Original Article

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Does Pregnancy after Renal Transplantation Affect Their Allograft and Pregnancy Outcomes?

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Background: The number of pregnancies in renal transplant recipients has increased. Many studies have shown that pregnancy increases the risk of graft, fetal, and maternal complications but does not affect the long-term outcome of the graft. We assessed the incidence and effect of pregnancy after renal transplantation and examined graft, fetal, and maternal outcomes.

Methods: Our study included 145 female recipients of child-bearing age (15～45 years) in our center from January 1990 to December 2011. The subjects were divided into two groups: pregnancy (n=17) and control (n=128). The 26 pregnancies in the 17 recipients were categorized as live births (n=10) or no-live births (n=16). These were analyzed for evaluation of pregnancy outcomes, graft function, and long-term graft survival.

Results: The pregnancy and control group had similar graft function and graft survival rates 5- and 10-year after renal transplantation. Outcomes of pregnancy were 10 live births, 8 therapeutic abortions, 7 spontaneous abortions, and 1 stillbirth. The mean serum creatinine levels of the pregnant recipients diminished during the first trimester (1.14±0.37 mg/dL) and increased slightly during the third trimester (1.18±0.37 mg/dL) to levels nearer the baseline (1.23±0.37 mg/dL). These ranges were stable. The mean time from transplantation to pregnancy was 20.73±3.57 months. Live birth rates were associated with the time from transplantation to pregnancy (71.78±37.75 months for live births and 19.38±12.71 months for no-live births, P=0.000). There were no significant differences in graft function, graft failure rates, and survival.

Conclusions: Pregnancy does not appear to have an adverse effect on graft function and the long-term outcomes of renal transplantation. Recipients with stable renal function who want to become pregnant can have successful pregnancies.

Key Words: Kidney transplantation, Pregnancy, Graft outcome
중심 단어: 신장이식, 임신, 예후

INTRODUCTION

Patients with end stage renal disease (ESRD) are frequently infertile or have a low incidence of pregnancy because of hypothalamic dysfunction(1). These endocrine and menstrual dysfunctions are restored after renal transplantation(2,3), which is one of the benefits of renal transplantation for women of child-bearing age. Fertility improves rapidly within a few months of renal transplantation, and most women who were previously infertile become able to conceive(4,5).

However, pregnancy in renal transplant recipients is considered high risk because of the maternal and fetal complications and the effect of the underlying conditions on graft outcomes(4,6). Rates of perinatal mortality and morbidity, preterm delivery, intrauterine growth retardation (IUGR), hypertension, anemia, renal function deterioration, and

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pre-eclampsia are higher in renal transplant recipients than in the general population(5-8).

As immunosuppressants improve, the rates of successful pregnancies and pregnancy outcomes increase. For patients with stable allograft function, pregnancy is thought to be safe 2 years after renal transplantation(3-5). Some studies have shown that renal transplant recipients who conceive in the first 6～12 months after renal transplantation can also have successful pregnancies(9). However, it is unclear whether renal function or the interval between transplantation and pregnancies do affect long-term maternal allograft and pregnancy outcomes.

In this study, we evaluated the rates and outcomes of pregnancies in women who underwent renal transplantation in our center to identify factors related to successful pregnancy and the effect of pregnancy on long-term graft outcomes.

MATERIALS AND METHODS

Between January 1990 and December 2011, 565 renal transplants were performed in Hanyang University Transplantation Center. One hundred forty-five of the women involved were of child bearing age (15～45 years). Of these, 18 (12.4%) went on to become pregnant, and between them had 27 pregnancies.

We retrospectively reviewed 26 of the pregnancies (the medical records were lost in one case). All patients received standard immunosuppressive therapy. Up to 1995, most patients received triple or dual therapy based on prednisolone, azathioprine, and cyclosporine A (CsA). For most of the patients azathioprine was replaced by mycophenolate mofetil and CsA replaced by tacrolimus from 1996. Baseline characteristics such as age of donor and recipients at transplantation and gender of donor, body weight and body mass index of recipient, number of human leukocyte antigen mismatches, acute and chronic rejection rate, viral infection rate, type or maintenance immune suppressive drug, and duration of follow-up were investigated and analyzed.

The pregnancy outcomes were classified as live birth, spontaneous abortion, therapeutic abortion, or still birth. Maternal details included age at the time at conception, times between pregnancy and transplantation, presence of hypertension or other comorbid conditions, changes in serum creatinine (sCr) levels and immunosuppressant dosage before and during pregnancy in each trimester. Neonatal outcomes were evaluated using gestational age, preterm delivery, birth weight, congenital abnormalities, and APGAR (Appearance, Pulse, Grimace, Activity, and Respiration) score 1 and 5 minutes after birth.

We compared the characteristics and graft outcomes of recipients who became pregnant with those of other recipients of child-bearing age. To evaluate the factors affecting a successful pregnancy, all pregnancy cases were categorized as either live birth or no-live birth (abortion and stillbirth). Clinical characteristics, renal function before and during pregnancy, and graft survival rates were analyzed.

Patients characteristics were compared using the chi-squire test and Student t-test were carried out. All analyses were performed using SPSS ver. 18.0 (SPSS Inc., Chicago, IL, USA) and P-values <0.05 were considered statistically significant.

RESULTS

Women in the pregnancy group were significantly younger and had experienced herpes zoster infection more frequently than those in the control group (P=0.002 and P=0.047, respectively). There were no differences in pregnancies according to their causes of ESRD.

There were no significant differences in other characteristics that are known to affect graft outcomes between the two groups. There was also no significant difference between two the groups in sCr levels, which reflect renal function before, or 1, 6, 12, 36 months and 10 years after renal transplantation. The 5- and 10-year graft survival rates were 85.8% and 70.2%, respectively, in the control group, and 87.8% and 74.8%, respectively in the pregnancy group (P=0.782).

There were 26 pregnancies among the 17 women. Ten were live births (10/26, 38.5%) and 15 (57.7%) were aborted (8 cases of therapeutic abortion [8/26, 30.8%] and 7 cases of spontaneous abortion [7/26, 26.9%]). Four cases of therapeutic abortion (4/8, 50.0%) were done therapeutic abortion because they were pregnant within 1 year after renal transplantation. One pregnancy ended in stillbirth. The

mean age of recipients at the time of pregnancy was 32.00±3.53 years (range; 27~41). The mean interval from transplantation to pregnancy was 20.73±3.57 months (range; 5~133). Mean gestational age was 20.07±13.82 weeks (range; 4~41).

To evaluate changes in renal function, we measured the sCr levels from 6 months before pregnancy to 6 months after delivery. The mean sCr level 6 months before conception was 1.23±0.37 mg/dL; it decreased to 1.14±0.37 mg/dL during the first trimester (P=0.650, compared with baseline), remained at 1.13±0.34 mg/dL throughout the second trimester (P=0.000), and increased slightly during the third trimester (1.18±0.37 mg/dL, P=0.000). The mean sCr level in these patients rose to 1.27±0.49 mg/dL 6 months after delivery (P=0.000) (Fig. 1). The same pattern of physiological change occurred after pregnancy. We investigated therapeutic levels of immunosuppressants from 6 months before pregnancy to 6 months after delivery. Twenty-three pregnancies were treated with cyclosporine (88.5%) and 3 tacrolimus (11.5%). Cyclosporine levels during the pregnancy (72.00±28.26 ng/mL in the first trimester, 56.93±22.87 ng/mL in the second trimester, and 86.43±35.72 ng/mL in the third trimester) were lower than before conception (135.71±34.58 ng/mL) and after delivery (116.70±24.70 ng/mL). Tacrolimus levels during pregnancy (5.54±1.53 ng/mL in the first trimester, 5.65 ng/mL in the second trimester, and 4.83 ng/mL in the third trimester) were also lower than those before conception (6.44±1.56 ng/mL) and after delivery (6.71 ng/mL,). Thus, in the pregnancy group, immunosuppressant levels were lower during pregnancy than before pregnancy.

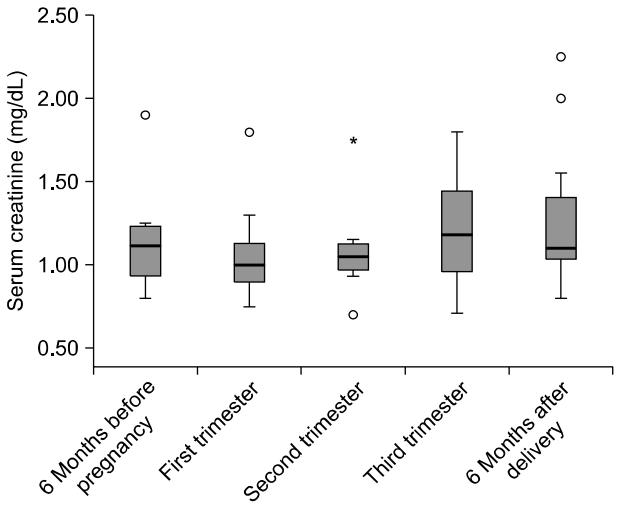

Fig. 1. Changes in serum creatinine levels from 6 months before pregnancy to 6 months after delivery.

All pregnancies were classified as either successful pregnancies that resulted in live births or as no-live births that ended in abortion or stillbirth. We compared the clinical characteristics of the two groups of pregnancies (Table 1). No significant differences were observed between the two groups except for the time from transplantation to pregnancy. This was much longer in the live births group than in the no-live births group (71.78±37.75 months vs. 19.38±12.71 months). The sCr levels before and after pregnancy and graft survival did not differ significantly. Although not statistically significant, immunosuppressant levels (cyclosporine/tacrolimus) during pregnancy and rates of chronic rejection tended to be higher in the no-live births group than in the live-births group (71.17/4.50 ng/mL vs. 102.67/6.04 ng/mL and 30% vs. 50%, respectively). One of the three recipients who experienced graft loss developed renal dysfunction after delivery, during which the sCr level increased to 2.2 mg/dL. Although sCr was transiently restored to 1.6 mg/dL after conservative treatment, the woman's allograft ceased to function 4 years after delivery (the periods used graft, 180 months; mean, 167.00±53.69). The other two recipients delivered their infants with IUGR; one was a preterm delivery (the periods used graft 94 and 108 months, respectively; mean, 167.00±53.69). Eight recipients among the no-live births developed chronic rejection (mean periods used graft, 126.57±77.01 months). One of these recipients had increased sCr levels of 2.0 mg/dL due to an infection at the episiotomy site after termination of the stillbirth; sCr level was restored after treating the infection. One recipient was repeatedly infected with herpes zoster from intrauterine period 6 weeks and the physician recommended that she terminate her pregnancy because the medication (acyclovir) had teratogenicity and toxic effects on the fetus. The woman wanted to maintain her pregnancy and continued to treat the infection. In 28 weeks of pregnancy, she had a stillbirth. The renal function of the other pregnant recipient deteriorated and her sCr levels increased to 2.7 mg/dL. She terminated her pregnancy because she needed to be treated with a high dose of immunosupp-

Table 1. Clinical characteristics of pregnancies between live births and no live births

Characteristic	Live births (n=10)	No-live births (n=16)
Recipient age (yr)	26.67±3.84	30.54±3.97
Time from transplantation to pregnancy (mo)	71.78±37.75	19.38±12.71
Age at pregnancy (yr)	32.33±3.20	31.46±3.35
Periods used graft (mo)	160.55±54.7	139.62±77.85
Donor type		
Living	9 (90)	14 (87.5)
Dialysis		
None	1 (10)	2 (12.5)
Hemodialysis	8 (80)	12 (75)
Peritoneal dialysis	1 (10)	2 (12.5)
Dialysis duration (mo)	44.11±42.73	49.23±45.81
Calcineurin inhibitors		
Cyclosporin	9 (90)	14 (87.5)
Tacrolimus	1 (10)	2 (12.5)
Anti-metabolic agents		
None	1 (10)	3 (18.8)
Azathioprine	6 (60)	9 (56.3)
Mycophenolate mofetil	3 (30)	4 (25.0)
Rejection		
Acute	1 (10)	2 (12.5)
Chronic	3 (30)	8 (50)
Bacterial infection	2 (20)	4 (25.0)
Cytomegalovirus infection	0	2 (12.5)
Herpes zoster infection	2 (20)	5 (31.3)
Serum creatinine (mg/dL)		
6 months before pregnancy	1.22±0.34	0.94±0.14
First trimester	1.14±0.33	0.88±0.04
Second trimester	1.12±0.34	0.93
Third trimester	1.24±0.36	0.95
Immunosuppressant level (cyclosporin/tacrolimus, ng/mL)		
6 months before pregnancy	133.64/4.70	114/7.32
First trimester	71.17/4.50	102.67/6.04
Second trimester	56.93	58
Third trimester	86.4/4.83	-

Data are presented as mean±SD or number (%).

ressants. Finally, she lost her graft function one month after termination.

We analyzed the 10 cases that resulted in live births (Table 2). Caesarian sections were performed in 9 of these. Of the 10 pregnancies, 1 (1/26, 3.9% of all pregnancies) resulted in preterm delivery (<37 weeks) and there were 3 cases (3/26, 11.5% of all pregnancies) of IUGR and low birth weight (LBW, <2,500 g). The APGAR score at 1 and 5 minutes after birth were significantly lower in the pre-term, IUGR, and LBW group than in the normal delivery group (7.0 vs. 3.7 at 1 minute, 8.7 vs. 6.0 at 5 minutes). Only one recipient experienced anemia during the pregnancy and after delivery. There were no other complications such as preeclampsia, gestational diabetes mellitus, urinary tract infection, and congenital anomalies of the fetus.

DISSCUSSION

ESRD is a risk factor for pregnancy-assisted and neonatal complications, as there is an association between degree of renal impairment and physiological adaptation to pregnancy(1). The expected increase in glomerular filtration

Table 2. Clinical outcomes of the delivery in renal transplant recipients (n=10)

Variable	Value
Gestational age (wk)	37.2±3.1 (3~41)
Infant birth weight (g)	2,807.8±1,131.5 (1,130~5,140)
APGAR score (min)	
1	5.89±2.03 (2~8)
5	7.78±1.64 (4~9)
Pregnancy outcome	
Preterm delivery	1 (10/3.9[a])
Intrauterine growth retardation	3 (30/11.5[a])
Low birth weight	3 (30/11.5[a])
Anemia	1 (10/3.9[a])

Data are presented as mean±SD (range) or number (%).
Abbreviation: APGAR, Appearance, Pulse, Grimace, Activity, and Respiration.
[a]In all pregnancy.

rate depends on the degree of impaired renal function(4,9,10). There is a considerable risk of impaired renal function after pregnancy and delivery and an increased likelihood of preterm delivery and pre-eclampsia(11). This is equally true of renal transplant recipients. During pregnancy, hyperfiltration may cause progressive loss of renal function because increased pressure and plasma flow induce glomerular sclerosis(12,13). However, the renal impairment is transient rather than permanent(3). So, if pre-pregnancy allograft function is good, renal transplant recipients of child-bearing age may be optimistic about a successful outcome to their pregnancy(14).

There have been many studies of the effects of pregnancy on allograft outcomes. Richman and Gohh(15) reviewed reports of 23 single center studies in 16 countries and one multicenter study in five Middle Eastern countries that were published after 1999. In that analysis, the women who became pregnant after renal transplantation did not generally suffer higher rates of rejection, and had excellent graft survival. A preliminary report from the National Transplant Pregnancy Registry which studied the outcome of pregnancies after transplantation in North America showed that women with suboptimal renal function (sCr > 1.5 mg/dL) were more likely to experience acute rejection during pregnancy. However, pregnancy did not affect long-term graft survival if pre-pregnancy renal function was stable(8). We compared sCr levels 6 months before pregnancy, during pregnancy, and 6 months after delivery to evaluate changes in renal function and graft outcomes. The physiological sCr levels of all the pregnant women changed, and there were no significant differences in those variables known to affect graft function between the pregnancy group and the control group. The 10-year graft survival rates were not significantly different: 70.2% in the control group and 74.8% in the pregnancy group. In the recipients with stable sCr levels, graft function and survival were not affected by pregnancy and delivery.

In the last decade, about 80% of recipients who had a functioning graft and became pregnant delivered a live birth(2,8). However, maternal and fetal complication rates are higher in renal transplant recipients than in the general population(8,15). Hypertension during pregnancy and after delivery, preeclampsia, gestational diabetes, anemia, and infections such as urinary tract infections have increased (16,17). The prevalence (30%~50%) of low-birth weight infants (<2,500 g), preterm delivery, and IUGR is higher than in the general population(2,7,8,15).

In our study, live birth rates (38.5%) were lower and abortion rates (57.7%) higher than in other studies. We advised recipients who wanted to become pregnant to wait for 2 years at least after renal transplantation, because of the higher risk of acute rejection, higher levels of immunosuppressants, viral or other infections, and fetal complications(3,5,8). Immunosuppressant levels (cyclosporine/tacrolimus) during pregnancy and rates of chronic rejection were higher in the no-live births group than in the live-births group. Recipients in both groups who contracted infections and whose renal function deteriorated during pregnancy tended to develop chronic rejection earlier than recipients without these complications, but the prevalence was higher in the no-live births group. Maternal and fetal complication rates (preterm delivery, LBW, IUGR, anemia) in live birth delivery were lower in our study than in other studies and there were no other complications. This was because sCr levels were stable when comorbid diseases such as hypertension and diabetes were well controlled during pregnancy and their immunosuppressant (cyclosporine/tacrolimus) were maintained at low dosage during pregnancy.

So, what is the optimal timing for pregnancy? The recom-

mendation is generally to wait until 2 years after renal transplantation(3,15). In our study, time from transplantation to pregnancy was significantly longer in the live-births group than in the no-live births group (P≈0.000). However, the recommendation has been changed to a minimum period of 1 year after transplantation if there have been no acute rejection episodes in the previous year and there is adequate graft function (sCr <1.5 mg/dL and < 500 mg/day protein excretion)(5,8,9,12,14).

CONCLUSION

Pregnancy does not adversely affect graft function and long-term graft survival. Good outcomes may be related to stable renal function and absence of infections during pregnancy and after delivery, absence of or well-controlled hypertension and proteinuria, minimal dosage of immunosuppressants, and the time from transplantation to pregnancy (at least 1 year). However, our study is retrospective study and involves relatively small number of cases. Large-scale prospective study should be undertaken.

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