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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

The first two authors equally contributed to the study

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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, parity, 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, date 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 Wilcoxon 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 chronic 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 renal 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.

References

1. Hou S. Pregnancy in renal transplant recipients. *Adv Chronic Kidney Dis.* 2013 ;20(3):253-9.
2. Watnick S, Rueda J. Reproduction and contraception after kidney transplantation. *Curr Opin Obstet Gynecol.* 2008;20(3):308-12.
3. Josephson MA, McKay DB. Pregnancy and kidney transplantation. *Semin Nephrol.* 2011 ;31(1):100-10.
4. Zachariah MS, Tornatore KM, Venuto RC. Kidney transplantation and pregnancy. *Curr Opin Organ Transplant.* 2009 ;14(4):386-91.
5. Deshpande NA, James NT, Kucirka LM, Boyarsky BJ, Garonzik-Wang JM, Montgomery RA, Segev DL. Pregnancy outcomes in kidney transplant recipients: a systematic review and meta-analysis. *Am J Transplant.* 2011 ;11(11):2388-404.
6. Levidiotis V, Chang S, McDonald S. Pregnancy and maternal outcomes among kidney transplant recipients. *J Am Soc Nephrol.* 2009 ;20(11):2433-40.
7. Armenti VT, Radomski JS, Moritz MJ, Gaughan WJ, Philips LZ, McGrory CH, Coscia LA: Report from the National Transplantation Pregnancy Registry (NTPR): Outcomes of pregnancy after transplantation. *Clin Transpl* 2002; 121–130.
8. Toma H, Tanabe K, Tokumoto T, Kobayashi C, Yagisawa T: Pregnancy in women receiving renal dialysis or transplantation in Japan: A nationwide survey. *Nephrol Dial Transplant* 1999; 14: 1511–1516.
9. Kozłowska-Boszko B, Durlík M, Kuczyńska-Sicińska J, Lao M. Predictor of transplanted kidney deterioration following pregnancy--daily urine protein loss or serum creatinine concentration? *Ann Transplant.* 1996;1(4):30-1.

10. You JY, Kim MK, Choi SJ, et al. Predictive factors for adverse pregnancy outcomes after renal transplantation. *Clin Transplant*. 2014 ;28(6):699-706.
11. Sibanda N, Briggs JD, Davison JM, Johnson RJ, Rudge CJ. Pregnancy after organ transplantation: a report from the UK Transplant pregnancy registry. *Transplantation*. 2007 ;83(10):1301-7.
12. Ghanem ME, El-Baghdadi LA, Badawy AM, Bakr MA, Sobhe MA, Ghoneim MA. Pregnancy outcome after renal allograft transplantation: 15 years experience. *Eur J Obstet Gynecol Reprod Biol*. 2005 ;121(2):178-81.
13. Armenti VT, Ahlswede KM, Ahlswede BA, Jarrell BE, Moritz MJ, Burke JF. National transplantation Pregnancy Registry--outcomes of 154 pregnancies in cyclosporine-treated female kidney transplant recipients. *Transplantation*. 1994 ;57(4):502-6.
14. López LF, Martínez CJ, Castañeda DA, Hernández AC, Pérez HC, Lozano E. Pregnancy and kidney transplantation, triple hazard? Current concepts and algorithm for approach of preconception and perinatal care of the patient with kidney transplantation. *Transplant Proc*. 2014;46(9):3027-31.
15. Perales-Puchalt A, Vila Vives JM, López Montes J, Diago Almela VJ, Perales A. Pregnancy outcomes after kidney transplantation-immunosuppressive therapy comparison. *J Matern Fetal Neonatal Med*. 2012 ;25(8):1363-6.
16. Nevis IF, Reitsma A, Dominic A, et al. Pregnancy outcomes in women with chronic kidney disease: a systematic review. *Clin J Am Soc Nephrol*. 2011 Nov;6(11):2587-98.
17. Piccoli GB, Attini R, Vasario E, et al. Pregnancy and chronic kidney disease: a challenge in all CKD stages. *Clin J Am Soc Nephrol*. 2010 ;5(5):844-55.

18. Alsuwaida A, Mousa D, Al-Harbi A, Alghonaim M, Ghareeb S, Alrukhaimi MN. Impact of early chronic kidney disease on maternal and fetal outcomes of pregnancy. *J Matern Fetal Neonatal Med.* 2011 ;24(12):1432-6.
19. Imbasciati E, Gregorini G, Cabiddu G, Gammara L, Ambroso G, Del Giudice A, Ravani P. Pregnancy in CKD stages 3 to 5: fetal and maternal outcomes. *Am J Kidney Dis.* 2007 ;49(6):753-62.
20. Fischer MJ, Lehnerz SD, Hebert JR, Parikh CR. Kidney disease is an independent risk factor for adverse fetal and maternal outcomes in pregnancy. *Am J Kidney Dis.* 2004 ;43(3):415-23.
21. Piccoli GB, Conijn A, Attini R, Biolcati M, Bossotti C, Consiglio V, Deagostini MC, Todros T. Pregnancy in chronic kidney disease: need for a common language. *J Nephrol.* 2011 May-Jun;24(3):282-99.
22. You JY, Kim MK, Choi SJ, Oh SY, Kim SJ, et al. Predictive factors for adverse pregnancy outcomes after renal transplantation. *Clin Transplant.* 2014 ;28(6):699-706.
23. Wyld ML, Clayton PA, Jesudason S, Chadban SJ, Alexander SI. Pregnancy outcomes for kidney transplant recipients. *Am J Transplant* 2013; 13(12):3173-82.
24. Alper AB, Yi Y, Rahman M, et al. Performance of estimated glomerular filtration rate prediction equations in preeclamptic patients. *Am J Perinatol.* 2011 ;28(6):425-30.
25. Smith MC, Moran P, Ward MK, Davison JM. Assessment of glomerular filtration rate during pregnancy using the MDRD formula. *BJOG.* 2008 ;115(1):109-12.

26. Larsson A, Palm M, Hansson LO, Axelsson O. Cystatin C and modification of diet in renal disease (MDRD) estimated glomerular filtration rate differ during normal pregnancy. *Acta Obstet Gynecol Scand.* 2010 ;89(7):939-44.
27. Piccoli GB, Cabiddu G, Attini R, et al. Pregnancy in CKD: Questions and answers in a changing panorama. *Best Pract Res Clin Obstet Gynaecol.* 2015 ;29(5):625-42.
28. Levey AS, Coresh J, Balk E, et al. National Kidney Foundation. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Ann Intern Med.* 2003 ;139(2):137-47.
29. Levin A. The advantage of a uniform terminology and staging system for chronic kidney disease (CKD). *Nephrol Dial Transplant.* 2003 ;18(8):1446-51.
30. Eknoyan G. Chronic kidney disease definition and classification: the quest for refinements. *Kidney Int.* 2007 ;72(10):1183-5.
31. Piccoli GB, Fassio F, Attini R, et al. Pregnancy in CKD: whom should we follow and why? *Nephrol Dial Transplant.* 2012 Oct;27 Suppl 3:iii111-8.
32. Piccoli GB, Attini R, Vigotti FN, Parisi S, Fassio F, Pagano A, et al. Is renal hyperfiltration protective in chronic kidney disease-stage 1 pregnancies? A step forward unravelling the mystery of the effect of stage 1 chronic kidney disease on pregnancy outcomes. *Nephrology (Carlton).* 2015 ;20(3):201-8.
33. Dejhalla M, Lahage N, Parvez B, Brumberg HL, La Gamma EF. Early Postnatal Growth in a Subset of Convalescing Extremely Low Birth Weight Neonates - Approximating the "Index Fetus" Ex Utero. *J Pediatr Gastroenterol Nutr.* 2015 ;61(3):361-6.

34. Jacob J, Kamitsuka M, Clark RH, Kelleher AS, Spitzer AR. Etiologies of NICU deaths. *Pediatrics*. 2015 ;135(1):e59-65.
35. Jarjour IT. Neurodevelopmental outcome after extreme prematurity: a review of the literature. *Pediatr Neurol*. 2015 ;52(2):143-52.
36. Bamoulid J, Staeck O, Halleck F, Khadzhyrov D, Brakemeier S, Dürr M, Budde K. The need for minimization strategies: current problems of immunosuppression. *Transpl Int*. 2015 ;28(8):891-900.
37. Hardinger KL, Brennan DC, Klein CL. Selection of induction therapy in kidney transplantation. *Transpl Int*. 2013 ;26(7):662-72.
38. Mezza E, Oggé G, Attini R, et al. Pregnancy after kidney transplantation: an evidence-based approach. *Transplant Proc*. 2004;36(10):2988-90.
39. Rupley DM, Janda AM, Kapeles SR, Wilson TM, Berman D, Mathur AK. Preconception counseling, fertility, and pregnancy complications after abdominal organ transplantation: a survey and cohort study of 532 recipients. *Clin Transplant*. 2014 ;28(9):937-45.
40. Piccoli GB, Conijn A, Consiglio V, et al. Pregnancy in dialysis patients: is the evidence strong enough to lead us to change our counseling policy? *Clin J Am Soc Nephrol*. 2010 Jan;5(1):62-71.
41. Bramham K, Lightstone L. Pre-pregnancy counseling for women with chronic kidney disease. *J Nephrol*. 2012;25(4):450-9.
42. Piccoli GB, Cabiddu G, Attini R, et al. Risk of Adverse Pregnancy Outcomes in Women with CKD. *J Am Soc Nephrol*. 2015 ;26(8):2011-22.
43. Cabiddu et al: abstract nazionale o lavoro gravidanze over time.

44. Joseph KS1, Liu S, Rouleau J, et al; Fetal and Infant Health Study Group of the Canadian Perinatal Surveillance System. Influence of definition based versus pragmatic birth registration on international comparisons of perinatal and infant mortality: population based retrospective study. *BMJ*. 2012;344:e746.
45. Piccoli GB, Minelli F, Versino E, et al. Pregnancy in dialysis patients in the new millennium: a systematic review and meta-regression analysis correlating dialysis schedules and pregnancy outcomes. *Nephrol Dial Transplant*. 2016 ;31(11):1915-1934.
46. Inal BB, Oguz O, Emre T, Usta M, Inal H, Altunoglu E, Topkaya C. Evaluation of MDRD, Cockcroft-Gault, and CKD-EPI formulas in the estimated glomerular filtration rate. *Clin Lab*. 2014;60(10):1685-94.
47. Parazzini F, Cortinovis I, Bortolus R, Soliani A, Fedele L. Weight at birth of singleton live births between the 23rd and 27th week of gestation delivered vaginally or by cesarean section. *Acta Paediatr*. 1994 ;83(11):1206-8.
48. Visintin C, Muggleston MA, Almerie MQ, Nherera LM, James D, Walkinshaw S; Guideline Development Group. Management of hypertensive disorders during pregnancy: summary of NICE guidance. *BMJ*. 2010 ;341:c2207.
49. <http://www.acog.org/Womens-Health/Preeclampsia-and-Hypertension-in-Pregnancy> last accessed April 12th 2015
50. Nguyen R, Wilcox A. Terms in reproductive and perinatal epidemiology: 2. Perinatal terms. *J Epidemiol Community Health* 2005; 59: 1019–1021.
51. Gardosi J, Chang A, Kalyan B, Sahota D, Symonds EM. Customised antenatal growth charts. *Lancet*. 1992 ;339(8788):283-7.

52. Gardosi J. New definition of small for gestational age based on fetal growth potential. *Horm Res.* 2006;65 Suppl 3:15-8.
53. Norris T, Johnson W, Farrar D, Tuffnell D, Wright J, Cameron N. Small-for-gestational age and large-for-gestational age thresholds to predict infants at risk of adverse delivery and neonatal outcomes: are current charts adequate? An observational study from the Born in Bradford cohort. *BMJ Open.* 2015;5(3):e006743.
54. Tyson JE, Parikh NA, Langer J, Green C, Higgins RD; National Institute of Child Health and Human Development Neonatal Research Network. Intensive care for extreme prematurity--moving beyond gestational age. *N Engl J Med.* 2008;358:1672-81.
55. Machado Júnior LC, Passini Júnior R, Rodrigues Machado Rosa I. Late prematurity: a systematic review. *J Pediatr (Rio J).* 2014;90 :221-31.
56. Tong A, Jesudason S, Craig JC, Winkelmayer WC. Perspectives on pregnancy in women with chronic kidney disease: systematic review of qualitative studies. *Nephrol Dial Transplant.* 2015 ;30(4):652-61.
57. Tong A, Brown MA, Winkelmayer WC, Craig JC, Jesudason S. Perspectives on Pregnancy in Women With CKD: A Semistructured Interview Study. *Am J Kidney Dis.* 2015 ;66(6):951-61.
58. Bulmer JN. Immune aspects of pathology of the placental bed contributing to pregnancy pathology. *Baillieres Clin Obstet Gynaecol.* 1992 Sep;6(3):461-88.
59. Matthiesen L, Berg G, Ernerudh J, Ekerfelt C, Jonsson Y, Sharma S. Immunology of preeclampsia. *Chem Immunol Allergy.* 2005;89:49-61.

60. Rusterholz C, Hahn S, Holzgreve W. Role of placentally produced inflammatory and regulatory cytokines in pregnancy and the etiology of preeclampsia. *Semin Immunopathol.* 2007 ;29(2):151-62.
61. Rolfo A, Attini R, Nuzzo AM, Piazzese A, Parisi S, Ferraresi M, et al. Chronic kidney disease may be differentially diagnosed from preeclampsia by serum biomarkers. *Kidney Int.* 2013 ;83(1):177-81.
62. Anonymous. Pregnancy and renal disease. *Lancet.* 1975 ;2(7939):801-2.
63. Stratta P, Canavese C, Quaglia M. Pregnancy in patients with kidney disease. *J Nephrol.* 2006 ;19(2):135-43.
64. Wiles KS, Bramham K, Vais A, Harding KR, Chowdhury P, Taylor CJ, Nelson-Piercy C. Pre-pregnancy counselling for women with chronic kidney disease: a retrospective analysis of nine years' experience. *BMC Nephrol.* 2015 ;16:28.
65. EBPG Expert Group on Renal Transplantation. European best practice guidelines for renal transplantation. Section IV: Long-term management of the transplant recipient. IV.10. Pregnancy in renal transplant recipients. *Nephrol Dial Transplant* 2002; 17 (suppl 4): S50-5.
66. Linee Guida della Società Italiana di Nefrologia: Rene e Gravidanza. <http://www.sin-italia.org>.
67. Stratta P, Canavese C, Giacchino F, Mesiano P, Quaglia M, Rossetti M. Pregnancy in kidney transplantation: satisfactory outcomes and harsh realities. *J Nephrol.* 2003;16(6):792-806.

68. Hladunewich MA, Hou S, Odutayo A, Cornelis T, Pierratos A, Goldstein M, et al. Intensive hemodialysis associates with improved pregnancy outcomes: a Canadian and United States cohort comparison. *J Am Soc Nephrol*. 2014 ;25(5):1103-9.
69. Piccoli GB, Cabiddu G, Daidone G, et al. Italian Study Group “Kidney and Pregnancy”. The children of dialysis: live-born babies from on-dialysis mothers in Italy--an epidemiological perspective comparing dialysis, kidney transplantation and the overall population. *Nephrol Dial Transplant*. 2014 ;29(8):1578-86.
70. Hildebrand AM, Liu K, Shariff SZ, Ray JG, Sontrop JM, Clark WF, Hladunewich MA, Garg AX. Characteristics and Outcomes of AKI Treated with Dialysis during Pregnancy and the Postpartum Period. *J Am Soc Nephrol*. 2015.
71. Jesudason S, Grace BS, McDonald SP. Pregnancy outcomes according to dialysis commencing before or after conception in women with ESRD. *Clin J Am Soc Nephrol*. 2014 ;9(1):143-9.
72. Schimmel MS, Bromiker R, Hammerman C, Chertman L, Ioscovich A, Granovsky-Grisaru S, Samueloff A, Elstein D. The effects of maternal age and parity on maternal and neonatal outcome. *Arch Gynecol Obstet*. 2015 ;291(4):793-8.
73. Laopaiboon M, Lumbiganon P, Intarut N, , et al; WHO Multicountry Survey on Maternal Newborn Health Research Network. Advanced maternal age and pregnancy outcomes: a multicountry assessment. *BJOG*. 2014 ;121 Suppl 1:49-56.

74. Gera M, Slezak JM, Rule AD, Larson TS, Stegall MD, Cosio FG. Assessment of changes in kidney allograft function using creatinine-based estimates of glomerular filtration rate. *Am J Transplant.* 2007 ;7(4):880-7.
75. Buron F, Hadj-Aissa A, Dubourg L, Morelon E, Steghens JP, Ducher M, Fauvel JP. Estimating glomerular filtration rate in kidney transplant recipients: performance over time of four creatinine-based formulas. *Transplantation.* 2011;92(9):1005-11.
76. Ibrahim HN, Rogers T, Tello A, Matas A. The performance of three serum creatinine-based formulas in estimating GFR in former kidney donors. *Am J Transplant.* 2006 ;6(6):1479-85.

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

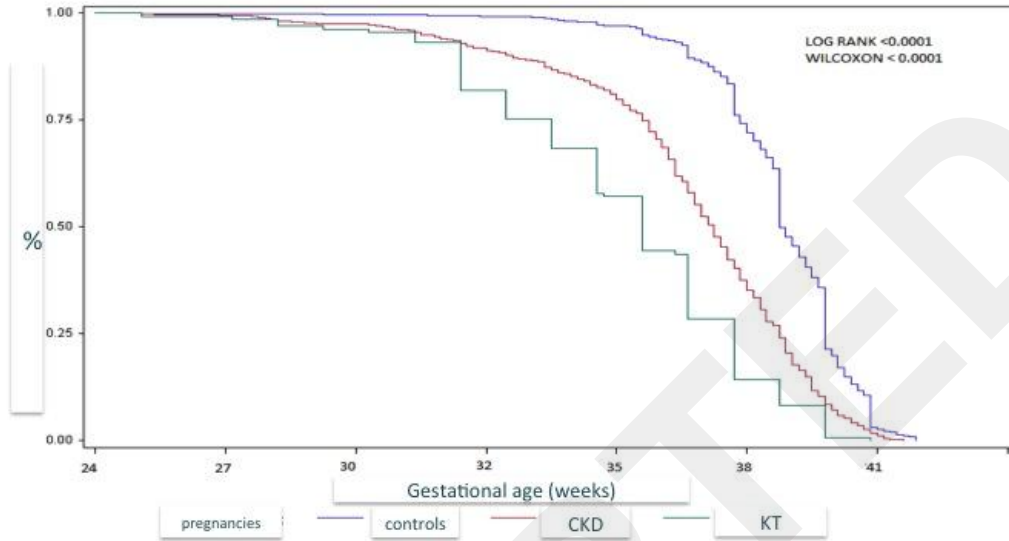


Figure 2

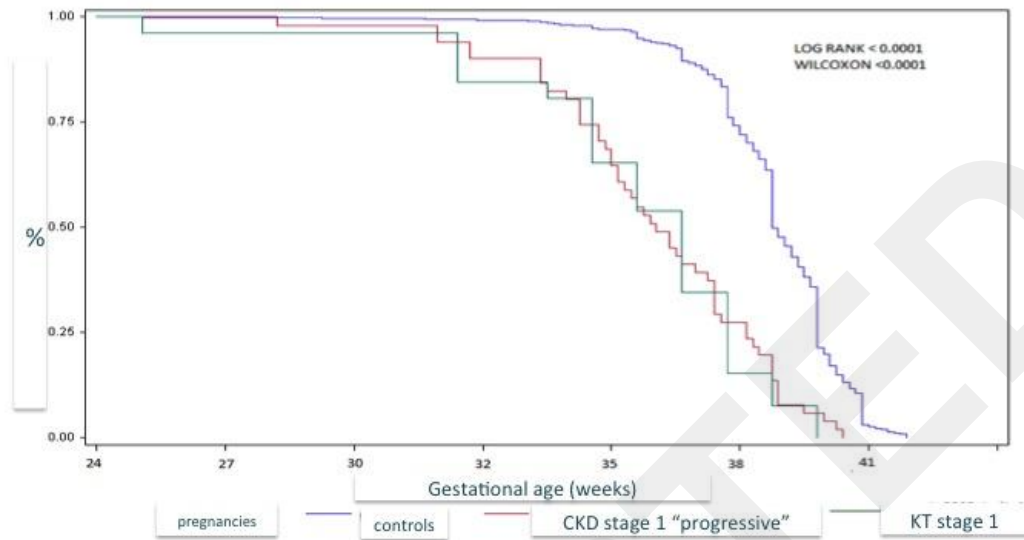


Figure 3

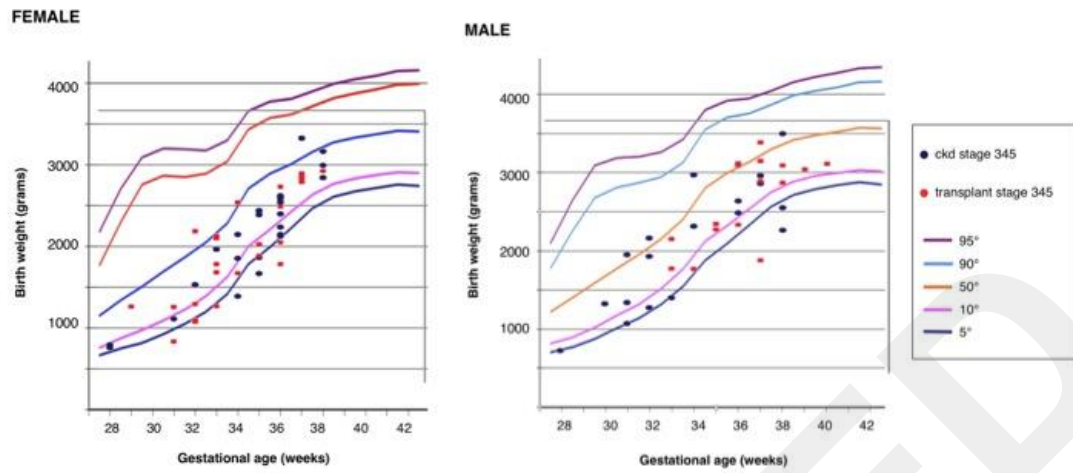


Figure 4

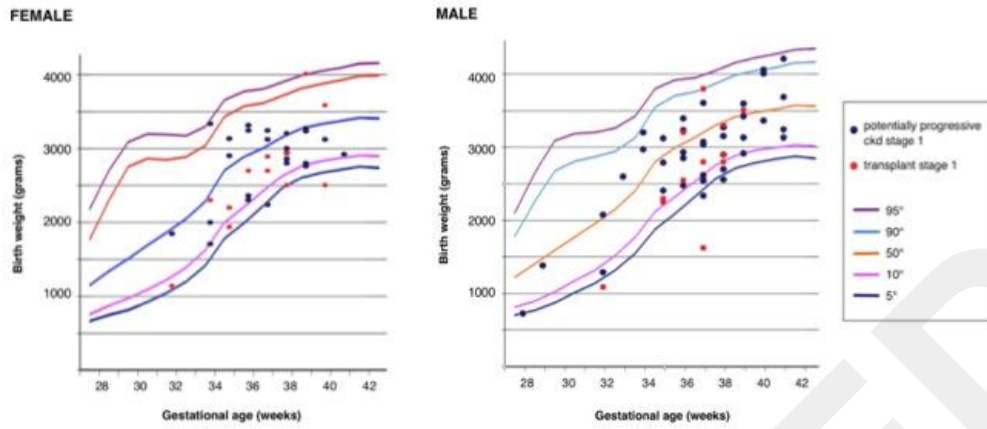


Table 1. Baseline characteristics of the study population: singletons, live-born deliveries

	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%)	
Interstitial diseases, including previous APN n (%)	9 (7.4%)	254 (41.6%)	<0.001
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%)	
CKD stage 2 n (%)	52 (43.0%)	87 (14.3%)	<0.001
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 calcineurin 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
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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.

ACCEPTED

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

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<10 th 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)	Stage 1 (25)	Stage 2 (52)	Stages 3-5 (42)
	N (%)	N (%)	N (%)	N (%)
Drug frequency				
<i>Steroid</i>	108 (90.0)	24 (96.0)	42 (80.8)	42 (97.7)
<i>CyA</i>	62 (51.7)	4 (16.09)	30 (57.7)	28 (65.1)
<i>Tacrolimus</i>	49 (40.8)	18 (72.0)	18 (34.6)	13 (30.2)
<i>AZA</i>	42 (35.0)	7 (28.0)	21 (40.4)	14 (32.6)
Drug combination frequency				
<i>Steroid alone</i>	2 (1.7)	1 (4.0)	1 (1.9)	-
<i>CyA alone</i>	1 (0.8)	-	1 (1.9)	-
<i>Tacrolimus alone</i>	1 (0.8)	-	1 (1.9)	-
<i>Steroid + CyA</i>	42 (35.0)	3 (12.0)	19 (36.5)	20 (46.5)
<i>Steroid + CyA + AZA</i>	14 (11.7)	1 (4.0)	6 (11.5)	7 (16.3)
<i>Cya + Aza</i>	5 (4.2)	-	4 (7.7)	1 (2.3)
<i>Steroid + Tacrolimus</i>	32 (26.7)	14 (53.8)	9 (17.3)	9 (20.9)
<i>Steroid + Tacrolimus +AZA</i>	11 (9.2)	3 (12.0)	4 (7.7)	4 (9.3)
<i>Tacrolimus + AZA</i>	5 (4.2)	1 (4.0)	4 (7.7)	
<i>Steroid + AZA</i>	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<10 th 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)