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Pregnancy after solid organ transplantation: Mother, child, and allograft outcome

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Pregnancy after solid organ transplantation: Mother, child and allograft outcome

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Keywords: pregnancy, kidney transplantation, immunosuppressive drugs, outcomes, risk factors, preeclampsia

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ABSTRACT

Background

Pregnancy can be associated with adverse outcome in women with chronic kidney diseases. As around 5-10% of kidney transplantations are performed in women of childbearing age (1,2), we must be able to advise and to support the patients who want to get pregnant. This study aims to describe mother, child, and allograft outcomes after pregnancy in our retrospective cohort of kidney transplant recipients, and to compare these data with other transplant cohorts as well as with the general population as descried in the literature.

Methods

We retrospectively reviewed the files of the cohort of kidney transplant recipients, regularly followed between 1990 and 2017 in Lausanne University hospital, a tertiary referral hospital. The studied outcomes were maternal, transplant, or newborn complications during and over a period of 2 years after pregnancy.

Results

There have been 16 pregnancies for 11 women, with 16 live births (100%). There was no graft loss during the pregnancy, but 2 patients (12.5%) lost their graft within 2 years after successful delivery. Twelve babies (75%) were born without complication or malformation. Four babies (25%) were born with respiratory, cardiac or chromosomic complications or malformations. Regarding the mothers, 10 pregnancies resulted into moderate or more severe complications, including 2 preeclampsia and 2 episodes of acute renal failure.

Conclusions

In conclusion, providing good kidney function before the conception, careful and regular specialized follow-up, pregnancy can be considered to be relatively safe for the transplanted mother and her child.

Keywords: pregnancy, kidney transplantation, immunosuppressive drugs, outcomes, risk factors, preeclampsia

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Introduction

Kidney transplantation decreases substantially patients' morbidity and mortality compared to those with severe stage 4-5 chronic kidney diseases (CKD) or on dialysis (3,4). Successful transplantation with a functioning kidney allograft also improves the quality of life (QoL) of patients, in part by restoring some physiological functions such as hormonal regulations and fertility within the first 6 months in average (5). This is an important point for women of childbearing age, who represent around 10% of transplant recipients.

Pregnancy is associated with physiological modifications such as hormonal and systemic hemodynamic changes in order to ensure better perfusion of peripheral organs such as the uterus but also the kidney. The consequence for the kidney is an increase in the plasma flow (40-50%) and the glomerular filtration rate (GFR). For patients with chronic nephropathy or with a single kidney and impaired function at the time of conception, the increase of GFR can contribute to chronic glomerular hyperfiltration and the progression of the pre-existing nephropathy.

Preeclampsia is defined as a new-onset or worsening of existing hypertension associated with one or more of the following conditions: maternal organ dysfunction (including acute renal insufficiency, liver involvement, neurological or hematological complications) and utero-placental dysfunction; occurring after 20 weeks of gestation (6). Proteinuria (>300 mg/day) is no longer an obligatory criterion, in particular in patients with preexisting kidney disease and after kidney transplantation. Preeclampsia may result in fetal growth restriction or fetal death, and, for the mother, the risks of preeclampsia are direct life-threatening complications during pregnancy and a trend towards cardiovascular diseases later in life (7). An increase in serum uric acid levels is indicative of a diminution of kidney perfusion (resulting in proximal tubular dysfunction) and has a diagnostic value for preeclampsia (8). More recently, plasma concentrations of angiogenic mediators have been proposed as diagnostic and prognostic value to follow at-risk pregnancies.(9) The risk of preeclampsia increases with the degree of kidney failure. For patients with CKD who envisage having a pregnancy with as little risk as possible, certain parameters must be stable and controlled before the conception, such as GFR, urinary protein levels (Uprot) and

blood pressure. In kidney transplant recipient, additional parameters must be taken into account, in particular medication and the choice of immunosuppressive drugs, as well as the immunological state at the time of conception.

In the context of transplantation, pregnancy represents an added risk of immunization in the presence of the semi-allogeneic foetus (paternal HLA antigens) that could trigger acute cellular or more delayed antibody-mediated rejection (10). Careful immunological monitoring and management of the immunosuppressive drugs before, during and after pregnancy is therefore very important to ensure the best graft outcome. Immunosuppressive drugs can therefore not be stopped during pregnancy, even if these drugs may affect the fetus as they can cross the placental barrier and enter into the fetal circulation (e.g. vascular toxicity related to calcineurin inhibitors, diabetogenic effects of glucocorticoids, medullar toxicity and aplasia in newborns caused by azathioprine). The choice of medication is important in anticipation of pregnancy. Studies in humans have shown that low dose glucocorticoids (GCs), calcineurin inhibitors such as cyclosporine (CsA) and tacrolimus (FK), azathioprine (AZT) and hydroxychloroquine (HCQ) do not seem to increase the risk of congenital abnormalities; while cyclophosphamide, leflunomide, mycophenolic acid derivatives (MMF) and methotrexate are contraindicated during pregnancy (11–13). The key to immunosuppression is a balance between efficacy and safety.

Given the expected restoration of fertility after transplantation in women of childbearing age, we must be able to advise patients on the possibility of pregnancy and accompany them to avoid complications. The aim of this study is to report our center's experience of pregnancy in kidney transplant recipients, in particular to explore the maternal, fetal and graft outcomes.

Patients and methods

Study population

This is a retrospective study, performed within the Lausanne University Hospital (CHUV) Transplantation Center's kidney cohort from 1990 to 2017. During this period, 920 kidney transplantations were performed, representing 577 men and 313 women recipients, respectively (we could not find the data regarding the sex for 30 patients). The number of women in childbearing age was 114, representing 36.3% of transplanted women. The collected data were retrieved from medical records from all the pregnancy during this period, which represents 16 pregnancies in 11 different women.

Data collection

For each pregnancy event, we collected the following patient's data: age of conception, type of donation (living *vs.* cadaveric), time between transplantation and conception, number of transplantations before conception, diagnosis of nephropathy, preexisting comorbidities (diabetes and other endocrine diseases, arterial hypertension) and weight of the mother. Regarding the pregnancy, we collected the following data: the gravidity and the parity, duration of gestation, type of birth (vaginal delivery *vs*. cesarean section), complications during the pregnancy, weight of the newborn and any peculiarity of the newborn. Regarding the kidney allograft, we reviewed serum creatinine levels [umol/l] and eGFR (MDRD, CKDepi), proteinuria [g/l or Uprot/creat], blood pressure [mmHg], immunosuppressive drugs, BK viremia, anti-HLA antibodies, graft rejection episodes and biopsies; at different time-points (within the 3-6 months before pregnancy; at 1st, 2nd and 3rd trimester; 6 months, 1 and 2 years after the delivery).

Statistics

Data are reported as mean [extreme] or median (interquartile range (IQR)) for unsymmetrically distributed values. All statistical analyses were performed using Microsoft Excel 365 version 2016.

Results

Patient characteristics

The demographics and clinical characteristics of the study population are summarized in **Table 1.** We could review 16 pregnancies in 11 patients for whom we had full data. Fifteen babies had a Caucasian mother and 1 an Asian mother. The mean age of the mothers at conception was 32.5 years [23-42], and the mean weight was 59.3 kg [47-69]. The mean time between transplantation and pregnancy was 47.5 months [11-112]. For 9 pregnancies (56.25%), it was the first kidney transplant and for 7 pregnancies (43.75%), it was the second. Twelve patients (75%) had received a kidney from a living donor and 4 (25%) from deceased donors. The indication for kidney transplantation was a glomerular disease for 8 women (50%), a tubulointerstitial disease for 7 (43.75%) and a genetic disease (Alport syndrome) for 1 patient (6.25%).

Table 1. Patients' characteristics.

Number of pregnancies analyzed during Tx	**n=16 pregnancies in 11 patients**
1st pregnancy	7 patients
2 pregnancies during the study period	3
3 pregnancies during the study period	1
Ethnic group	
Caucasian	15 patients
Asian	1
Diagnosis of initial nephropathy	
Glomerular disease	8 patients
Tubulointerstitial or malformative disease	7
Genetic disease	1
Age at conception	
Mean [range]; years	32.5 [23-42]
Number of transplantations before pregnancy	
1	9 patients
2	7
Type of donation	
Living donor / cadaveric donor	12 patients / 4 patients
Time between transplantation and pregnancy	
Mean [range]; months	47.5 [11-112]

Tx, transplantation.

Mean baseline serum creatinine levels before pregnancy were of 130.1 umol [80-235] (average value of the 3 last values before the conception) with a mean eGFR-MDRD of 53.3 ml/min/1,73m2 [23-80]. The average systolic and diastolic blood pressure was of 114.4 mmHg and 73.6 mmHg, respectively. In 5 pregnancies, the patients received an antihypertensive treatment before the conception. Three patients (18.75%) had moderate proteinuria before the conception.

Immunosuppressive treatment

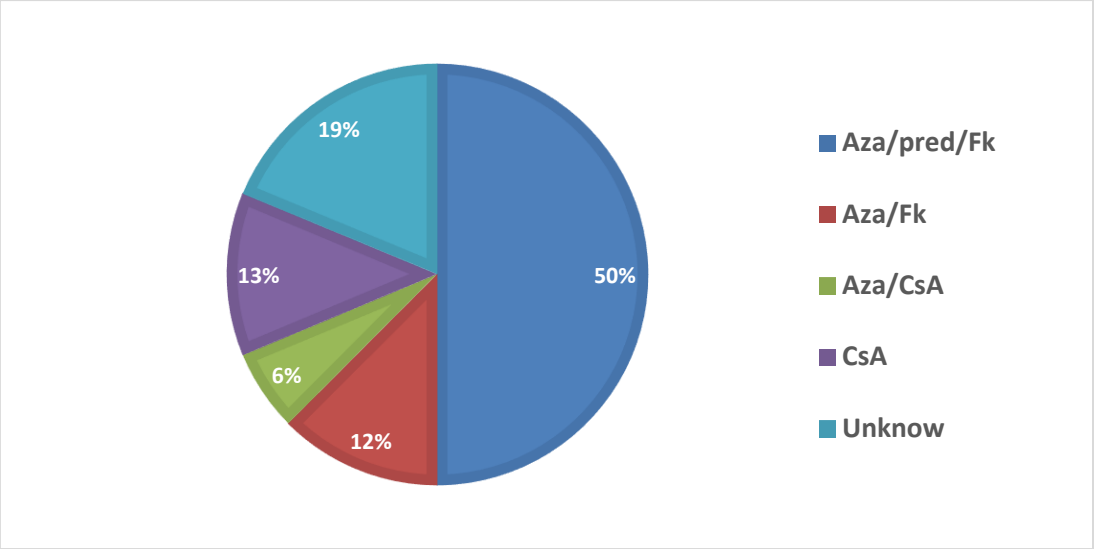
The immunosuppressive treatment before conception was a combination of azathioprine (Aza), prednisone (P) and tacrolimus (FK) for 7 of the 16 pregnancies (43.75%), a combination of Aza and FK for 2 (12.5%), a combination mycophenolate mofetil (MMF), P and FK for 1 (6.25%), and a combination of Aza and cyclosporine (CsA) for 1 of 16 pregnancies (6.25%). For 2 of 16 pregnancies (12.5%) CsA was given in monotherapy. Data on immunosuppressive treatment before conception are missing for 3 pregnancies, the patients being followed by their own nephrologists and not referred to CHUV for initial counselling.

During pregnancy, the immunosuppressive treatment was a combination of Aza, P and FK for 8 of 16 pregnancies (50%), a combination of Aza and FK for 2 (12.5%), a combination of Aza and CsA for 1 (6.25%), and for 2 of 16 pregnancies (12.5%) it remained CsA as monotherapy (**Figure 1**). Therefore, besides the switch of MMF to Aza, there was no other modification of the immunosuppressive treatment. Moreover, besides the adjustment of FK and CsA in accordance to measured trough levels (due to the hemodilution that occurs during pregnancy), there was no significant change in the administered dose of P or Aza. In the absence of acute rejection or any other immunological event, none of the patients received additional immunosuppressive therapy during pregnancy.

The immunosuppressive treatment was changed after the delivery for 7 of the 16 pregnancies and remained the same for 7 of the 16 pregnancies (data are incomplete for 2 pregnancies after the delivery). The new immunosuppressive treatment was a combination of MMF and FK for 4 of 16 pregnancies (25%), a combination of MMF, P and Fk for 2 (12.5%), and a combination of MMF and CsA for 1 of the 16 pregnancies

(6.25%).

Figure 1. Immunosuppressive therapy during pregnancy.
The immunosuppressive treatment was recorded at conception, during pregnancy (1st, 2nd, 3rd trimester) and after delivery. Aza, azathioprine; CsA, cyclosporine; FK, tacrolimus; P, prednisone. The data shown here represent the therapy during pregnancy.



Pregnancy outcome

The transplant recipients delivered at an average of 35.7 weeks of gestation [27.2-40.5] with an average birthweight of 2407.2 grams [860-3550]. Nine of the 16 babies (56.25%) were born preterm, including one very preterm (30.5 weeks) and one extremely preterm (27.2 weeks). All 16 pregnancies (100%) resulted in live births. The mode of delivery was cesarean section for 11 pregnancies (68.75%) including 5 in emergency. Three women (18.75%) had spontaneous vaginal delivery and 2 women (12.5%) had induced vaginal delivery. Of note, 4 couples had required fertility treatment to conceive (25%); 2 by intra-uterine insemination, 2 in-vitro fertilization with one preceded by hormonal stimulation. There was no multiple pregnancies.

Maternal complications

Maternal complications during pregnancy included acute kidney failure in three patients (18.75%), suspicion of preeclampsia in two (12.5%), preeclampsia in one (6.25%), progression of proteinuria in one (6.5%), severe anemia of unknown origin in

one (6.5%), oligohydramnios in one (6.5%), polyhydramnios in one (6.5%), and hypoglycemia in one patient (6.5%).

Ten episodes of urinary tract infections (UTI) were observed during the pregnancy, some patients having more than one episode of UTI while others had none. Six patients (37.5%) had UTI episodes, the majority during the 2nd semester (60%). Only one woman had a pyelonephritis, all the others had lower urinary tract infections and cystitis. Two patients were under antibiotic prophylaxis (cefuroxime) during all the pregnancy. One woman had a postpartum hemorrhage, one suffered from chickenpox at 31 weeks of gestational age, and another patient had a postpartum endometritis due to group B streptococci.

We did not observe *de novo* onset gestational diabetes in our study. There were however two type 1 diabetic patients in our cohort. The first patient had received a simultaneous kidney and pancreas allograft 44 months before her first pregnancy. Glucose levels remained controlled throughout pregnancy without need of any treatment, demonstrating excellent function of the pancreatic allograft. The second patient had 3 pregnancies while being transplanted with a kidney and under intensive insulin therapy. The first pregnancy was 24 months, the second 39 months and the last 71 months after kidney transplantation from a living related (her mother) donor. The patient experienced poor glycemic controls during all 3 pregnancies with frequent episodes of hypo- and hyperglycemia, in part due to hyperemesis and digestive dysmotility.

Neonatal outcome

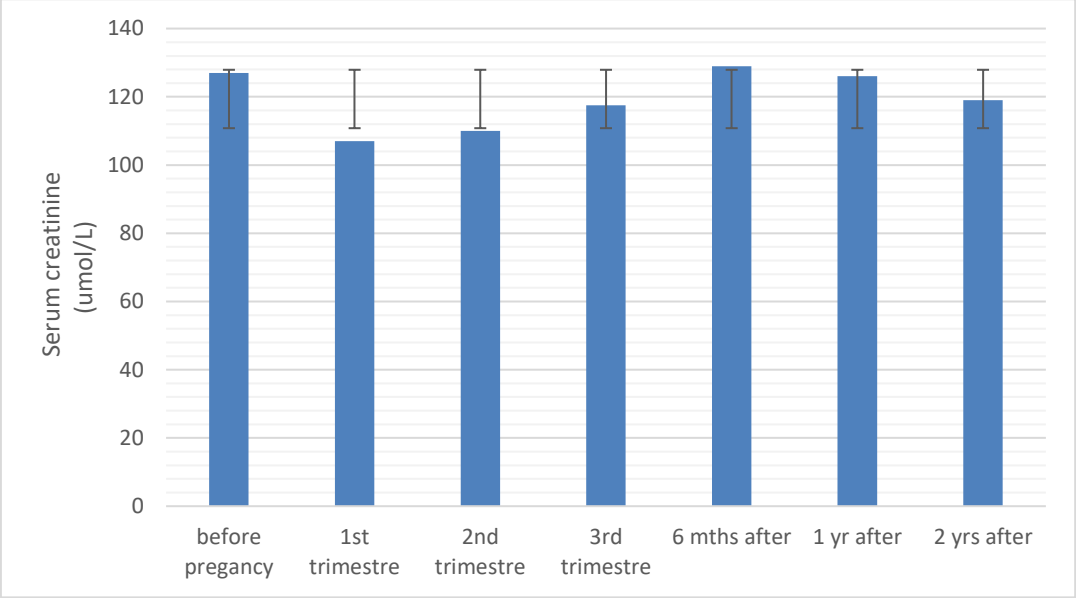
Two of the 16 newborns were small for gestational age (SGA), while four (25%) had neonatal complications, mainly respiratory. One newborn suffered from transient tachypnea (neonatal wet lung syndrome), two were diagnosed with newborn respiratory distress syndrome (NRDS, hyaline membrane disease) concomitant with a patent ductus arteriosus (PDA) and in one child also with pneumothorax, one had apnea of prematurity. One child was diagnosed as a mosaic Turner syndrome with malformations.

Kidney allograft outcome

None of the women in our cohort had an acute rejection episode during pregnancy. Two patients (12.5%) lost their grafts within 2 years after the birth of their child (of note, these patients were advised against pregnancy as they did not meet the recommended criteria with preexisting moderate-to-severe kidney allograft dysfunction at the time of conception) and 7 women (43.75%) more than two years after the childbirth. Anti-HLA antibodies and the presence of donor-specific antibodies (DSA) were regularly monitored during and after pregnancy. For the majority of our patients there was no significant change, i.e. no increase in preexisting DSA, nor occurrence of *de novo* DSA. One patient in our cohort developed class II DSA antibodies at delivery, with no immediate consequences. Five patients had a kidney graft biopsy (31.25%), none during the pregnancy (2 within 6 months after delivery, 1 after one year and 2 after 2 years). Out of the 6 biopsies performed, 3 (18.75%) showed chronic calcineurin inhibitor toxicity, one (6,25%) revealed severe acute cellular tubulointerstitial and vascular rejection grade Banff IIb and the last showed borderline acute cellular rejection (6,25%).

Figure 2.1. Evolution of kidney function during and after pregnancy.
Serum creatinine values (**A**) and MDRD eGFR (**B**) before, at 1st, 2nd, and 3rd trimester during pregnancy, and at 6 months (mths), 1 and 2 years (yr) after delivery. Data are represented as median values with standard deviation.

A.



B.

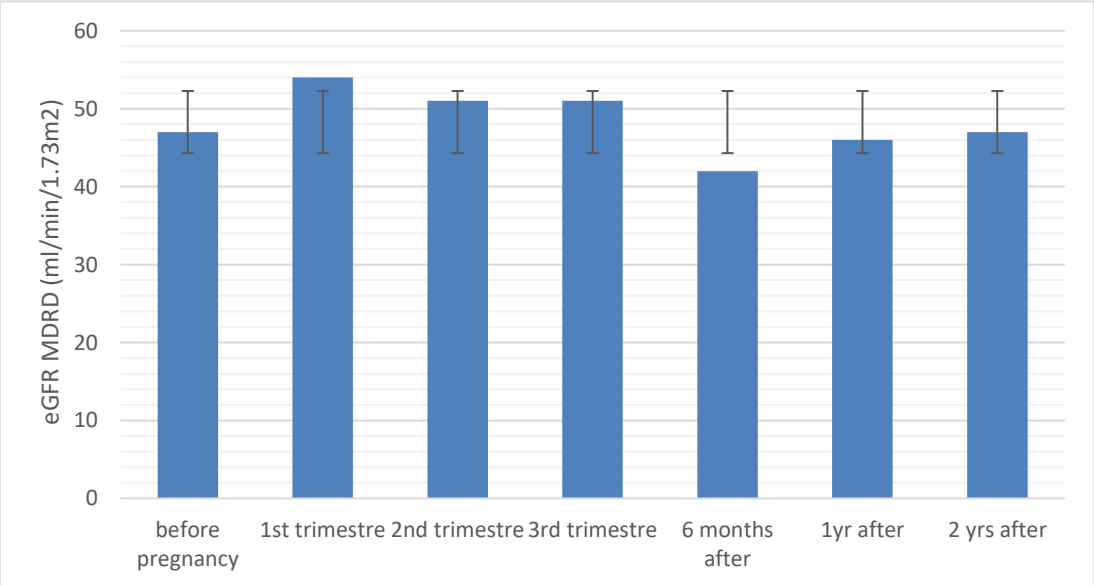
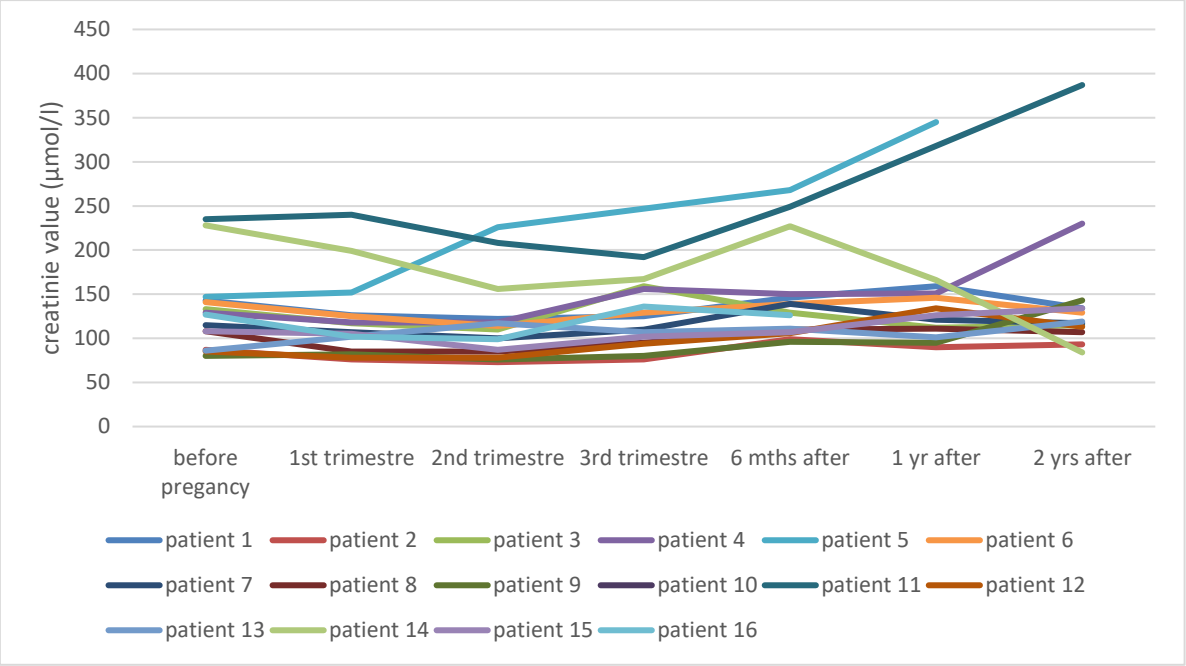


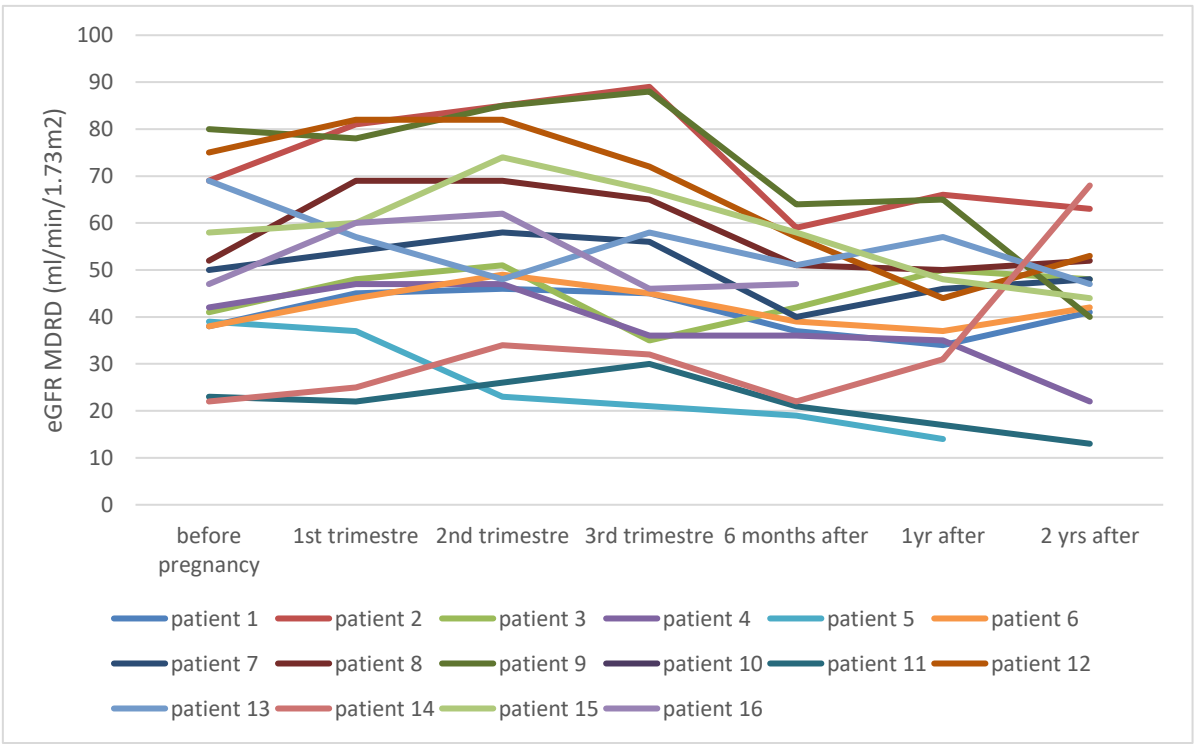
Figure 2.2. Evolution of kidney function during and after pregnancy.

Serum creatinine values (**A**) and MDRD eGFR (**B**) for individual patients before, at 1st, 2nd, and 3rd trimester during pregnancy, and at 6 months (mths), 1 and 2 years (yr) after delivery.

A.



B.



Regarding kidney function, median serum creatinine values before pregnancy were of 127 umol/L (range 97.5-142), with median eGFR-MDRD of 47 ml/min/1.73m² (IGR 38.5-63.5). As expected for normal pregnancies, we observed a decrease in the median creatinine value during the pregnancy, in particular during the 1st trimester (-20 umol/L), with a median creatinine value of 107 umol/L (IQR 93.5-125.5) and 15% increase in median eGFR. This was the consequence of physiological hyperfiltration during pregnancy and reflected preserved functional nephrotic mass within the transplanted kidney. After delivery, creatinine levels almost returned to the levels before pregnancy (+2 umol/L), except for 3 patients (**Figure 2.1 and 2.2**). However, 6 months after childbirth, the median eGFR was lower than before the pregnancy (-11%), but with a slight improvement over the next 1.5 years (**Figure 2.1 and 2.2**). Of note, patient 14 was transplanted with a new kidney, within 2 years after pregnancy, explaining the good eGFR value at 2-years follow-up.

Discussion

This retrospective study shows that pregnancy remains a risk factor after kidney transplantation, in particular considering fetal and maternal outcomes. First, the number of preterm babies (56%) was higher in this study than in the Swiss general population (7%), according to figures from the Swiss Federal Statistical Office (OFS). Consistent with higher preterm births, mean birth weights were significantly smaller in children from transplanted mothers, as compared to the general population (mean birth weight 2407.2 and 3288 grams, in transplanted patients and in the general Swiss population, respectively) (14). For preterm babies, low birth weight (<2500gr) is expected. However, 12.5 % of the preterm babies were small for the gestational age (<10th percentile), which is 2.5% more than to the normal range (10% under the 10th percentile). The prematurity rate in our study was slightly higher compared to previous reports (43-45%) (15–17), as well as the rate of small for gestational age (24%) (18). If we calculate the average age and weight of premature babies, we obtain 33.66 [27.2-36.3] weeks of gestation and 2085g [860-2800], respectively. The 50 percentile for a premature baby of this age is 1890g in our center (P90 at 2310g). So, we can observe that the issue in our center was a higher proportion of premature babies but that the

weight was appropriate to their age. Second, the prevalence of malformations was 12.5% (one baby with cardiac malformation and one with chromosome anomaly). In a nationwide controlled cohort study in Denmark with 124 children, the prevalence was 11.8%. According to the authors, it is a plausible result of exposure in fetal life to the immunosuppressive and antihypertensive treatment (19). However, other studies report a lower number of malformations (5%) (18). For our study, we did not have detailed information on prenatal mortality or miscarriage in our cohort of kidney transplant recipients, but the majority of the literature does not suggest an increase in risk compared to the general population (15,16,20). Of note however, a study by Gill et al. highlights a much lower rate of live births (55,4% against 73.5%) and suggests that certain biases have led to underestimating fetal loss in the other studies (21). Chronic hypertension despite treatment at the time of conception (TAM > 105 mmHg) has been reported to be associated with a higher risk of fetal death, but there was no significant difference in women with preeclampsia (22).

Concerning the obstetrical complications, the literature supports the results of our study with a significantly higher risk as compared to the general population. The systematic review and meta-analysis of Deshpand et al. reports a 52% rate of chronic hypertension, 27% of preeclampsia, 56.9% of cesarean section delivery, and 8.0% of gestational diabetes (16). In our study, the cesarean section rate was twice higher than in the general Swiss population (32.8%) (23). In two cases (12.5%) there was no medical indication other than that the fact that the patient was a kidney transplant recipient. While the guidelines recommend vaginal delivery, it is acknowledged that in about 50% of the cases, caesarian sections are necessary (24).

Considering maternal outcome, few studies have investigated the repercussions of hypertension both at the level of the graft and regarding obstetric complications. Hypertension affects between 50-80% of all kidney transplant patients during pregnancy (25), and the prevalence seems to be similar in kidney transplant recipients prior to conception (52-69%). Fetal death, preeclampsia and graft loss have been cited as complications possibly resulting from poorly controlled hypertension, but further studies would be needed to confirm this (22,26,27).

The rate of preeclampsia was reported to be six times higher than in the general population (4-5%), affecting up to 25% of the women who get pregnant after kidney transplantation (16,28,29). An association between kidney transplantation and preeclampsia was shown, even after controlling for known confounding factors such as twin pregnancy, hypertension at the beginning of pregnancy, age, and gestational diabetes mellitus (28). Chronic hypertension, history of preeclampsia, and high serum creatinine levels in early pregnancy (> 125 umol/l) are prognostic factors for the development of preeclampsia. Data are however discordant regarding the prevalence of preeclampsia in transplant recipients. A study with 105 pregnancies does not report an increased proportion of preeclampsia among women with chronic hypertension while another cohort study reports that 2/3 of women with chronic hypertension developed preeclampsia (18,28). Some consequences of preeclampsia have been identified, such as significantly higher postpartum serum creatinine levels, higher risks of preterm delivery, cesarean delivery, and small for gestational age infants (22). However, recent reports have shown no association with long-term renal dysfunction or graft loss despite a high rate of preeclampsia (22,30).

Following on maternal complications, the rate of urinary tract infections during pregnancy was similar to the 40-45% rates found in the literature, which is significantly higher than in the general non-transplanted pregnant population (1-2.3%) (31). As an explanation we can propose some degree of vesicoureteral reflux and, mild hydronephrosis of the transplanted kidney, as well as pregnancy hormones-related dilatation of renal collecting ducts and ureters (26,32). Hence, this highlights the importance of regular screening for UTI. Finally, despite potential diabetogenic drugs such as prednisone or tacrolimus, gestational diabetes does not appear to be increased after kidney transplantation compared to the general population. Our study is too small to be representative (0 case), but other studies have reported incidence rates between 3-8% (16,18), which is quite similar to the general population (33).

Regarding graft function during and after pregnancy, 18.75% of our patients have experienced acute renal failure and, the median eGFR was lower after the delivery (values at 6 months post-pregnancy) than before pregnancy. There was no acute rejection episode or significant immunization during pregnancy according to the regular monitoring of anti-HLA DSA. Nevertheless, there was a slight improvement of

kidney function 1.5 years after the delivery, which can be encouraging as compared to current literature. A meta-analysis found 4.2% of acute rejection episodes during the pregnancy and highlighted 5.8% of graft loss 1-year post-pregnancy and 8.1% at 2 years. (16). The main factor associated with worsening graft function was decreased renal graft function pre-pregnancy (34,35). This is something we observed in our study. The patients who had the highest deterioration in kidney function were the ones with a higher pre-pregnancy creatinine value. In a cohort of 117 transplant patients followed during 14 years, there was no significant difference in graft survival, long term patient survival, and kidney function between patients who conceived and the controls (36). There was also no relationship between the type of donor organs (deceased versus live donors) and pregnancy outcome (18).

Overall, our cohort is too small to define potential predictive factors for a poor pregnancy outcome after kidney transplantation. In the literature, the factors that stand out include, >1 previous kidney transplant, first-trimester serum creatinine >125 µmol/L, hypertension and, proteinuria (16,18,26). Lastly, the time recommended between transplantation and pregnancy is still debated. American guidelines (2003, American Society of Transplantation Women's Health Committee) recommend to wait 1 year and the European guidelines (European Dialysis and Transplant Association, EDTA) 2 years post-transplantation (37,38). According to a study that followed 729 pregnancies, the risk of allograft failure extends to the second year after the transplantation (39). In our center, we advise the patient to wait 2 years before the conception. This is the time needed to achieve stability in kidney function, metabolic and immunological parameters, as well as medication including maintenance immunosuppression. Besides obstetrical concerns (age, history of previous pregnancies etc.), pregnancy is discouraged in the case of severe graft dysfunction (creatinine >250 µmol/L), non-controlled hypertension and moderate proteinuria (>1-2g/24 hours), recent episodes of cellular or antibody-mediated rejection, uncontrolled recurrence of initial nephropathy. Once the decision of pregnancy is taken, immunosuppressive and other drugs must be adapted 3-6 months before conception to avoid toxicity to the fetus, while maintaining stable graft function.

Our study has several limitations. It is a retrospective single-center study and the number of patients included is small. For some patients, there is a lack of information

due in part to different follow-up protocols as the study covers a large period. Despite this, the study illustrates our current practice where although relatively safe, pregnancies remain rare after transplantation (around 1 per year in our center). The main reasons are the evolving trend in the age and comorbidities of women with end-stage renal disease accessing kidney transplantation, but possibly also patients and physicians reluctance to undergo a potential added risk after successful transplantation.

In conclusion, pregnancy is possible after kidney transplantation. There are however significant risks of maternal, fetal and graft complications that need to be discussed and weighed with the patient. Therefore, counselling and preparation before conception, as well as regular monitoring and multidisciplinary collaboration with an obstetrician are needed.

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Disclosure

All the authors have no conflicts of interest to disclose.

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