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Full Review

Pregnancy after renal transplantation: a review of registry and single-center practices and outcomes*

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Abstract

Registries from North America, Australia and Europe are rich sources of clinical data on pregnancy after kidney transplantation. Single-center reports of pregnancy outcomes are limited by small sample sizes but not by the potential reporting bias that can impact registry data. Despite the differences in data pools, the obstetric and graft outcomes reported by single centers and registries have been similar. The majority of pregnancies are successful in renal transplant patients, but the risk of complications like pre-eclampsia, low birth weight and premature birth is high. Pregnancy has no significant impact on graft function or survival when baseline function is normal.

End-stage renal disease can have a devastating impact on the quality of life. Plans for education, work and family are often interrupted or abandoned completely as patients cope with illness and the demands of treatment. Kidney transplantation not only improves mortality but it can revive opportunities to pursue personal and professional goals [1]. Although a growing number of successful pregnancies are being reported in chronic kidney disease patients [2], dialysis-dependent women of childbearing age are usually unable to conceive [2–4]. Transplantation restores fertility and has given hundreds of women the opportunity to bear children [5].

Registries from North America, the UK, Europe and Australia have recorded outcomes from >1000 pregnancies [5–8]. While registries are a rich source of data, they may be affected by reporting bias. This review will attempt to summarize the findings of multiple single-center studies from around the world and compare outcomes with registry data.

Registry data

The National Transplantation Pregnancy Registry (NTPR), established in 1991 at Thomas Jefferson University, has compiled data from 1356 pregnancies among 857 North American kidney transplant recipients. Overall, the registry data show that kidney transplant recipients have a good chance of having successful pregnancies but are at a higher risk of complications than the general population

Table 1 Pregnancy outcomes reported by major registries

Pregnancy outcomes	NTPR [5]	ANZDATA [6]	UK [7]
N= pregnancies	709*	577	188
Live births	72–80%	76.9%	79%
Mean gestational age (weeks)	35–36		35.6
Premature (<37 weeks)	48–54%		50%
Low birth weight(<2500 g)	43–48%		54%
Cesarean section	42–61%		72%
Neonatal deaths	1–3%		0
Maternal Complications	NTPR	ANZDATA	UK
N = pregnancies	903*	577	188
Hypertension during pregnancy	52–68%		50%
Pre-eclampsia	28–31%	27%	
Median creatinine before pregnancy	106–123 μmol/L** [1.2–1.4 mg/dl]	99 μmol/L [1.13 mg/dl]	125 μmol/L [1.42 mg/dl]
Median creatinine after pregnancy	123–141 μmol/L ** [1.4–1.6 mg/dl]	109 μmol/L [1.24 mg/dl]	129 μmol/L [1.47 mg/dl]
Graft Loss within 2 years of delivery	8–11%		6%

Data from the National Transplantation Registry (NTPR), Australia and New Zealand Dialysis and Transplant Registry (ANZDATA), and The United Kingdom Transplant Registry (UK).
*For NTPR data, obstetric outcomes were calculated according to the number of live births reported while maternal outcomes were based on the total number of pregnancies.
**NTPR reported mean creatinine before and after pregnancy, the other 2 registries provided median creatinine.

(Table 1). For patients treated with calcineurin inhibitors, 76–80% of reported pregnancies resulted in live births. Spontaneous abortions occurred in 12–24% of pregnancies and the remainder ended with therapeutic abortions and still births [5].

Premature birth (<37 weeks) and low birth weight (<2500 g) were among the most common neonatal complications and affected nearly half of all newborns. Transplant patients frequently required treatment for pre-eclampsia (28–31%) and hypertension (52–68%), but few patients had rejections (1–3%) or graft loss during pregnancy. According to data from the NTPR, newborn and maternal outcomes remain favorable with successive pregnancies [5].

The outcomes reported by The Australian and New Zealand Dialysis and Transplant (ANZDATA) Registry and the NTPR were similar. The ANZDATA reported a live birth rate of 76.9% among 577 pregnancies. The registry matched 120 parous with 120 nulliparous transplant recipients by year of transplant, duration of transplant and predelivery creatinine, and found no difference in 20-year graft survival [6].

Data from the UK transplant registry were consistent with other registry data and reported a live birth rate of 79%. Graft dysfunction was present in at least 27% and hypertension in 69% of UK registry patients at the start of pregnancy. Patients with normal pre-pregnancy graft function and blood pressure were more likely to have successful pregnancies (defined as live births) and less likely to have complications than those with inferior renal function or hypertension [7].

Comparable to the NTPR data, the most common neonatal complications in the UK were preterm delivery and low birth weight, which were reported in ∼50% of cases. Low birth weight is an inevitable consequence of abbreviated gestation, and the data revealed no independent risk factors for low birth weight beyond preterm delivery. A pre-pregnancy serum creatinine of >150 μmol/L (1.7 mg/dL) was associated with a greater risk of preterm delivery as was the presence of drug-treated hypertension [7].

Better pre-pregnancy renal function was also associated with superior graft outcomes. Patients with a pre-pregnancy creatinine >150 μmol/L (1.7 mg/dL) were more likely to see a rise in their baseline creatinine after pregnancy than patients entering pregnancy with better renal function. Nevertheless, 2-year post-pregnancy graft survival was 94%, which was not different than in matched, non-pregnant controls [7].

Single center data

Twenty-three single-center studies from 16 countries [9–31] and one multicenter study from five Middle Eastern countries [32] were reviewed. All reports were published after 1999 but data collection spanned from 1977 to 2008. The sample sizes ranged from 7 to 140 patients (mean 40.3) with 10 to 234 pregnancies (mean 56.4).

Obstetric outcomes

Similar to registry data, most centers reported live birth rates >70% (43.2% to 85.7%). The most common neonatal complications remained preterm labor and low birth weight. Of the 19 centers providing data on fetal outcomes, only Pakistan and Mexico reported an incidence of preterm labor <20% [9, 10]. Neonatal deaths and congenital anomalies were infrequent (Table 2).

Sgro *et al.* compared the pregnancy outcomes of transplant patients with controls without kidney disease. Pregnancies in transplant patients were significantly shorter

Table 2. Fetal outcomes

Author	Duration of study	Country	Subjects	Pregnancies	Live births		Mean gestational age	Premature		Low birth weight		Congenital abnormalities & neonatal deaths
					N	%	Weeks	N	%	N	%	
Al Duraihimh *et al*.[32]	1996-2006	Multiple	140	234	174	74.4	33.2	78	40.8		43.1	No congenital defects, 4.2% neonatal deaths
Ghanem *et al*. [14]	1984-1999	Egypt	41	67	52	77.6		21	40.3	10	19.2	2 inguinal hernias, 1 congenital hypotonia
Naqvi *et al*. [9]	1985-2005	Pakistan	31	47	36	76.5		6	12.7			0
Oliveira *et al*. [20]	2001-2005	Brazil	52	52				20	38			1 neonatal death
Gorgulu *et al*. [17]	1983-2008	Turkey	19	22				10	53	3	16	3 cases of fetal anomaly (not specified), 0 neonatal deaths
Cruz Lemini *et al*. [10]	1990-2005	Mexico	60	75	64	85.3	36.1	10	13.3			0
Kuvacic *et al*. [21]	1986-1996	Croatia	15	23	15	65.2	38.1	5	21.7	2	8.7	0
Framarino *et al*. [22]	1990-2006	Italy	70	70	60	85.7		20	33.3			1 hip dislocation
Bouattar *et al*. [23]	1998-2007	Morocco	7	10	8	80.0		2	25			0
Areia *et al*. [13]	1989-2007	Portugal	28	34	27	79.4	35.7	16	59.3	13	48.1	0
Abe *et al*. [24]	1977-2002	Japan	20	29	23	79.3	35.4	13	57.1	16	70	double-outlet right ventricle, unilateral hydro, 1 neonatal death
Han *et al*. [25]	1990-1998	Korea	14	23	11	47.8		4	36	1	9	0
Kok *et al*. [26]	1986-2000	Singapore	25	42	29	69.0						
Sgro *et al*. [11]	1988-1998	Canada	26	44	32	72.7	36.5	14	44			1 child with bilateral club feet, imperforate anus & hypospadias. 1 child with pervasive developmental disorder
Gutierrez *et al*. [18]	1976-2007	Spain	27	30								
					N	%	Weeks	N	%	N	%	
DiLoreto *et al*. [27]	1997-?	Italy	12	13	11	84.6	35.4	4	36.4			1 Klinefelters
Rahamimov *et al*. [15]	1983-1998	Israel	39	69	55	79.7		33	60			
Pezeshki *et al*. [28]	1991-1998	Iran	18	20	17	85.0	34.8	7	35	8	40	2 neonatal deaths
Ghafari and Sanadgol[29]	1991-2007	Iran	53	61				14	26.4			1 club foot, 1 facial hemangioma, 4 neonatal deaths
Yassaee and Moshiri[30]	1996-2001	Iran	74	95	72	75.8		21	22.1	45	62.5	No congenital defects, 4 neonatal deaths
Kashanizadeh *et al*.[16]	1996-2002	Iran	86	86	62	72.0						
Pour-Reza-Gholi *et al*. [31]	1984-2004	Iran	60	74		43.2						
Kim *et al*. [19]	1991-2005	Korea	48	74	49	66.0	37.1	22	45	14	27	Tracheoesophageal atresia & spinal bifida in 1 infant exposed to MMF, 1 neonatal death
Willis *et al*. [12]	1977-1995	UK	34	71	56	78.0		30	54	25	45	Epigastric hernia, hydrocele, claw hand, cystic hygroma, 2 neonatal deaths

MMF = Mycophenolate mofetil

Table 3. Maternal outcomes

Author	Pre-eclampsia		Rejection		Graft loss in 1st year		Long-term graft survival
	N	%	N	%	N	%	
AlDuraihimh *et al*. [32]	61	26.1	4	2.9	0		No graft loss within 2 years of delivery
Ghanem *et al*. [14]			0	0.0			
Naqvi *et al*. [9]			0	0			1 graft loss within 38-months follow-up
Oliveira *et al*. [20]	16	31.0			1	2	
Gorgulu *et al*. [17]	2	11.0					Renal function similar to controls at 10 years
Cruz Lemini *et al*. [10]	6	8.2	4	5.3			
Kuvacic *et al*. [21]			2	8.6	2	8.6	
Framarino and Dei Malatesta *et al*. [22]	4	6.6	1	1.6	1	1.6	
Bouattar *et al*. [23]	1	10.0	0	0.0			No graft loss at 59 months
Areia *et al*. [13]	2	5.8	3	8.8	1	2.9	
Abe *et al*. [24]	8	38.1	1	4.7	0		5 year graft survival 85.1%, 10 year 74.4%
Han *et al*. [25]	8	35.0	0	0.0			
Kok *et al*. [26]			0	0.0	0	0	92% graft survival at 86.6 months
Sgro *et al*. [11]							
Gutierrez *et al*. [18]	10	37.0	0	0.0	0	0	Renal function similar to controls at 10 years
DiLoreto *et al*. [27]	4	30.7	0	0.0	0	0	No graft loss at 2 years.
Rahamimov *et al*. [15]	6	15.3	0	0.0			Graft survival 77.6% at 10 years, 61.6% at 15years
Pezeshki *et al*. [28]	9	45.0	2	11.0			
Ghafari and Sanadgol *et al*. [29]	14	26.4			3	5.6	
Yassaee and Moshiri *et al*. [30]	45	47.4	2	2.1			Graft loss 3 (3.2%) over 2 years
Kashanizadeh *et al*. [16]	4	5.0			2	2	5-year graft survival 91%, similar to controls.
Pour-Reza-Gholi *et al*. [31]			5	6.7	0	0	Graft survival 94.5% at 5 years, 77.1% at 10 years No difference from controls
Kim *et al*. [19]	14	27.0					10 year graft survival 78.5%, 15 year 67.3% All outcomes similar to controls
Willis *et al*. [14]							

than in controls. The average gestational age at delivery was 36.5 weeks in the study group and 40.2 weeks in the control group. With a mean birth weight of 2.54 ± 0.67 kg, infants born to transplanted women weighed less than infants in the control group who weighed 3.59 ± 0.53 kg, on average [11]. Other single-center studies reported similar data with an overall mean gestational age of 35.2 weeks and a birth weight of 2.4 kg, which meets the definition of low birth weight [33].

Despite a high incidence of prematurity and low birth weight, the majority of children born to women with kidney transplants have a normal, healthy development [11–13]. Long-term studies show that most children achieve a normal height and weight and usually perform well in school [11, 13]. Problems such as learning disabilities, pervasive developmental disorder and hearing loss have been reported but are not common [11]. Children of renal transplant recipients have been followed up to 18 years, but little is known about their adulthood. Whether or not disruptions to health and well-being emerge at later ages remains to be seen. One case report suggests that *in utero* exposure to immunosuppression increases the risk of autoimmune disorders later in life, but more data are needed to establish the risk [34].

Maternal renal function and hypertension probably have an impact on fetal outcomes [10, 12, 14] and most centers encourage only the healthiest patients, with stable graft function, to pursue pregnancy. Sub-optimal renal function has been linked to a higher risk of spontaneous abortion [12]. Among transplant patients with successful pregnancies, a pre-pregnancy serum creatinine of 1.5 mg/dL or higher has been associated with premature delivery and low birth weight [10]. Ghanem *et al*. found that patients with proteinuria and hypertension were more likely to have offsprings with intrauterine growth retardation (IUGR), but Willis *et al.* found no association between renal function and risk of IUGR [12, 14].

Maternal and graft outcomes

The single-center data showed that women pursuing pregnancy after renal transplantation generally had excellent patient and graft survival, but were at an increased risk for developing potentially serious complications during pregnancy. Five centers compared long-term outcomes in transplant patients with a history of pregnancy with nulliparous controls [15–19] and no investigator found a significant difference in graft function or survival. The 15-year patient survival rates were 84.8% in patients with a history of pregnancy and 78.8% in controls[15]. Graft survival was 61.6–67.3% in study groups and 58.1–68.7% in control groups at the 15-year follow-up [15, 19] (Table 3).

Patients with a history of pregnancy had graft function similar to controls at 1, 5 and 10 years [15]. Moreover, higher rates of rejection were not found in parous women [19]. Multiple studies have reported no difference in mean pre- and post-pregnancy creatinine [17, 23, 25, 32]. Favorable outcomes are most likely found in patients with normal baseline renal function. Al Duraihimh *et al*. reported that patients who had a pre-pregnancy serum creatinine of ≥150 μmol/L (1.7 mg/dL) saw a decline in renal

function with pregnancy significantly more often than those with normal baseline creatinine [32].

Data on graft survival are reassuring, but transplant patients are at high risk of complications. Transplant registry data estimates 27–31% of pregnancies are complicated by pre-eclampsia [5, 6], a substantially higher incidence than 5–8% reported in the general population [35]. Of the 17 centers reporting pre-eclampsia data [10, 13, 15–20, 22–25, 27–30, 32], 10 had an incidence greater than 25% [18–20, 24, 25, 27–30, 32]. Hypertension, urinary tract infections and anemia were also among the most common complications reported.

Timing of pregnancy

The American Society of Transplantation (AST) advises delaying conception for at least 1 year after kidney transplantation. The committee noted that pregnancy timing should be an individualized decision, taking factors such as risk of acute rejection, risk of infection, need for potentially teratogenic medications and graft function into consideration [36]. Prior to 2005, a 2-year waiting period was recommended but improvements in immunosuppression and lower rates of early rejection prompted the AST to make the policy less restrictive. The consensus statement further acknowledges that the opportunity to bear children may be abbreviated by long wait times for organs. The more recent recommendation is based on sound reasoning but data on optimal pregnancy timing are lacking.

Pezeshki *et al*. found a significantly higher incidence of hypertension during pregnancy and pre-eclampsia in patients who conceived within 2 years of transplantation compared with those who delayed pregnancy. Choosing to proceed with pregnancy earlier did not significantly increase the risk of preterm labor, low birth weight, miscarriage, premature rupture of membranes, infection or graft dysfunction [28]. Kuvacic *et al*. reported that pregnancies occurring sooner than 2 years after transplantation had a higher rate of spontaneous abortion and preterm delivery but these differences were not significant [21].

In a review of 74 pregnancies among 48 women, Kim *et al*. found no difference in maternal or fetal outcomes or complications in pregnancies conceived within 1 year of transplantation [19]. A study of a similar size reported 100% graft survival at 2 years in patients who conceived within the first transplant year. Four patients conceived within 3 months of transplantation and had 100% graft survival at 2 years [31].

It is possible that the studies were underpowered to detect the impact of timing on pregnancy outcomes. Counseling patients to wait at least a year before conceiving to confirm graft stability and minimize the risk of teratogenic infections may be the most judicious practice until larger studies are available to guide recommendations. Reproductive function and fertility can be restored within weeks of receiving a kidney, making it important to start pregnancy counseling prior to transplantation [37].

Fertility

Uremia is known to disrupt the hypothalamic-pituitary axis and commonly results in irregular menses, anovulation and infertility [38]. Among 75 female renal transplant patients surveyed, a majority recalled amenorrhea (41.7%) or irregular menstruation (33.3%) while on dialysis. Following transplantation, amenorrhea was less common (15.5%) and almost half of women reported regular menses (47.2%). Menstruation resumed in 5.1 months, on average, and became regular 6.9 months after transplantation [39].

Advances in dialysis efficiency and obstetric care may be improving fertility rates but successful pregnancies are still uncommon in dialysis-dependent women [2, 40]. The outcomes clearly improve after transplantation but reported fertility rates are variable. The single centers reported fertility rates ranging from 6.2% to 42.4% with an average of 20.7%. The ANZDATA found no difference in fertility rates among transplanted women and the general population over a period of 40 years, but the lack of statistical significance may be due to small sample sizes [6].

A review of Medicare data from 16 195 female kidney transplant patients of reproductive age revealed a pregnancy rate of 20 per 1000 women in transplant patients and 104 per 1000 women in the general population in the Year 2000, suggesting a much lower fertility rate in transplant patients. The study excluded patients with private insurance and only looked at data up to 3 years post-transplantation. A rise in the pregnancy rate from 10 per 1000 in the first post-transplant year to 15 per 1000 in the third post-transplant year suggests that a 3-year study is inadequate to assess the fertility rates in transplant patients [41]. Most patients are advised to delay pregnancy at least 1 year after transplantation, and the single-center data demonstrates that patients wait an average of 22.6 to 65.8 months before conceiving. Studies spanning only a few years probably underestimate fertility rates in transplant patients.

Even if fertility rates are lower among transplant patients, this tells us little about the incidence of infertility in this population. Transplant patients face many complex medical and psychosocial issues, and lower fertility rates, at least in part, could reflect patients' choice.

Two studies report infertility in ∼10% of transplant patients, which is similar to the general population, but larger studies are needed to confirm this finding [42, 43]. Ovulatory cycles resume in many patients after transplantation but certainly not all. As many as 50% of women report menstrual cycle irregularities after kidney transplantation [39, 44]. In addition, changes in estrogen, progesterone, testosterone and prolactin levels have been described in women post-transplantation, making it likely that infertility is more common among transplant patients than in the general population [45, 46].

Transplant patients are among the growing number of women seeking fertility treatments. At least five cases of successful *in vitro* fertilization in kidney transplant patients have been reported in the literature [47]. One pregnancy was complicated by ovarian hyperstimulation syndrome and ovarian enlargement causing graft obstruction. Renal function ultimately recovered with conservative management [48]. The remaining case reports found no adverse effects on graft survival [47].

Immunosuppression

Most centers maintained pregnant patients on two or three-drug regimens with various combinations of calcineurin inhibitors, prednisone and azathioprine. Mycophenolate mofetil (MMF) and sirolimus were used infrequently.

Tacrolimus and cyclosporine have been widely used in pregnancy and neither has been associated with an increased risk of congenital malformations [49–53]. Cyclosporine has been associated with low birth weight but multiple investigations have shown favorable long-term outcomes in children with *in utero* exposure [5, 51–53]. Nulman *et al*. found no significant difference in full-scale intelligence quotient (IQ), verbal IQ or behavioral performance when comparing children exposed to cyclosporine during gestation with controls [51].

The NTPR reported structural malformations, including hypoplastic nails, shortened fingers, microtia, cleft palate, facial malformations and Tetralogy of Fallot, in 11 of 48 children (22.9%) with *in utero* MMF exposure [5]. Among the single-center pregnancies reported, one infant with spinal bifida and tracheoesophageal atresia was born to a mother who took MMF during the first 8 weeks of gestation [19]. In a review of 61 pregnancies, Ghafari and Sanadgol found no significant differences in clinical, obstetric or perinatal outcomes when MMF was used rather than azathioprine [29]. Nonetheless, the malformations reported by other investigators are enough to deter most centers from using MMF.

Many years of experience with azathioprine have shown it to be a safe drug during pregnancy, and it can serve as an alternative to MMF [23, 54]. The fetus lacks the enzyme required to convert azathioprine to its active metabolite, 6-mercaptopurine, thereby limiting the drug's toxicity [55]. Corticosteroids readily cross the placenta but are generally considered safe during pregnancy. Modest doses of glucocorticoids can lead to maternal adrenal insufficiency, and stress dose steroids at the time of delivery are recommended [56].

The teratogenicity of sirolimus has yet to be determined [5, 57]. The availability of alternative therapies with established safety profiles makes it an unpopular choice for pregnant transplant patients. Only two centers reported its use in a few patients and one center stopped it after pregnancy was diagnosed. No adverse outcomes were reported [18, 32].

Although most standard immunosuppressive regimens have not been linked to a pattern of congenital abnormalities [58], the agents could contribute to the high complication rate observed in the pregnancies of transplant patients. Cyclosporine and prednisone can induce or exacerbate hypertension during pregnancy, thereby increasing the risk of pre-eclampsia and early delivery [37, 59].

Conclusion

Single centers from around the world report findings consistent with data from large transplant pregnancy registries. The majority of pregnancies are successful in transplanted women but maternal and fetal complication rates are high. Pre-eclampsia, low birth weight and premature birth are among the most common complications. Investigators consistently show that pregnancy has no adverse effects on graft function or survival. Prior to transplantation, women of reproductive age should be thoroughly counseled on fertility, contraception and potential risks of pregnancy. The restoration of fertility with transplantation may have a substantial impact on the quality of life and the data suggest that pregnancy need not be discouraged in patients who are well-informed and healthy.

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