Nephrol Dial Transplant (2016) 31: 1957–1965
doi: 10.1093/ndt/gfw232
Advance Access publication 5 July 2016

Pregnancy outcomes after kidney graft in Italy: are the changes over time the result of different therapies or of different policies? A nationwide survey (1978–2013)

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ABSTRACT

Background. Kidney transplantation is the treatment of choice to restore fertility to women on renal replacement therapy. Over time, immunosuppressive, support therapies and approaches towards high-risk pregnancies have changed. The aim of this study was to analyse maternal–foetal outcomes in two cohorts of transplanted women who delivered a live-born baby in Italy in 1978–2013, dichotomized into delivery before and after January 2000.
Methods. A survey involving all the Italian transplant centres was carried out, gathering data on all pregnancies recorded since the start of activity at each centre; the estimated nationwide coverage was 75%. Data on cause of ESRD, dialysis, living/cadaveric transplantation, drug therapy, comorbidity, and the main maternal–foetal outcomes were recorded and reviewed. Data were compared with a low-risk cohort of pregnancies from two large Italian centres (2000–14; Torino and Cagliari Observational Study cohort).
Results. The database consists of 222 pregnancies with live-born babies after transplantation (83 before 2000 and 139 in 2000–13; 68 and 121 with baseline and birth data, respectively), and 1418 low-risk controls. The age of the patients significantly increased over time (1978–99: age 30.7 ± 3.7 versus 34.1 ± 3.7 in 2000–13; $P < 0.001$). Azathioprine, steroids and cyclosporine A were the main drugs employed in the first time period, while tacrolimus emerged in the second. The prevalence of early preterm babies increased from 13.4% in the first to 27.1% in the second period ($P = 0.049$), while late-preterm babies non-significantly decreased (38.8 versus 33.1%), thus leaving the prevalence of all preterm babies almost unchanged (52.2 and 60.2%; $P = 0.372$). Babies below the 5th percentile decreased over time (22.2 versus 9.6%; $P = 0.036$). In spite of high prematurity rates, no neonatal deaths

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occurred after 2000. The results in kidney transplant patients are significantly different from controls both considering all cases [preterm delivery: 57.3 versus 6.3%; early preterm: 22.2 versus 0.9%; small for gestational age (SGA): 14 versus 4.5%; $P < 0.001$] and considering only transplant patients with normal kidney function [preterm delivery: 35 versus 6.3%; early preterm: 10 versus 0.9%; SGA: 23.7 versus 4.5% ($P < 0.001$); risks increase across CKD stages]. Kidney function remained stable in most of the patients up to 6 months after delivery. Multiple regression analysis performed on the transplant cohort highlights a higher risk of preterm delivery in later CKD stages, an increase in preterm delivery and a decrease in SGA across periods.

Conclusions. Pregnancy after transplantation has a higher risk of adverse outcomes compared with the general population. Over time, the incidence of SGA babies decreased while the incidence of 'early preterm' babies increased. Although acknowledging the differences in therapy (cyclosporine versus tacrolimus) and in maternal age (significantly increased), the decrease in SGA and the increase in prematurity may be explained by an obstetric policy favouring earlier delivery against the risk of foetal growth restriction.

ORIGINAL ARTICLE

BACKGROUND

Kidney transplantation is frequently cited as the best way to restore fertility in a woman with severe CKD or on renal replacement therapy (RRT) [1–6]. However, in spite of decades of clinical experience, several problems remain unsolved, and counselling may still be difficult, given also the important differences in culture and in clinical management all over the world [5, 7–13]. Despite the availability of large databases, systematic reviews and guidelines, the need for new data as underlined by an editorial in 2010 is still felt [14].

Kidney transplantation and obstetric care are fields undergoing continuous evolution, and these changes may be relevant for interpretation of results that are mainly based on large, historical databases/registries or on single-centre series often encompassing several decades [15–20]. A recent, large systematic review of 50 papers from 25 countries highlighted some of the limitations of the present evidence, including patient overlap between studies; unmeasured, confounding differences in classification criteria, in particular for pre-eclampsia, baseline and pregnancy-induced hypertension; and selection and/or reporting biases mainly linked to the fact that most of the registries are voluntary [21]. Only 6 papers of the 50 analysed provided information on at least 100 pregnancies, thus underlining the need for gathering further large patient series [21].

In many western countries, the age of women undertaking pregnancy has progressively increased and the advances in maternal–foetal medicine have anticipated timing of a 'viable' delivery, easing the way to pregnancies in chronic diseases at high risk for preterm delivery and low birthweight [22–26]. High-risk pregnancies are thus increasing in several conditions, including CKD and dialysis, reaching previously unmet targets while presenting new challenges [27–30]. Chronic dialysis is one of the fields in which the advances are most dramatic, not only in terms of the incidence of live-born babies, but also with regard to the reduction in severe prematurity, in particular with the new long dialysis approaches [28].

According to two recent studies from almost opposite regions of the world (Italy and Australia), the probability of giving birth to a live-born baby is between 10 and 20% for a kidney graft patient as compared to the general population (in turn about 10 times higher as compared to dialysis) [31, 32]. While pregnancies are increasing in dialysis patients, the advances in transplantation have probably affected fertility and pregnancy-related outcomes less, and both are still less favourable as compared with the overall population. However, few studies are specifically addressed to these issues and, in particular, the differences occurring over time, with specific regard to the obstetric policy have never been extensively analysed [18, 22, 33–35]. An analysis of the observed changes could provide an additional key for interpretation of the available evidence, potentially adding to our knowledge on the reasons why maternal–foetal outcomes are still different with regard to low-risk pregnancies [21, 36].

This multicentre, nationwide collaborative study was designed to analyse the changes in maternal–foetal outcomes of pregnancies after kidney transplantation that have taken place since the start of kidney transplantation in Italy (1978–2013).

MATERIALS AND METHODS

Study design and source of data

The present study was planned in the context of the activities of the study group 'Kidney and Pregnancy' of the Italian Society of Nephrology in collaboration with the study group on kidney transplantation.

In the absence of a national registry gathering data on pregnancy after renal transplantation, the present analysis was based on a survey involving all the Italian transplant centres (37 centres, all of which are public; 24 answered).

The coverage of the transplant population was estimated at ~60% in the period prior to 2000 and at ~80% between 2000 and 2013. In the latter period, >95% of the patients were transplanted in Italian centres, and most of them were grafted at the nearest regional centre. The coverage has increased since the previous nationwide study that focused on pregnancy after dialysis [31].

Collected data

The following information was selected: code, centre, date of birth, date of RRT start, type of kidney disease, gestational age, birthweight, preterm delivery, small for gestational age (SGA), follow-up of the mother [functioning graft, on dialysis, dead (in the case of death, date and cause death)] and of the child. Functional data [serum creatinine, GFR (calculated according to the Chronic Kidney Disease Epidemiology Collaboration) were gathered at the start of pregnancy, at 20 weeks, at delivery and 6 months after delivery; blood pressure was also recorded at the same intervals. Proteinuria had not been systematically collected in the clinical charts, unless significantly increased, and was therefore not included in the original database.

At birth, data concerning Apgar score, weight, sex, centile (according to Parazzini charts) and malformations were

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collected. The main maternal problems in pregnancy were also recorded as free text.

Since the study period was very long (1978–December 2013), early pregnancy losses were collected in the database but were not included in the present analysis in order to reduce the reporting bias; similar considerations apply to miscarriages after the 24th gestational week, which were collected but not included in the analysis, which focused on live-born babies whose data are less subject to reporting biases.

Definitions

Hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg or antihypertensive therapy; patients on antihypertensive therapy prior to conception were included even when antihypertensive therapy was discontinued in pregnancy.

Due to the high prevalence of missing data on proteinuria at baseline, and to the difficulties in defining pre-eclampsia (PE) or 'superimposed PE' in the context of pre-existing kidney disease, we did not include pre-eclampsia as an outcome in this study [36, 37].

A newborn was defined as SGA when the birthweight was below the 5th or 10th centile according to the Italian birthweight references that were used most often throughout the study period (Parazzini charts) [38].

Preterm delivery was defined as delivery before 37 completed weeks of gestational age, 'early' preterm deliveries were defined as deliveries before 34 completed weeks and extreme preterm delivery was defined as delivery before the 28th completed gestational week [39–42].

Control group

The control group consisted of low-risk pregnancies recruited in two Italian Units (Torino and Cagliari), and data were updated on 31 March 2015. This is an update of the Torino Cagliari Observational Study (TOCOS) cohort, which can be referred to for further details [43]. Low-risk cases are defined as pregnancies occurring in the absence of hypertension, obesity, diabetes, CKD, cardiovascular diseases or any other disease or condition potentially affecting pregnancy outcomes.

We chose for comparison 1421 patients (including 3 intrauterine deaths and 1418 singleton live-born deliveries) from among 1484 low-risk singleton pregnancies (after excluding 39 miscarriages and 24 patients lost to follow-up).

Statistical analysis

A descriptive analysis was performed as appropriate (mean and standard deviation for parametric data and median and range for non-parametric data). Paired *t*-test, chi-square test, Fisher's test, Kruskal–Wallis test, Mann–Whitney *U* test, analysis of variance and *t*-test with Bonferroni correction were used where indicated for comparisons between cases and controls and among groups. Significance was set at <0.05.

Multiple regression analysis was performed considering the outcomes (i.e. preterm delivery, early preterm delivery, SGA baby) and the following covariates: age, dichotomized at the median (33 years), period of graft (dichotomized at 2000), CKD stage at start of pregnancy (1–2 versus 3 and 1 versus 2–3) and hypertension at start of pregnancy (SPSS version 18.0 for Windows; SPSS, Chicago IL, USA).

Kaplan–Meier analysis was performed as time-to-event analysis, starting the observation at 24 weeks (previous deliveries were considered miscarriages) and continuing until the date of delivery. The analysis was performed as implemented on SAS 9.2 (SAS Institute, Cary, NC, USA). Differences were assessed by log-rank and Wilcoxson tests.

Ethical issues

The observational study protocol was performed in the context of the institutional activities of the Study Group on Kidney and Pregnancy of the Italian Society of Nephrology. The study was approved by the ethics committee of 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).

RESULTS

Baseline data

Overall, excluding abortions (before the 24th gestational week: 4 cases), 219 pregnancies were reported (79 in 1978–99 and 136 in 2000–12). By also ruling out subjects for whom kidney function data concerning the first 12 weeks of pregnancy (11 cases before and 15 cases after 2000) were not available, and intrauterine deaths (1 case), 189 live-born babies were selected for the present analysis: 68 who were born between 1978 and 1999 and 121 between 2000 and 2013.

Maternal age significantly increased over time (in the first period, median age was 30.7 ± 3.7 years versus 34.1 ± 3.7 in the second period; P < 0.001); kidney function was similar in both periods (median serum creatinine 1.05 and 1.07, respectively, with roughly half of the cases in stage 2 CKD in both periods), as was the prevalence of the main kidney diseases. Approximately half of the patients had baseline hypertension, with a non-significant increase from the first to the second period.

Overall, 17.5% of the patients had received a living donor graft, which was more frequently the case in the first period than in the second, albeit non-significantly (Table 1).

Azathioprine, steroids and cyclosporine A were the main drugs employed in the first period, while tacrolimus emerged in the second. In the first period, about one-fourth of the patients were on calcineurin-free regimens versus 7.5% in the second; steroids were used in all patients in the first period and in 90% in the second (Table 1).

Main maternal–foetal outcomes

Caesarean sections were almost the rule in this population, even if a non-significant trend towards a reduction was observed (in parallel to what was observed in the overall population in Italy [44]) (Table 2).

The overall prevalence of preterm babies (<37 gestational weeks) was not significantly different in the two periods (52.2 and 60.2%; P: ns), while the increase in early preterm delivery was significant (13.4 and 27.1%; P = 0.049) (Table 2). Conversely, the incidence of SGA babies below the 5th centile significantly

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Table 1. Baseline characteristics of the study population: singleton live-born deliveries (with available baseline and birth data)

	KT 1978–1999	KT 2000–2013	P-value before versus after 2000	All KT
Pregnancies, *n*	68	121		189
Age at pregnancy (years)	30.7 ± 3.7	34.1 ± 3.7	<0.001	32.8 ± 4.1
Glomerular, *n* (%)	25 (36.8)	62 (51.2)	0.078	87 (46)
Diabetic nephropathy, *n* (%)	2 (2.9)	4 (3.3)	0.768	6 (3.2)
Interstitial, *n* (%)	8 (11.8)	9 (7.4)	0.464	17(9)
ADPKD, *n* (%)	1 (0.8)	3 (2.5)	0.949	4 (2.1)
Stage 1, *n* (%)	14 (20.6)	26 (21.5)	0.487	40 (21.2)
Stage 2, *n* (%)	36 (52.9)	52 (43)		88 (46.6)
Stage 3, *n* (%)	18 (26.5)	42 (34.7)		60 (31.7)
Stages 4–5, *n* (%)	0	1 (0.8)		1 (0.5)
sCr (before or first updating)	1.05 (0.6–1.8)	1.07 (0.6–2.4)	0.993	1.07 (0.6–2.4)
Hypertension at referral, *n* (%)	29 (42.6)	67 (55.4)	0.127	96 (50.8)
Pre-pregnancy follow-up				
Median (min–max)	37.5 (0–192)	27.5 (0–194)	0.198	28 (0.194)
Pre-emptive, *n* (%)	2 (2.9)	6 (5)	0.780	8 (4.2)
Living donor KT, *n* (%)	15 (22.1)	18 (14.9)	0.294	33 (17.5)
Treatment with CyA, *n* (%)	50 (74.6)	62 (51.7)	0.004	112 (59.9)
Treatment with tacrolimus, *n* (%)	1 (1.5)	49 (40.8)	<0.001	50 (26.7)
No calcineurin inhibitors, *n* (%)	16/67 (23.9)	9/120 (7.5)	0.003	25/187 (13.4)
Treatment with steroids, *n* (%)	67/67 (100)	108/120 (90)	0.018	175/187 (93.6)
Months between KT and pregnancy, median (min–max)	52 (5–178)	62 (14–278)	0.086	59 (5–278)

1418 low-risk controls; age 31.2 ± 5.6 years (P < 0.001 versus transplantation).
ADPKD: autosomic dominant polycystic kidney disease; KT: kidney transplantation; CyA: cyclosporine A; sCr: serum creatinine; min: minimum; max: maximum. Pre-pregnancy: follow-up on dialysis before renal transplant (months of dialysis). Pre-post: pregnancy with delivery before or after 2000.

Table 2. Deliveries according to period of analysis: all cases, stage 1 only versus low-risk controls

	KT 1978–1999	KT 2000–2013	P-values before versusafter 2000	KT all cases	Controls	P-values, all KT low-riskcontrols
Kidney transplantation: all stages versus controls						
Pregnancies, *n*	68	121	–	189	1418	
Age at pregnancy (years)	30.71 ± 3.72	34.06 ± 3.73	<0.001	32.85 ± 4.05	31.2 ± 5.6	<0.001
Caesarean section	60/67 (89.6%)	95/121 (79.2%)	0.108	155/187 (82.9%)	379/1418 (26.7%)	<0.001
Gestational week	36.15 ± 2.63	35.32 ± 2.97	0.060	35.62 ± 2.88	39 ± 1.7	<0.001
Preterm (<37 weeks)	35/67 (52.2%)	71/118 (60.2%)	0.372	106/185 (57.3%)	89/1418 (6.3%)	<0.001
Early preterm (<34 weeks)	9/67 (13.4%)	32/118 (27.1%)	0.049	41/185 (22.2%)	13/1418 (0.9%)	<0.001
Extreme preterm (<28 weeks)	0	2/118 (1.7%)	0.535	2/185 (1.1%)	2/1418 (0.1%)	0.068
Weight at birth (g)	2458.38 ± 547	2399.61 ± 686	0.530	2420 ± 640	3232 ± 476	<0.001
SGA <10% (Parazzini)	19/63 (30.2%)	24/115 (20.9%)	0.230	43/178 (24.2%)	157/1413 (11.1%)	<0.001
SGA <5% (Parazzini)	14/63 (22.2%)	11/115 (9.6%)	0.036	25/178 (14%)	63/1413 (4.5%)	<0.001
Kidney transplantation: stage 1 versus controls						
Pregnancies, *n*	14	26		40	1418	
Age at pregnancy (years)	30.2 ± 2.9	33.4 ± 4.4	0.019	31.24 ± 5.6	31.2 ± 5.6	0.126
Caesarean section	11/14 (78.6%)	19/26 (73.1%)	0.999	30/40 (75%)	379/1418 (26.7%)	<0.001
Gestational week	37.86 ± 1.5	36 ± 3.2	0.047	36.65 ± 2.8	39 ± 1.7	<0.001
Preterm (<37 weeks)	2/14 (14.3%)	12/26 (46.2%)	0.081	14/40 (35%)	89/1418 (6.3%)	<0.001
Early preterm (<34 weeks)	0	4/26 (15.4%)	0.278	4/40 (10%)	13/1418 (0.9%)	<0.001
Extreme preterm (<28 weeks)	0	1/26 (3.8%)	1.000	1/40 (2.5%)	2/1418 (0.1%)	0.080
Birthweight (g)	2706 ± 406	2573.6 ± 810	0.582	2619 ± 695	3232 ± 476	<0.001
SGA <10% (Parazzini)	6/13 (46.2%)	6/25 (24%)	0.055	12/38 (31.6%)	157/1413 (11.1%)	<0.001
SGA <5% (Parazzini)	5/13 (38.5%)	4/25 (16%)	0.026	9/38 (23.7%)	63/1413 (4.5%)	<0.001

Parazzini: growth curves according to Parazzini *et al.* [38]; KT: kidney transplantation.

decreased over time in the two time periods (22.2 versus 9.6%; P = 0.036). As a consequence of increased prematurity but decreased SGA, birthweight was not significantly different in the two periods.

As expected, most of the outcomes differ significantly with respect to the low-risk controls (Table 2); the most important differences were observed for prematurity, in particular for early preterm delivery (22.2 versus 0.9%; P < 0.001) and for SGA babies (<5th percentile: 14 versus 4.5%). The only exception is extreme preterm delivery (1.1 versus 0.1%, although not reaching statistical significance). The differences maintain a high statistical significance for all the previous items, even when considering only stage 1 patients versus controls (Table 2).

The results observed across CKD stages are reported in Table 3. Of note, the duration of pregnancy decreased and

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the risk of prematurity increased across CKD stages, while the prevalence of SGA babies did not vary significantly (Table 3).

A decrease in kidney function from the first to the last update in pregnancy, leading to a 'stage shift' from a lower to a higher CKD stage, was recorded overall in ∼18% of the cases in both periods (18.5 versus 18%; P: ns). One intrauterine death was reported in the transplant group and three in the low-risk population; in the second period, none of the babies died in the first month of life.

Kidney function 1 year after delivery

Table 4 reports the functional data of the transplanted women 6 months and 1 year after delivery. None of the women died in the first year after delivery and only one started dialysis within 1 year (age 29 years; baseline disease: glomerulonephritis, hypertensive at the start of pregnancy, serum creatinine 1.5 mg/dL at the 20th gestational week and 3.4 mg/dL at the end of pregnancy; she delivered a female baby at 32 gestational weeks, adequate for gestational age; she died of a cerebral accident 2 years after delivery).

Within the limits of retrospective collections, the data suggest that kidney transplant patients who start pregnancy in CKD stages 2–3 do not necessarily undergo worsening of renal function either during pregnancy (Table 3) or after delivery (Table 4).

Logistic regression and time to delivery analysis

Logistic regression analysis, undertaken for the most important outcomes, confirms the importance of the classic elements associated with pregnancy outcomes in CKD patients, i.e. being in stages 2–5 bears a 3-fold risk for preterm delivery as compared with stage 1 CKD, the presence of non-significant increases in the risk of being SGA and of prematurity, a correlation that becomes significant in the combined outcome.

Interestingly, the second study period is associated with a higher risk of early preterm birth and a lower risk of delivering an SGA baby (below the 5th centile). The difference depending on the study period is offset if we consider combined outcomes by merging data for preterm delivery and SGA babies (Table 5).

The relationship between time of delivery, birthweight and study period is graphically depicted in Figure 1. Follow-up starts at 24 weeks (due to the exclusion of abortions); the relevant difference between the curves is for the period between 31 and 36 weeks. However, statistical significance is not reached, although it is borderline by Wilcoxon's test, which is more sensitive to 'geometric' variations of the curves.

Figures 2 and 3 report the birthweight and growth curves at delivery in male and female newborns in the same period: the figures suggest a different policy towards delivery in the first period (more small babies with older gestational age) as compared to the second period (babies are delivered before becoming growth restricted).

DISCUSSION

Pregnancy after kidney transplantation is proof of success, but it is not devoid of risks; patient counselling is essential [5, 7–13].

Table 3. Pregnancy-related outcomes across CKD stages

	Stage 1			Stage 2			Stages 3–5		
	KT 1978–1999	KT 2000–2013	P-value, before and after 2000	KT 1978–1999	KT 2000–2013	P-value, before and after 2000	KT 1978–1999	KT 2000–2013	P-value, before and after 2000
Pregnancies, *n*	14	26		35	51		18	43	
Age (years)	30.2 ± 2.9	33.4 ± 4.4	0.019	30.81 ± 3.8	33.63 ± 3.6	0.001	30.89 ± 4.1	34.56 ± 3	<0.001
Caesarean section	11 (78.6%)	19 (73.1%)	1.0	32 (91.4%)	39 (76.5%)	0.088	17 (94.4%)	37 (86%)	0.662
Gestational week	37.86 ± 1.5	36 ± 3.2	0.047	36.29 ± 2.3	35.24 ± 3.2	0.563	34.56	35	0.563
Preterm (<37 weeks)	2 (14.3%)	12 (46.2%)	0.081	20 (57.1%)	31 (60.8%)	0.824	13 (72.2%)	28 (68.3%)	1.0
Early preterm (<34 weeks)	0	4 (15.4%)	0.278	3 (8.6%)	14 (27.5%)	0.052	6 (33.3%)	14 (34.1%)	1.0
Extreme preterm (<28 weeks)	0	1 (3.8%)	1.0	0	1 (2%)	1.0	0	1 (3.8%)	1.0
Birthweight (g)	2706 ± 406	2573.6 ± 810	0.582	2497 ± 553	2454 ± 610	0.744	2173.75 ± 536	2229.17 ± 672	0.769
SGA <10% (Parazzini)	6/13 (46.2%)	6/25 (24%)	0.055	9/34 (26.5%)	8/50 (16%)	0.277	4/16 (25%)	10/40 (25%)	1.0
SGA <5% (Parazzini)	5/13 (38.5%)	4/25 (16%)	0.026	5/34 (14.7%)	4/50 (8%)	0.475	4/16 (25%)	3/40 (7.5%)	0.094
CKD stage shift	4/13 (28.6%)	6/19 (31.6%)	1.0	8/35 (22.9%)	9/38 (23.7%)	1.0	0/16	1/32 (3.1%)	1.0

Parazzini: growth curves according to Parazzini *et al.* [38]; KT: kidney transplantation.

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Table 4. Kidney functional data over pregnancy and up to 12 months after delivery

	KT 1978–1999	KT 2000–2013	All cases	P-value, before and after 2000
Patients, *n*	68	121	189	
sCr before pregnancy	1.05 (0.51–1.8)	1.07 (0.6–2.4)	1.07 (0.51–2.4)	0.993
sCr 20 weeks	0.9 (0.5–1.9)	0.9 (0.4–2.3)	0.9 (0.4–2.3)	0.642
	N = 53	*N* = 93	*N* = 146	
sCr 6 months after delivery	1.0 (0.4–2.1)	1.0 (0.6–2.5)	1.0 (0.4–2.5)	0.749
	N = 55	*N* = 89	*N* = 144	
sCr 1 year after delivery	1.1 (0.4–2.1)	1.1 (0.5–2.6)	1.1 (0.4–2.6)	0.543
	N = 61	*N* = 102	*N* = 163	
eGFR CKD-EPI before pregnancy	72 (36–129)	71 (25–123)	71 (25–129)	0.473
eGFR CKD-EPI 20 weeks	86 (36–132)	80 (27–133)	82 (27–133)	0.238
	N = 53	*N* = 93	*N* = 146	
eGFR CKD-EPI 6 months after delivery	73 (31–142)	71 (24–123)	71.5 (24–142)	0.425
	N = 55	*N* = 89	*N* = 144	
eGFR CKD-EPI 1 year after delivery	67 (31–141)	66.5 (22–133)	67 (22–141)	0.997
	N = 61	*N* = 102	*N* = 163	
CKD-EPI stages before pregnancy				
Stage 1	14/68 (20.6%)	26/121 (21.5%)	40/189 (21.2%)	0.487
Stage 2	36/68 (52.9%)	52/121 (43.0%)	88/189 (46.6%)	
Stage 3	18/68 (26.5%)	42/121 (34.7%)	60/189 (31.7%)	
Stages 4–5	–	1/121 (0.8%)	1/189 (0.5%)	
CKD-EPI stages 1 year after delivery				
Stage 1	7/61 (11.5%)	17/102 (16.7%)	24/163 (14.7%)	0.188
Stage 2	36/61 (59.0%)	48/102 (47.1%)	84/163 (51.5%)	
Stage 3	18/61 (29.5%)	32/102 (31.4%)	50/163 (30.7%)	
Stages 4–5	–	5/102 (4.9%)	5/163 (3.1%)	

Data expressed as median (minimum-maximum); sCr: serum creatinine; eGFR: estimated glomerular filtration rate; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; KT: kidney transplantation.

In 1978–99: information on outcomes available in 45 cases. Dialysis was restarted by 25 women after delivery (none within the first year); 6 mothers died (none in the first year after delivery). In 2000–13: dialysis was restarted by 9 women after delivery (one only within the first year); 2 mothers died (1 after dialysis start, 2 years after delivery, and one 3 years after delivery).

Table 5. Multiple regression results: KT patients in the different CKD stages (ORs and CIs)

	Pretermdelivery <34 weeks	Preterm delivery <37 weeks	SGA <10th centile	SGA <5th centile	Preterm delivery <37 weeks and/or SGA <10th centile	Preterm delivery <34 weeks and/or SGA <5th centile
KT CKD stage 1	1	1	1	1	1	1
KT CKD stages 2–5	**3.2 (1.06–9.72)**	**3.39 (1.61–7.12)**	0.65 (0.29–1.46)	0.42 (0.16–1.09)	1.94 (0.93–4.06)	1.34 (0.62–2.86)
Normal BP	1	1	1	1	1	1
High BP	1.07 (0.52–2.19)	1.45 (0.79–2.66)	1.78 (0.87–3.66)	1.68 (0.68–4.15)	**2.00 (1.05–3.80)**	1.37 (0.74–2.55)
KT 1978–1999	1	1	1	1	1	1
KT 2000–2013	**2.45 (1.07–5.59)**	1.36 (0.73–2.56)	0.55 (0.27–1.14)	**0.33 (0.14–0.80)**	0.88 (0.46–1.72)	0.98 (0.52–1.86)

1: reference; Parazzini: growth curves according to Parazzini *et al.* [38]; KT: kidney transplantation; BP: blood pressure.

However, even if the history of pregnancy after kidney transplantation is very long, our knowledge is still incomplete [14, 21].

Available data share the limits of observational studies and come from a few large, mostly voluntary registries, and from many smaller more homogeneous series that are subject to a strong 'centre effect', also mirroring social, financial and medical differences [21]. Obstetric policies vary widely around the world, and this may be relevant in analysing the results [45–49].

In this context, the present study was undertaken to account for the lack of a systematic study in our country; it was initially aimed at censusing the 'children of transplantation', analogous to a previous study on the 'children of dialysis', and was further developed to try to understand the differences that were reported over two macro periods (1978–99 and 2000–13) [31].

Over time, patients' age significantly increased, while diseases causing uraemia, kidney function at start of pregnancy and the prevalence of hypertension remained unchanged, possibly reflecting the lack of substantial changes in the young female population starting RRT in Italy and/or a policy of conservative counselling for pregnancy (good renal function, no hypertension) [8, 9, 11, 12, 50, 51]. In keeping with what is observed in the overall transplanted population in our country, in the new millennium therapy has shifted from cyclosporine to tacrolimus, steroid use decreased while calcineurin use increased, living donations decreased and there has been an increase in pre-emptive transplantation (Table 1) [3, 19, 21].

As expected, pregnancy outcomes of women with kidney transplantation differ significantly from those of low-risk pregnancies, and the differences are significant even when considering patients with normal kidney function (stage 1 patients) (Table 2). In keeping with what is observed in the non-transplanted CKD population, there is a significant relationship between CKD stages

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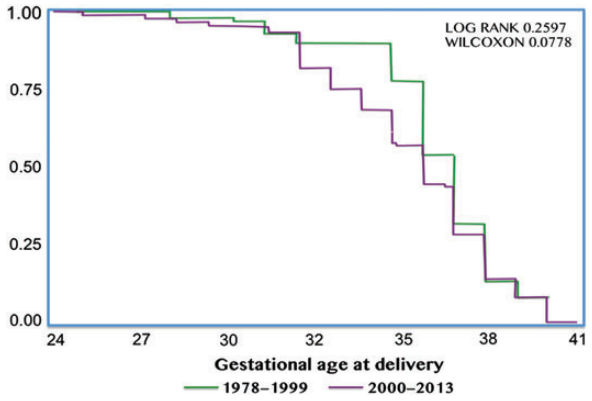

FIGURE 1: Time to event (delivery) analysis, from 24 to 41 gestational weeks (live-born deliveries, singletons).

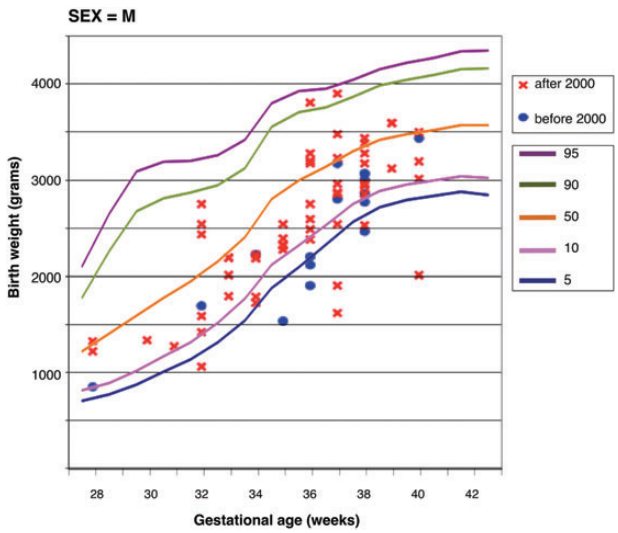

FIGURE 2: Birth weight and growth curves at delivery in male newborns.

and pregnancy-related outcomes, with an overall increase in adverse outcomes with increasing CKD stage (Table 3).

Of note, kidney function worsening may be less frequent than previously reported since 'stage shifts' from pre-pregnancy to 1 year after delivery occurred in only ~20% of patients (Table 4).

The main point of interest in our study is highlights the two main differences in pregnancy-related outcomes over time: the incidence of 'early preterm' deliveries almost doubled over time, but conversely, the incidence of SGA age babies decreased by almost 70% in the second period. Interestingly, when these merge into a combined outcome, either 'general' (preterm delivery and/or SGA <10th centile) or 'severe' (early preterm and/or SGA <5th centile), no differences over time are observed, thus suggesting that the two outcomes are interrelated and an increase in one compensates for a decrease in the other (Tables 2, 3 and 5).

This interpretation may be supported by the changes in obstetric policies that have been made in recent decades [52–54]. Our hypothesis is that the greater attention to utero-placental flow and foetal growth has led to earlier delivery in the presence of initial growth impairment, even before the baby becomes

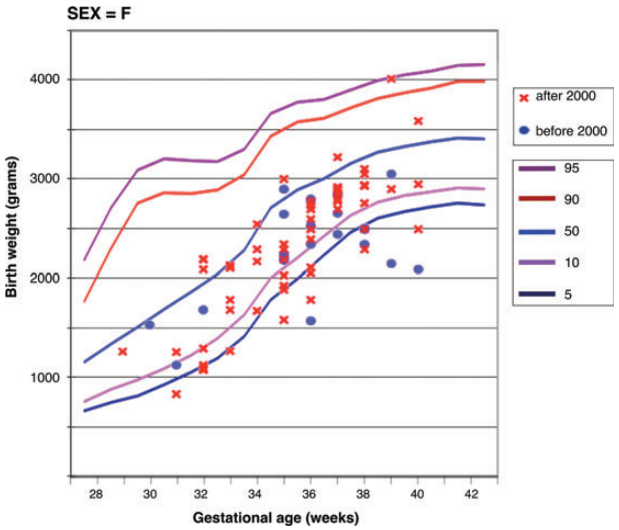

FIGURE 3: Birth weight and growth curves at delivery in female newborns.

SGA (Figures 1–3). In keeping with this hypothesis, the difference is mainly observed at 32–35 weeks (during which the obstetric choices play a major role) after having reached the first major developmental goals (28–32 gestational weeks; Figure 1) [55]. The main impact of this finding is to suggest contextualizing data employed for counselling to similar periods of time and clinical settings, with particular attention on obstetric policy, which is particularly important in modulating the results of late preterm babies.

The main strength of our study, which is the first comprehensive Italian survey, is that it evaluates ~35 years of observation, the novelty is that it compares results over time and the advantage is that it relates data with a dataset from a large, low-risk population. However, it has several weaknesses: it is retrospective and therefore some important outcomes, such as early foetal loss, were not evaluable; it has a large, but incomplete nationwide enrolment (coverage of ~60% in the first period and 80% in the second period); some important information such as proteinuria before and during pregnancy and long-term follow-up of the babies is not available. These biases are, however, shared by most of the largest datasets, which are derived from voluntary registries, and share the same problem of incomplete coverage [21].

While acknowledging these limitations, the study group hopes that this first analysis might be the basis for a systematic, prospective evaluation of pregnancies after kidney transplantation in Italy.

CONCLUSIONS

The main features of women delivering a live-born baby after kidney transplantation have changed over time, with a significant increase in maternal age and a shift from cyclosporine to tacrolimus in the new millennium.

In spite of high prematurity rates, no perinatal deaths were reported, thus confirming an overall good prognosis in

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pregnancies that continue after the first 24 weeks of gestation. In both periods, graft loss did not appear to increase after delivery.

In this context, the incidence of 'early preterm' deliveries almost doubled over time and was counterbalanced by a corresponding decrease in SGA babies. We therefore suggest that increased obstetric attention may have led to earlier delivery of babies whose *in utero* growth slowed. These variations should be kept in mind when comparing data obtained in different periods and in different settings and underline the need for careful contextualization of the results that are used when counselling our patients. Further prospective studies are needed to highlight the pathophysiological mechanisms that are the basis of the observed results, and to compare different populations, including not only low-risk controls, but also other CKD stages and phases, observed in similar settings and over comparable periods of time.

ACKNOWLEDGEMENT

The first two authors and the last three authors equally contributed to the study.

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CONFLICT OF INTEREST STATEMENT

The results presented in this paper have not been published previously in whole or part, except in abstract format.

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Received for publication: 14.11.2015; Accepted in revised form: 2.5.2016

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