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## Original Article

## Pregnancy outcomes after kidney transplantation—A single-center experience in Taiwan



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## ABSTRACT

**Objective:** This study investigated the pregnancy outcomes of women who had undergone kidney transplantations from 1992 to 2013 in a single medical center.**Materials and Methods:** Records for patients who had undergone kidney transplantations between 1992 and 2013 at National Taiwan University Hospital, Taipei, Taiwan were retrospectively reviewed, and data on obstetric conditions, neonatal outcomes, and maternal and neonatal complications were collected.**Results:** Data for a total of 15 pregnancies in 13 women who had undergone kidney transplantation between 1992 and 2013 were included in this study. The live birth rate was 87%. The mean gestational age was  $35.4 \pm 3.2$  weeks, and the mean birth body weight was  $2208.8 \pm 678.8$  g. Forty percent of the neonates were small for their gestational age ( $< 10^{\text{th}}$  percentile); 53.3% of the pregnancies resulted in preterm deliveries ( $< 37$  weeks); and 26.7% of the neonates needed Neonatal Intensive Care Unit admission. The prevalence rates of preeclampsia and gestational diabetes were 23.0% and 13.3%, respectively.**Conclusion:** The pregnancy outcomes after kidney transplantation were favorable and the mean birth body weight was  $2208.8 \pm 678.8$  g at  $35.4 \pm 3.2$  weeks gestational age. However, the maternal and neonatal complication rates were still high, such as preterm labor, preeclampsia, and small for gestational age.Copyright © 2016, Taiwan Association of Obstetrics & Gynecology. Published by Elsevier Taiwan LLC. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## Introduction

There are more than 500 kidney transplantations performed in Taiwan each year [1] and Taiwan has the highest rate of end-stage renal disease (ESRD) and dialysis rate in the world [2]. Pregnancy is uncommon in women with ESRD on chronic dialysis [3]. Kidney transplant recipients appear to have a better pregnancy rate and live birth rate. Physiologically, hypothalamic gonadal function [4] and ovulation functions [5] in females with ESRD normalized mostly after kidney transplantation. In a previous study, Gill et al [6] reported that the unadjusted pregnancy rate was 3.3% in the United States during the first three posttransplant years. Various studies on renal allograft recipients have reported successful pregnancy outcomes [7–9]. In a meta-analytical study, Deshpande

et al [10] reported the overall post kidney transplantation live birth rate and miscarriage rate to be 73.5% and 14.0%, respectively. However, kidney transplant recipients might have a higher risk of both maternal and neonatal complications, such as preeclampsia, gestational diabetes, preterm labor, and small for gestational age [11].

Premature birth ( $< 37$  weeks) and low birth weight ( $< 2500$  g) were among the most common neonatal complications, affecting nearly half of all newborns. Fortunately, newborn and maternal outcomes seem to remain favorable with successive pregnancies [12]. Improved prepregnancy renal function is also associated with superior graft outcomes [13]. Patients with a prepregnancy creatinine  $> 150$   $\mu\text{mol/L}$  (1.7 mg/dL) are more likely to encounter renal function deterioration and a rise in their baseline creatinine after pregnancy than patients with better prepregnancy renal function [13].

Today,  $> 15,000$  pregnancies have been recorded in  $> 12,000$  kidney transplant recipients worldwide, with a favorable outcome in 65–92% of the cases [14]. However, few studies have been

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published in East Asia, and no data are available for Taiwan, which has the highest rate of ESRD and dialysis in the world. In this report, we describe our experiences in the National Taiwan University Hospital, Taipei, Taiwan and present a retrospective study for the period 1992–2013.

## Material and methods

Records for patients who had undergone kidney transplantations at the National Taiwan University Hospital were retrospectively reviewed between January 1, 1992 and December 31, 2013. We used the Electronic Medical Record system at the National Taiwan University Hospital, and patients with International Classification of Diseases codes of “V22: normal pregnancy” and “V42.0 kidney replaced by transplant” were searched between January 1, 1992 and December 31, 2013. Women who became pregnant before kidney transplantation or ongoing dialysis were excluded. Women who had undergone kidney transplantation and who became pregnant without follow-up until delivery were also excluded.

The medical records were reviewed including: maternal age at delivery, parity, duration between transplantation and pregnancy, serum creatinine level, birth body weight, gestational age, the percentile of body weight, and Apgar scores at the 1<sup>st</sup> minute and 5<sup>th</sup> minute after birth. Maternal and neonatal complications such as preeclampsia, gestational diabetes, birth complications, small for gestational age (< 10<sup>th</sup> percentile), and prematurity were also collected. The statistical method was calculation of mean and standard deviation (SD), recorded as mean  $\pm$  SD.

This study received ethics approval from the Institutional Review Board of National Taiwan University Hospital, (No. 201312107RINA) on January 29, 2014.

## Results

Eighteen pregnancies in 16 women who had undergone kidney transplantation between January 1, 1992 and December 31, 2013 were included in this study. All of the pregnancies were conceived naturally. Two of the women decided to terminate their pregnancies. One decision arose from the concern of the use of immunosuppressant as well as economic issues. The other resulted from maternal prior history of hypoxic encephalopathy in the patient, complicated by mental retardation (IQ = 75). In addition, another case was excluded as a result of right tubal ectopic pregnancy. After

exclusion, the study comprised 15 pregnancies in 13 women who underwent kidney transplantation in our hospital.

A total of 271 childbearing-age (range, 18–49 years) women had undergone kidney transplantation in our hospital for the period 1992–2013. The fertility rate was approximately 6.6%, without any artificial reproductive technologies. Furthermore, two patients experienced perinatal deaths. The overall rate of successful pregnancies was 5.5% for each childbearing age (range, 18–49 years) woman after kidney transplantation.

The maternal background data is summarized in Table 1. The mean age of the patients at the time of delivery was  $33.8 \pm 5$  years (range, 21–41 years). The mean age at the time of transplantation was  $28.5 \pm 4.5$  years (range, 16–36 years). Immunosuppressant therapy comprised cyclosporine and prednisolone in eight patients, mycophenolate mofetil, sirolimus and prednisolone in one patient, cyclosporine and mycophenolate mofetil in one patient, tacrolimus, sirolimus, and prednisolone in one patient, tacrolimus and prednisolone in two patients, and tacrolimus in two patients.

Tables 2 and 3 summarizes the pregnancy outcomes. The mean gestational age was  $35.4 \pm 3$  weeks (range, 26.1–38.3 weeks). The mean birth body weight was  $2208.8 \pm 678.8$  g (range, 524–3308 g). Forty percent of the neonates were born small for their gestational ages (< 10<sup>th</sup> percentile). Preterm deliveries comprised 53.3% (20.0%, < 34 weeks and 33.3%, 34–37 weeks), and 26.7% of the neonates needed NICU admission. Sixty percent of the neonates were born via cesarean sections and the remaining six women underwent vaginal deliveries.

Table 4 summarizes the maternal complications and graft outcomes. The mean serum creatinine level prior to pregnancy was  $1.15 \pm 0.3$  mg/dL (range, 0.7–2.5 mg/dL). The prevalence rate of preeclampsia of pregnancy was 26.7% ( $n = 4$ ). The maternal gestational diabetic rate was 13.3% ( $n = 2$ ). None of the patients died during pregnancy or delivery. The graft survival rates at 1-, 5-, and 10-years after delivery were 100%, 100%, and 92.3%, respectively. Only one woman experienced graft failure at 7 years post-delivery. In Case 2, graft failure was noted 7 years later, which resulted from chronic rejection proved by kidney biopsy.

Several unfavorable cases were noted in our study, including two perinatal mortalities and one neonatal morbidity. In Case 3-1, the patient received an emergent cesarean section due to previous cesarean section and fetal distress at gestational age (GA) 35 + 4 weeks. The initial Apgar score was 0–0–>3 and the birth body weight was 1698 g. Intubation was performed, but the neonate nevertheless expired due to respiratory failure on the same

**Table 1**  
Maternal transplantation related data.

Patient	Underlying disease	Type of dialysis	Age at Transplantation	Immunosuppressant	Duration from transplantation to pregnancy
1	RPGN	HD	28	CyA + Pred	3 y 2 mo
2	CGN	HD	30	CyA + Pred	1 y 3 mo
3-1	CGN	HD	33	CyA + Pred	3 y 10 mo
3-2				CyA + Pred	6 y 5 mo
4-1	SLE	HD	30	CyA + Pred	1 y 11 mo
4-2				CyA + Pred	3 y 7 mo
5	CGN	HD	23	MMF + Sir + Pred	2 y 5 mo
6	CGN	HD	16	CyA + MMF	4 y 8 mo
7	CGN	PD	21	CyA + Pred	11 y 4 mo
8	SLE	HD	30	Tac + Sir + Pred	2 y 3 mo
9	CGN	PD	36	CyA + Pred	3 y 10 mo
10	CGN	HD	30	Tac + Pred	1 y 11 mo
11	IgA nephropathy	HD	30	Tac	9 y 1 mo
12	CGN	HD	30	Tac	4 y 7 mo
13	CGN	HD	26	Tac + Pred	11 y 1 mo
Mean		HD:PD = 11:2	28.5 $\pm$ 4.8		4 y 6 mo

CGN = chronic glomerulonephritis; CyA = cyclosporine; HD = hemodialysis; MMF = mycophenolate mofetil; PD = peritoneal dialysis; Pred = prednisolone; RPGN = rapidly progressive glomerulonephritis; Sir = sirolimus; SLE = systemic lupus erythematosus; Tac = tacrolimus.

**Table 2**  
Pregnancy outcomes.

Patient	Age at delivery (y)	History of pregnancy during hemodialysis	History of pregnancy after transplantation	Sex	Gestational age (wk)	Birth weight (g)	Birth weight percentile	Apgar score (1 <sup>st</sup> min)	Apgar score (5 <sup>th</sup> min)
1	31	G0P0	G2P0SA1	F	36+6	2276	5.20	8	9
2	32	G0P0	G1P0	F	38+3	3308	61.80	9	9
3-1	36	G2P1AA1	G3P1AA1	F	35+4	1698	< 5	0	0
3-2	40		G4P2AA1	M	36+0	2438	22.90	8	9
4-1	32	G0P0	G1P0	F	34+5	2080	17.60	7	9
4-2	33		G2P1	F	37+0	1948	< 5	8	9
5	26	G0P0	G3P0SA1AA1	M	37+0	2150	< 5	6	8
6	21	G0P0	G1P0	M	36+1	2368	17.70	8	9
7	37	G0P0	G1P0	M	37+0	2488	12.20	9	9
8	31	G0P0	G1P0	M	26+1	524	< 5	0	0
9	41	G0P0	G1P0	M	37+5	2549	8.10	9	9
10	32	G0P0	G2P0AA1	M	36+3	3136	76.30	9	9
11	39	G0P0	G1P0	M	32+3	2062	75	6	8
12	38	G1P1	G2P1	M	37+5	2800	22.60	9	9
13	38	G0P0	G3P0SA1AA1	F	31+3	1307	6.60	3	7
Mean	33.8 ± 5			M:F = 6:9	35.4 ± 3	2208.8 ± 678.8		6.6	7.5

day. Her consecutive pregnancy after kidney transplantation produced a favorable outcome, with a birth body weight of 2438 g at GA 36 weeks.

In Case 8, the woman was a victim of systemic lupus erythematosus, and her renal function during pregnancy did not deteriorate, with serum creatinine 1.1 mg/dL. This woman received kidney transplantation from a cadaveric donor, using tacrolimus, sirolimus, and prednisolone as immunosuppressants. Neither pre-eclampsia nor evidence of systemic lupus erythematosus flare up was noted. However, reversed end diastolic velocity was noted during prenatal examination at GA 26 weeks. Emergent delivery was suggested, but the patient and her family hesitated. Intrauterine fetal demise was found 2 days later.

In Case 5, the woman received kidney transplantation from a related living donor, using mycophenolate mofetil, sirolimus, and prednisolone as immunosuppressants. The fetus was adequate for the gestational age prior to GA 29 weeks. However, intrauterine growth restriction and oligohydramnios was noted starting GA 32 weeks. Prenatal obstetric ultrasound showed no other obvious fetal anomaly, and no maternal fever or other signs of infection were noted. After birth, pediatrics brain echo showed generalized megacystic brain lesion with calcification. Bilateral elbow and ankle arthrogryposis and coarctation of aorta were also noted. Congenital

infection was highly suspected by the pediatrics, but the Toxoplasmosis, Other (syphilis, varicella-zoster, parvovirus B19), Rubella, Cytomegalovirus (CMV), and Herpes (TORCH) study yielded all negative results. Furthermore, failure to thrive and cerebral palsy were diagnosed at 5 months of age.

## Discussion

In this study, the live birth rate was 87%, which is slightly higher than the one in the meta-analysis reported by Deshpande et al [10] (78.3%). The most common obstetric complication found in our study is cesarean section, reported at 60%, which is equal to the rate reported by Deshpande et al [10] (60%). The rate of preterm delivery is 53.3%, which is higher than the rate reported by Deshpande et al [10] (44.8%). Furthermore, the mean gestational age is 35.4 weeks, which is similar to the outcomes reported by Wyld et al [16] (35.4 weeks), the most recent report using data from the Australia and New Zealand Dialysis and Transplant Registry. The mean birth body weight in our study is 2208 g, smaller than the outcomes reported by Wyld et al [16] (2485 g).

The data from our center in Taiwan are consistent with those reported in previous studies of single center experiences worldwide. As shown in Table 5, mean birth body weights and gestational

**Table 3**  
Perinatal morbidities.

Patient	Mode of delivery	Reasons for cesarean delivery	SGA (< 10%)	Preterm (< 34 wk)	Preterm (34–37 wk)	NICU admission	Other complication
1	NSD	—	+	—	+	—	—
2	C/S	Cephalopelvic disproportion	—	—	—	—	—
3-1	C/S	Fetal distress & previous C/S	+	—	+	+	Fetal death
3-2	C/S	Previous C/S	—	—	+	—	—
4-1	C/S	Severe preeclampsia	—	—	+	—	—
4-2	C/S	Severe preeclampsia	+	—	—	—	—
5	NSD	—	+	—	—	+	Cerebral palsy
6	C/S	Cephalopelvic disproportion	—	—	+	—	—
7	C/S	Induction failure	—	—	—	—	—
8	NSD	—	+	+	—	—	REDV, IUFD
9	C/S	Induction failure	—	—	—	—	—
10	Vacuum assist	—	—	—	—	—	—
11	C/S	Severe preeclampsia	—	+	—	+	—
12	NSD	—	—	—	—	—	—
13	NSD	—	+	+	—	+	—
Rate (%)	NSD: 40 C/S: 60		40.0	20.0	33.3	26.7	

C/S = cesarean section; IUFD = intrauterine fetal demise; NICU = neonatal intensive care unit; NSD = normal spontaneous delivery; REDV = reversed end diastolic velocity; SGA = small for gestational age.

**Table 4**

Graft outcome.

Patient	Hypertension prior to pregnancy	Proteinuria prior to pregnancy	Preeclampsia	Gestational diabetes	Serum creatinine prior to pregnancy (mg/dL)	Postpartum serum creatinine (1 mo)	Postpartum serum creatinine (6 mo)	Graft loss	Further maternal mortality
1	–	–	–	–	0.9	1	1.1	–	Lymphoma (at 34 y)
2	–	±	–	–	1.3	1.4	1.9	+	Graft failure, Sepsis (at 39 y)
3.1	–	+	–	–	1.2	1.4	1.4	–	Gastric cancer (at 57 y)
3.2	–	+	–	–	1.9	2.2	2.3	–	
4.1	–	–	+	–	0.7	0.7	0.9	–	
4.2	–	–	+	–	0.8	0.8	0.9	–	
5	–	±	–	–	1	1.2	1	–	
6	–	–	–	–	1.1	1.2	0.8	–	
7	–	–	–	–	1	1.1	2.7	–	
8	–	±	–	–	1.1	1	1.1	–	
9	+	–	+	+	1	0.9	0.9	–	
10	–	–	–	–	1.1	1.2	1.0	–	
11	+	+	+	+	0.9	1.1	1.1	–	
12	–	–	–	–	0.8	0.9	0.9	–	
13	–	–	–	–	2.5	2	2.2	–	
Rate (%)	13.3	20.0	26.7	13.3				6.7	

ages from our center and the others listed ranged from 2208 g to 2631 g and from 34.4 weeks to 37.1 weeks, respectively. Cesarean rates were generally high, ranging from 27.3% to 100%. Preeclampsia rate were also fairly high, ranging from 18.1% to 38.1%. The gestational diabetes rate was 13.3% in our study, while the other studies either did not report a rate or reported a rate of 0%.

As for graft and patient survival, previous studies reported that pregnancy in women with a functioning graft does not have an adverse impact on patient survival and does not affect long-term graft survival [8,9,17]. In our study, none of the patients died during pregnancy or delivery and the graft survival rates at 5 years after delivery were 100%.

However, particular attention should be paid to obstetric complications such as hypertension, preeclampsia, gestational diabetes, as well as delivery outcomes such as cesarean section rates and preterm deliveries [10].

Current recommendations for pregnancy after kidney transplantation included: (1) a waiting period of at least 1 year for patients who received a kidney from a living related donor and 2 years for those who received a kidney from a living nonrelated donor; (2) serum creatinine < 177 mmol/L (< 2 mg/dL), preferably < 133 mmol/L (< 1.5 mg/dL), with no recent episodes of acute rejection or evidence of ongoing rejection; (3) normal blood pressure or with minimal hypertensive treatment (a single drug); (4) absence of or minimal proteinuria (< 0.5 g/d); (5) normal renal ultrasound

without pyelocaliceal dilatation; and (6) a low dose of immunosuppressive drugs (prednisone < 15 mg/d, azathioprine < 2 mg/kg/d, cyclosporine < 4 mg/kg/d, and tacrolimus at a therapeutic dose), withdrawal of mycophenolate mofetil and sirolimus [18–21].

A recent review by Wyld et al [16] described the usage of immunosuppressant regimens over the past 30 years. Before 1990, most women used a combination of azathioprine and prednisone as an immunosuppressant, then, from 1991 to 2000, most women used cyclosporine A-based regimens. Since 2001, 54% of women have used cyclosporine A-based regimens and 35% of women have used tacrolimus-based regimens. Although it was still under debate [22], azathioprine was used less because it was reported to increase the risk of congenital malformations, specifically ventricular/atrial septal defect [23,24], and it was assigned to FDA pregnancy category D.

Two patients in our study (Cases 5 and 8) received mycophenolate mofetil and sirolimus as immunosuppressants. They both experienced poor pregnancy outcomes. Mycophenolate mofetil was FDA pregnancy category C before and was then reassigned to pregnancy category D in 2008. A previous study reported that the use of mycophenolate mofetil during pregnancy was associated with an increased risk of malformations and first trimester pregnancy loss [25]. As for sirolimus, its use was reported to be associated with two birth defects in nine live births in the National Transplantation Pregnancy Registry [26], and it was assigned to

**Table 5**

Comparison between Taiwan and single center experience worldwide.

Parameter	Japan	South Korea	USA	Italy	Mexico	NTUH
Period	1977–2002	1991–2005	1993–2002	1997–2010	1990–2005	1992–2013
Number of patients	20	48	19	60	60	15
Number of pregnancies	29	74	13	13	75	13
Live birth rate	79%	66%	NA	NA	NA	87%
Mean maternal age	32.1	31.6	32.2	33.9	26.97	33.8
Mean gestational age (wk)	35.4	37.1	34.4	35.4	37.1	35.4
Mean birth body weight (g)	2229	2631	2373	2350	2439	2208
Premature birth rate (%)	57.10	45.00	45.40	30.00	13.30	53.3
Low birth body weight (%)	15	NA	24	15	7.70	40.0
Cesarean section (%)	40.00	39.00	27.30	100	71.30	60.0
Gestational diabetes (%)	NA	0	NA	0	0	13.3
Preeclampsia (%)	38.10	19.00	18.10	33.30	NA	26.7
Chronic hypertension (%)	25.00	49.00	NA	NA	NA	13.3
Reference	[15]	[18]	[30]	[31]	[32]	

NA = not available; NTUH = National Taiwan University Hospital.

FDA pregnancy category C. However, Jones et al [27] reported a different conclusion that the outcomes of pregnancies in women treated with mycophenolic acid products were similar to the outcomes in the general population in the National Transplantation Pregnancy Registry.

As mentioned earlier, Taiwan has the highest rate of ESRD and dialysis in the world [2]. Chou et al [28] reviewed the pregnancy outcomes for patients on chronic dialysis in Taiwan, and the overall rate of successful delivery was 57.1% among women on chronic hemodialysis, with a mean gestational age of  $30.8 \pm 1.6$  weeks with a mean birth body weight of  $1511 \pm 284$  g. Comparison of those findings with the results of the current study indicate that the gestational age and birth body weight means for pregnancies in post kidney transplant women are better. In Japan, Toma et al [29] documented a significant difference in the ratio of live births at 49% and 82%, respectively. These findings suggest that when patients with renal failure wish to become pregnant, a higher chance of favorable results can be expected if pregnancy is delayed until after kidney transplantation [15].

## Conclusion

The pregnancy outcomes after kidney transplantation were favorable and the mean birth body weight was  $2208.8 \pm 678.8$  g at  $35.4$  weeks  $\pm 3.2$  weeks gestational age. However, the maternal and neonatal complication rates were still high, such as preterm labor, preeclampsia, and small for gestational age.

## Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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