Pregnancy Outcomes After Kidney Transplantation and Long-Term Evolution of Children: A Single Center Experience

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ABSTRACT

Background. Pregnancies in women who underwent kidney transplants are at high risk compared with the general population.

Methods. In this study, we aimed to retrospectively assess the obstetrical complications, delivery outcomes, and impact of pregnancy on kidney allograft function in a single-center cohort of kidney transplant recipients (KTRs). We provide data regarding the long-term evolution of children.

Results. Thirty-two KTRs underwent a total of 57 pregnancies between 1994 and 2010. Fourteen pregnancies (24 %) did not survive caused by miscarriages (n = 9), stillborn (n = 1), ectopic pregnancies (n = 2), and medical abortion (n = 2). Live birth occurred in 76% of pregnancies. Delivery was by cesarean in 66%. The mean gestational age was 30.45 ± 11.3 weeks and 65% of newborns were premature. A low birth weight <2500g was noted in 46%. Obstetric complications were de novo hypertension in 4%, pre-eclampsia in 9%, and gestational diabetes in 2%. The 5- and 10-year post-delivery death-censored graft loss rates were 3.1% and 12.5%, respectively. Data on 21 children were collected via a self-questionnaire. After a median follow-up time of 17 years, they appeared in good medical and psychological health. None of them suffered from chronic disease (especially uronephrological condition) or was taking chronic medication.

Conclusions. Long-term evolution of children born to women who underwent kidney transplants seems favorable. Pregnancies in KTRs are successful in two-thirds of cases but are at increased risk of prematurity, delivery by cesarean, and low birth weight.

KIDNEY transplantation (KT) is the best way to restore fertility and sexual function in women with kidney failure [1]. Over the last decade, there has been an increased incidence of pregnancy in KT recipients (KTR). In 2011, over 11.000 births after KT have been reported worldwide [2]. However, pregnancy in KTR remains challenging regarding graft and patient outcomes, as well as delivery and fetal outcomes [3]. A recently published meta-analysis from van Buren et al showed reassuring long-term data regarding the impact of pregnancy on graft survival and graft function [4]. However, compared with the general population, pregnancy in KT women is associated with higher incidence of preeclampsia, cesarean section (C-section), preterm delivery, low birth weight, neonatal deaths, and stillbirths, as demonstrated in 2 meta-analyses [2,5] and in the 2017 Transplant Pregnancy Registry International annual report [6].

The Kidney Disease Improving Global Outcomes and European Renal Best Practices guidelines recommend to delay pregnancy after KT by 1 to 2 years, respectively [7,8]. Moreover, stable graft function with no recent episode of acute rejection, serum creatinine <1.5 mg/dL, proteinuria <500 mg/24 h, and normal or controlled hypertension are predictors of good maternal and fetal outcomes, and are required by most kidney

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transplant centers before allowing a planned pregnancy in a KT patient [2,9,10]. Surprisingly, data on the long-term evolution of children born to women who underwent transplants are scarce.

The aim of this retrospective single center study is to report our experience and to assess the obstetrical complications, delivery outcomes, and impact of pregnancy on kidney allograft function in our single-center kidney transplant cohort. We also assessed the long-term evolution of children.

MATERIAL AND METHODS

Patient Selection

We included all kidney transplant recipients with at least one documented pregnancy followed in our center between 1994 and 2010. Demographic data of KT patients at transplantation and at delivery were recorded, as obstetrical complications (de novo hypertension, preeclampsia, and gestational diabetes), and pregnancy outcomes (rate of live birth, characteristics of deliveries). Graft function and survival also were assessed until the end of follow-up in 2016.

This study was approved by our local ethics committee.

Definitions

De novo hypertension was defined as the need to add a hypotensive drug. Preeclampsia was defined as new onset hypertension >20 weeks (systolic >140 mm Hg and/or diastolic > 90 mm Hg) in association with one of the following: proteinuria >300 mg/day (P/creat >30 mg/mmol), maternal organ dysfunction (liver, kidney, neurologic, etc.), and uteroplacental dysfunction. Gestational diabetes was defined as a diagnosis of new-onset diabetes (fasting blood glucose concentration >92 mg/dL and/or blood glucose concentrations >180 mg/dL and/or >153 mg/dL at 1 and 2 hours, respectively, following a 75-g oral glucose tolerance test) at 24 to 28 weeks of gestation.

Patient Follow-up During Pregnancy

Patients were followed at our institution by an obstetrical team dedicated to high-risk pregnancies including patients who underwent transplants under immunosuppressive therapy. Visits were scheduled at the KTR outpatient clinic monthly or earlier when needed.

Long-term Follow-up of Live Born Children

A questionnaire was sent to children of all KTRs included in the study to assess their medical evolution. It included their current situation (weight, height, familial status, and treatment), medical history (hypertension, diabetes, and depression), addictions (smoking, etc.), and educational achievements/difficulties.

Statistics

Results are presented as median (ranges) or n and %, as appropriate. Survival rates were calculated using the product limit function (Kaplan-Meier estimator). Statistical analyses were performed using JMP software.

RESULTS

Patients Characteristics

Thirty-two women were included. Eighty-three percent of patients were on chronic dialysis for a median time of 23.6 (range, 0-138) months before KT. Median age was 24 (range, 7-35) years at KT and 42% received a living donor graft. Sixty-nine percent received induction therapy and overall were more commonly treated with a combination of cyclosporine (78%), azathioprine (81%), and steroids (100%) Table 1. summarizes the main baseline characteristics at kidney transplantation.

Pregnancy and Mother Outcomes

Fifty-seven pregnancies (including 2 twin pregnancies) were recorded during the study period. As illustrated in Fig 1, half of the pregnancies (56%) occurred >5 years of transplantation, and no patient had a pregnancy in the first year post transplant. Median age at delivery was 32 (range, 22-39) years. The incidences of de novo hypertension during pregnancy, preeclampsia, and gestational diabetes were 4%, 9%, and 2%, respectively (Table 2). Serum creatinine levels at delivery and 5 years after were 1.3 mg/dL (range, 0.8-4.6) and 1.35 mg/dL (ranges, 0.7-2.5), respectively (Table 3). After a median follow-up time of 14 years (range, 4-21), 1 patient had a biopsy-proven acute rejection (T-cell mediated rejection 10 days after delivery, successfully treated with steroids), 5 lost their grafts (at 4, 6, 7, 9, and 17 years after delivery), and 1 died of post-transplant lymphoproliferative disorder 2 years after delivery (Table 3). The death-censored post-delivery graft loss rates at 5 and 10 years were 3.1% and 12.5%, respectively.

Table 1. Baseline Characteristics

	Total Kidney Transplantations (N = 36) Corresponding to 32 Patients
Characteristics before transplantation	
Under dialysis, n (%)	30 (83%)
Hemodialysis, n (%)	25 (69%)
Peritoneal dialysis, n (%)	5 (14%)
Time of dialysis, median months (range)	24 (0-138)
Causes of kidney failure	
Glomerulonephritis, n (%)	12 (38%)
Interstitial nephritis, n (%)	13 (40%)
Genetic, n (%)	3 (10%)
Others, n (%)	4 (12%)
Characteristics at transplantation	
Age, median years (range)	24 (7-35)
Living donor, n (%)	15 (42%)
Immunosuppression	
Induction therapy, n (%)	25 (69%)
Tacrolimus, n (%)	7 (19%)
Cyclosporine, n (%)	28 (78%)
Mycophenolate mofetil, n (%)	4 (11%)
Azathioprine, n (%)	29 (81%)
Steroids, n (%)	36 (100%)

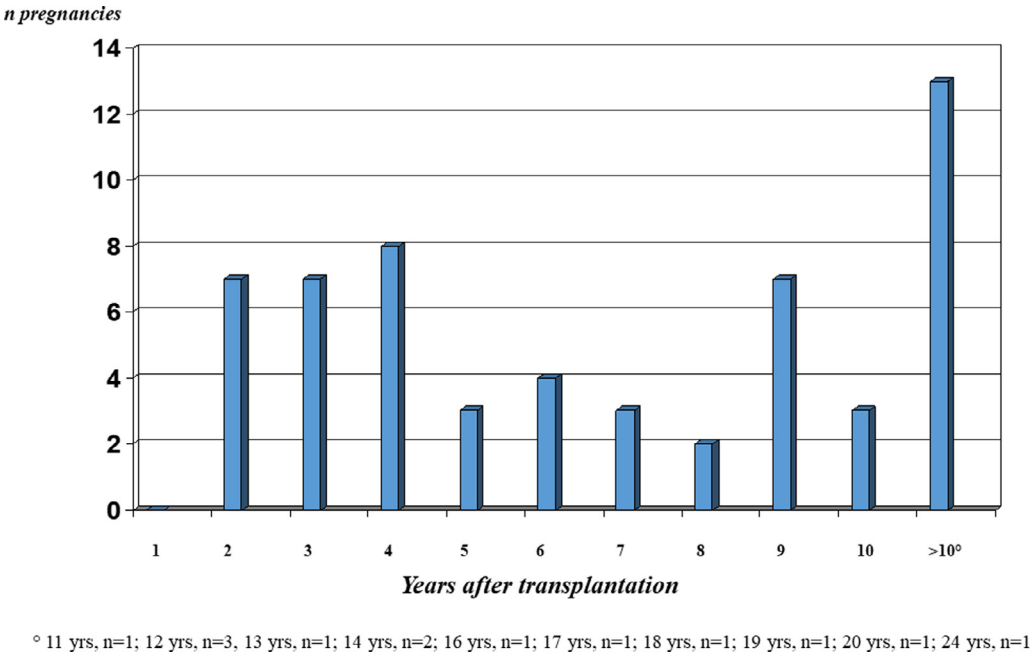


Fig 1. Distribution in time of pregnancies.

Outcomes of Patients With Chronic Allograft Dysfunction Before Delivery

Six patients had serum creatinine >1.5 mg/dL before pregnancy. As illustrated in Fig 2, serum creatinine slowly increased in 3 patients (patient 2, 3, and 6) who eventually lost their graft 7, 9, and 17 years after delivery, respectively. Patient 3 was also the only patient from the cohort who had abnormal proteinuria before delivery (0.5 g/g of creatinuria) that remained stable thereafter. The 3 other patients (patient 1, 4, and 5) had relatively stable kidney function after delivery and still have a functioning graft today >10 years after delivery.

Table 2. Characteristics, Complications, and Outcomes of Deliveries

	Total Pregnancies (N = 57)
Age at delivery, median years (range)	32 (22-39)
Obstetrical complications	
De novo hypertension, n (%)	2 (4%)
Preeclampsia, n (%)	5 (9%)
Gestational diabetes, n (%)	1 (2%)
Pregnancy outcomes	
Live birth, n (%)	43 (76%)
Causes of pregnancy failure (n = 14)	
Miscarriage, n (%)	9 (64%)
Stillborn, n (%)	1 (7%)
Ectopic pregnancy, n (%)	2 (14%)
Medical abortion, n (%)	2 (14%)
Characteristics of live birth deliveries (n = 43)	
C-section, n (%)	29 (66%)
Preterm, n (%)	37 (86%)
Birthweight <2500g, n (%)	21 (46%)

Pregnancy Outcomes

Out of the 57 pregnancies recorded, 14 (24%) failed secondary to miscarriage (n = 9), stillborn (n = 1), ectopic pregnancy (n = 2) and medical abortion (n = 2), and 43 (76%) led to live birth deliveries. At live birth deliveries, the rate of C-section, preterm (<37 weeks of gestational age), and low birthweight (<2500g) were 66%, 86%, and 46%, respectively (Table 2). No neonatal death occurred.

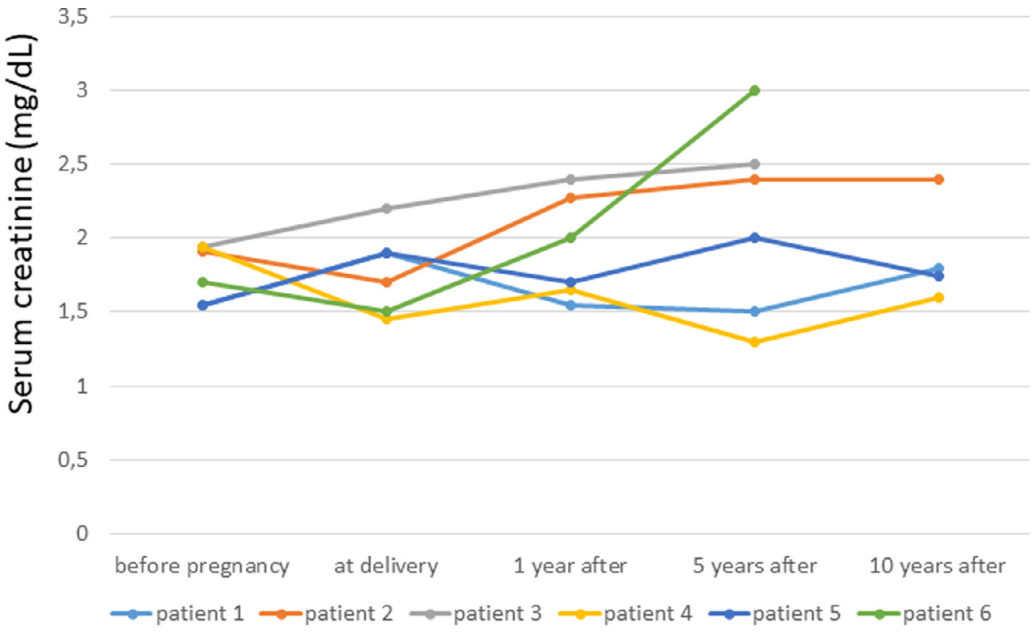
Children's Evolution

A self-questionnaire was sent in 2019 to the 43 children (or to their parents if the child was <18 years) born during the study period. The response rate was 49% (n = 21). Median age was 17 years (range, 7-25) with 48% of female. Ninety-five percent

Table 3. Graft Outcome After Delivery

	Total Population (N = 32)
Acute rejection after delivery, n (%)	1 (2%)*
Serum creatinine at delivery, median mg/dL (range)	1.3 (0.8-4.6)
Serum creatinine 5 y after delivery, median mg/dL (range)	1.4 (0.7-2.5)
Graft loss in the 5 y post delivery, n (%)	1 (2%)
Graft loss during follow-up, n (%)	5 (9%)
Death during follow-up, n (%)	1 (2%)
Follow-up time after delivery, median years (range)	14 (4-21)

* T-cell mediated rejection 10 d after delivery, successfully treated with steroids.



Patient 2 had a second pregnancy two years after the first one, and lost her graft 17 years after the first pregnancy.
Patient 3 lost her graft 7 years after delivery.
Patient 6 had a second pregnancy two years after the first one and lost her graft 9 years after the first prenancy.

Fig 2. Evolution of serum creatinine in patients with baseline >1.5 mg/dL.

(n = 20) were students (primary/secondary school, n = 12; high-school, n = 5; and university, n = 3) and 1 patient worked as a specialized engineer. Two children had a medical history including transient hypothyroidism and recurrent otitis. Two had surgical history, one for phimosis and one for bilateral uretro-vesical reflux procedure. None of the children reported taking any chronic medication, including hypotensive or diabetic treatment. None reported history of chronic kidney disease, hearing impairment, renal stone, gross hematuria, or pathologic urine dipstick test screening at school medicine. Eight children (38%) reported grade repetition and 2 were followed for attention deficit disorder during childhood. On a 1 to 10 scale, median self-estimation of physical and psychological health were 9.4 (range, 7.5-10) and 9.5 (range, 7-10), respectively.

DISCUSSION

Even if limited and needing validation on larger scales studies, our work provides for the first time reassuring long-term data on the evolution of children born from women who underwent kidney transplants. After a median follow-up time of 17 years, none of the children suffered from obvious chronic disease (especially uronephrological condition) or were taking any chronic medication. None reported history of severe infection. One patient had retrovesical reflux procedure during childhood. Moreover, their psychosocial development seems similar than in the general population. The rate of grade repetition (38%) was lower than the one reported in the general population in Belgium (60%) [11].

Data on children born to mothers with kidney transplants are currently very scarce [12]. Ono et al [13] published an interesting study that assessed immunophenotypic profile and immune function in 28 children born to women who underwent transplants on immunosuppressive medication compared with 40 healthy controls. All women were on azathioprine and prednisolone, and 70.4% were on tacrolimus. The transplanted group had a significantly lower mean birth weight and 29% of babies born to mothers who underwent transplants were hospitalized for infections in the first year of life compared with 3.6% in matched controls. All children who were hospitalized were exposed to tacrolimus during pregnancy. Furthermore, 80% of infants born to mothers who underwent transplants had low platelets, and leukocytes encompassing neutrophils, B-cells, CD8- and CD4-positive T cells, NK cells, and eosinophils. Follow-up data on this cohort showed that after birth, the observed weight discrepancies resolved [14]. At 12 months, all children were in the normal range for weight, and there was no difference in renal function between treatment and control groups. Kovač et al recently published a retrospective analysis of 22 pregnancies in 18 women who underwent kidney transplants. They found a similar incidence of major congenital anomalies to that seen in immunocompetent women [15].

Nearly 75% of pregnancies led to live births in our cohort. This is in line with other studies [2,5] and similar to what is observed in the general population [10]. Pre-eclampsia is a major concern in pregnant women who underwent kidney transplants. Indeed, it has been suggested that the risk of pre-eclampsia was 6 times higher than in the general population [16]. Our

incidence of pre-eclampsia (9%) was Please note changed After to Post inmuch lower than in other studies. Indeed, Deshpande et al reported an incidence of 27% [2], and Shah et al reported 21.5% [5]. In a national survey of Norway, the incidence of pre-eclampsia was even higher at 37% [17]. In this study, the authors showed that chronic hypertension (adjusted odd ratio [aOR] = 5.02), previous preeclampsia (aOR = 3.26), and elevated serum creatinine at the start of pregnancy (1.41 mg/dL) (aOR = 5.79%) were independent risk factors for preeclampsia occurrence. However, without any of these factors, they calculated that the risk was lower at 19%. As mentioned above, the high rate of our patients in ideal conditions (normal creatinine, no proteinuria), and tight combined transplantation-obstetrical follow-up might have contributed to the better outcomes observed in our cohort. We observed a higher incidence of preterm delivery (86%, with a mean gestational age of 30 weeks) compared with those previously described (43%-51%, with a mean gestational age around 35 weeks) [2,5,6]. The incidence of C-section (66%) was high, but in line with those previously reported (43%-64%) in kidney transplant patients [2,5,6,18]. It was much higher than in the general population, around 20% in Belgium [19]. In their retrospective study about 105 pregnancies, Bramhan et al reported a 64% incidence of C-section, mainly driven by concern about fetal wellbeing [18].

Our study also shows good long-term kidney allograft outcomes after delivery. Indeed, the 5- and 10-year post-delivery death-censored graft loss rates were 3.1% and 12.5%, respectively, especially as 56% and 28% of pregnancies occurred after 5 and 10 years after KT, respectively. In comparison, in 2 previously published meta-analyses [2,5] including 6712 pregnancies in 4174 recipients and 4706 pregnancies in 3570 KT recipients, the graft loss rates at 2 years post delivery were 9.2% and 8.1%, respectively. Van Buren et al [4] recently published another meta-analysis including 2453 patients and showed a pooled incidence of graft loss of 9.4% within 2 years after pregnancy, 9.2% within 2 to 5 years, 22.3% within 5 to 10 years, and 38.5% >10 years postpartum. Levidiotis et al reported a 5-,10-, and 15-year graft loss rates at 11%, 23.6%, and 43.5%, respectively, in their cohort of 298 women after a first live birth [20]. Results in our cohort seem better. One explanation could be the ideal conditions for pregnancy [7,8] with stable normal kidney function and no proteinuria for the majority of our patients. However, in the patients (n = 6) who had chronic allograft dysfunction (defined as prepregnancy serum creatinine >1.5 mg/dL) before delivery, long-term allograft survival was also acceptable; no patient experienced graft failure in the 5 years post delivery and only one 10 years after delivery. It is important to note that all of our patients were followed regularly at the outpatient clinic, including on the long run after delivery, and none was lost to follow-up.

We acknowledge the limitations of this study. It is a retrospective study, making it subject to reporting bias. Patients were in the optimal conditions to carry a pregnancy, and no patient with chronic renal dysfunction and serum creatinine >2 mg/dL was included. Consequently, our results cannot be extrapolated to patients with severely impaired graft dysfunction. Also, only half of the children born to mothers who underwent transplants responded to our questionnaire, making it subject to interpretation bias. Nevertheless, our cohort has the advantage over registry data of reporting granular outcomes of included patients, long-term follow-up, and innovatively, data on the outcome of children.

In conclusion, our study shows that children born to mothers with kidney transplants seem to have normal long-term medical and psychosocial evolution. Pregnancies in kidney transplant recipients are successful in two-thirds of cases but are at increased risk of preterm delivery, delivery by C-section and low birth weight. Long-term graft outcome is favorable after delivery. Care in specialized centers with close collaboration between obstetricians, neonatologists, and the transplant team is advisable.

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