Obstetric and long-term kidney outcomes in renal transplant recipients: a 40 year single-centre study.

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Abstract

Female renal transplant recipients of childbearing age may ask what the outcomes are for pregnancy and whether pregnancy will affect graft function. We analysed obstetric and transplant outcomes among renal transplant recipients in our centre who have been pregnant between 1973 and 2013. A case-cohort study was performed identifying 83 pairs of pregnant and non-pregnant controls matched for sex, age, transplant vintage and creatinine. There were 138 pregnancies reported from 89 renal transplant recipients. There were live births in 74% of pregnancies with high prevalence of prematurity (61%), low birth weight (52%) and preeclampsia (14%). Lower eGFR (OR 0.98; p=0.05) and higher uPCR (OR 1.86; p=0.02) at conception were independent predictors for poor composite obstetric outcome. Lower eGFR (OR 0.98; p=0.04), higher uPCR (OR 1.50; p=0.04) and live organ donation (OR 0.35; p=0.02) were predictors of ≥20% loss of eGFR between immediately pre-pregnancy and 1 year after delivery. There was no difference in eGFR at 1, 5 and 10 years in pregnant women compared with non-pregnant controls and a pregnancy was not associated with poorer 10-year transplant or 20-year patient survival. Despite high rates of obstetric complications, most women had successful pregnancies with good long-term transplant function.

Keywords: pregnancy, kidney transplant, obstetric, transplant outcomes

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Introduction

Fertility is restored within a few months following kidney transplantation. Approximately 2% of female kidney transplant recipients of childbearing age become pregnant(1). Published data on pregnancy outcomes after kidney transplantation derive from self-reporting registries and single-centre studies(2-6). Transplant function(3, 5, 7), pre-existing hypertension(5), and time since transplantation(2, 7, 8) may predict risk to the mother, kidney and fetus. Data on transplant and maternal survival suggest that live birth does not adversely affect patient or allograft survival(4) but these are limited by patient overlap (in registries), classification differences, reporting biases or single-centre studies with short follow-up and no adequate control group.

This study aimed to examine obstetric and kidney outcomes in women with kidney transplants, investigate changes in outcomes over four decades and explore factors influencing obstetric and kidney outcomes. We compared maternal and transplant outcomes in pregnancy to matched patients, who did not become pregnant over this period.

Patients and Methods

Study population and baseline data

This was a single-centre retrospective cohort study from Glasgow Transplant Unit, where almost 3000 adult renal transplants have been performed between 1970 and 2014 with a prevalent transplant population of approximately 900 adults at December 2014.

All women reporting a pregnancy between January 1st, 1973 and February 28th, 2013 whilst having a functioning kidney transplant were identified from

the electronic patient record. Those requiring temporary dialysis during pregnancy or returning to long-term dialysis shortly before delivery were included. All women delivered at three different obstetric units across the region. Two investigators (SS, MG) extracted the information needed independently using a data collection form.

The following characteristics were recorded: age, ethnicity, weight, previous pregnancies, last menstrual period, delivery date, clinic blood pressure (BP), cause of established renal failure (ERF), time on renal replacement therapy (RRT), prior kidney transplant, decade of transplantation, time since transplant, transplant source (deceased or live donation), prior acute rejection, pre- and post-pregnancy serum creatinine and urinary protein quantification. Maintenance immunosuppression regimen used prior to and during pregnancy was recorded.

Outcome data were gestational age, birth weight, pregnancy outcome, obstetric complications (gestational hypertension, preeclampsia and caesarean section), neonatal survival (>28 days), and presence of congenital anomaly. Transplant outcomes were acute rejection during pregnancy, transplant loss during pregnancy and within two years post-partum, and deterioration of renal function associated with pregnancy. Patient and transplant outcomes were analysed from time of delivery.

We analysed obstetric outcomes in two subgroups of patients according to estimated glomerular filtration rate (eGFR) (≤ or >45ml/min/1.73m^2) assuming that women with normal or mildly impaired renal function have better outcomes. The cut-off was selected as being consistent with the KDIGO

classification of Stage 3a and 3b chronic kidney disease (CKD) and was felt to be clinically meaningful.

Estimated glomerular filtration rate was calculated using the Modification of Diet in Renal Disease formula(9). Urine protein:creatinine ratio (uPCR) was used as an estimation of proteinuria. If no uPCR value was available, 24-hour urine protein excretion was used, dividing the value in mg by 10 to achieve equivalent in mg/mmol(10). Small for gestational age was calculated from birth weight compared to UK references(11).

Outcome definitions

Pregnancy outcomes were live birth, miscarriage (<20 weeks gestation), termination, ectopic pregnancy and stillbirth (≥20 weeks gestation)(12).

Gestational hypertension was defined as new onset hypertension (BP>140/90mmHg) after 20 weeks gestation without proteinuria in a previously normotensive woman. Preeclampsia was defined as gestational hypertension with proteinuria.

Due to low event rates in each individual adverse obstetric outcome, we defined a composite adverse obstetric outcome incorporating reported first or second trimester losses, stillbirths, neonatal mortality (death in first 28 days of life), very preterm births (<32 weeks gestation) and fetal congenital anomalies. Pregnancy associated transplant dysfunction was defined as ≥20% loss of eGFR between results immediately pre-pregnancy and 1 year after delivery. This threshold has been used by previous studies(3) as a 20% fall in eGFR reflects a clinically important change in renal function for an individual patient. The clinical and research activities reported are consistent

with the Principles of the Declaration of Istanbul as outlined in the 'Declaration of Istanbul on Organ Trafficking and Transplant Tourism'.

Case-cohort study

Long-term transplant and maternal survival rates were compared to a control cohort of non-pregnant renal transplant recipients using matched survival analyses. The electronic patient record, case notes and clinic letters were viewed to ensure that the non-pregnant controls did not become pregnant over the study period. Non-pregnant women receiving a kidney transplant matched for age (±5 years), transplant vintage (±10 years) and serum creatinine (±30mmol/L or 0.34mg/dL) were chosen as controls whilst blinded for outcomes. To match the age of the graft at conception for non-pregnant women, transplantation to pregnancy interval was calculated for each pregnant woman to define a 'matching day' and to assign a 'pre-pregnancy eGFR' in each control. For comparisons between groups, the 'matching day' in controls and the last menstrual period day in pregnant renal allograft recipients were used. Once the match was made, pregnancy to delivery interval was used to define a 'simulated delivery day' and to calculate 'gestational period' in control subjects. Serum creatinine was retrieved at 1, 5 and 10 years after 'delivery day'. Follow-up was censored on date of transplant failure, death, loss to follow-up or last entry in the electronic patient record, whichever was first. For women with multiple pregnancies, first pregnancy post-transplant was matched. Each non-pregnant control was selected only once.

Statistical analyses

Categorical variables were reported as frequencies and percentages, with mean and standard deviation or medians and interquartile ranges (for skewed data) reported for continuous variables. Categorical data were compared by chi-squared test, Fisher's exact test or logistic regression. Continuous data were compared by Student's t-test or linear regression. The Mann-Whitney U test was used for comparisons of differences in medians.

Univariate binomial logistic regression models were used to assess prognostic factors for composite adverse obstetric outcome and pregnancy associated transplant dysfunction. Variables tested were maternal age at pregnancy, time since transplant, cause of ERF, pre-pregnancy eGFR and proteinuria, decade of transplant, transplant source, calcineurin inhibitor (CNI) use at time of pregnancy, presence of hypertension, time on RRT, prior kidney transplant and prior rejection. Statistically significant factors were tested in separate multivariable logistic regression models with composite adverse obstetric outcome and pregnancy associated transplant dysfunction as dependent variables.

In the case-cohort study mean eGFR at 1, 5 and 10 years were compared by t-test. Patient survival, overall transplant survival and transplant survival censored for patient death were plotted using Kaplan–Meier estimates and compared using log-rank test.

Analyses were performed using SPSS (version 21.0, SPSS Inc.). In all analyses, p-value <0.05 was considered statistically significant.

Results

There were 138 pregnancies to 89 transplant recipients reported between 1973 and 2013. Median duration of follow-up from first pregnancy was 8.2 years (IQR: 3.8, 16.9). Fifty-seven women had one pregnancy (64.0%), 22 had two pregnancies (24.7%), 7 had three pregnancies (7.9%) and 3 had four pregnancies (3.4%). Four women had pregnancies with two different kidney transplants. There was one triplet pregnancy.

One patient required temporary dialysis during pregnancy. Three women conceived with a functioning transplant for most of their pregnancy but returned to dialysis before delivery. Median time between transplantation and pregnancy was 3.6 (IQR: 1.9, 7) years. Median RRT time pre-pregnancy was 6.9 (IQR: 3.8, 10.4) years (Table 1).

Maternal demographics

Mean ages at time of transplantation and pregnancy were 25.2 (SD 6.4) and 30.3 (SD 5.1) years respectively. The most common primary kidney disease was reflux nephropathy (48.3%), followed by glomerulonephritis (36.0%), cystic disease (2.2%), diabetes (1.1%) and other/unknown (12.4%). Approximately two-thirds of transplanted kidneys were from deceased donors and 30 (21.7%) women had one previous kidney transplant. Mean systolic and diastolic BP at conception was 126.9 (SD 16.6) and 80.5 (SD 9.8) mmHg. Fifty-six (40.6%) women were on antihypertensive therapy before pregnancy. Six women (4.3%) had an episode of acute rejection of the current transplant before pregnancy (Table 1).

Immunosuppression

Six immunosuppression regimens (all steroid based) were used. The most common combinations are shown in Figure 1. In the 1970's, 13 women (86.7%) were on prednisolone and azathioprine and in the 1980's prednisolone with either azathioprine (44.2%) or cyclosporine (42.3%) were used equally. In the 1990's, 44 women (89.8%) received CNI-based regimens and during the last decade, tacrolimus was used more commonly than cyclosporine (17 vs. 3 women). Four women were taking mycophenolate mofetil (MMF) at conception despite routine advice issued to all women at our centre not to become pregnant on MMF.

Pregnancy outcomes

In the 138 pregnancies, there were 102 (73.9%) live births, 23 (16.7%) miscarriages, 8 (5.8%) terminations, 3 (2.2%) ectopic pregnancies and 2 (1.4%) stillbirths. There were 16 pregnancies during the first post-transplant year, resulting in 9 (56.2%) live births, 4 (25.0%) miscarriages and 3 (18.8%) terminations.

Two women underwent in vitro fertilisation resulting in early miscarriage and stillbirth.

Gestational age and mode of delivery

Median gestational age at delivery was 34.3 (IQR: 23.8, 37.4) weeks. Of 102 live births, 62 (60.8%) were preterm (<37 weeks). 5.9% of babies were born at <32 weeks gestation.

Of the 102 live births, 22 (21.6%) were vaginal deliveries and 80 (78.4%) were caesarean deliveries (43 elective, 32 emergency and 5 unknown). Seven (11.3%) preterm births were vaginal deliveries and the remaining 55 (88.7%) were caesarean deliveries (28 elective, 24 emergency and 3 unknown).

Birth weight

Six birth weights were missing. Mean birth weight of all newborns was 2464 (SD 727) g. Forty-one (45.1%) had low birth weight (<2500g), and 6 (6.6%) had very low birth weight (<1500g).

Of 96 singleton pregnancies with gestational age and birth weight data, 13 (13.5%) and 9 (9.4%) had birth weights below the 10^{th} and 3^{rd} centile for gestational age respectively.

Preeclampsia

Data to identify preeclampsia were missing for 8 pregnancies. Preeclampsia occurred in 15 (14.2%) pregnancies and gestational hypertension occurred in 8 (7.5%).

Median gestational age of babies born to women developing preeclampsia was less than women who did not [34.1 (IQR: 32.7, 36.0) vs. 36.4 (IQR: 33.8, 38.0) weeks; p=0.005] with lower mean birth weights [2016 (SD 1060) g vs. 2418 (SD 823) g; p=0.12]. Of 11 infants born prematurely due to preeclampsia with gestational age and birth weight data, only 2 (18.2%) had birth weights below the 10^{th} centile for gestational age.

Obstetric outcomes according to eGFR subgroups (≤ or >45ml/min/1.73m^2) are shown in Table 2.

Neonatal Outcomes

Three (2.9%) congenital abnormalities were reported - one atrial septal defect and two babies had vesicoureteral reflux. None of these occurred in women taking MMF at conception. Neonatal death (in first 28 days of life) occurred in two (2.0%) separate pregnancies.

Successive pregnancies

Thirty-two women had more than one pregnancy post-transplant. Of 45 subsequent pregnancies, 34 (75.6%) had gestation >20 weeks. Seventeen (37.8%) reached term, 16 (35.5%) were preterm while 12 (26.7%) ended with early losses. Rates of live and preterm births, gestational age and birth weight during subsequent pregnancies were not significantly different compared with first pregnancies (p=1.00, p=0.28, p=0.88 and p=0.51, respectively).

Transplant survival and function

Sixteen patients lost their transplant, 3 during pregnancy and a further 13 women within 2 years following delivery. Six women had biopsy-proven acute rejection (BPAR) during pregnancy from which 2 lost their transplant. All rejection episodes were treated with high dose oral or intravenous steroids and a dose increase in the calcineurin inhibitor (or switch from cyclosporine to tacrolimus). In 3 patients, tacrolimus or cyclosporine levels were deemed subtherapeutic the period before the rejection episodes.

Pregnancy associated transplant dysfunction occurred in 38 (27.5%) pregnancies including the women who returned to dialysis. Pre-pregnancy

serum creatinine was available for 132 pregnancies. Mean eGFR fell from 55.0ml/min/1.73m^2 (SD 20.4) to 27.9ml/min/1.73m^2 (SD 25.9, n=99) over 10 years in pregnant women. There was no significant difference in pre-pregnancy mean eGFR over the 4 decades examined (p=0.41). Pre-pregnancy proteinuria was available for 125 pregnancies. Median pre-pregnancy uPCR was 15mg/mmol (IQR: 10, 33) compared with 26mg/mmol (IQR: 10, 43, n=55) at 10 years.

Deceased kidney donation was associated with a larger drop between pre-pregnancy and post-partum eGFR (from 50ml/min/1.73m^2 to 42) as compared with live donation (from 62ml/min/1.73m^2 to 60) at 1 year. When we compared women with single to women with multiple pregnancies, there was no difference in 10-year eGFR (p=0.68) and transplant survival (p=1.00).

Univariate and multivariable analysis

Approximately one-third of the cohort (34.1%) had a poor pregnancy outcome, defined as at least one of first or second trimester loss, stillbirth, neonatal mortality, very preterm birth and congenital anomaly. Univariate analysis for the composite adverse obstetric outcome demonstrated reduced eGFR (OR 0.98 per mL/min/1.73m^2; 95% CI, 0.96 to 1.00; p=0.05) and increased uPCR (OR 1.86 for each additional 100mg/mmol; 95% CI, 1.11 to 3.10; p=0.02) at conception as independent predictors of poor obstetric outcome (Table 3). Reduced eGFR (OR 0.98 per mL/min/1.73m^2; 95% CI, 0.96 to 0.99; p=0.04), increased uPCR (OR 1.50 for each additional 100mg/mmol; 95% CI, 1.02 to 2.20; p=0.04) and live versus deceased donor source (OR 0.35; 95% CI, 0.15 to 0.85; p=0.02) were predictors of pregnancy associated transplant

dysfunction (Table 4). Multivariable analysis did not demonstrate any independent predictors of either obstetric or kidney outcomes (Tables 3, 4).

Matched cohort study

Of 93 women with first pregnancy, 83 could be matched to non-pregnant renal transplant controls. Baseline characteristics of pregnant women and non-pregnant controls are shown in Table 5. There were no significant differences between pregnant women who were matched and the 10 women who were not matched.

Transplant function declined in both groups but there were no significant differences in eGFR between pregnant women and non-pregnant controls at 'matching day', 1 year, 5 years or 10 years after the 'matching day' (Figure 2). Acute rejection episodes occurred in 5 pregnant women during the gestational period and 2 non-pregnant controls during the corresponding time period, respectively. By Kaplan Meier analysis, overall transplant survival was similar for pregnant and control subjects (1-year transplant survival 98.8% vs. 98.8%, 5-year 75.9% vs. 81.1%, and 10-year 54.2% vs. 68.5%; p=0.79). Transplant survival censored for death with functioning kidney was similar for pregnant and control subjects (1-year death censored transplant survival 98.8% vs. 98.8%, 5-year 79.6% vs. 81.1%, and 10-year 59.8% vs. 69.8%; p=0.60) (Figure 3A). There was no difference in patient survival between pregnant women and non-pregnant controls (1-year survival 100% vs. 100%, 5-year survival 95.5% vs. 100%, 10-year survival 88.1% vs. 98.1%, and 20-year survival 88.1% vs. 72.0%; p=0.77) (Figure 3B).

Discussion

We report on 138 pregnancies in 89 transplant recipients over four decades. To the best of our knowledge, this is the largest number of pregnancies reported from a single centre with long-term follow-up and adequate controls and the first one that uses pre-pregnancy eGFR instead of serum creatinine. Our data suggest the majority of pregnancies in renal transplant recipients have a good outcome with live birth occurring in 74% of all pregnancies and 96% of pregnancies reaching 20 weeks gestation. Rates of prematurity (61%), low birth weight (52%) and preeclampsia (14%) are high. 23% of babies were small for gestational age. The majority of preterm births were due to medical intervention (89%) for fetal and maternal complications including fetal growth restriction, deteriorating kidney function, uncontrolled hypertension and preeclampsia. The majority of deliveries were by caesarean section (80%), of which almost half were emergency procedures. Not all caesarean deliveries were due to medical reasons. In our experience obstetricians have a low threshold for performing caesarean section in kidney transplant patients, based on perceived higher risks associated with proceeding to term vaginal delivery in this population.

The 74% live birth rate is similar to various registry reports(2, 5, 6, 13). Early pregnancy losses (miscarriages and ectopic pregnancies) were more frequent in our study (19% vs. 14%(8)).

Live birth rates did not change over four decades. Spontaneous miscarriage and ectopic pregnancy rates increased from 13% in the 1970's to 36% after 2000 despite reduction in terminations. This may represent willingness to support higher risk pregnancies in recent times or prior under-reporting of

early pregnancy losses. However, the mean eGFR prior to pregnancy did not decline over the decades.

Renal impairment and proteinuria were associated with poor pregnancy outcome, as reported previously(3, 14). Historically, pre-pregnancy serum creatinine of >1.5mg/dL predicts adverse pregnancy outcomes(5, 15, 16). We used a pre-pregnancy eGFR cut-off of 45ml/min/1.73m^2, which corresponds to serum creatinine of 1.5mg/dL, and we showed that women with CKD stage 3B or more advanced renal disease are at greater risk for small gestational age and low birth weight. We found no relationship between deceased and live donation and pregnancy outcome(3, 17) but live donation was associated with smaller drops in eGFR and better renal function 1 year after delivery probably because the women with living kidney donors had better renal function at the time of pregnancy. Others have reported preexisting hypertension(5), time from transplantation(2, 7, 8), pre-pregnancy dialysis vintage(18), and number of previous transplants(3) as predictive of adverse events; however, we did not observe these relationships.

This is the first study to report on a large number of multiple pregnancies with the same transplant. Women who had multiple pregnancies had similar obstetric and long-term kidney outcomes to women who had single pregnancies.

Perinatal mortality among babies born to transplant recipients was 2.9% compared to <1% in the general UK and US population and between 1% to 5.8% in women with transplants(2, 3, 19).

Incidence of birth defects in our cohort was similar to the general population of 3–5%. We do not have data on long-term developmental outcomes.

All neonatal deaths, congenital anomalies and very preterm deliveries occurred in pregnancies 3 or more years post-transplant. The average age at time of pregnancy for women with pregnancies ≥3 years post-transplant was 30.2 years.

There were 6 episodes of BPAR during pregnancy compared with 6 episodes before pregnancy. In the case-cohort study, rejection episodes were more common in pregnant women compared with non-pregnant controls (5 versus 2) but this did not translate into worse transplant or patient survival. This is likely the consequence of adjustment of immunosuppression or pharmacokinetic changes in calcineurin inhibitors during pregnancy which make interpretation of whole blood trough concentrations particularly challenging. Sixteen patients returned to dialysis during pregnancy or within 2 years following delivery.

Renal transplant recipients are traditionally counselled to wait two years after transplantation before conceiving(20). More potent immunosuppressive strategies have decreased rejection rates at one year post-transplant, whilst waiting time for deceased donor organs has increased, leaving women fewer potential childbearing years. In 2005, the American Society of Transplantation decreed that pregnancy may be considered after 1 year in women at lower risk(21) based on existing evidence(22, 23). Our data support this approach.

In the case-cohort study there was no significant difference in eGFR at 1, 5 and 10 years after study entry between pregnant women and non-pregnant controls; mean eGFR fell in both groups, however there was no difference in transplant survival, death censored transplant survival or patient survival. The immunosuppression regimens used in both groups were similar but as

422 expected more patients in the control group used mycophenolate mofetil. Our
423 data showed that 90% of mothers survive 20 years from first pregnancy to
424 raise the child to adulthood. However at the child's 10th birthday, there is
425 approximately 40% chance that the mother's transplant will have failed. This
426 is useful information for physicians involved in pre-conception counselling.
427 We acknowledge this study has limitations. The analysis was retrospective
428 although data were retrieved mainly from prospectively maintained
429 comprehensive electronic records. Single centre studies have the advantage
430 of uniformity of therapeutic approach but treatments, including
431 immunosuppressive regimens, have changed substantially over this time
432 period. Therefore we analysed different eras but were unable to detect any
433 era effect. Single centre studies may lack generalisability but it is reassuring
434 that our outcomes compare with high-quality national data(2, 4) and a recent
435 meta-analysis(8). The number of cases available for study was higher than
436 previous single centre reports but the low rate of serious obstetric
437 complications means some analyses may be underpowered to detect
438 important associations. Under-reporting of early pregnancies is likely so we
439 can be less definitive about incidence of conception and early pregnancy
440 complications. Diagnostic criteria for renal transplant rejection have changed
441 over the era of this study, with the introduction of C4d staining and routine
442 testing for donor specific antibodies occurring only during the last 10 years of
443 this study. Therefore we cannot definitively exclude a component of antibody-
444 mediated rejection in the patients who had episodes of rejection.
445 In this large single-centre study of pregnancy and kidney outcomes extending
446 over 40 years we observe the majority of pregnancies in renal transplant

recipients to have good outcomes. Rates of live and preterm births have not changed over this period despite advances in immunosuppression. We confirm previous reports of high rates of prematurity, low birth weight and preeclampsia and emphasise the influence of transplant function and proteinuria on obstetric and renal risks. Compared with appropriately matched non-pregnant female renal transplant recipients, there were no significant differences in long-term transplant and patient survival in renal transplant mothers. This information is reassuring for patients and clinicians when counselling women with transplants contemplating pregnancy.

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Author contributions

Dr Sokratis Stoumpos: Conception and design, collection and analysis of data, wrote the paper, final approval of the version to be published.

Dr Susan H McNeill: Collection and analysis of data, revised the paper, final approval of the version to be published.

Dr Morag Gorrie: Collection and analysis of data, revised the paper, final approval of the version to be published.

Dr Patrick B Mark: Revised the paper, final approval of the version to be published.

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Dr Colin C Geddes: Conception and design, analysis and interpretation of data, revised the paper, final approval of the version to be published.

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575 **Table 1**

Baseline characteristics of study patients	
Age at transplantation (mean [SD])	25.2 (6.4)
Age at pregnancy (mean [SD])	30.3 (5.1)
Time since transplant (yr; median [IQR])	3.6 (1.9 – 7.0)
Cause of ERF Glomerulonephritis (n [%]) Reflux nephropathy (n [%]) Other (n [%])	 32 (36.0) 43 (48.3) 14 (15.7)
Donor source Deceased (n [%]) Live (n [%])	 87 (63.0) 51 (37.0)
Previous kidney transplant (n [%])	30 (21.7)
Years on RRT (median [IQR])	6.9 (3.8 – 10.4)
Treatment for hypertension (n [%])	56 (40.6)
Systolic BP (mmHg; mean [SD])	126.9 (16.6)
Diastolic BP (mmHg; mean [SD])	80.5 (9.8)
Pre pregnancy eGFR (ml/min/1.73m^2; mean [SD])	55 (20.4)
Post pregnancy eGFR[a] (ml/min/1.73m^2; mean [SD])	50 (23.0)
Pre pregnancy uPCR (mg/mmol; median [IQR])	15 (10 – 33)
Post pregnancy uPCR[a] (mg/mmol; median [IQR])	30 (10 – 70)
Pre pregnancy acute rejection (n [%])	6 (4.3)

[a] at six months

ERF, established renal failure; RRT, renal replacement therapy; BP, blood

pressure; eGFR, estimated glomerular filtration rate; uPCR, urine protein:creatinine ratio.

Table 2

Obstetric outcomes according to pre-pregnancy eGFR[a]			
	≤45ml/min/1.73m^2 N=41	>45ml/min/1.73m^2 N=91	P value[b]
Live birth (n; [%])	27 (65.9)	71 (78.0)	0.51
Gestational age (wk; median (IQR))	34.3 (33.3, 36.7)	36.5 (33.9, 37.9)	0.02
Birth weight (g; mean [SD])	2128 (832)	2599 (670)	0.007
Preeclampsia (n [%])[c]	7 (25.9)	8 (11.3)	0.08

[a] excludes 6 cases with missing data

[b] t-test or chi-squared test or Mann-Whitney-U test where appropriate

[c] excludes <20wk gestation

eGFR, estimated glomerular filtration rate;

609 **Table 3**

Factors associated with composite adverse obstetric outcome[a]				
Factor	**Unadjusted OR (95% CI)**	**P Value**	**Adjusted OR (95% CI)**	**P Value**
Age at pregnancy (each additional year)	1.04 (0.97-1.12)	0.23	1.20 (0.94-1.50)	0.67
Time since transplant (each additional year)	1.03 (0.95-1.12)	0.40	1.03 (0.95-1.12)	0.44
Cause of ERF				
Glomerulonephritis	1.03 (0.22-4.70)	0.97	-	
Reflux nephropathy	3.20 (0.78-13.0)	0.11	-	
Pre pregnancy eGFR (each additional ml/min/1.73m^2)	0.98 (0.96-1.00)	0.05	0.99 (0.97-1.01)	0.32
Pre pregnancy uPCR (additional 100mg/mmol)	1.86 (1.11-3.10)	0.02	1.68 (0.98-2.88)	0.06
Era of transplant				
1973 to 1980	1.53 (0.40-5.82)	0.53	-	
1981 to 1990	0.65 (0.22-1.87)	0.42	-	
1991 to 2000	1.02 (0.36-2.89)	0.98	-	
2001 to 2013	0.65 (0.17-2.48)	0.53	-	
Live vs. Deceased donor	1.09 (0.53-2.26)	0.82	-	
CNI-based IS regime	0.80 (0.37-1.74)	0.57	-	

[a] first or second trimester loss, stillbirth, neonatal mortality, very preterm birth and fetal congenital anomaly

ERF, established renal failure; eGFR, estimated glomerular filtration rate; uPCR, urine protein:creatinine ratio; CNI, calcineurin inhibitor; IS, immunosuppression.

631 **Table 4**

Factors associated with pregnancy associated transplant dysfunction[a]				
Factor	**Unadjusted OR (95% CI)**	**P value**	**Adjusted OR (95% CI)**	**P value**
Age at pregnancy (each additional year)	0.96 (0.89-1.04)	0.29	0.94 (0.86-1.03)	0.18
Time since transplant (each additional year)	0.93 (0.84-1.03)	0.15	0.98 (0.96-1.01)	0.14
Cause of ERF				
Glomerulonephritis	2.35 (0.44-12.6)	0.32	-	
Reflux nephropathy	2.60 (0.51-13.3)	0.25	-	
Pre pregnancy eGFR (each additional ml/min/1.73m^2)	0.98 (0.96-0.99)	0.04	0.98 (0.96-1.01)	0.13
Pre pregnancy uPCR (additional 100mg/mmol)	1.50 (1.02-2.20)	0.04	1.24 (0.82-1.88)	0.31
Era of transplant				
1973 to 1980	0.52 (0.09-3.14)	0.48	-	
1981 to 1990	1.13 (0.35-3.68)	0.84	-	
1991 to 2000	1.97 (0.62-6.26)	0.25	-	
2001 to 2013	1.91 (0.32-11.5)	0.48	-	
Live vs. Deceased donor	0.35 (0.15-0.85)	0.02	0.48 (0.18-1.27)	0.17
CNI-based IS regime	1.85 (0.76-4.50)	0.18	1.24 (0.42-3.72)	0.70

[a] ≥20% loss of eGFR between immediately pre-pregnancy and 1 year after delivery

ERF, established renal failure; eGFR, estimated glomerular filtration rate; uPCR,

urine protein:creatinine ratio; CNI, calcineurin inhibitor; IS, immunosuppression.

653 **Table 5**

Baseline characteristics cases vs. controls			
	Pregnancies N=83	Controls N=83	P value[a]
Age at study entry (years; mean [SD])	29.4 (5.3)	31.1 (5.9)	0.05
Months since transplant (median [IQR])	34 (17.5 - 64.5)	32 (14.0 – 59.0)	0.97
Glomerulonephritis (n [%])	34 (41.0)	24 (28.9)	0.1
Reflux nephropathy (n [%])	36 (43.4)	33 (39.8)	0.64
Immunosuppression			
Cyclosporine (n [%])	53 (63.9)	52 (62.7)	0.9
Tacrolimus (n [%])	17 (20.5)	17 (20.5)	1
No calcineurin inhibitor (n [%])	13 (15.7)	14 (16.9)	0.8
Azathioprine (n [%])	55 (66.3)	43 (51.8)	0.23
Mycophenolate mofetil (n [%])	0 (0)	16 (19.3)	<0.001
Systolic BP (mmHg; mean [SD])	126.2 (15.4)	128.3 (15.3)	0.4
Diastolic BP (mmHg; mean [SD])	80.9 (10.3)	80.6 (8.9)	0.8
eGFR at matching day (ml/min/1.73m^2; mean [SD])	53.9 (18.2)	53.6 (17.0)	0.9
uPCR at matching day (mg/mmol; median [IQR])	15 (10 - 30)	20 (10 - 50)	0.13
uPCR>100mg/mmol at matching day (n [%])	10 (12.5)[b]	9 (11.4)[c]	0.83

Follow-up (yr; median [IQR])	8.1 (3.8 - 17.3)	9.0 (3.8 - 16.6)	0.94

[a] t-test or chi-squared test or Mann-Whitney-U test where appropriate

[b] excludes 3 cases with missing data

[c] excludes 4 cases with missing data

BP, blood pressure; eGFR, estimated glomerular filtration rate; uPCR, urine protein:creatinine ratio.

Figure 1: Four most common maternal immunosuppression regimens by decade of transplant. No immunosuppression information was recorded for 2 patients between 1981 and 1990 and 4 patients between 1991 and 2000. One patient between 1991 and 2000 did not require immunosuppression (transplant from identical twin). Pred, prednisolone; Aza, azathioprine; CsA, cyclosporine A; Tac, tacrolimus.

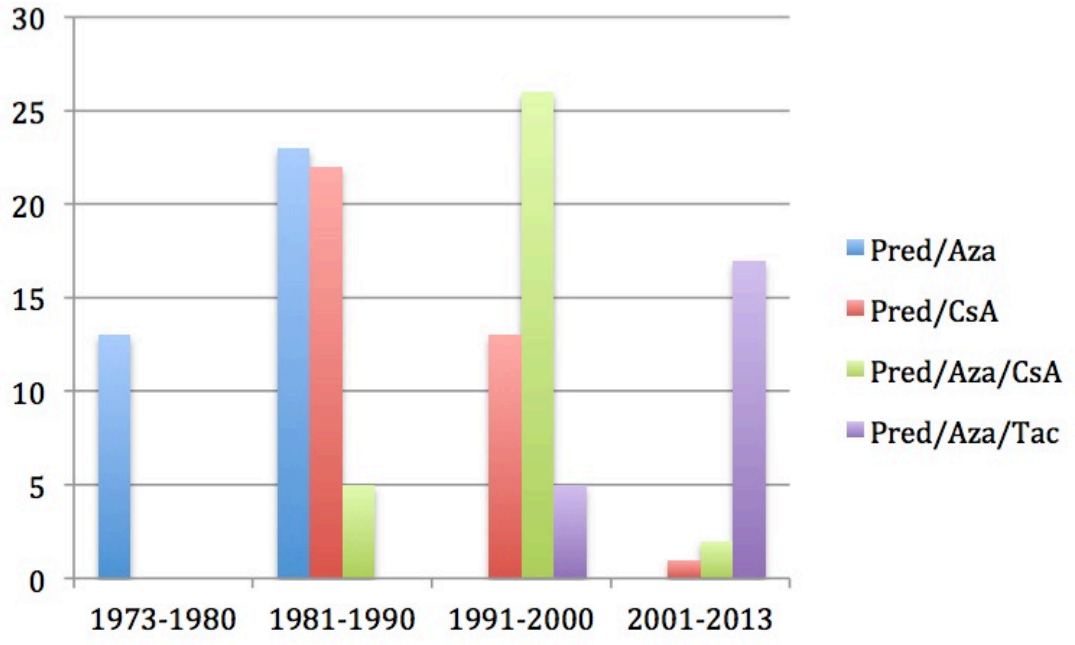

Figure 2: Estimated mean eGFR and standard deviation in pregnant women and non-pregnant controls with a transplant kidney. The difference in eGFR between cases and controls was not statistically significant at 'matching day', 6 months, 1 year, 5 years or 10 years after the 'matching day'.

eGFR counted as '0' from time of transplant failure and return to dialysis.

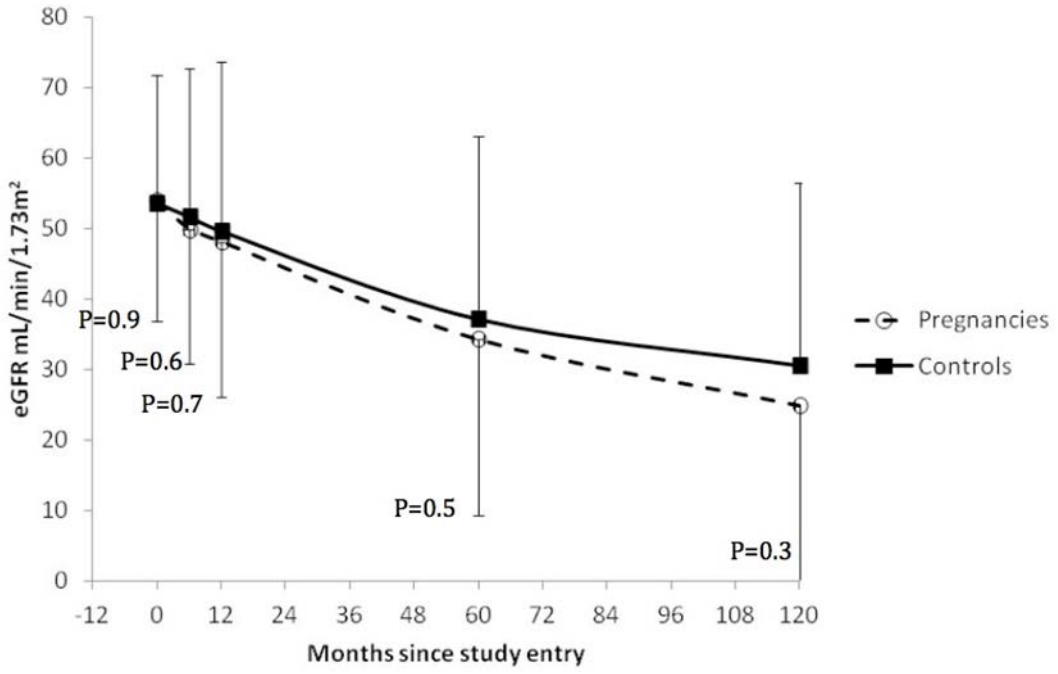

Figure 3. Kaplan Meier survival estimates in pregnant women and non-pregnant controls with a transplant kidney. (A) Transplant survival censored for death. (B) Patient survival.