(Article begins on next page)

Transplantation Publish Ahead of Print
DOI: 10.1097/TP.0000000000001645

Outcomes of pregnancies after kidney transplantation: lessons learned from CKD. A comparison of transplanted, nontransplanted chronic kidney disease patients and low-risk pregnancies: a multicenter nationwide analysis

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Abbreviations:

SGA: small for gestational age

CKD: chronic kidney disease;

KT: kidney transplantation

PE: pre-eclampsia

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Funding

Funding sources: Società Italiana di Nefrologia (editing and publication funds).

Disclosure

None

Abstract

Background

Kidney transplantation (KT) may restore fertility in CKD. The reasons why materno-foetal outcomes are still inferior to the overall population are only partially known. Comparison with the CKD population may offer some useful insights for management and counselling.

Aim of this study was to analyse the outcomes of pregnancy after KT, compared with a large population of non-transplanted CKD patients and with low-risk control pregnancies, observed in Italy the new millennium.

Methods

We selected 121 live-born singletons after KT (Italian study group of kidney in pregnancy, national coverage about 75%), 610 live-born singletons in CKD and 1418 low-risk controls recruited in 2 large Italian Units, in the same period (2000-2014). The following outcomes were considered: maternal and foetal death; malformations; preterm delivery; small for gestational age baby (SGA); need for the neonatal intensive care unit (NICU); doubling of serum creatinine or increase in CKD stage. Data were analysed according to kidney diseases, renal function (staging according to CKD-EPI), hypertension, maternal age, partity, ethnicity.

Results.

Materno-foetal outcomes are less favourable in CKD and KT as compared with the low-risk population. CKD stage and hypertension are important determinants of results. KT patients with e-GFR >90 have worse outcomes compared with CKD stage

1 patients; the differences level off when only CKD patients affected by glomerulonephritis or systemic diseases ("progressive CKD") are compared with KT. In the multivariate analysis, risk for preterm and early-preterm delivery was linked to CKD stage (2-5 versus 1: RR 3.42 and 3.78) and hypertension (RR 3.68 and 3.16) while no difference was associated with being a KT or a CKD patient.

Conclusions.

The materno-foetal outcomes in patients with kidney transplantation are comparable with those of nontransplanted CKD patients with similar levels of kidney function impairment and progressive and/or immunologic kidney disease.

Introduction

Among the many advantages of kidney transplantation over dialysis, pregnancy is of particular relevance for young patients, and successful delivery after transplantation is considered by patients and physicians as one of the main achievements of this therapy (1-4).

According to a recent in-depth systematic review that includes over 4,700 transplanted patients, post-KT pregnancy is feasible, but complication rates are still relatively high as compared to the general population in the USA (5). The reasons for this are not fully understood: the presence of impaired renal function, hypertension and proteinuria were identified as important determinants of the outcomes (6-10), as were interval between transplantation and pregnancy (5, 11-12), maternal age (4-5) and immunosuppressive drugs (1, 13-15).

While it may be intuitive that patients with a transplanted kidney and impaired renal function are at higher risk for adverse pregnancy-related outcomes, as is extensively described in nontransplanted patients with CKD, the degree of risk has never been fully assessed (16-20). This is also due to the high heterogeneity of the study populations and of the controls, as well as to the lack of common terminology and of reliable measurements of kidney function in both physiological pregnancies and in pregnancies complicated by preeclampsia or kidney disease (21-27).

One of the effects of CKD reclassification in the new millennium was to focus attention on various situations, including pregnancy, in the early stages of the disease (16-17, 28-32). Changes in the definition of CKD went hand in hand with the progress being made in Maternal-Fetal medicine and neonatal care, which included anticipated the timing of "viable" delivery, while the new therapies allowed the indications for kidney transplantation to be further broadened (33-37).

The new millennium is also the era of patient empowerment, making way for counseling in delicate situations, such as pregnancy in CKD or after kidney transplantation (38-41).

The aim of this collaborative study was to analyze the risks for adverse pregnancy-related outcomes in the new millennium in a nation-wide Italian cohort of kidney transplant patients and to compare the data to a large multi-center cohort of CKD patients and low-risk pregnancies using the data from the 2014 update of the Torino-Cagliari Observational Study on CKD and pregnancy (TOCOS study) and applying the stratification criteria previously established in CKD (42). The results of such a comparison may cast light on the weight of immunosuppressive therapies and of renal function derangements in determining pregnancy outcomes in KT and CKD patients.

Materials and methods

Data sources

The present study was planned in the context of the activities of the Study group on "Kidney and Pregnancy" of the Italian Society of Nephrology. In the absence of Registry data on pregnancy after renal transplantation, the present analysis was based on systematic phone interviews and e-mail contacts with all the Italian transplant Centers. The study database we built will be the basis for a prospective update.

By June, 2014, answers had been obtained from 24/37 Kidney Transplant Centers that were active at December, 2013. Based on the data of the Italian Regions with fully updated archives, we estimated that the survey covers about 75% of the Italian kidney transplant population. The database includes data on pregnancies that have been reported since 1978; however, due to differences recorded over time in obstetrics, only deliveries as of January 1st, 2000 were included in the present analysis (43).

Data regarding CKD patients and low-risk controls were obtained from the 2014 update of the TOCOS database (Torino-Cagliari Observational Study), described in detail elsewhere (42). At December 2014, after excluding pregnancies in dialysis or after kidney transplantation, the TOCOS cohort consisted of 610 live-born singletons from CKD mothers and 1,418 low-risk live-born singleton deliveries.

Selection criteria

We decided to focus on the more robust data of live-born babies since these data are less subject to reporting biases, which are common in retrospective analyses, considering also that the definitions of intrauterine death, abortion, and perinatal death may be difficult to interpret and may overlap, an important issue in international comparisons as it is also encountered in pregnancies in dialysis patients (21, 44-45). Consequently, data on intrauterine deaths and abortions (pregnancy losses <24 gestational weeks) were collected but not included in the present analysis.

Collected data

The following information was retrieved whenever appropriate in CKD and kidney transplant pregnancies: general data and maternal information: name (code), Center, date of birth, date of RRT start, data of kidney transplant, type of kidney transplant (cadaveric, living donor), maternal age at the start of pregnancy, type of kidney disease; functional data (serum creatinine, e-GFR calculated by CKD-EPI formula on account of its widespread use (46), blood pressure, anti-hypertensive medications) at the start of pregnancy and at delivery. Proteinuria (24-hour urine collection) was not included in the original survey in transplant patients and was available only for CKD subjects; a follow-up call to all transplant centers showed that these data were not available before or at the start of pregnancy for over 70% of patients, thus leading to our decision not to include proteinuria in the present analysis.

Information on gestation and delivery: gestational week at delivery, birth weight, centile (according to the Italian reference Parazzini charts, the reference in the period of study (47)), Apgar score, weight, sex, major malformations; follow up of the mother (alive, in conservative treatment, on dialysis, functioning kidney graft) and of the child; in case of death, date and cause death. The main maternal problems in pregnancy were also recorded.

Definitions

Causes of end-stage kidney disease were classified into broad categories: glomerulonephritis and systemic immunologic diseases; interstitial nephropathy and chronic pyelonephritis; diabetic nephropathy; polycystic kidney disease; other-unknown. In the CKD population 2 further categories were considered: persistent urinary anomalies; previous pyelonephritis with kidney scars. Furthermore, a subset which includes diabetic nephropathy, glomerulonephritides and systemic diseases was defined as "potentially progressive CKD".

Hypertension was defined as systolic blood pressure ≥140 and/or diastolic blood pressure ≥90, or anti-hypertensive therapy; patients on anti-hypertensive therapy prior to conception were considered hypertensive even when anti-hypertensive therapy was discontinued in early pregnancy.

Pre-eclampsia (PE) was defined by employing the classic definition of hypertension accompanied by proteinuria ≥300 mg/24 hours after 20 weeks of gestational age in a previously normotensive, non proteinuric woman, in the absence of other signs or symptoms indicating a different nephrological diagnosis; doppler flow alterations were considered further support PE diagnosis. This strict diagnosis applies only to subjects who were normotensive and non proteinuric; since the definition of "superimposed PE" is not absolute, and as the overlap with CKD is higher, we did not include it in this study (42, 48). Due to the characteristics of CKD and kidney transplant patients, we did not employ the recent ACOG definitions which also consider an increase in serum creatinine as diagnostic (49).

A newborn was defined as small for gestational age (SGA) when the birth weight was below the 5th or 10th centile according to Italian birth weight references (Parazzini charts (47)); again, this is not an absolute definition, and while acknowledging its limits, we chose the 2 most frequently used cut-off points, 5th and 10th centile (50-53).

Preterm delivery was defined as delivery occurring before 37 completed gestational weeks; early preterm delivery as delivery occurring before 34 completed gestational weeks and extreme early preterm delivery as delivery occurring before 28 completed gestational weeks (50, 54-55).

Statistical analysis

A descriptive analysis was performed as appropriate (mean and standard deviation for parametric data and median and range for non-parametric data). Independent t-test, Chi-square test, Fisher's test, and Mann-Whitney U test were used, where indicated, for comparisons between patients and controls and among groups. Significance was set at <0.05.

Multiple regression analysis was performed considering the outcomes: preterm delivery, early preterm delivery, SGA baby, and the following covariates: age; CKD or kidney transplant; CKD stage at start of pregnancy; hypertension at start of pregnancy (SPSS vers. 18.0 for Windows, Chicago IL, USA).

Kaplan Meier analysis was performed as time to event analysis, with observation going from the 24th week until the date of live-born delivery. The analysis was performed as implemented on SAS 9.2. Differences were assessed by Log-Rank and Wilcoxson tests.

Study design: first of all, the 2 patient populations of CKD and kidney transplant patients were compared as per baseline data; secondly, stratification according to CKD stage was performed in both subsets of patients; thirdly, the "potentially progressive" patients were selected from the large CKD stage 1 population for comparison with stage 1 kidney transplant patients. Low-risk controls were used to contextualize the results.

Ethical issues

The observational study protocol was approved and supported by the Italian Society of Nephrology (Gruppo di Studio Rene e Gravidanza). The epidemiological and outcome study on CKD in pregnancy and the related low-risk controls was approved by the Ethics Committee of O.I.R.M.-Sant'Anna Hospital (protocollo di studio 11551/c28.2;Delibera n. 335 del 4/3/2011). The observational study on kidney transplantation was approved by the Ethics Committee of the san Luigi Gonzaga hospital of the University of Torino, Italy (nota prot. n. 11655 del 26/06/13 - studio osservazionale pratica comitato etico n. 90/2013 Delibera n. 363 del 17/06/13).

The clinical and research activities being reported are consistent with the Principles of the Declaration of Istanbul as outlined in the 'Declaration of Istanbul on Organ Trafficking and Transplant Tourism

Results

Baseline data

One hundred twenty-one pregnancies in KT patients resulting in a live-born singleton baby were compared with 610 deliveries in CKD patients; mean age of the mothers was significantly higher in KT patients and, as expected by the different clinical histories, KT patients were more often affected by glomerulonephritides and immunologic diseases as compared to CKD patients in whom less severe diseases, mainly interstitial nephropathies, were more often present (Table 1).

These differences affect also the distribution of CKD stages ($p<0.001$). Consequently, serum creatinine before pregnancy or at referral is almost twice as high in KT patients, and the prevalence of hypertension rises from 24.4% in CKD to 55.4% in KT pregnancies. The overall characteristics reflect the Italian KT population during the study period, with a low prevalence of preemptive and living donor transplantations and a high prevalence of calcineurin inhibitors and of steroid treatments, that, albeit at low doses, are usually employed in patients with immunologic diseases who make up the majority of KT subjects (Table 1).

In spite of the higher age, grafted patients were more often primigravidae, as compared with the CKD and low risk population (table 1, table 2). This finding may be explained by the long waiting time for transplantation: in fact, only a minority of cases was transplanted pre-emptively (5%) or received a living donor graft (14.9%).

The main immunodepressive medications were steroids, employed in 90% of the cases, and calcineurin inhibitors (Cyclosporine A, in 51.7% and Tacrolimus, in 40.8%); Azathyoprine was used in 35% of the cases, resulting in 10 different drug combinations (Table S1, SDC, http://links.lww.com/TP/B390). No difference according to the main calcineurin inhibitor was found in the logistic regression analysis (Table S2, SDC, http://links.lww.com/TP/B390).

Main outcomes and outcomes across CKD stages

Given the baseline differences, timing of delivery is not surprisingly significantly different between KT and CKT patients, and in both situations versus low-risk pregnancies ($p<0.0001$) (Figure 1).

Stratification for CKD stage, which is reported in Table 2, shows an increase of incidence of preterm delivery and early preterm delivery across functional stages, significant in CKD patients (Chi square $p < 0.05$), but not reaching significance in the smaller KT cohort.

The KT cohort is characterised by a higher incidence of caesarean sections (CS) across all CKD stages. The pattern suggests a widespread policy of CS in KT patients, regardless of stage and comorbidity, to be further addressed in dedicated analyses.

With the exception of cesarean sections, the comparison between KT and CKD highlighted a substantial equivalence of the outcomes in stage 2 and in stage 3-5 patients that were taken into consideration, as also shown in Figure 2 which depicts centile distribution and age at birth in male and female babies born to CKD and KT patients in CKD stages 3-4-5.

However, in stage 1 patients, preterm, early and extremely preterm delivery, as well as small for gestational age newborns are significantly more common in KT patients (Table 2). Due to the impossibility to clearly diagnose preeclampsia in the CKD population, this outcome was not considered; none of the patients with a kidney graft developed HELLP syndrome in pregnancy or immediately after.

Multivariate logistic regression analysis, shown in Table 3, was performed for preterm delivery, early preterm delivery and small for gestational age baby, while cesarean section was not analyzed, because of colinearity with KT; the analysis confirms the relevance of CKD stage (RR of 3.42 and 3.78 for early preterm and preterm delivery) and of baseline hypertension (RR of 3.68 and 3.16 for early and preterm delivery) but not of being a KT recipient versus being a CKD patient, even if differences may be offset by the small sample size.

Furthermore, the multivariate analysis confirms the significant effect of parity on early preterm delivery (but not on preterm delivery an SGA); adding parity to the model does not affect the equivalence between KT and CKD (table 3).

Main outcomes in CKD stage 1 patients: KT, CKD and "potentially progressive" CKD versus the low risk control population.

On account of the high heterogeneity of the CKD population, by including patients with a single kidney scar as well as patients with systemic, potentially progressive diseases, such as glomerulonephritis or diabetic nephropathy, a further comparison was carried out on patients with "potentially progressive" CKD. All patients were also compared to low-risk controls (Tables 4-5, Figures 3-4).

While all subsets of stage 1 patients differ from the low-risk controls with regard to most or all of the outcomes we considered, the differences between KT and CKD pregnancies disappear if only "potentially progressive" diseases are considered (Table 4). Timing of delivery and the distribution of weight according to gestational week at delivery follow the same distribution in these 2 subsets (Figures 3-4).

Hypertension was confirmed as a significant outcome modulator by logistic regression analysis, while parity or being a KT or CKD patient had no effect on the outcomes (Table 5).

Discussion

Pregnancy is a great achievement for many women with chromic kidney disease before or after the start of renal replacement therapy; the decision to undertake a pregnancy may be extremely difficult, and the communication of medical risks should be balanced by respect of life priorities (38, 56-57).

Risk assessment on which counseling is based usually considers pregnancy outcomes in the overall population or in low-risk pregnancies (5-6, 17, 27).

The aim of the present study is to offer some insight into a complementary point of view: the patients' risks throughout their disease evolution, from CKD to KT. Our data show that the risk for 2 of the main pregnancy-related outcomes are similar in patients with comparable degrees of renal function impairment, in the pre-ESRD phase or after KT, and are modulated by the presence of hypertension (Tables 2-3, Figures 1-2).

While the highly heterogeneous group of stage 1 CKD patients has overall better outcomes than KT patients, the differences disappear when only patients with "potentially progressive disease" are selected from among the large subset of stage 1 CKD patients. This is probably due to the fact that in our CKD cohort there is a high prevalence of interstitial diseases, with normal renal function, no hypertension and no proteinuria. Hence, we selected subjects with "potentially progressive disease", more similar to KT patients, in whom the immunological challenges and the reduced nephron mass make progression over time almost the rule (Tables 4-5, Figures 3-4).

From the physiopathologic point of view, our data suggest that once kidney function impairment is present, it represents a major determinant of the outcomes, thus offsetting the influence of therapy and of type of disease, and underlining the importance of the functioning nephron mass, as already reported in CKD patients (19-20, 31, 42). Conversely, the results observed in patients with normal kidney function may support either the role of the nephron mass (since patients with "potentially progressive" CKD may be in the "gray area" in which a substantial parenchymal reduction is not detected by conventional renal functional tests), or the role of the immunologic challenge shared by glomerulonephritides, systemic diseases and KT.

The latter explanation is in line with the immunological hypothesis of the pathogenesis of preeclampsia and related hypertensive disorders of pregnancy, whose role in the development of adverse outcomes in CKD is only partially understood (58-61).

From the clinical point of view, our data may add support to the counseling of both non-transplanted CKD and KT patients. In fact, in the past, non-KT patients with advanced CKD were often discouraged from undertaking pregnancy, although in some cases they were told that their chances could be improved by a successful KT (41, 62-64). However, the conditions that were classically considered "safe" for pregnancy following KT identified only a subset of "best patients" (1-2 years after KT, good real function, no or low-grade proteinuria normotension). In both conditions, therefore, a gray area encompassed the patients with severe renal functional reduction (62-67).

The great advances in pregnancy on dialysis have led to a paradigm shift; the increasingly good results with extended dialysis reduce the fear that the need to start or restart dialysis in pregnancy will invariably lead to adverse outcomes (40, 45, 68-71). Consequently, we may also expect an increase in patients with advanced CKD before or after KT who want to have a baby, in particular when increasing maternal age leads the patients to consider age-related sub-fertility.

The demonstration that the risk of adverse pregnancy outcomes for KT patients is similar to that of non transplanted CKD patients with a corresponding degree of kidney function impairment and hypertensive status, should reassure KT patients about the lack of detrimental effects of their immunosuppressive therapy, at least on "macro-events", such as delivery of a small for gestational age, preterm baby (Tables 3-5). Further, our study suggests that the broad creatinine-based categories that are

employed to distinguish high and low risk KT pregnancies should be broken down into more precise staging (Table 2). Our observation of similar risks in CKD and KT patients may support undertaking pregnancy in the pre-ESRD stage, at least in patients without a living donor, given the long waiting lists, the impossibility to foresee kidney function after KT and the consideration that increasing maternal age is associated not only with fertility reduction but also with an increase in adverse pregnancy-related outcomes (72-73).

Although ours is a novel study, it has several limitations, partly shared by other studies on pregnancy in CKD or after KT (5, 16, 21, 45).

Relatively large numbers became small after stratification, thus reducing the statistical power.

The databases are heterogeneous: while data on CKD patients was gathered prospectively, the database on KT was the result of a retrospective inquiry, and reporting biases cannot be completely ruled out. Therefore, we hope that the data here discussed may raise attention and lead to running further large prospective studies on these issues.

While no GFR formula is devoid of biases, errors may increase in pregnancy after KT, considering also that CNIs may cause a decrease in GFR (however measured) with an indirect effect on outcome (25-26, 39-30, 32, 46, 74-76). However, a common, simple assessment, as the CKD-EPI formula, chosen for its wide diffusion, is probably at present the only way to carry out clinical comparisons.

Considering the importance of proteinuria in pregnancy-related outcomes, a major bias is the absence of this information in our database; this was due to lack of sufficient information in the original clinical charts, probably because attention to kidney function assessment and 24-hour proteinuria is only relatively recent in this setting (and patients with relevant proteinuria were probably often discouraged from

undertaking pregnancy). The data has been added to the prospective database for future studies, once more stressing the need for new, detailed, and sharable information to support counseling and manage pregnancies in KT and CKD patients.

Caesarean sections were more common in KT patients, in all stages; this pattern may suggest a policy preferring a priori this mode of delivery in KT patients, but this important issue should be assessed by dedicated analyses.

Lastly, we do not have data on assisted fertilization techniques in our CKD and KT populations (low-risk cases are by definitions spontaneous pregnancies). This item was added in the prospective database; however, since in Italy until recently the access to assisted fertilization techniques was limited to cases without comorbidity, the role of in vitro fertilization was probably negligible in the present study population.

In summary, the present study, based upon a large multicenter cohort of pregnancies in KT patients whose data were compared to nontransplanted CKD and low-risk pregnancies, suggests that the patterns observed in KT closely correspond to those observed in non transplanted CKD with a comparable degree of kidney function impairment or with normal renal function and "potentially progressive" disease.

These findings, reassuring on lack of a clear detrimental effect of immunosuppressive treatments, stress the importance of kidney function and hypertension as determinants of pregnancy-related outcomes and suggest the need for more detailed stratification of kidney function for risk assessment after KT. They also confirm that the differences versus the low-risk population are also observed in patients with normal renal function, and may support the usefulness of tailoring counseling on the various phases of CKD.

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Figures:

Figure 1: Gestational age at delivery in low-risk controls, kidney transplant patients and CKD patients.

Figure 2: Gestational age at delivery in low-risk controls, kidney transplant patients and stage 1 CKD patients with "potentially progressive" disease.

Figure 3: Relationship between weight and gestational age, with respect to the Parazzini graphs, in KT stage 3-4-5 patients and in CKD stage 3-4-5 patients.

Figure 4: Relationship between weight and gestational age, with respect to the Parazzini graphs, in KT stage 1 patients and in CKD stage 1 patients with "potentially progressive disease".

Figure 1

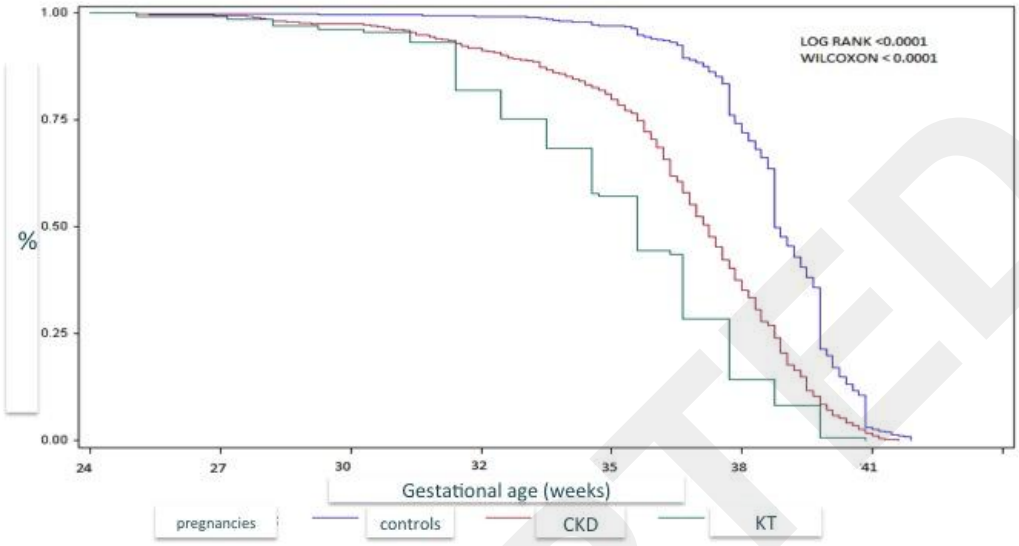

Figure 2

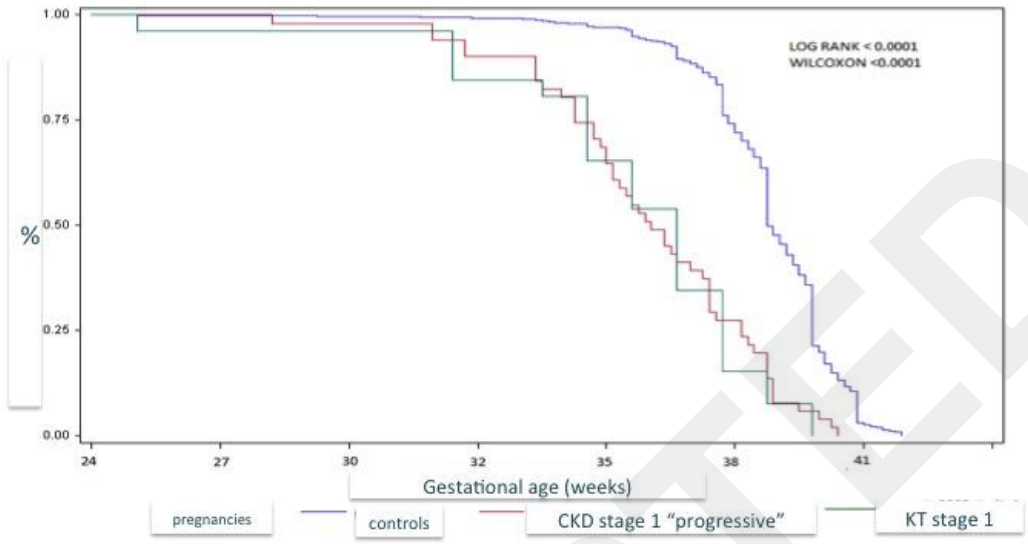

Figure 3

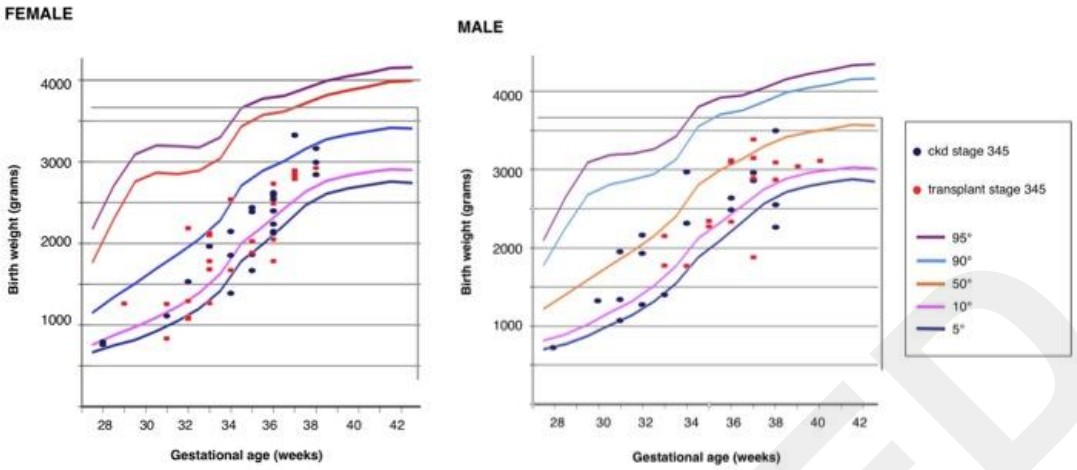

Figure 4

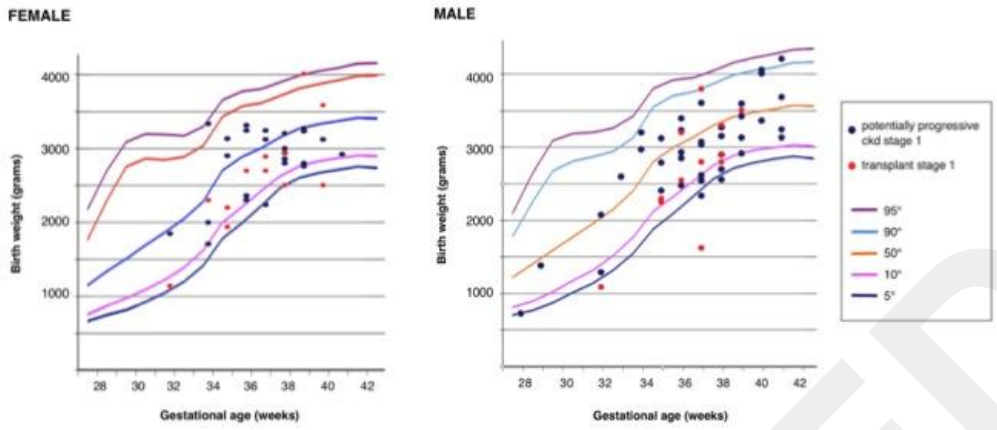

Table 1. Baseline characteristics of the study population: singletons, live-born deliveries

	Kidney transplant (KT)	Chronic kidney disease (CKD)	P KT - CKD
N pregnancies	121	610	
Age at pregnancy (mean and std; years)	34.1 ± 3.7	31.9 ± 5.5	<0.001
Primiparous (*)	85 (75.2%)	341 (55.9%)	<0.001
Glomerular, diabetes and immunological disease n (%)	66 (54.5%)	127 (20.8%)	<0.001
Interstitial diseases, including previous APN n (%)	9 (7.4%)	254 (41.6.%)	
ADPKD n (%)	3 (2.5%)	30 (4.9%)	
Other not known n (%)	43 (35.6%)	199 (32.6%)	
CKD stage 1 n (%)	26 (21.5%)	481 (78.9%)	<0.001
CKD stage 2 n (%)	52 (43.0%)	87 (14.3%)	
CKD stage 3 n (%)	42 (34.7%)	32 (5.2%)	
CKD stage 4-5 n (%)	1 (0.8%)	10 (1.6%)	
Serum creatinine (before or referral) (median, min-max; mg/dL)	1.07 (0.6-2.4)	0.61 (0.3-7.9)	<0.001
Hypertension (before or referral) n (%)	67 (55.4%)	148 (24.4%)	<0.001
Months of dialysis pretransplantation (median, min-max)	27.5 (0-194)	-	
Months between transplantation and pregnancy (median, min-max)	62 (14-278)	-	
Preemptive transplantation n (%)	6 (5%)	-	
Living donor transplantation n (%)	18 (14.9%)	-	
Cyclosporine A therapy n (%)	62 (51.7%)	-	
Tacrolimus therapy n (%)	49 (40.8%)	-	
No calineurin inhibitors	9/120 (7.5%)	-	
Treatment with steroids	108 (90%)	-	

Legend: ADPKD: autosomal dominant chronic kidney disease; CKD: chronic kidney disease; control low-risk pregnancies: primiparous: 57.5% (ns versus CKD and <0.001 vs KT). * KT: data on parity available in 113 cases.

Table 2. Main materno-foetal outcomes across CKD-EPI stages in kidney transplant and in patients with CKD (pre- ESRD)

	CKD-EPI stage 1 (n)			CKD-EPI stage 2 (n)			CKD-EPI stages 3-5 (n)		
	KT	CKD	p	KT	CKD	p	KT	CKD	P
N pregnancies	26	481		52	87		43	42	
Primiparous n (%)	17 (68.0%)	264 (54.9%)	0.280	39 (78.0%)	50 (57.5%)	0.025	29 (76.3%)	27 (64.3%)	0.353
Age at pregnancy (yrs)	33.4±4.4	31.4 ± 5.7	0.077	33.6 ± 3.6	33.7 ± 4.6	0.861	34.9 ± 3.3	33.0 ± 4.5	0.030
Cesarean sections (%)	19 (73.1%)	212 (44.2%)	0.007	39 (76.5%)	59 (67.8%)	0.375	37 (86%)	29 (69%)	0.100
Gestational week	36 ± 3.1	37.6±2.4	0.001	35.24±3.2	35.8 ± 3.1	0.290	35 ± 2.5	34.0 ± 3.2	0.140
Preterm (<37 w)	12 (46.2%)	106 (22.1%)	0.010	31 (60.8%)	44 (50.6%)	0.325	28 (68.3%)	33 (78.6%)	0.420
Early preterm (<34 w)	4 (15.4%)	30 (6.2%)	0.088	14 (27.5%)	17 (19.5%)	0.388	14 (34.1%)	15 (35.7%)	0.999
Extreme preterm (<28 w)	1 (3.8%)	2 (0.4%)	0.147	1 (2%)	3 (3.4%)	0.999	0	1 (2.4%)	0.999
Weight at birth (g)	2573 ± 810	2960 ± 623	0.003	2454 ± 610	2509 ± 692	0.640	2229 ± 672	2089 ± 747	0.370
SGA <10% (Parazzini)	6/25 (24.0%)	63 (13.2%)	0.134	8/50 (16%)	13 (15.5%)	0.999	10/40 (25%)	12 (29.3%)	0.850
SGA <5% (Parazzini)	4/25 (16.0%)	23 (4.8%)	0.038	4/50 (8.2%)	4 (4.8%)	0.471	3/40 (7.5%)	4 (9.8%)	0.999
SGA <10% (Ines)	4/25 (16.0%)	53 (11.1%)	0.511	4/49 (8.2%)	9 (10.3%)	0.770	8/40 (20%)	8 (19%)	0.999
SGA <5% (Ines)	3/25 (12.0%)	17 (3.5%)	0.070	2/49 (4.1%)	3 (3.4%)	0.999	4/40 (10%)	2 (4.8%)	0.430

CKD stage shift	6/19 (31.6%)	32/481 (6.7%)	0.002	9/38 (23.7%)	10/87 (11.5%)	0.14	1/32 (3.1%)	6/42 (14.3%)	0.13

Legend: CKD: chronic kidney disease; KT: kidney transplantation; ESRD: end stage renal disease; SGA: small for gestational age.
P: between CKD and KT patients in each stage.

Table 3. Multivariate logistic regression analysis: transplantation versus CKD (all cases, all stages)

	Preterm delivery <34 weeks (N= 92/717)	Preterm delivery <37 weeks (N= 248/717)	SGA (Parazzini) <10th centile (N= 110/709)
Age < 33 years	1	1	1
Age >=33 years OR (IC)	1.38 (0.84-2.29)	1.21 (0.85-1.73)	0.68 (0.45-1.05)
CKD Stage 1	**1**	**1**	1
CKD stages 2+3+4 OR (IC)	**3.25 (1.92–5.49)**	**3.81 (2.57-5.65)**	1.48 (0.90-2.43)
Normotension	**1**	**1**	1
Hypertension OR (IC)	**3.86 (2.35-6.32)**	**3.18 (2.20-4.59)**	1.13 (0.71-1.80)
CKD	1	1	1
KT OR (IC)	1.04 (0.58-1.88)	1.16 (0.71-1.92)	1.23 (0.67-2.25)
Primiparous	1	1	1
Multiparous OR (IC)	**0.43 (0.25-0.74)**	0.83 (0.58-1.19)	0.86 (0.56-1.32)

Legend: CKD: chronic kidney disease; KT: kidney transplantation; SGA: small for gestational age.

Table 4. Main Materno-foetal outcomes in CKD-EPI stage 1 transplanted patients, CKD patients, CKD patients with "progressive disease" and low-risk controls

	KT stage 1	CKD stage 1	CKD stage 1 with "potentially progressive" disease	Low-risk controls	P (KT vs CKD)	P (KT vs progressive CKD)	P (KT vs controls)	P (CKD vs controls)
N pregnancies	26	481	63	1418				
Primiparous n (%)	17 (68.0%)	264 (54.9%)	43 (68.3%)	815 (57.5%)	0.280	1.000	0.394	0.348
Age at pregnancy (yrs)	33.4 ± 4.4	31.4 ± 5.7	30.9 ± 5.9	31.2 ± 5.5	0.077	0.323	0.470	0.559
Cesarean sections (%)	19 (73.1%)	212 (44.2%)	39 (61.9%)	379 (26.7%)	**0.007**	0.446	**<0.001**	**<0.001**
Gestational week	36.0 ± 3.1	37.6 ± 2.4	36.8 ± 2.7	39.0 ± 1.6	**0.001**	0.362	**<0.001**	**<0.001**
Preterm (<37 w)	12 (46.2%)	106 (22.1%)	25 (39.7%)	89 (6.3%)	**0.010**	0.744	**<0.001**	**<0.001**
Early preterm (<34 w)	4 (15.4%)	30 (6.2%)	6 (9.5%)	13 (0.9%)	0.088	0.470	**<0.001**	**<0.001**
Extreme preterm (<28 w)	1 (3.8%)	2 (0.4%)	0	2 (0.1%)	0.147	-	0.053	0.267
Weight at birth (g)	2573 ± 810	2960 ± 623	2879 ± 627	3232 ± 476	**0.003**	0.070	**<0.001**	**<0.001**
SGA <10%	6/25	63	7	157	0.134	0.181	0.055	0.262

(Parazzini)	(24.0%)	(13.2%)	(11.1%)	(11.1%)				
SGA <5% (Parazzini)	4/25 (16.0%)	23 (4.8%)	2 (3.2%)	63 (4.5%)	**0.038**	0.052	**0.026**	0.854
SGA <10% (Ines)	4/25 (16.0%)	53 (11.1%)	7 (11.1%)	120 (8.5%)	0.511	0.500	0.266	0.110
SGA <5% (Ines)	3/25 (12.0%)	17 (3.5%)	0	45 (3.2%)	0.070	-	**0.048**	0.811

Legend: CKD: chronic kidney disease; KT: kidney transplantation; ESRD: end stage renal disease; SGA: small for gestational age.

Table 5. Logistic regression analysis: transplantation versus CKD with "progressive disease" (stage 1 according to CKD-EPI)

	Preterm delivery <34 weeks	Preterm delivery <37 weeks	SGA Parazzini<10th centile
Age < 33 years	1	1	1
Age >=33 years OR (IC)	0.18 (0.03 – 1.01)	0.94 (0.37 – 2.38)	0.54 (0.15 – 1.99)
Normotension	1	1	1
Hypertension OR (IC)	2.99 (0.69- 12.96)	**3.07 (1.18 – 8.02)**	1.78 (0.48- 6.51)
CKD	1	1	1
KT OR (IC)	1.70 (0.37 - 7.72)	0.80 (0.29– 2.27)	2.46 (0.64 – 9.48)
Primiparous	1	1	1
Multiparous OR (IC)	1.13 (0.24-5.26)	1.01 (0..38-2.72)	0.67 (0.16-2.86)

Legend: CKD: chronic kidney disease; KT: kidney transplantation; SGA: small for gestational age.

Table S1: Immunosuppressive medications. The different combinations in kidney transplant recipients

	All KT (120) N (%)	**Stage 1 (25) N (%)**	**Stage 2 (52) N (%)**	**Stages 3-5 (42) N (%)**
Drug frequency				
Steroid	108 (90.0)	24 (96.0)	42 (80.8)	42 (97.7)
CyA	62 (51.7)	4 (16.09	30 (57.7)	28 (65.1)
Tacrolimus	49 (40.8)	18 (72.0)	18 (34.6)	13 (30.2)
AZA	42 (35.0)	7 (28.0)	21 (40.4)	14 (32.6)
Drug combination frequency				
Steroid alone	2 (1.7)	1 (4.0)	1 (1.9)	-
CyA alone	1 (0.8)	-	1 (1.9)	-
Tacrolimus alone	1 (0.8)	-	1 (1.9)	-
Steroid + CyA	42 (35.0)	3 (12.0)	19 (36.5)	20 (46.5)
Steroid + CyA + AZA	14 (11.7)	1 (4.0)	6 (11.5)	7 (16.3)
Cya + Aza	5 (4.2)	-	4 (7.7)	1 (2.3)
Steroid + Tacrolimus	32 (26.7)	14 (53.8)	9 (17.3)	9 (20.9)
Steroid + Tacrolimus +AZA	11 (9.2)	3 (12.0)	4 (7.7)	4 (9.3)
Tacrolimus + AZA	5 (4.2)	1 (4.0)	4 (7.7)	
Steroid + AZA	7 (5.8)	2 (8.0)	3 (5.8)	2 (4.7)

Note: information is missing in 1 case

Table S2. Logistic regression analysis: transplantation

	Preterm delivery <34 weeks	Preterm delivery <37 weeks	SGA Parazzini<10th centile
Age < 34 years	1	1	1
Age >=34 years OR (IC)	2.27 (0.89 – 5.79)	1.61 (0.72 – 3.61)	0.40 (0.14 – 1.11)
Normotension	1	1	1
Hypertension OR (IC)	1.07 (0.45- 2.54)	1.52 (0.69- 3.37)	1.25 (0.45- 3.49)
Stage 1	1	1	1
Stages 2+3+4 OR (IC)	2.94 (0.73 – 11.79)	2.16 (0.76 – 6.16)	1.60 (0.37 – 6.87)
Cyclosporine	1	1	1
Tacrolimus OR (IC)	1.07 (0.42-2.71)	1.001 (0.42-2.39)	1.02 (0.34-3.06)