73%, 45%, and 56%, respectively (10). In a report from United Kingdom, 105 pregnant kidney recipients were observed for three years (11). During pregnancy TAC, AZA, and prednisolone were most commonly received. 24% of those developed eclampsia. 64% had cesarean delivery and 91% of births were live births. Birth weights lower than 2500 grams were observed in 24%. 52% of births were premature. Mean serum creatinine level was lower than 1.3 mg/dL in those with good outcomes. Deterioration in renal function was observed in 38%. In another study from Australia (12), an analysis of 40-year follow-up (1966 to 2005) was reported. Mean age was 29±5 years. 27% of those developed preeclampsia. Rates of live birth, termination, and abortion were 62%, 30%, and 9%, respectively, between the years 1966-2005. Gill et al (13) reported the assessment of 16195 women in reproductive age between the 1990-2003. Pregnancy and live birth rate were 33/1000 and 19/1000, respectively. CsA (71%), and AZA (49%) were most commonly used medications. Pregnancy rate in 20-24 aged group was 93%. In pregnant recipients, rates of live births and abortion were observed 55% and 21%, respectively.

In the study of Alfay et al. (14), mean age of twenty pregnant recipients was 30.5±4.5 years. The mean time from transplantation to pregnancy was 21±5.7 months. In 2 patients, graft loss occurred. In one of those, the time between transplantation and pregnancy was lower than one year. The other patient had prenatal serum creatinine greater than 1.5 mg/dL. Mean duration of pregnancy was 36.3±3.9 weeks. 30% of patients had preterm delivery, and 30% of those had normal vaginal birth. In 25% of those, preeclampsia and urinary tract infection was observed. Mean birth weight of infants was 2349±574 g and Apgar score was 9-10.

In an another report conducted in Iran (15), 95 pregnancies in 74 kidney transplant recipients were assessed (mean age: 29.3±6.7 years). In 17.8% of those, pregnancy was not planned. Mean TTB was 41±9.5 months. 94 pregnancies resulted in 72 live births in 81.1% of those, cesarean sections were performed. Mean birth weight of infants was 2385±161.7 grams and 62.5 of those had birth weight lower than 2,500 grams. 61.1% of infants needed monitoring in intensive care unit, and mean Apgar score was 7.9±0.7. Preeclampsia was developed in 47.4% of pregnancies. In two-year follow-up after pregnancy, graft dysfunction (serum creatinine >2.0 mg/dL) was observed in 6.3% of the patients, and also graft loss in 3.2% of those. Thompson et al. (16) reported that 54.2% of 48 pregnant patients with renal transplantation took AZA plus prednisone, 29.2% took CsA plus AZA plus prednisone, and 8.3% took CsA plus prednisolone. In nearly one-third of patients, urinary tract infections, and preeclampsia occurred. Mean serum creatinine level was 90±38.14 mmol/L before pregnancy, 90.5±51.6 mmol/L 6 months after pregnancy. 16.0% of those had graft dysfunction. In 3.3 of them, graft loss was observed in two-year period after transplantation. 56.5% of infants were born preterm, and 50% of those had low birth weight (<2500 grams)

In a study (17) conducted in our country, Turkey, 57 women with renal transplant were included (19 pregnant, 38 non pregnant). 74% of pregnant patients were recipients from a living donor. Mean TTB was 5±3 years. Mean age of pregnant patients was 29±3 years. In 89.5 of those, serum creatinine level was lower than <1.5 mg/dL during pregnancy. Mean serum creatinine level was 1.15±0.29 mg/dL one-year after birth. Complications during pregnancy were listed as follows; anemia (68%), chronic hypertension (37%), urinary tract infection (21%) and preeclampsia (11%). In 88.2 of patients, cesarean section was performed. 53% of infants were born preterm. 16% of those had IUGR and low birth weight. In two patients, graft loss was diagnosed after 12.5±0.7 years.

Hypertension was observed in 18 of 34 pregnant patients followed during the years 1989-2007. 10 of those had urinary tract infection. 2 patients developed preeclampsia and in 2 of those, acute graft rejection occurred during follow-up. Mean serum creatinine levels in one year before and after pregnancy were 1.29±0.34 mg/dL and 1.34±0.95 mg/dL, respectively. 65.5% of the births delivered via cesarean section. 79.4% of the births were live births and 59.3% of those were preterm. Median birth weight was 2465 (1300-3530) grams. 13.8% of those had IUGR (8). The results of the pregnant recipients and the infants in our study are consistent with findings of similar studies in the literature (Table 5). Recommendations of EBPG are as follows: at least two-year period of good graft function (serum creatinine ≤1.5 mg/dL) before pregnancy, six weeks in that level of calcineurin inhibitor is kept at optimal level before conception, to substitute AZA for MMF (9). During follow-up, no graft loss was observed. In our study, lower rate of preeclampsia and graft dysfunction may be related to presence of relatively low number of patients, close monitoring and effective antihypertensive treatment.

In conclusion, pregnancies are fairly possible in renal transplant recipients of reproductive age. Close monitoring of pregnant patient in terms of complication and graft function is crucial for maternal and fetal health. Maternal age, low serum creatinine and urinary proteinuria effect pregnancy. In patients receiving appropriate medication (including optimal level of calcineurin inhibitor and AZA instead of MMF), pregnancy, which occurs after graft function remains stable for post-transplant two years, was found not to have negative effect on graft function. A multidisciplinary approach is important in patients planning pregnancy.

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Table 1. Demographic characteristics of pregnant and non-pregnant groups

Age, years	Pregnant Group (n=24)		Non-pregnant Group (n=116)		p value
	Postop 6th month	Last follow-up	Postop 6th month	Last follow-up	
Distribution of age, n (%)	32.5(24.41)				0.014
18-25	16(66.7)	23(95.8)	23(19.8)	53(45.7)	0.008
26-35	7(29.2)	53(45.7)	0.014		
>35	1(4.2)	40(34.5)	<0.001		
BMI, kg/m ²					
<25	11(45.8)	63(54.3)	0.449		
25-30	12(50)	31(26.7)	0.034		
>30	1(4.2)	22(19)	0.126		
Primary disease, n (%)					
Hypertension	7(29.2)	35(30.2)	0.214		
Glomerulonephritis	3(12.5)	12(10.3)	0.181		
Pyelonephritis	6(25)	14(12.1)	0.066		
vesicoureteral reflux	4(16.7)	11(9.5)	0.117		
Polycystic kidney disease	-	9(7.8)	<0.001		
Lupus nephritis	-	6(5.2)	<0.001		
Diabetic neuropathy	-	5(4.3)	<0.001		
AA amyloidosis	-	4(3.4)	<0.001		
Histiocytic	4(16.7)	20(17.2)	0.285		
Type of Dialysis, n (%)					
HD	16(66.7)	60(51.7)	0.415		
PD	16(66.7)	23(19.8)	0.243		
HD + PD	3(12.5)	10(9)			
PD + HD	0	7(6)			
No dialysis	4(16.7)	25(21.6)			
Duration of HD, months	30 (1-192)		48 (1-264)		0.415
Duration of PD, months	36 (30-48)		56 (7-144)		0.243
Age at transplantation, years	24(18-36)		32(15-47)		<0.001
Follow-up time, months	50(20-178)		42(13-168)		0.285
Age of donor, years	45(12-61)		49(21-69)		0.034
Type of Ex, n (%)					0.181
Preemptive	4(16.7)	25(21.6)			
Living	16(66.7)	54(46.6)			
Cadaveric	4(16.7)	37(31.9)			

Table 4. Characteristics of pregnant women and babies

Pregnant (n,%) (24, 17,14)	
Birth age, year	29 (23-39)
Time between tx and birth, month	32.5 (20-178)
The mode of delivery	
C/S	17 (70.8)
Normal	4 (16.7)
Miscarriage	3 (12.5)
Week of pregnancy (n,%)	
>37 weeks	38 (84)
32-37 weeks	13 (54.2)
27-32 weeks	5 (20.8)
<27 weeks	6 (25)
Pregnancy outcome	
Live birth	20 (83.3)
Miscarriage	3 (12.5)
Termination (Loss)	1 (4.2)
Preeclampsia	
Yes	2 (8.3)
None	22 (91.7)
Birth weight (gram) (n,%)	2850 (1450-4100)
>2500	11 (45.8)
1500-2500	6 (25)
<1500	7 (29.2)
IUGR	
Yes	2 (8.3)
None	22 (91.7)
Hospitalization in ICU	
Yes	5 (20.8)
None	19 (79.2)
HT in pregnancy	
Yes	6 (25)
None	18 (75)
ApgAR	
	9 (4-10)

Tx: Transplantation; C/S: Cesarean section; IUGR: Intrauterine growth retardation; ICU: Intensive care unit; HT: Hypertension; ApgAR: Activity, pulse, grimace, appearance, respiration.

Table 2. Level of hemoglobin, serum creatinine and dipstick urine protein in groups

	Pregnant Group (n=24)		Non-Pregnant Group (n=116)		p value
	Postop 6th month	Last follow-up	Postop 6th month	Last follow-up	
Creatinine mg/dL	1.1	0.9	1.2	1.1	0.576
	(0.6-3.1)	(0.6-2.1)	(0.6-3.1)	(0.6-6.3)	
Hemoglobin g/dL	12.2	11	12	12	0.442
	(8.2-18.8)	(8.7-15.4)	(8.2-18.8)	(7.7-16.6)	
Proteinuria	1+	2+	1+	1+	0.153
	(1-5)	(1-2)	(1-5)	(1-5)	

Table 3. Comparison of immunosuppressive therapy between the groups

Immunosuppressive therapy, n (%)	Non-Pregnant Group (n=116)	Pregnant Group (n=24)	p value
TAC + MMF + CS	68(58.6)	-	<0.001
CsA + MMF + CS	25(21.6)	-	0.008
TAC + AZA + CS	5(4.3)	14(58.3)	<0.001
TAC + AZA	3(2.6)	-	1.0
CsA + AZA	2(1.7)	7(29.2)	<0.001
TAC + MMF	2(1.7)	-	1.0
CsA + MMF	10(9)	-	1.0
EVR + MMF + CS	2(1.7)	-	1.0
SRL + MMF + CS	10(9)	-	1.0
TAC + SRL + CS	2(1.7)	-	1.0
CsA + EVR + CS	2(1.7)	-	1.0
TAC + EVR	2(1.7)	-	1.0
mTOR + AZA	10(9)	-	1.0
AZA + CS	-	2(8.3)	0.028
CS	-	1(4.2)	0.171

TAC: tacrolimus; MMF: mycophenolate mofetil; mTOR: Mammalian target of rapamycin; CS: prednisolone; CsA, cyclosporine A; EVR, everolimus; AZA, azathioprine; SRL; sirolimus.

Table 5. Clinical outcomes during pregnancy

Factors	Ayar et al. (2015) (n=114, pregnancy n=24)	Bramham et al. (2013) (Pregnancy n=105, Outcome n=81, poor pregnancy n=24) Control n=1807	Leviolati et al. (2009) (Pregnancy n=57)	Gill et al. (2009) (Pregnancy n=50, all transplant patient n=1819)
Maternal age	48.39 (1.26-1860.72) ^a	1	-	1.42 (1.12-1.81) ^a
Diastolic age	-	2.08 (0.50-8.71)	-	0.26 (0.20-0.32) ^a
Proteinuria	13/81 (2.58-92.45) ^a	0.05 (1.19-21.4) ^a	0.2 (0.1-0.7) ^a	-
Hypertension	-	0.22 (1.96-19.85) ^a	-	NA
Diabetes mellitus	-	-	-	NA
Serum creatinine	0.901 (0.4-3.6) ^a	0.59 (2.12-20.55) ^a	-	-
BMI	<25	-	NA	NA
25-30	-	-	-	-
>30	-	-	-	-
Timing of transplantation to conception	1.25 (1.11-9.48) ^a	NA	-	-
Live or cadaveric kidney donor	-	NA	NA	-

