An Examination of Pregnancy Cases After Kidney Transplantation: Single-Center Experience

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ABSTRACT

Introduction. The number of young women who wish to become pregnant opting for kidney transplants is increasing, as becoming pregnant under hemodialysis or peritoneal dialysis is associated with many risks. However, there have been reports indicating that these patients are subject to a higher risk of miscarriage compared to women with normal renal function. We examine and report cases of patients that experienced pregnancy after undergoing kidney transplantation at our hospital.

Subjects and method. Of the kidney transplantation cases that were performed at our hospital between 1985 and 2016, there were 7 cases of pregnancy. The serum creatinine levels, urine protein findings, etc, of these 7 cases were examined during the pre-pregnancy, pregnancy, childbirth, and postpartum periods.

Results. All 7 cases were able to give birth. There were two cases of transient postpartum hypertension. There were no cases of obvious pregnancy toxemia or fetal growth retardation. Two of the cases resulted in the failure of the transplanted kidneys.

Discussion. According to previous studies on pregnancy and childbirth after kidney transplantation, the presence of high blood pressure and proteinuria as well as the renal function at the time of pregnancy is closely associated with postpartum renal function. Urine protein was detected prior to pregnancy in both cases and resulted in the failure of the transplanted kidneys. The influence of immunosuppressants on the mother and fetus is also an important consideration.

Conclusion. We believe it is extremely important to ensure a thorough informed consent process prior to pregnancy and systematic use of immunosuppressants for young female transplant recipients.

THE number of end-stage renal disease patients is increasing in Japan and around the world. Transplantation is an established method of renal replacement therapy, and the number of transplants is increasing. As hemodialysis or peritoneal dialysis during pregnancy are accompanied by several risks, more young women who wish to become pregnant are opting for renal transplantation. An important benefit associated with kidney transplantation in women of childbearing age is increased fertility. However, women with renal transplants are reported to have a higher rate of miscarriage than women with normal renal function. Although these patients are carefully managed by their transplant surgeon and obstetrician, there are many challenges to overcome. In kidney transplantation, pregnancy and childbirth are very important tasks. We report our hospital experience with patients who became pregnant and delivered after receiving a kidney transplant.

SUBJECTS AND METHOD

Between 1985 and 2016, 537 patients underwent kidney transplantation at our hospital, of whom 7 became pregnant

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Table 1. Criteria

1. At least 2 years post-transplantation.
2. Stable renal function with creatinine < 2 mg/dL (1.5 or less mg/dL is desirable).
3. No recent episodes of acute rejection.
4. Blood pressure < 140/90 mm Hg on medication.
5. Proteinuria < 500 mg/d.
6. Normal allograft ultrasound.

and delivered. Of these 7, 6 patients had 1 pregnancy and 1 had 2 pregnancies. We evaluated blood creatinine levels, urinary protein, and the presence of hypertension or complications before, during, and after pregnancy.

The criteria used for our outpatient pre-pregnancy evaluation of transplant patients are shown in Table 1: 1. ≥2 years since the transplant; 2. stable function of the transplanted kidney, with serum creatinine ≤2 mg/dL; 3. no recent history of rejection reactions; 4. stable blood pressure; 5. urinary protein <500 mg/day; and 6. no abnormal ultrasound findings in the transplanted kidney. This criteria referred to European Renal Association–European Dialysis and Transplant Association criteria [1].

RESULTS

Pre-pregnancy patient characteristics are shown in Table 2. Transplantation was performed at a mean age of 27.3 ± 4.6 (19–31) years, with 6 receiving a live donor kidney and 1 receiving a deceased donor kidney. Pre-transplant dialysis duration was 3 to 126 months, and none received a preemptive transplant. Creatinine levels were ≤1.5 in all patients. Urinary protein was 2+ in 1 patient and 1+ in 1 patient, but was negative in 5 others. No patients had a history of hypertension.

Table 3 shows the patients' characteristics at the time of pregnancy. The mean age at pregnancy was 34.2 ± 2.5 (31–39) years. The duration between transplantation and pregnancy was ≥2 years in all patients (34–117 months) (Table 3). Gestational albuminuria occurred in 2 patients (1+). Other gestational complications included dyslipidemia in 2 patients and hyperuricemia in 4.

Table 4 shows the patients' profiles during labor. Pregnancy duration was 37 to 43 weeks (normal term) in 5 patients, with premature births (<37 weeks) in 2 patients. All deliveries were by cesarean section. The newborns weighed between 2220 g and 2750 g, with low birth weight (<2500 g) in 3 cases (unknown in 1 patient).

Postnatal characteristics are shown in Table 5. Changes in postnatal blood creatinine levels were monitored for up to 1 year after birth, and are shown in Fig 1. In all cases serum creatinine was below 1.5 before childbirth, but in 3 cases it increased to 1.5 or more after childbirth. With regard to perinatal events, 1 patient was transferred to another hospital for a threatened premature delivery, and 1 was delivered by emergency cesarean section. Two patients had postnatal hypertension and were medically treated, but both cases were transient and remitted. No patients had toxemia or fetal growth retardation. Two experienced failure of the transplanted kidney (both were positive for urinary protein before pregnancy). Of these 2, 1 underwent retransplantation.

Table 6 shows pre- and post-pregnancy immunosuppressant use. In general, patients considering pregnancy are controlled with a combination of methylprednisolone, a calcineurin inhibitor, and azathioprine in our department. One of the patients in this study was switched from mizoribine to azathioprine when pregnancy was confirmed. Five of the 7 had no change in medication. However, azathioprine was discontinued in one patient after becoming pregnant because it caused anemia as a side effect.

DISCUSSION

A review of the literature on pregnancy and delivery after renal transplantation suggests that hypertension, albuminuria, and renal function during the pregnancy affect postnatal renal function, and may be associated with serious maternal and fetal complications [2]. The 2 patients who developed transplanted kidney failure were positive for urinary protein before pregnancy. All but 1 of the remaining patients continue to have stable renal function. Although pregnancy and delivery after organ transplantation are considered high-risk, pregnancy and delivery in general are associated with risk. It is a misconception that avoiding exposure to drugs or radiation during early pregnancy prevents deformities–the rates of spontaneous miscarriage and defects are 15% and 3%, respectively. The risks of pregnancy and delivery after organ transplantation must be analyzed in comparison to the rates of spontaneous events,

Table 2. Case (Pre-Pregnancy)

	Cause of Disease	Age of Tx	Donor	Dialysis Period (Months)	S-Cr	Proteinuria	HT
1.	Nephrotic syndrome	19	Living	24	1.0	2+	-
2.	Unknown	31	Living	121	1.1	-	-
3.	IgA nephropathy	30	Living	6	1.0	-	-
4.	Unknown	22	Cadaveric	78	1.3	1+	-
5.	Nephrotic syndrome	27	Living	3	1.3	-	-
6.	Unknown	31	Living	126	1.04	-	-
7.	Unknown	31	living	126	1.22	-	-

Abbreviations: HT, hypertension; S-Cr, serum creatinine; Tx, transplantation.

Table 3. Case (Found Out Pregnancy)

	Age	Post-Transplant Period	S-Cr (mg/dL)	Proteinuria	HT	Other Disease
1.	33	13 y, 4 mo	1.0	1+	-	Hypercholesterolemia Hyperuricemia HCV (+)
2.	33	3 y, 4 mo	1.03	-	-	None
3.	37	7 y, 4 mo	1.02	-	-	Hyperuricemia
4.	31	9 y, 9 mo	1.8	1+	-	Hyperuricemia
5.	33	6 y, 6 mo	1.3	-	-	Hypercholesterolemia Hyperuricemia
6.	34	2 y, 10 mo	1.03	-	-	None
7.	39	8 y, 1 mo	1.18	-	-	None

Abbreviations: HCV, hepatitis C virus; HT, hypertension; S-Cr, serum creatinine.

Table 4. Case (Delivery)

	Age	Pregnancy Period	S-Cr (mg/dL)	Method of Delivery	Apgar Score 1 min/5 min	Fetal Sex and Body Weight
1.	33	35 wk	1.1	Cesarean section	8/-	F 2220 g
2.	34	37 wk	1.26	Cesarean section	Unknown	M 2248 g
3.	37	37 wk, 2 d	1.22	Cesarean section	9/-	M 2750 g
4.	31	28 wk, 2 d	1.6	Cesarean section	Unknown	F Unknown
5.	33	41 wk, 1 d	1.9	Cesarean section	7/9	M 2608 g
6.	35	37 wk, 3 d	1.22	Cesarean section	Unknown	M 2248 g
7.	40	38 wk, 4 d	1.26	Cesarean section	Unknown	F 2580 g

Abbreviations: F, female; M, male; S-Cr, serum creatinine.

Table 5. Case (Post-Delivery)

	Event of Perinatal Period	Post-Delivery (1 mo) S-Cr (mL/min) Proteinuria	Post-Delivery (3 mo) S-Cr (mL/min) Proteinuria	Post-Delivery (1 y) S-Cr (mL/min) Proteinuria	Outcome (Present) S-Cr (mL/min) Proteinuria
1.	Start to hypotensive drug (temporary)	1.1 1+	1.4 3+	1.7 2+	Re-transplanted (19 y after childbirth)
2.	Start to hypotensive drug (temporary)	1.03 -	1.17 -	1.08 -	Graft is engrafted 1.34 Proteinuria (-)
3.	None	1.21 1+	1.25 -	1.14 -	Graft is engrafted 1.54 Proteinuria (±)
4.	Hospital transfer due to imminent abortion	1.9 -	2.0 1+	2.2 1+	Restart of dialysis (15 y after childbirth)
5.	Urgent cesarean section	2.0 -	1.7 -	1.8 ±	Unknown
6.	None	1.03 ±	1.09 -	1.18 -	Graft is engrafted 1.23 Proteinuria (-)
7.	None	1.15 -	1.25 ±	1.28 -	Graft is engrafted 1.23 Proteinuria (-)

Abbreviation: S-Cr, serum creatinine.

and the use of immunosuppressant drugs complicate the assessment. Antimetabolites such as mycophenolate mofetil are teratogenic, and administration in early pregnancy is problematic. Antihypertensive drugs such as angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are highly toxic to fetuses and should be avoided during the second and third trimesters. The most important post-transplantation drugs are immunosuppressants. Azathioprine and calcineurin inhibitors are required or recommended under certain conditions, even during pregnancy. A meta-analysis of 5 cohort studies on azathioprine exposure within 3 months before conception and during pregnancy analyzing 3045 patients revealed no association with the rates of congenital abnormalities or low birth weight. Although there was an association with an increase in premature delivery, the results suggested this was due to the severity of underlying disease [3]. Hematological abnormalities such as severe transient anemia and

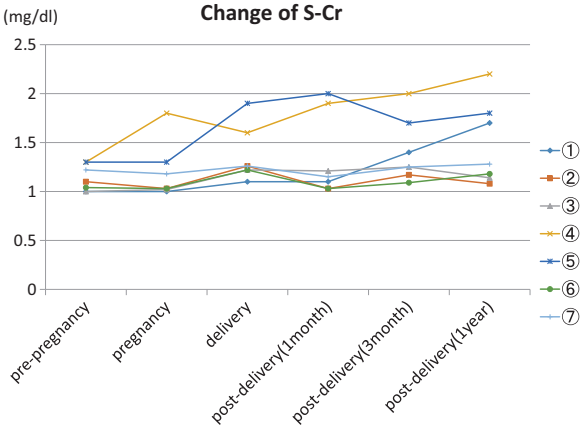

Fig 1. Changes of serum creatinine.

thrombocytopenia have been reported in newborns whose mothers were given continuous azathioprine therapy, but there were no reports of severe complications [4–6]. The use of cyclosporine in over 850 pregnant women has been reported, but the rate of congenital defects was not dramatically higher than in the general population [7–9]. Although the rate of intrauterine growth retardation was higher in children exposed to cyclosporine, this may also be due to the underlying disease itself [9,10]. Sirolimus and everolimus are contraindicated. Thus, appropriate informed consent should be obtained from recipients who wish to become pregnant, and immunosuppressive management must be carefully planned. Two of the patients in this study had hypertension during pregnancy. Fortunately, this was controlled without progression to severe hypertension, but monitoring for complications, including preeclampsia, is crucial in pregnant renal transplant recipients. There are no guidelines on pregnancy and delivery after transplantation in Japan and patients have been managed through trial and error at each institution. A guideline is now finally being prepared. The experience at our institution implies that pregnancy and delivery following renal transplantation are safe and feasible when carefully managed.

Table 6. Immunosuppression

	Pre-Pregnancy	Post-Pregnancy
1.	Methylprednisolone 4 mg Cyclosporine 125 mg Mizoribine 25 mg	Same dose Cyclosporine 150 mg ↑ Azathioprine 12.5 mg (convert)
2.	Methylprednisolone 2 mg Cyclosporine 100 mg Azathioprine 50 mg	Methylprednisolone 4 mg ↑ Same dose Same dose → drop out (anemia)
3.	Cyclosporine 100 mg Azathioprine 50 mg	All same dose
4.	Methylprednisolone 6 mg Cyclosporine 150 mg Azathioprine 75 mg	All same dose
5.	Methylprednisolone 4 mg Cyclosporine 150 mg Azathioprine 75 mg	All same dose
6.	Methylprednisolone 4 mg Cyclosporine 100 mg	All same dose
7.	Methylprednisolone 2 mg Cyclosporine 100 mg Azathioprine 50 mg	All same dose

CONCLUSION

Medical facilities in Japan have established their own standards regarding pregnancy and delivery following kidney transplantation. Although all 7 cases had safe deliveries, regulation of immunosuppressants was difficult. Future increases in the number of kidney transplants necessitates safe deliveries along with graft protection. Particular caution is considered necessary for patients preoperatively positive for proteinuria, which caused transplanted kidney function failure in 2 patients. Kidney transplant recipients intending to conceive need to provide thorough informed consent to enable primary care physicians to clearly understand their condition during delivery.

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