Association Between the Fertile Period and Live Birth Post–Kidney Transplantation: A Retrospective Single-Center Cohort Study

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ABSTRACT

Background. Despite restoration of fertility after kidney transplantation, the benefit is limited in female kidney recipients. Our objective is to determine the reasons for this discrepancy.

Methods. We evaluated 315 women who underwent kidney transplantation from 1983 to 2015 (a median of age at transplantation [10th–90th percentile] of 32 years [7–55 years]); 230 recipients between the ages of 15 to 49 years old as of March 2016 were observed.

Results. We experienced 10 abortions and 21 live births from our 23 recipients and 2 abortions and 7 live births in 7 recipients from other transplant center. The live birth rate was 8.9 per 1000 female transplant recipients of childbearing age. Seven recipients received either treatments of artificial insemination or in vitro fertilization. Average age at pregnancy was 33.2 ± 3.2 years old, and the fertile period post-transplantation was longer in recipients with live births than those without live births (14.1 ± 7.1 vs 9.9 ± 7.3 years, $P < .05$). In 42.9% of recipients with live birth, pregnancy-induced hypertension was observed in the last trimester. The gestational age and the average birth weight were 32.8 ± 5.0 months and 2184 ± 632 g, respectively. During follow-up of 14.5 years, there was one case of graft loss, which is a rate of 2.5 per 1000 female recipients.

Conclusion. Although pregnancy complications are often observed in kidney recipients, graft survival is less influenced by pregnancy. Importantly, kidney disease at childbearing age disrupts pregnancy even after kidney transplantation.

ONE of the many perceived benefits of kidney transplantation is restoration of fertility in women of childbearing age (15–49 years old). In many cases, pituitary-ovarian function is restored within the first few months after kidney transplantation [1]. Safe conception can be achieved as early as 1 to 2 years following kidney transplantation [2,3]. The proportion of live births to total pregnancy outcomes after kidney transplantation, including incidences of live birth, miscarriage, abortion, stillbirth, and ectopic pregnancy, has been reported at 73.5%; this proportion is higher than that for the general population of the United States [4]. Many studies have suggested that pregnancy has no deleterious effect on allograft function [5–7].

Despite the acceptable and favorable outcomes of treatment, overall pregnancy and live birth rates for kidney transplant recipients remain markedly lower than in the general population [8]. Factors influencing these statistics may include age at transplantation, baseline disease, duration of dialysis treatment, era of kidney transplantation, mycophenolate mofetil administration, and household income [8]. However, few studies have verified the factors

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related to pregnancy and live birth rate in kidney transplant recipients.

Live birth rate in the general population is calculated as the number of live births during a given period. Total fertility rate indicates the average number of children a woman delivers in her lifetime, which is calculated from the number of live births in a year by women of childbearing age. According to the Ministry of Health, Labour and Welfare, the total fertility rate in the general Japanese population in 2015 was 1.42. The average age of first live birth for women was 30.6 years. In Japan, as in many other developed countries in the world, later marriage has a considerable impact on live birth rates.

The main objectives of our current study were to assess reasons for live birth rates in kidney transplant patients to be markedly lower than in the general population, and to investigate the effects of chronic kidney disease (CKD) onset time and kidney transplantation time on live birth rates.

MATERIALS AND METHODS

This study employed a retrospective, cross-sectional design based on pre-existing medical records. A total of 315 women with end-stage renal disease underwent kidney transplantation during 1983 to 2015 in our treatment center (the median age at kidney transplantation [10th–90th percentile] is 32 years [7–55 years]). In Fig 1A, each line shows observational period from the age of kidney transplantation to the age in 2016 and the shaded area shows the period of childbearing age (15–49 years old). Evaluation of medical records was possible for 230 of these patients after application of the following exclusion criteria: age over 50 years at the time of kidney transplantation (n = 57), age under 15 years at the time of survey (n = 26), and graft loss before the age of 15 years (n = 2). Two hundred eleven recipients with no live birth were observed (91.7%), including 6 abortions. Of the remaining 19 recipients from our transplant center, we observed 4 abortions and 21 live births. In addition, 7 recipients from another transplant center visited an obstetric service in our hospital, of whom we observed 2 abortions and 7 live births (Fig 1B). Mycophenolate mofetil was converted to azathioprine when they planned pregnancy. We did not observe incidents of fetal malformation.

Records of age, date of kidney transplantation and pregnancy, disease underlying end-stage renal disease, dialysis modality, donor type, HLA, height, weight, blood pressure at pregnancy, serum creatinine, proteinuria, marital status, gestational age, birth weight, and live births were collected. Estimated glomerular filtration rate was calculated according to the revised formula for Japanese patients, which is 194 × creatinine − 1.094 × age − 0.287 (× 0.739 for women), according to the Modification of Diet in Renal Disease method [9]. To calculate live birth rates after kidney

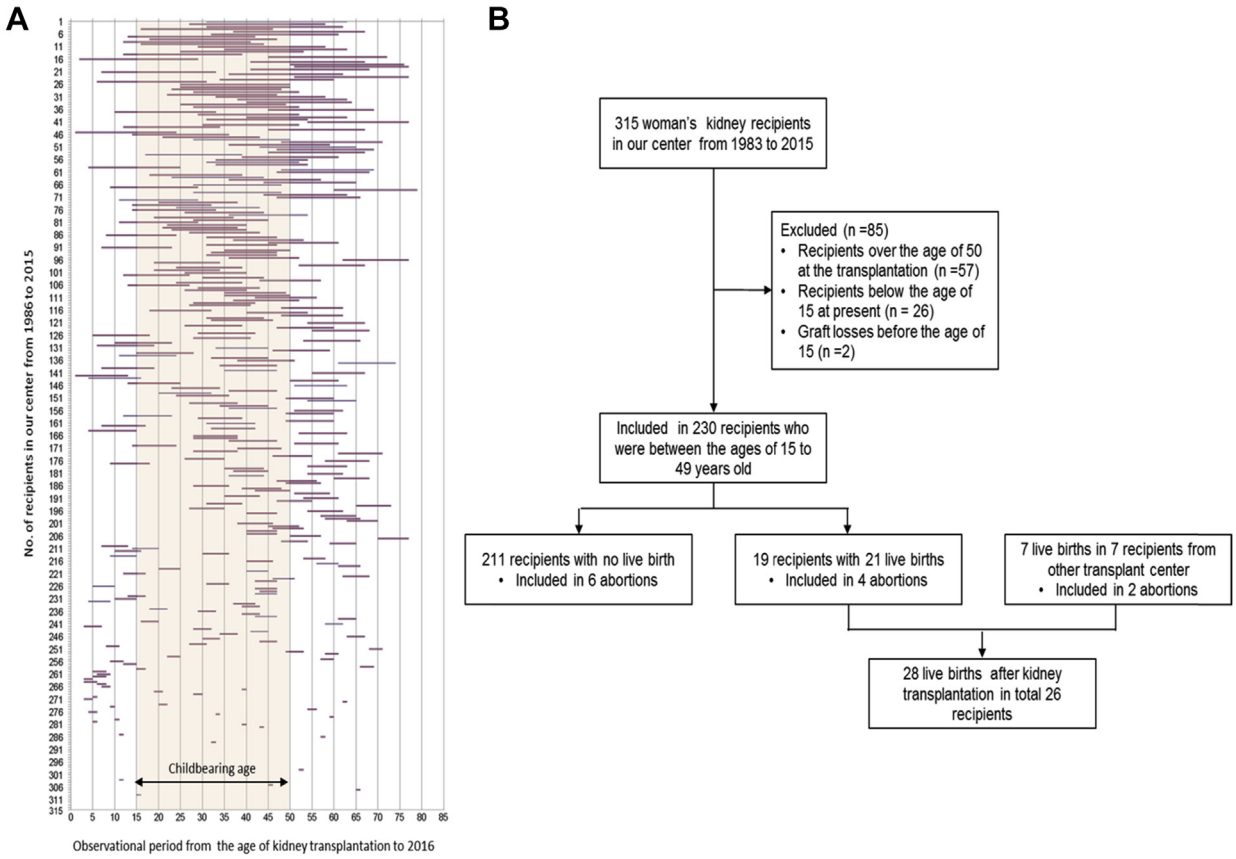

Fig 1. (**A**) Observational periods from the age of kidney transplantation to the age in 2016 and (**B**) flowchart of female transplant recipients. Each line shows observational period from the age of kidney transplantation to the age in 2016, and the shaded area shows the period of childbearing age (15–49 years old).

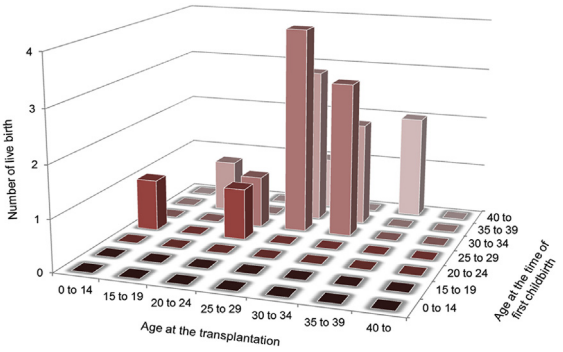

Fig 2. Association between age at kidney transplantation and age at pregnancy.

transplantation, follow-up periods during childbearing age after the first 2 years post–kidney transplantation were taken into consideration for the counting. Childbearing age was defined as 15 to 45 years in this study.

The measured values were expressed as the means ± standard deviations and percentages. Continuous variables between the 2 groups were compared using Mann-Whitney *U* tests, whereas categorical variables were compared using Pearson χ^2 tests. Significance was accepted at $P < .05$. This study was approved by the Ethics Committee of Toho University Omori Medical Center, Tokyo, Japan (approval number: 23–159) and has adhered to the principles of the Declaration of Helsinki governing the ethical use of human subjects for medical research.

RESULTS

Association of Age at the Transplantation With Pregnancy

Pregnancy was observed in women between the age of 25 and 45 years, most of whom received transplantation in their 20s and gave birth in their 30s. Three recipients gave birth in their 40s (Fig 2). Live birth rate after kidney transplantation was 8.9 per 1000 women transplant recipients of childbearing age.

Demographic Characteristics of Recipients With or Without Live Birth

The population characteristics in relation to the occurrence of live birth are presented in Table 1. Live birth occurred in 19 (8.3%) female recipients, and they had longer periods of childbearing age after kidney transplantation (14.1 ± 7.1 vs

Table 1. Demographic Characteristics by Recipients With or Without Live Birth

Recipients' Characteristics	Recipients in Childbearing Age After Kidney Transplantation (n = 230)		*P* Value
	No Live Birth, n = 211 (91.7%)	Live Birth, n = 19 (8.3%)	
Age at kidney transplantation (y)	29.4 ± 12.7	28.2 ± 6.3	.45
Age at the present day (y)	43.0 ± 14.2	42.5 ± 6.2	.76
Period of childbearing age after kidney transplantation (y)	9.9 ± 7.3	14.1 ± 7.1	.022
Period of dialysis therapy (d)	1189 ± 1614	816 ± 700	.07
Graft loss in childbearing age, n (%)	10 (4.7%)	0 (0.0%)	.26
Graft loss after childbearing age, n (%)	38 (18.0%)	2 (10.5%)	
Height (cm)	147 ± 20	153 ± 9	.024
Weight (kg)	42.9 ± 13.3	40.7 ± 7.4	.27
Body mass index (kg/m^2)	18.9 ± 3.8	17.3 ± 2.5	.023
ABO incompatibility	51 (24.3)	6 (31.6)	.53
HLA A/B/DR mismatches			.46
0	14	3	
1	21	1	
2	73	4	
3	66	9	
4	13	2	
5	8	0	
6	6	0	
Unknown	11	1	
Underlying disease			.94
Congenital anomalies of the kidney and urinary tract, n (%)	43 (20.4%)	5 (26.3%)	
Hereditary kidney disease, genetic disorder, or Wilms tumor, n (%)	13 (6.2%)	1 (5.3%)	
Glomerulonephritis, n (%)	109 (51.7%)	10 (52.6%)	
Type 1 diabetes mellitus, n (%)	6 (2.8%)	1 (5.3%)	
Type 2 diabetes mellitus, n (%)	7 (3.3%)	0 (0.0%)	
Others, n (%)	4 (1.9%)	0 (0.0%)	
Unknown, n (%)	29 (14.2%)	2 (10.5%)	
Modality of dialysis therapy			.49
Preemptive, n (%)	28 (13.3%)	1 (5.3%)	
PD or PD to HD, n (%)	53 (25.1%)	4 (21.1%)	
HD, n (%)	130 (61.6%)	14 (73.7%)	

Abbreviations: HD, hemodialysis; PD, peritoneal dialysis.

9.9 ± 7.3 years, $P = .022$), greater height (153 ± 9 vs 147 ± 20 cm, $P = .024$), and lower body mass index (17.3 ± 2.5 vs 18.9 ± 3.8 kg/m^2, $P = .023$). The period of dialysis therapy tended to be shorter in recipients with live birth than in those without live birth (816 ± 700 vs 1189 ± 1614 days, $P = .07$), but it was not a statistically significant difference. Moreover, there were no significant differences in the proportions of ABO incompatibility, HLA mismatches, underlying kidney disease, and modality of dialysis therapy.

Pregnancy Outcomes

Pregnancy outcomes in the 26 recipients with live birth are presented in Table 2. Average age at kidney transplantation and average age at pregnancy were 24.8 ± 8.1 years and 34.4 ± 3.9 years, respectively. The average period from transplantation to pregnancy was 9.3 ± 6.9 years. A total of 34 pregnancies, including 6 (17.6%) abortions and 28 live births, were observed in these recipients. Seven of them received either treatments of artificial insemination or in vitro fertilization. The average gestational age was 32.8 ± 5.0 weeks, and 7 vaginal deliveries (25%) and 21 caesarean sections (75%) were observed. The average birth weight was 2184 ± 632 g, and low birth-weight and extremely low birth-weight were recorded in 13 and 5 neonates, respectively. Pregnancy-induced hypertension was observed in 12 (42.9%) recipients and was categorized into 3 types: 2 gestational hypertension, 6 preeclampsia, and 4 superimposed preeclampsia. Pregnancy-induced hypertension occurred in the last trimester of pregnancy (median gestational age [10th–90th percentile] of 32.5 weeks [23.6–36.7 weeks]). Threatened premature delivery and/or premature rupture of the membrane were observed in 7 recipients. The onset of those was 31.6 ± 7.1 weeks. Hydronephrosis of kidney graft by enlarged uterus was observed in 2 recipients.

Kidney Graft Outcomes

Graft function deteriorated temporarily in the last trimester of pregnancy for some recipients, and a progressive creatinine increase was observed in one recipient. Gestation outcome of this patient was relatively favorable except for a creatinine level of 1.48 mg/dL (estimated GFR 34.8 mL/min per 1.73 m^2) before pregnancy (Fig 3).

DISCUSSION

The results of this study revealed that (1) only 8.3% of female kidney transplant recipients achieved live birth; (2) longer periods of childbearing age after kidney transplantation contributed importantly to giving birth; (3) some recipients received infertility treatment; (4) maternal comorbidity and complications, such as hypertension, preeclampsia, proteinuria, and deterioration of graft function, occurred with high frequency; and (5) graft survival after pregnancy was favorable.

Table 2. Pregnancy Outcomes in 26 Recipients With Live Birth

Recipients' Characteristics	Recipients With Live Birth After Kidney Transplantation (n = 26)
Age at kidney transplantation (y)	24.8 ± 8.1
Age at pregnancy (y)	34.4 ± 3.9
Period from transplantation to pregnancy (y)	9.3 ± 6.9
Pregnancy (n)	34
Abortion, n (%)	6 (17.6%)
Live birth (n)	28 (82.4%)
Fertilization	
Spontaneous pregnancy or timed intercourse (n)	27
Artificial insemination (n)	4
In vitro fertilization (n)	3
Systolic blood pressure at pregnancy (mm Hg)	144 ± 26
Diastolic blood pressure at pregnancy (mm Hg)	87 ± 13
Creatinine at pregnancy (mg/dL)	1.25 ± 0.73
$eGFR_{MDRD}$ at pregnancy (mL/min per 1.73 m^2)	40 ± 27
GFR categories in KDIGO 2012 at pregnancy	
G1 or 2, n (%)	12 (46.1)
G3a, n (%)	8 (30.8)
G3b, n (%)	6 (23.1)
G4 or 5, n (%)	0 (0.0)
Immunosuppressive drugs at pregnancy	
Methylpredonisolone in 24 recipients (mg)	4.0 ± 1.7
Predonisolone in 2 recipients (mg)	5.0 ± 0.0
Azathioprine in all recipients	46 ± 12
Calcineurin inhibitors	
Cyclosporin in 11 recipients	134 ± 64
Tacrolimus in 14 recipients	3.3 ± 1.5
None in 1 recipient	
Vaginal delivery, n (%)	7 (25%)
Caesarean section, n (%)	21 (75%)
Gestational age (wk)	32.8 ± 5.0
Birth weight (g)	2184 ± 632
Low-birth-weight baby (<2500 g)	13
Extremely low-birth-weight baby (<1500 g)	5
Pregnancy-induced hypertension	12 (42.9%)
Gestational hypertension	2
Preeclampsia	6
Superimposed preeclampsia	4
Other complications of pregnancy	
Gestational proteinuria with increased creatinine	1
Threatened premature delivery and/or premature rupture of membrane	7
Hydronephrosis of kidney graft by enlarged uterus	2

Abbreviations: eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; MDRD, Modification of Diet in Renal Disease.

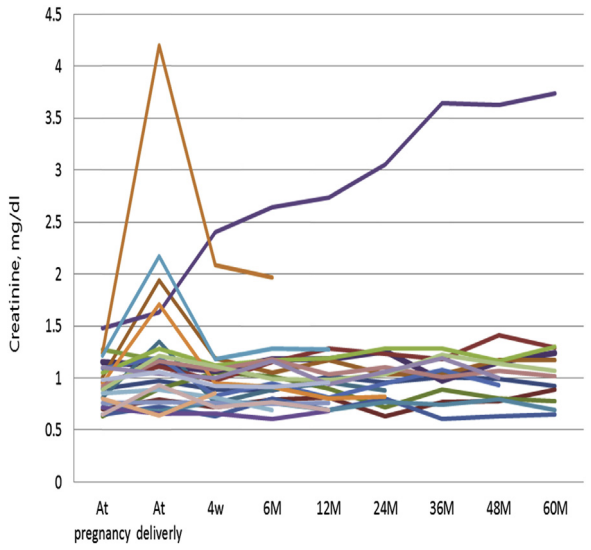

Fig 3. Kidney graft outcomes. Each line shows changes in serum creatinine during observational period in 26 female kidney recipients with live birth.

Live birth rates in the United States, Australia, and New Zealand were reported at 19 per 1000 female kidney transplant recipients per year between 1990 and 2003 [8] and 16 per 1000 female kidney transplant recipients per year between 1996 and 2005 [6]. The markedly low live birth rate in kidney transplant recipients is a common global concern.

This study provides information regarding the factors underlying low live birth rates in female kidney transplant recipients of childbearing age. One of the reasons for the low live birth rates is that patients who have a pretransplant reproductive history seldom try to have children after kidney transplantation as they may be focused on the risks, rather than the benefits, of giving birth. If the onset of CKD occurs during childbearing age, live birth is difficult regardless of the timing of kidney transplantation. Previous studies reported that pregnancy rates after kidney transplantation were highest in females aged 20 to 24 years [8] and that the median age at the time of pregnancy significantly increased across decades to a peak of 32 years in the last decade [6]. Although no significant difference was found in age at kidney transplantation in our study, it is nevertheless important that the maximum possible number of childbearing years should be preserved after kidney transplantation. As CKD onset may occur before adulthood, in cases of CKD onset overlapping with childbearing age, early kidney transplantation is optimal for the possibility of future live births.

Delaying marriage is an increasing trend in Japan today. In our study, average age at pregnancy was 34.4 years. The differences in cumulative conception rates between women aged more or less than 30 years was found to be statistically significant [10]. In fact, some recipients in our cohort received infertility treatment. We recommend that recipients with a desire to bear children should visit a clinic for infertility treatment even if they assume that pituitary-ovarian function is restored. In contrast, maternal comorbidity and complications were observed in approximately 40% to 50% of recipients, and favorable pregnancy outcomes were found mostly in recipients with normal baseline graft function.

Our study has limitations that should be considered when interpreting the results. First, the study included only 230 female kidney transplant recipients at a single center. A few patients were excluded due to change of hospital, and these patients might have gone on to experience live births. The actual difference in live birth rates with respect to those reported in the general population may vary according to the small sample size of the study. It is necessary to investigate these rates using a multicenter epidemiologic study on a larger scale. Second, we conducted a visit to the fertility clinic and the in vitro fertilization center only upon request of the recipients. Live birth rate may have increased if we collaborated with obstetrician before pregnancy.

CONCLUSIONS

The study found that only 8.3% of female recipients achieve live birth within 14.1 years of kidney transplantation. Although pregnancy complications are often observed in kidney recipients, graft survival is less influenced by pregnancy. Live birth after kidney transplantation is an exhilarating experience that can be interrupted by kidney disease during childbearing age even after kidney transplantation.

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