

Pregnancy and Kidney Transplantation: A Single-Center Experience

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ABSTRACT

Objective: The possibility of pregnancy increases with kidney transplantation in patients with chronic kidney disease. However, graft dysfunction, risk of fetal growth retardation, and fetal anomaly should be monitored closely. In this study, renal and obstetric outcomes were analyzed in pregnant kidney recipients who were followed in our center.

Methods: We analyzed 140 reproductive-aged patients who underwent renal transplantation between January 2009 and May 2015, and clinical and laboratory data were evaluated retrospectively.

Results: Twenty-four patients became pregnant (17.1%). In pregnant group, median age was significantly lower than non-pregnant group ($P = .014$). The median age of pregnant group at the time of transplantation was also significantly lower than non-pregnant patients ($P < .001$). The rate of pregnant patients was 66.7% in 18-25 year age group ($P = .008$). The rate of urinary tract infection in non-pregnant group was higher than pregnant group ($P = .03$). Live birth rates were 83.3% and 45.8% of those whose birth weight was higher than 2500 g. The increased level of daily urinary proteinuria and the time from diagnosis of renal failure to transplantation had significant effect on pregnancy (odds ratio = 13.81; 95% CI: 2.06-92.45; $P = .007$ and odds ratio = 3.25; 95% CI: 1.11-9.48; $P = .031$, respectively). Low serum creatinine level had significant protective effect (odds ratio = 0.001; 95% CI: 0-0.30, $P = .018$). The patients in 18-25 age group were 48.39 times more eligible for pregnancy compared to those in >35 age group (odds ratio = 48.39; 95% CI: 1.26-1860.72; $P = .037$). Rejection episodes were observed in 1 of pregnant women and 11 of non-pregnant women ($P > .05$).

Conclusion: Pregnancy is possible in kidney transplant recipients of reproductive age. Calcineurin inhibitors and azathioprine seem to be safe. Maternal age, low-serum creatinine, and urinary proteinuria affect pregnancy. The close monitoring of renal function and fetal parameters is very important.

Keywords: Renal transplantation, pregnancy, fetal complication, immunosuppression

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INTRODUCTION

In women with chronic kidney disease, inhibition of gonadotropin-releasing hormone (GnRH) results in hypothalamo-pituitary dysfunction and leads to anovulation, abnormal menstrual cycle, amenorrhea, and infertility. Furthermore, the drugs used for that disease 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 post-transplantation patients 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 pregnancy. Controlling blood pressure, keeping immunosuppressive drugs at 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), pre-eclampsia, gestational diabetes, proteinuria, rejection,



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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 the present study, outcomes of pregnancy after kidney transplantation were evaluated retrospectively.

METHODS

In the study, 140 women of reproductive age (15-49 years old) who had kidney transplantation between January 1, 2009, and June 30, 2015, were analyzed. The patients wishing to conceive were allowed after post-transplant of 2 years of stable trend in renal function (serum creatinine <1.5 mg/dL). Mycophenolate changed with AZA. 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 2 groups based on pregnancy; pregnant and non-pregnant control. Serum creatinine, hemoglobin, amount of urinary protein excretion, age of pregnant women at birth, time from transplantation to birth (TTB), pregnancy termination week, 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 the comparison of intragroup; Mann-Whitney, Fisher's exact test, and Fisher-Freeman-Halton tests were used for the comparison of intergroup. Independent risk factors for pregnancy were assessed by logistic regression analysis, and the forward method was used to select variables. In all analyses, $P < .05$ was accepted as a significance level. Data were statistically processed by IBM Statistical Package for the Social Sciences (SPSS) version 21 software (IBM SPSS Corp., Armonk, NY, USA).

MAIN POINTS

- Kidney transplantation improves patient survival and social adaptation compared to other renal replacement therapy.
- Motherhood, pregnancy is an important concept in women socially and psychologically.
- It contributes to patients self-esteem, socialization and maintaining their well-being.
- Recovery of maternity and pregnancy after transplantation is important in terms of patient survival and returning to the pre-disease process, family and social support. In our study we evaluated and shared pregnancy and birth data after transplantation.

RESULTS

Twenty-four patients became pregnant and were included in the pregnant group. The median age of pregnant women was lower than the non-pregnant group ($P = .014$). When age distribution was evaluated, pregnant women were presented in the age group of 18-25 years significantly compared to the non-pregnant group (66.7% vs. 19.8%, $P = .008$). The median age at the time of transplantation was lower in the pregnant group ($P < .001$). In our study, 16.7% of the pregnant group and 31.9% of the non-pregnant group had cadaveric transplantation. Live relative-related transplantation was more common in the pregnant group (84.4%, 16.7% preemptive). In the live transplantation, 5 patients in the non-pregnant group were transplanted from their spouses (4.3%). All patients in the pregnant group were transplanted from their first-degree relatives (sibling, parents). In a comparison of both groups based on primary disease, body mass index (BMI), dialysis modalities, duration of dialysis, types of transplantation, donor age, and follow-up period after transplantation were not different ($P > .05$) (Table 1). In pregnant group, ratio of patients who were overweight (BMI; 25-30 kg/m²) was significantly higher (50% vs. 26.7%, $P = .024$). Although the acute rejection rate in the non-pregnant group was higher, it was not statistically different ($P > .05$). Urinary tract infection was detected more in the non-pregnant group compared to the pregnant group ($P = .03$). Levels of serum creatinine, hemoglobin, and amount of urinary protein excretion were assessed at the sixth month after transplantation and last visit in the non-pregnant group; at the sixth month, after transplantation and first post-partum visit in the pregnant group. Only, hemoglobin levels at the end of gestation were significantly lower in the pregnant group ($P = .001$) (Table 2).

In non-pregnant group, immunosuppression regimens of tacrolimus (TAC), MMF, prednisolone (PRED), and cyclosporine A (CSA), MMF, and PRED were used more commonly. Whereas, medication including TAC, AZA, and PRED was more common in pregnant group (Table 3). Two pregnant patients had husbands who received kidney transplantation. Pregnant patients received TAC+AZA+PRED, so husbands received TAC / CSA+MMF, and prednisolone. The median time from transplantation to pregnancy was 52.5 (20-178) months. The median age at the time of birth in pregnant group was 29 (23-39) years. The median duration of pregnancy was 38 weeks (8-41). In 13 patients, the duration of pregnancy was longer than 37 weeks, and 6 patients had pregnancy less than 32 weeks. During pregnancy, rejection episodes occurred in 1 patient who had not been in AZA for a long time. Her immunosuppressive regimen consisted of TAC and steroid, and she did not receive any follow-up for 6 months. Her serum creatinine level increased from 0.8 mg/dL to 1twenty.8 mg/dL. Spontaneous abortion occurred in the ninth week of pregnancy, and she underwent renal biopsy, in which findings were consistent with cellular rejection. 500 mg prednisolone for 3 days and antithymocyte globulin (ATG) for 7 days were given. She was discharged with a creatinine level of 2.1 mg/dL. Preeclampsia developed in 2 patients. In 6 patients,

Table 1. Demographic Characteristics of Pregnant and Non-pregnant Groups

	Pregnant Group (n = 24)	Non-pregnant Group (n = 116)	P
Age, years	32.5 (24-41)	35 (20-49)	.014
Distribution of age, n (%)			
18-25	16 (66.7)	23 (19.8)	.008
26-35	7 (29.2)	53 (45.7)	.014
>35	1 (4.2)	40 (34.5)	<.001
BMI, kg/m ²			
<25	11 (45.8)	63 (54.3)	.449
25-30	12 (50)	31 (26.7)	.024
>30	1 (4.2)	22 (19)	.126
Primary disease, n (%)			
Hypertension	7 (29.2)	35 (30.2)	.214
Glomerulonephritis	3 (12.5)	12 (10.3)	.181
Pyelonephritis	6 (25)	14 (12.1)	.066
Vesicoureteral reflux	4 (16.7)	11 (9.5)	.117
Polycystic kidney disease	-	9 (7.8)	<.001
Lupus nephritis	-	6 (5.2)	<.001
Diabetic neuropathy	-	5 (4.3)	<.001
AA amyloidosis	-	4 (3.4)	<.001
Idiopathic	4 (16.7)	20 (17.2)	.285
Type of dialysis, n (%)			
HD	16 (66.7)	60 (51.7)	
PD	16 (66.7)	23 (19.8)	
HD + PD	3 (12.5)	1 (0.9)	
PD + HD	0	7 (6)	
No dialysis	4 (16.7)	25 (21.6)	
Duration of HD, months	30 (1-192)	48 (1-264)	.415
Duration of PD, months	36 (30-48)	56 (7-144)	.243
Age at transplantation, years	24 (18-36)	32 (15-47)	<.001
Follow-up time, months	50.5 (20-178)	42 (13-168)	.285
Age of donor, years	45 (12-61)	49.5(21-69)	.054
Type of Tx, n (%)			.181
Preemptive	4 (16.7)	25 (21.6)	
Living	16 (66.7)	54 (46.6)	
Cadaveric	4 (16.7)	37 (31.9)	
Acute rejection, n (%)	1 (4.2)	11 (9.5)	.691
Urinary tract infection, n (%)	6 (25)	57 (49.1)	.030

BMI, body mass index; HD, hemodialysis; PD, peritoneal dialysis; Tx, transplantation.

hypertension was observed during pregnancy and they were treated with alpha-methyldopa, calcium channel blockers (diltiazem, amlodipine, nifedipine), or beta-blockers (carvedilol). Seventeen of pregnant patients had a cesarean section (70.8%), and 4 pregnant patients had a normal vaginal delivery. In 20 patients, pregnancies resulted in a live birth, and in 1 patient, pregnancy was terminated because of oligohydramnios. Three patients' pregnancies resulted in a miscarriage.

Independent risk factors for pregnancy were evaluated with logistic regression analysis (LRA). The forward method was used in variable selection. In the final step, the LRA model was significant ($P < .001$). Age, age categories (18-25, 26-35, >36), BMI, weight categories (according to BMI; <25, 26-30, >30), duration of dialysis, types of transplantation, donor age, duration of transplantation, presence of hypertension, diabetes mellitus, serum creatinine level, hemoglobin, and amount of daily urinary protein excretion at the sixth month after transplantation were assessed. Increased level of daily urinary proteinuria and the time from diagnosis of renal failure to transplantation had significant effect on pregnancy (odds ratio (OR) = 13.81; 95% CI: 2.06-92.45; $P = .007$ and OR = 3.25; 95% CI: 1.11-9.48; $P = .031$, respectively).

Low serum creatinine level had significant protective effect (OR = 0.001; 95% CI: 0-0.30, $P = .018$). 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: 1.26-1860.72; $P = .037$).

The median birth weight was 2850 g (1450-4100). In 11 patients (45.8%), birth weights were higher than 2500 g and in 7 patients (29.2%) were lower than 1500 g. Two infants had IUGR and 5 had been monitored in the intensive care unit. Median Apgar scores of infants were 9 (4-10). Two pregnancies were unplanned. Both of the patients had been receiving medication consisting of calcineurin inhibitor, prednisolone, and MMF. Their pregnancies resulted in a miscarriage at 8 and 14 weeks. In one patient, oligohydramnios and hypertension developed and miscarriage occurred at 24 weeks. In another patient with oligohydramnios, fetal heartbeat was not heard; therefore, pregnancy was terminated at 30 weeks (Table 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 of fetuses were increased in pregnancy. Therefore, especially pregnancy should be monitored more closely in the 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,

Table 2. Levels of Hemoglobin, Serum Creatinine, and Dipstick Urine Protein in Groups

	Pregnant Group (n = 24)			Non-pregnant Group (n = 116)		
	Post-op, 6th ,Month	Last Follow-Up	P	Post-op, 6th m=Month	Last Follow-Up	P
Creatinine, mg/dL	1.1 (0.6-3.1)	0.9 (0.6-2.1)	.488	1.2 (0.6-3.1)	1.1 (0.6-7.63)	.576
Hemoglobin, g/dL	12.2 (8.2-18.8)	11 (8.7-15.4)	.001	12 (8.2-18.8)	12 (7.7-16.6)	.442
Proteinuria, 0-5+	1+ (1-5)	2+ (1-2)	.317	1+ (1-5)	1+ (1-5)	.153

Table 3. Comparison of Immunosuppressive Therapy Between the Groups

Immunosuppressive Therapy, n (%)	Non-Pregnant Group (n = 116)	Pregnant Group (n = 24)	P
TAC + MMF + CS	68 (58.6)	-	<.001
CsA + MMF + CS	25 (21.6)	14 (58.3)	.008
TAC + AZA + CS	5 (4.3)	7 (29.2)	<.001
TAC + AZA	3 (2.6)	-	1.0
CsA + AZA	2 (1.7)	-	<.001
TAC + MMF	2 (1.7)	-	1.0
CsA + MMF	1 (0.9)	-	1.0
EVR + MMF + CS	2 (1.7)	-	1.0
SRL + MMF + CS	1 (0.9)	-	1.0
TAC + SRL + CS	2 (1.7)	-	1.0
CsA + EVR + CS	2 (1.7)	2 (8.3)	1.0
TAC + EVR	2 (1.7)	1 (4.2)	1.0
mTOR + AZA	1 (0.9)	-	1.0
AZA + CS	-	-	.028
CS	-	-	.171

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

rates of pre-eclampsia, live births, preterm birth, and cesarean delivery were 27%, 73%, 45%, and 56%, respectively.¹⁰

In a report from the United Kingdom, 105 pregnant kidney recipients were observed for 3 years.¹¹ During pregnancy TAC, AZA, and PRED were most commonly received. Eclampsia developed in 24% of these patients. Sixty-four percent of pregnancies had a cesarean delivery and 91% of births were live births. Birth weights were observed lower than 2500 g in 24%. Fifty-two of births were premature. Mean serum creatinine level was lower than 1.3 mg/dL with good outcomes. Deterioration in kidney function was detected in 38%. In another study from Australia,¹² an analysis of 40-year follow-up (1966-2005) was reported. Mean age was 29 ± 5 years. Preeclampsia developed in 27% of pregnant. Rates of live birth, termination, and abortion were 62%, 30%, and 9%, respectively, between the

Table 4. Characteristics of Pregnant Women and Babies

	Pregnant (n, %) (24, 17.14)
Birth age, year	29 (23-39)
Time between tx and birth, months	52.5 (20-178)
The mode of delivery	
C/S	17 (70.8)
Normal	4 (16.7)
Miscarriage	3 (12.5)
Week of pregnancy (n, %)	38 (8-41)
>37	13 (54.2)
32-37	5 (20.8)
<32	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 (g) (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, internal care unit; HT, hypertension; APGAR, activity, pulse, grimace, appearance, respiration.

years 1966 and 2005. Gill et al¹³ reported the assessment of 16 195 women of reproductive age between 1990 and 2003. Pregnancy and live birth rates were 33/1000 and 19/1000, respectively. Cyclosporine A (71%) and azathioprine (49%) were the most commonly used medications. Pregnancy rate in 20-24 age groups was 93%. In pregnant recipients, rates of live births and abortion were observed to be 55% and 21%, respectively.

In the study by Alfi et al,¹⁴ mean age of 20 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. The time between transplantation and pregnancy was lower than 1 year in one of pregnant patients. The other patient had prenatal serum creatinine greater than 1.5 mg/dL. Mean duration of pregnancy was 36.3 ± 3.9 weeks. Thirty percent of patients had a preterm delivery, and 30% of those had a normal vaginal birth. In 25% of those, preeclampsia and urinary tract infection were observed. The mean birth weight of infants was 2349 ± 574 g, and the Apgar score was 9-10.

In 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. Ninety-four pregnancies resulted in 72 live births. In 81.1% of birth, cesarean sections were performed. The mean birth weight of infants was 2385 ± 161.7 g and 62.5% of those had birth weight lower than 2500 g. Sixty-one percent of infants needed monitoring in the intensive care unit, and the mean Apgar score was 7.9 ± 0.7 . Preeclampsia was developed in 47.4% of pregnancies. In 2-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 al¹⁶ reported that 54.2% of 48 pregnant patients with renal transplantation took AZA plus PRED, 29.2% took CsA plus AZA plus PRED, and 8.3% took CsA plus PRED. In nearly one-third of patients, urinary tract infections and preeclampsia occurred. The mean serum creatinine level was 90 ± 38.14 mmol/L before pregnancy and 90.5 ± 51.6 mmol/L after the sixth month of pregnancy. Sixteen percent of patients had graft dysfunction. In 3.3% of them, graft loss was observed in 2-year period after transplantation. Infants were born 56.5% as preterm and 50% of those had low birth weight (< 2500 g).

In a study¹⁷ conducted in our country, Türkiye, 57 women with renal transplants were included (19 pregnant, 38 non-pregnant). Seventy-four percent of pregnant patients were recipients from a living donor. Mean TTB was 5 ± 3 years. The mean age of pregnant patients was 29 ± 3 years. In 89.5% of them, serum creatinine level was lower than < 1.5 mg/dL during pregnancy. Mean serum creatinine level was 1.15 ± 0.29 mg/dL 1 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, a cesarean section was performed. Fifty-three percent of infants were born preterm. Intrauterine growth retardation and low birth weight were detected as 16%. In 2 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 1 year before and after pregnancy were 1.29 ± 0.34 mg/dL and 1.34 ± 0.95 mg/dL, respectively. A birth rate of cesarean section was observed as 65.5%. Live and preterm births were observed at 79.4% and 59.3%, respectively. The median birth weight was 2465 (1300-3530) g. Intrauterine growth retardation was identified as 13.8%.⁸ Recommendations of EBGP are as follows: at least 2-year period of good graft function (serum creatinine ≤ 1.5 mg/dL) before pregnancy, 6 weeks in that level of calcineurin inhibitor is kept at the optimal level before conception, to substitute AZA for MMF.⁹ During follow-up, no graft loss was observed. In our study, a lower rate of preeclampsia and graft dysfunction may be related to the presence of a relatively low number of patients, close monitoring, and effective antihypertensive treatment.

CONCLUSION

Pregnancies are fairly possible in kidney transplant recipients of reproductive age. Close monitoring of pregnant patients in terms of complication and graft function is crucial for maternal and fetal health. Maternal age, low serum creatinine, and urinary proteinuria affect pregnancy. In patients receiving appropriate medication (including the optimal level of calcineurin inhibitor and AZA instead of MMF), pregnancy, which occurs after graft function remains stable for post-transplant 2 years, was found not to have a negative effect on graft function. A multidisciplinary approach is important in patients planning for pregnancy.

Ethics Committee Approval: This study approved by The Ethics Committee for Uludağ University (Date: January 1, 2019, Decision no: 2011-KAEK-26/20)

Informed Consent: Written informed consent was obtained from patient who participated in this study.

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