ORIGINAL ARTICLE

Pregnancy outcomes in simultaneous pancreas and kidney transplant recipients: a national French survey study

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SUMMARY

Simultaneous pancreas and kidney transplantation (SPK) is currently the best therapeutic option for patients with type 1 diabetes and terminal renal failure. Renal transplantation restores fertility enabling women to pursue pregnancies. However, scarcity of available data on pregnancy outcomes in SPK impedes fair medical counseling. Medical files of all pregnancies that lasted ≥3 months among recipients of functional SPK performed between 1990 and 2015 in France were retrospectively analyzed. Twenty-six pregnancies in 22 SPK recipients were identified. Main maternal complications included gestational hypertension (53.8%) and infections (50%). Cesarean section was performed in 73% of cases. Overall fetal survival was 92.6% with a mean gestational age of 34.2 ± 3 weeks. Four children (16.7% of live births) had a birth weight <10th percentile. Endocrine pancreas graft function remained stable during pregnancy. An acute kidney rejection occurred in two patients, one of which resulting in graft loss. Kidney and pancreas graft survival was, respectively, 96% and 100% at 1 year postconception and did not differ from controls. Pregnancy in SPK is feasible, but patients should be informed of the risks for the fetus, the mother, and the grafts. Planning of pregnancy in SPK women is key to allow a personalized multidisciplinary monitoring, which represents the most straightforward approach to optimize outcomes.

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Introduction

Fertility decreases in parallel with renal function in chronic kidney disease [1].

Renal transplantation partially restores women fertility, which may enable to pursue pregnancies [2]. Data available from registries have shown that pregnancy is feasible in solid organ transplant recipients, with a slightly higher maternal and fetal complication rates, but without significant impact on long-term graft function [3,4]. Despite these reassuring data, a recent study reported that one-third of transplanted women were still actively being counseled against pregnancy by one or more care providers [5].

Simultaneous pancreas and kidney transplantation (SPK) is recognized as the best therapeutic option for patients with type 1 diabetes complicated with end-stage renal failure [6]. In addition to liberating patients from exogenous insulin therapy, which contributes to improve their quality of life [7], several lines of evidence suggest that pancreas transplantation has also long-term beneficial effects both on patient survival [8,9] and on the course of diabetic complications (including retinopathy [10], neuropathy [11], and cardiovascular morbi-mortality [12]).

Type 1 diabetes affects young patients: Half of the cases are diagnosed before the age of 20 with evolution toward end-stage renal failure within a 15- to 20-year interval [13]. Women eligible to SPK transplantation may therefore expect to become pregnant. Because SPK is much less frequent than other solid organ transplantation (i.e., 3232 kidney transplantations were performed in France in 2014, compared to 70 SPK [14]), only few isolated case reports and very small series of pregnancies in SPK recipients have been published so far. This lack of data represents an important hurdle for a fair counseling of SPK women enquiring about the safety of a pregnancy.

We therefore decided to undertake a retrospective study among all French transplant centers to better define maternal, fetal, and graft outcomes in SPK recipients. Due to the retrospective nature of the study and the high risk of under-reporting of spontaneous early miscarriage, neither fertility nor incidence of miscarriage before 3 months was analyzed in this study.

Materials and methods

Study population

The electronic database (CRISTAL) of the national agency in charge of organizing solid organ transplantation in France (Agence de la Biomédecine; https://www.agence-biomedecine.fr/) was interrogated to retrieve all the cases of childbearing age women that received a SPK between January 1990 and December 2013 in France. Among a total of 265 recipients, 22 women with a functional pancreas grafts (i.e., insulin independent) became pregnant and were retrospectively enrolled in the present study. Because patients could easily miss spontaneous miscarriage before 3 months and due to the retrospective nature of the study, we considered the risk of under-reporting these events too high and therefore decided to exclude them from the study.

A control cohort was constructed with the remaining 243 childbearing age women that received a SPK over the same period but did not carried out a pregnancy. Given the facts that (i) in our cohort the median delay between SPK transplantation and time of conception was 28 months, (ii) in our study, survival of the renal and pancreas graft was analyzed from the time of conception, we decided to include in the control cohort only the 156 SPK recipients with at least 28 months of follow-up (this time point being considered as the starting point for survival analyses for the controls).

Data collection and definitions

In accordance with the French law on descriptive research, this study received approval by the CNIL (Comité Informatique et Liberté) on December 16, 2016 (No. 2018255).

Patients' data were obtained either from CRISTAL national electronic database or from medical files of transplantation and obstetric departments. Clinical data, including maternal demography (age at conception, duration of dialysis, and diabetes before transplantation), obstetrical complications (preeclampsia, Cesarean section), fetal outcome (birth weight, gestational age, intrauterine growth retardation (IUGR)) and biological parameters including creatininemia, proteinuria, fasting blood glucose, insulinemia, C-peptide, lipasemia, glycated hemoglobin, were collected from hospital records for all patients. The biological data were collected at each trimester of pregnancy, 3 months before and 1 year after delivery, as well as at last follow-up. Glomerular filtration rate was estimated (eGFR) using the MDRD formula.

Graft loss was defined as resuming of dialysis for kidney and of exogenous insulin for pancreas, as well as retransplantation and death with functioning grafts. Intrauterine growth retardation (IUGR) was defined as a fetus weight inferior to the 10th percentile and severe IUGR when the fetus growth was inferior to the third percentile, according to AUDIPOG chart [15]. Stillbirth

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was defined as the occurrence of intrauterine fetal death after 24 weeks of gestation. Neonatal death was defined as a live infant dying within 28 days after delivery. Prematurity was defined as a live birth before the 37th week of gestation. Pregnancy was considered successful if it resulted in a live infant discharged from the hospital.

Statistical analysis

Continuous variables were expressed as mean and SD, and categorical variables were expressed absolute and relative frequencies. Survival curves were estimated with the Kaplan–Meier method and compared between groups with the log-rank test.

Paired *t*-tests were used to compare evolutions of estimated glomerular filtration rate, proteinuria, HbA1c, and fasting C-peptide for each patient during pregnancy (GRAPH PAD PRISM 6; Graph Pad Software Inc., La Jolla, CA, USA). A *P*-value of <0.05 was considered statistically significant.

Results

Maternal and graft characteristics at conception

Over the study period, 27 children were born from 26 pregnancies of 22 SPK recipients in France (one mother delivered twins and three had more than one pregnancy).

The main maternal and transplant characteristics at conception are summarized in Table 1.

Most pancreatic grafts were anastomosed end to side to the recipient common iliac artery (13/20, 65%, two missing data) and to the inferior vena cava (10/22, 45%). Exocrine secretions were drained via the donor duodenum anastomosed to recipient small bowel, except for one graft, which was anastomosed directly to the bladder.

Seventeen women (65.4%) were primiparous, and 45% of them had experienced at least one miscarriage prior to described pregnancy. There was no pregnancy secondary to *in vitro* fertilization. Median maternal age at conception was 34.1 ± 4.0 years (range 25–43 years). Duration of diabetes and time on dialysis before transplantation was, respectively, 20 ± 4.9 years (range from 10 to 30 years) and 7.1 ± 9.3 months (range from 0 to 30 months). Median time between transplantation and pregnancy was 28 months (range 5–108 months).

Four patients (18.2%) had a past medical history of biopsy-proven acute transplant rejection before pregnancy: Two women received steroids pulses for a cellular rejection 2 and 7 years before conception (pregnancy #9 et #26); one required anti-thymocyte globulin for a steroid-resistant cellular rejection of the pancreas 15 months before conception (pregnancy #10). The remaining patient was diagnosed with mixed rejection of the kidney and treated with three pulses of corticosteroids, six plasma exchanges and anti-CD20 mAb (monoclonal antibody) therapy 19 months before pregnancy (pregnancy #22). Donor-specific antibodies disappeared after treatment and were not detected in the circulation at conception.

Table 1. Characteristics of the study population at conception.

	n (%) or mean ± SD
Patients	
Number of SPK patients	22 (100)
Duration of diabetes (years)	20 ± 4.9
Duration of dialysis (months)	7.1 ± 9.3
Preemptive transplantation	10 (45.4%)
Donor age (years)	31 ± 11
Number of HLA mismatches(A, B, DR, DQ)	5.8 ± 1.3
Pancreas cold ischemia time (h)	10.7 ± 2.2
Pancreas transplantation type	
SPK	20 (91)
PAK	2 (9)
Pregnancies	
Number of pregnancies	26 (100)
HBP before pregnancy	7 (26.9)
Age at conception (year)	34.1 ± 4.0
Transplant to conception (months)	38.3 ± 25
Primiparous	17 (65.4)
History of miscarriage prior to described pregnancy	10 (45)

HLA for Human Leukocyte Antigen SPK for Simultaneous Pancreas and Kidney transplantation. PAK for Pancreas after Kidney transplantation. HBP for High Blood Pressure.

Changes in immunosuppressive regimen

The vast majority of patients (*n* = 20, 90.9%) received anti-thymocyte globulin for induction therapy. The remaining two received, respectively, anti-CD3 and anti-CD25 mAb.

Modulation of maintenance immunosuppression regimen due to pregnancy is summarized in Fig. 1a. Most pregnancies (*n* = 24, 92.3%) occurred in patients on calcineurin inhibitor-based therapy: 22 (84.6%) on tacrolimus and two (7.7%) on cyclosporine. In this case, the treatment was not modified. Mean tacrolimus trough level before pregnancy was 8.0 ± 3.1 μg/l and remained unchanged over the follow-up period

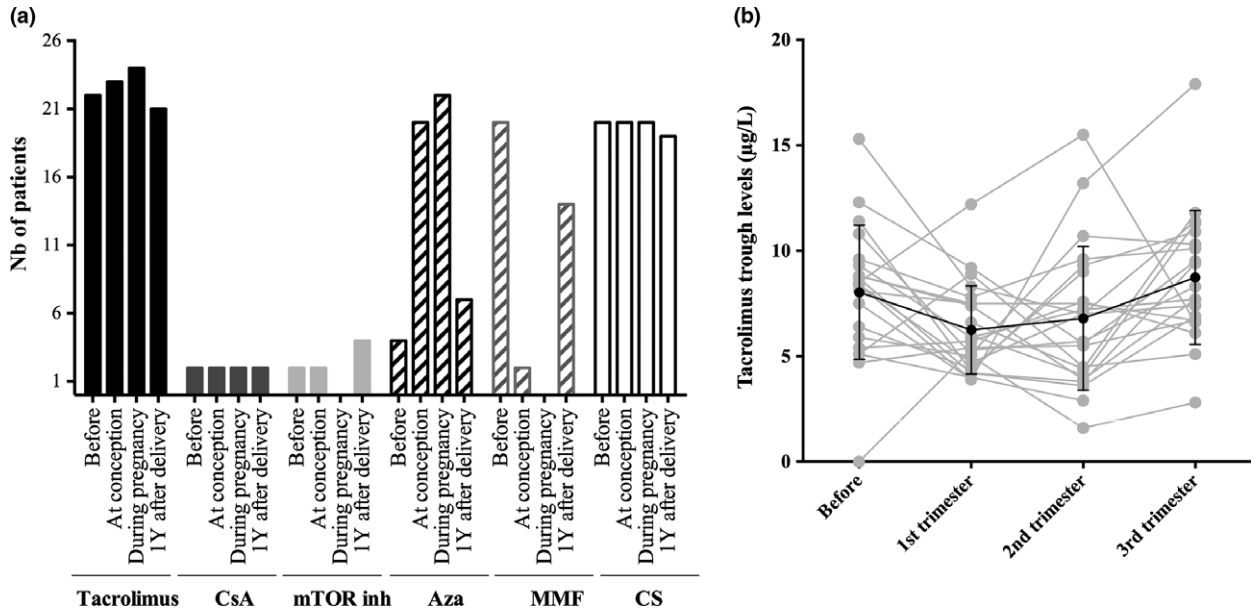

Figure 1 Changes in immunosuppressive regimen. (a) Histogram detailing the number of patients on each immunosuppressive drug before pregnancy, at conception (whether the pregnancy was planned with the physician or not), during pregnancy (indicates the regimen adapted by the physician) and 1 year after delivery. CsA, cyclosporin A; m-TOR inh, m-TOR inhibitor; AZA, azathioprine; MMF, mycophenolate mofetil; CS, corticosteroids. (b) Evolution of tacrolimus trough levels during pregnancy in SPK recipients. Gray circles indicate individual values. Black circles are mean ± SD.

(Fig. 1b). Two pregnancies occurred in patients on mTOR inhibitor-based (calcineurin inhibitor free) regimen. Tacrolimus was introduced as a replacement of mTOR inhibitors in these two patients (pregnancies #15 et #17). However, due to lack of planning and delayed diagnosis, the switch was only made 6 weeks after the onset for both pregnancies.

Two patients (7.7%) had no antiproliferative agent (neither azathioprine nor mycophenolate mofetil) in their immunosuppressive regimen before, during, and after pregnancy. Four patients (15.4%) were on azathioprine before conception and remained on this drug during pregnancy. The remaining 20 cases were on mycophenolate mofetil (MMF) before pregnancy. In accordance with guidelines, MMF was stopped (n = 2, 7.7%) or switched for azathioprine (n = 16, 61.5%) before pregnancy. However, due to lack of planning, the switch for azathioprine was delayed in two cases (Pregnancy#15 and Pregnancy#17 that were also on mTOR inhibitor see above), which therefore remained on MMF for the first 6 weeks of gestation (Fig. 1a).

Maternal outcomes

All 22 mothers survived their pregnancies and were alive at last follow-up. The courses of the 26 pregnancies are summarized in Table 2.

Table 2. Maternal outcomes.

Pregnancies	*n* (%) – total = 26
Gestational hypertension	14 (53.8)
Preeclampsia	12 (46.1)
HELLP syndrome	2 (7.7)
Infections	13 (50)
Urinary tract	9 (34.6)
Gastrointestinal tract	2 (7.7)
CMV	1 (3.8)
Pneumocystis	1 (3.8)
Renal BPAR	2 (7.7)
Cancer	1 (3.8)

HELLP for Hemolysis, elevated liver (enzymes), low platelet count.

BPAR for Biopsie Proven Acute Rejection

Cesarean section delivery was used in 19 (73%) of pregnancies. Only one procedure was complicated by a bladder wound and postpartum hemorrhage. The causes for Cesarean section were as follows: fetal heart rhythm abnormalities (1 case), uterine prerupture (1 case), but mostly gestational hypertension.

Gestational hypertension indeed occurred in 14 (53.8%) cases, from which 12 (46.1%) developed preeclampsia and 2 (7.7%) a HELLP syndrome. Of note, seven patients (31.8%) had hypertension before

conception (among them, six developed gestational hypertension).

One patient experienced EBV-related vulvar epidermoid carcinoma.

Infections occurred in 13 (50%) of all pregnancies. Nine patients experienced uncomplicated urinary tract infection (all treated with antibiotics), and two had a gastrointestinal infection (one Clostridium difficile colitis treated with metronidazole and one Campylobacter gastroenteritis with favorable outcome on symptomatic treatment). The two remaining patients had severe infectious complications leading to fetal death. The first experienced a CMV reactivation leading to chorio-amnionitis despite valganciclovir treatment. Premature rupture of membranes occurred at 20 weeks of gestation leading to fetal death. The second patient was diagnosed with pneumocystis pneumonia complicated with acute respiratory distress syndrome at the end of the second trimester of gestation. She was transferred in intensive care unit, intubated and treated with sulfamethoxazole–trimethoprine, corticosteroids, and noradrenaline. During resuscitation, she developed acute renal failure and immunosuppressive drugs had to be suspended. Three weeks later, while on recovery in the transplantation department, she suddenly delivered a 26-week-old baby, suffering from neurological malformations, who died an hour later.

Fetal outcomes

Fetal outcomes are summarized in Table 3.

Table 3. Fetal outcomes.

All births	*n* (%) – total = 27
Death	2 (7.4)
Death *in utero*	1 (3.7)
Neonatal death	1 (3.7)
Fetal malformation	2 (7.4)
Live births	25 (100)
Prematurity (<37 weeks)	20/25 (80)
Mild prematurity (32–37 weeks)	14 (56)
Significant prematurity (28–32 weeks)	4 (16)
Extreme prematurity (<28 weeks)	2 (8)
Mean gestational age (weeks)	
Mean ± SD	34.2 ± 3
Range	20–38
Mean birth weight (g, mean ± SD)*	2088 ± 680
Low birth weight (<2500 g)*	17/24 (70.8)
Very low birth weight (<1500 g)*	4/24 (16.7)
IUGR (<10th percentile)*	4/24 (16.7)

*Data missing for 1/25 live birth.

Fetal survival was 92.6%. Two children were lost due to maternal infectious complications (see details in the section above).

Among live births, 20 of 25 (80%) infants were preterm with a mean gestational age of 34.2 ± 3.0 weeks (range 26–38 weeks) (Fig. 2a).

Mean birth weight of live births was 2088 ± 680 g (range 530–3180 g). Sixteen of 24 (1 missing data) children (70.8%) had a low birth weight (<2500 g), among which four newborns (16%) had to be transferred to the neonatal intensive care unit. Prematurity was likely the main culprit for this finding because when birth weight was adjusted for the term of delivery, only 16.7% of cases were below the 10th percentile (i.e., the

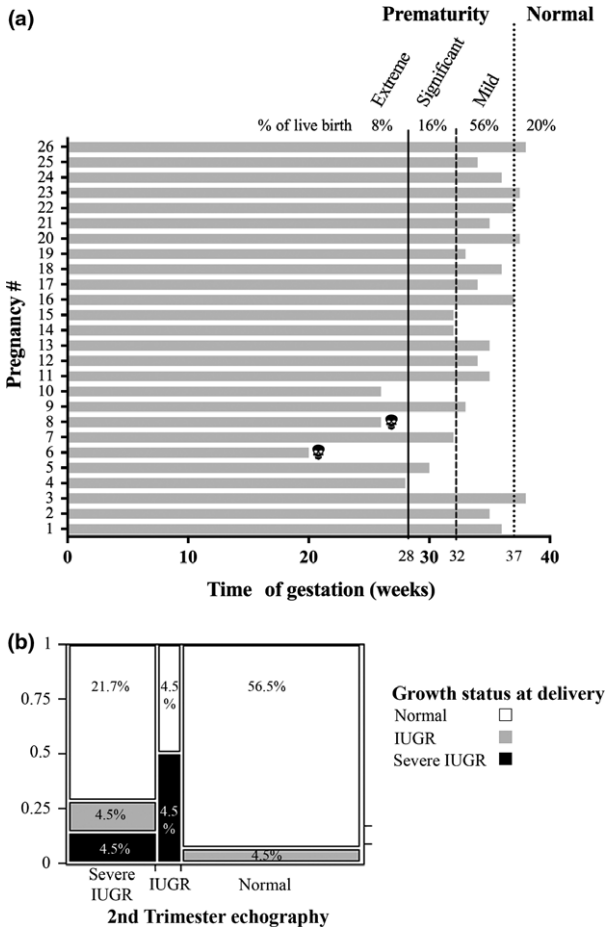

Figure 2 Term and fetal growth. (a) Histogram indicating the term of each of the 26 pregnancies. Limits for mild (37 weeks), significant (32 weeks) and extreme (28 weeks) prematurity are indicated, respectively, with a dotted line, a dashed line and a black line. The two fetal deaths are indicated with a symbol. (b) Contingency table indicating the evolution of 23 analyzable fetal growth between the second trimester of gestation (evaluated with echography, shown in x axis) and the delivery (color coded). Percentages of each possible evolution are indicated.

limit for IUGR). Figure 2b shows the details of fetal growth between the second trimester (evaluated with ultrasound) and the delivery. Interestingly, neither creatininemia, proteinuria, fasting glucose nor HbA1c levels before pregnancy were predictive of birth weight superior to the 10th percentile.

Four mothers breast-fed their infant (16% of live births).

Two fetal malformations were diagnosed (Table 3): one ventriculomegaly due to stenosis of the mesencephalic duct (pregnancy #8) and one congenital heart disease (common arterial trunk, associated with a possible pulmonary artery stenosis for pregnancy #15). The neurological malformation was possibly related to severe maternal infectious complication (pneumocystis). Because this neurological malformation was not compatible with life, a decision of therapeutic abortion was made but spontaneous abortion occurred before the procedure (at 26 weeks). The congenital heart disease occurred in a fetus exposed *in utero* to sirolimus and MMF for the first 6 weeks of pregnancy (pregnancy #15, see above). The baby underwent two neonatal surgical procedures and was alive at the last follow-up (32 months postdelivery).

Renal and pancreas graft outcomes

Survival of kidney and pancreas grafts was, respectively, 96% and 100% at 12 months and 72.7% and 68.7% at 84 months after conception (Fig. 3a and b). These results were not statistically different from what observed in the control cohort of childbearing age women transplanted with SPK over the same period but who did not carry out a pregnancy (Fig. 3a and b; log-rank tests, respectively, $P = 0.94$ and $P = 0.61$ for kidney and pancreas).

Two acute kidney rejections occurred among the 26 pregnancies. One patient (pregnancy #4) with low tacrolimus trough level (mean value 4 $\pm$ 1.6 ng/ml) developed an acute kidney failure 5 months after conception. Proteinuria and detection of donor-specific antibodies in the circulation led to perform a graft biopsy, which confirmed the diagnosis of acute antibody-mediated rejection. Despite anti-rejection therapy including high-dose steroids, six plasma exchanges and intravenous immunoglobulin for 6 months, she resumed hemodialysis at 24 weeks of gestation (Fig. 3a). At 27 weeks of gestation, she developed preeclampsia and delivered a baby of 990 g by Cesarean section at 28 weeks. The baby was transferred to the neonatal intensive care unit and survived with no sequelae. The mother remained on hemodialysis until she received a second kidney transplantation in July 2015. Pancreatic function remained stable over the follow-up period. The second patient (pregnancy #10) experienced an acute kidney failure at the end of the first trimester of gestation without proteinuria or DSA. Graft biopsy showed acute cellular rejection that was treated with three pulses of corticosteroids. Renal function stabilized ~eGFR 20 ml/min. A new biopsy performed 1 month after delivery showed persistence of borderline lesions and interstitial fibrosis/tubular atrophy grade II-III. Sixteen months after the delivery, chronic graft dysfunction led to her re-inscription on the kidney transplant waiting list. Pancreatic function remained stable over the follow-up period.

Five other patients experienced "nonimmune" acute kidney graft dysfunction episode during pregnancy. One patient (pregnancy #8) had an acute renal failure related to sepsis while on intensive care unit for treatment of a pneumocystis infection. Three mothers were diagnosed with functional renal failure due to either dehydration complicating infectious gastroenteritis (pregnancies #9 and #18), or acute calcineurin-inhibitor (CNI) overdose (pregnancy #11).

The remaining patient (pregnancy #15) had an acute renal failure of unknown cause (despite a biopsy of the graft), which spontaneously recovered.

Estimated glomerular filtration rate (MDRD) during first, second, and third trimester was not statistically different from baseline. However, eGFR value 1 year after delivery was significantly lower (63.81 $\pm$ 17.72 vs. 52.02 $\pm$ 17.34 ml/min, $P = 0.037$; Fig. 3c). Proteinuria was also statistically higher during the third trimester (0.11 $\pm$ 0.08 vs. 0.54 $\pm$ 0.70 g/24H, $P = 0.023$; Fig. 3d) and one-year postdelivery compared to baseline (0.11 $\pm$ 0.08 vs. 0.25 $\pm$ 0.15 g/24H, $P < 0.001$; Fig. 3d).

Pancreas graft function is notoriously complicated to evaluate. No pancreas graft biopsy was performed in any patient during all declared pregnancies.

Four patients (15.4%) developed reversible gestational diabetes (among which only one had HbA1c >6% before pregnancy). Regarding long-term outcomes, neither HbA1c (5.37 $\pm$ 0.64 vs. 5.45 $\pm$ 0.78%, $P = 0.64$; Fig. 3e) nor fasting C-peptide (1.28 $\pm$ 1.2 vs. 1.2 $\pm$ 0.46 mol/l, $P = 0.14$, Fig. 3f) worsens at 1-year postdelivery compared to baseline value.

Finally, regarding the risk for developing DSA (Donor Specific Antibody) due to pregnancy, in addition to patient #4, who was diagnosed with an acute antibody-mediated rejection at 5 months of pregnancy, two other patients of the cohort developed *de novo* DSA. Both patients had two pregnancies and develop DSA a long time after the second delivery. DSA appeared 3 years after the second delivery for the first patient, at a time when she was also diagnosed with

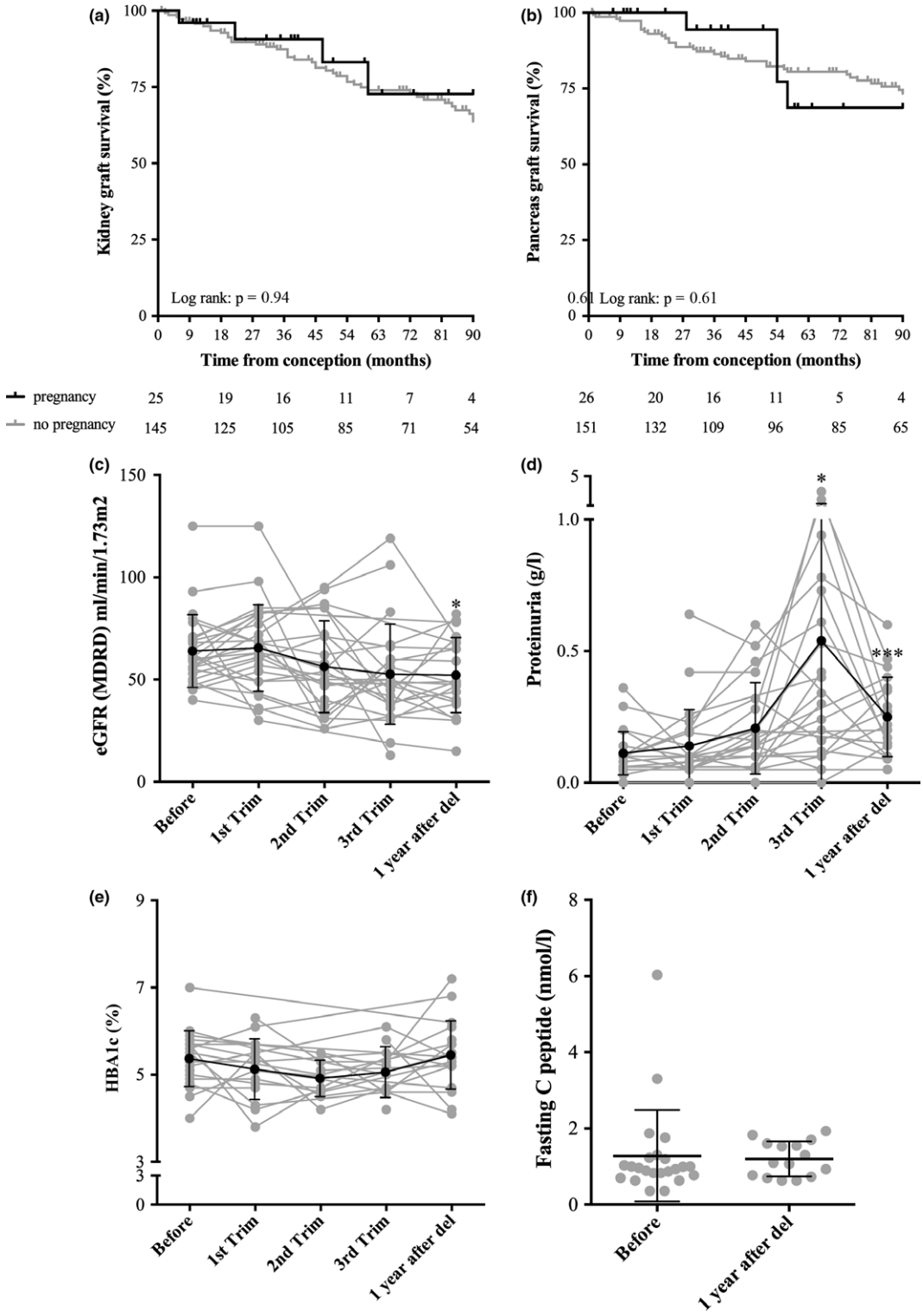

Figure 3 Renal and pancreas graft outcomes. Survival curves of, respectively, renal (a) and pancreas (b) graft are shown for simultaneous pancreas and kidney transplantation (SPK) women who carry a pregnancy (full line; survival is plotted from conception) and SPK women who did not carry a pregnancy over the same period (dashed line; survival is plotted from 28 months post-transplantation, the median delay between SPK transplantation and conception in the previous cohort). Evolution of, respectively, eGFR (c), proteinuria (d), and HbA1c (e) during pregnancy in SPK recipients. Gray circles indicate individual values. Black circles are mean ± SD. Comparison of serum fasting C-peptide values before pregnancy and 1 year after delivery (f). Gray circles indicate individual values. Black lines are mean ± SD. *P < 0.05; ***P < 0.001; Trim, trimester; del, delivery.

kidney transplant borderline rejection. She received three pulses of corticosteroids, and maintenance immunosuppressive regimen was switched from mTOR inhibitors to tacrolimus-based therapy. For the second patient, DSA were detected 22 months after the second delivery while kidney function was stable with no significant proteinuria.

Discussion

The present study, which reports 26 pregnancies in 22 patients, one of the largest cohort published so far [3,16–19], highlights that pregnancy outcomes are acceptable in SPK patients. Fetal survival rate was indeed 92.6%, a percentage significantly higher than the 69% live births rate recently reported by the 2015 NTPR (National Transplantation Pregnancy Registry) registry [20] for pregnancies in SPK patients between 1989 and 2015 (Table 4). This fetal prognosis remains, however, significantly lower compared to the general population in France (996/1000) [21], emphasizing the importance for planning and following carefully these high-risk pregnancies.

As expected, the incidence of low birth weight was high (70.8%). Prematurity likely represented the main cause for this problem in our cohort as the incidence of IUGR (defined after adjustment on term) was only 16.7%. Our cohort exhibited a 80% rate of preterm births, comparable to 2015 NTPR data [20] (Table 4). Prematurity, a known complication in SOT (Solid Organ Transplantation) recipients [20], is even more frequent in SPK [16,18,19] (Table 4). This difference could be related to the high incidence of gestational hypertension and preeclampsia observed in the "ex-diabetic" SPK population.

Infants born preterm are exposed to several complications, including respiratory distress syndrome, chronic lung disease, bowels disorders, compromised immune system, cardiovascular disorders, hearing and vision problems, and neurological injuries [22]. Unfortunately, follow-up data were lacking and long-term consequences of prematurity in children born from SPK mothers remain unknown.

Over the past years, the benefits of breast-feeding low birthweight and preterm infants have been demonstrated in the general population [23]. In our cohort, only four mothers breast-fed their infant. This low percentage is likely the consequence of the mindset of transplant community, who has concerns regarding immunosuppressive therapy toxicity on newborns. Recent studies have reported reassuring data demonstrating that excretion of immunosuppressive drugs in the milk is lower than through the placenta [24]. Breast-feeding seems therefore safe in transplanted mothers [25] and should be encouraged during the first 6 months [26] as long as maintenance immunosuppressive regimen does not include mycophenolate mofetil and m-TOR inhibitors.

Two children were diagnosed with severe malformations (7.7%), a proportion similar to what reported by Bar *et al.* [27] for renal transplantation. Of note, one of these fetal malformations occurred in a women who started her pregnancy without planning, which resulted in a delayed adjustment of her immunosuppressive regimen. MMF and m-TOR inhibitors need indeed to be replaced before conception to avoid their potential teratogenicity [28].

Table 4. Comparison between our cohort and data from NTPR registry

% or mean ± SD	Our SPK recipients *n* = 27 (%)	NTPR-SPK recipients* (*n* = 106)	NTPR-kidney recipients* (*n* = 1810)
Live births	24 (92.6)	69%	75%
Gestational hypertension	14 (53.8)	58%	49%
Preeclampsia	12 (46)	27%	30%
Gestational diabetes	4 (15.4)	3%	8%
Rejection during pregnancy	2 (7.7)	4.9%	0.8%
Gestational age (weeks)	34.2 ± 3	34.3 ± 3.1	35.9 ± 3.4
Preterm delivery(live births)	20/25 (80)	73%	51%
Birth weight (g)	2088 ± 680	2135 ± 706	2567 ± 766
Low birth weight (<2500 g)	17/24 (70.8)	62%	42%
Neonatal death	1 (3.7)	1.3%	1.6%
Cesarean section	19/26 (73)	69%	54%

g, grams.

*According to NTPR Annual Record 2015.

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The incidence of maternal complications was high. Besides infections, which occurred in half of cases, gestational hypertension was common in our cohort (53.8%), close to the reported 58% of hypertension treated in the 2015 NTPR cohort [20] (Table 4). This might be explained by confusing factors, which could lead to over-diagnosing preeclampsia in SPK recipients (i.e. pre-existing hypertension and proteinuria) [29]. Moreover, CNI can also increase acid uric level (one of the preeclampsia diagnosis criteria) [30]. Measurement of circulating angiogenic factors [31] might be helpful to monitor these high-risk pregnancies, but their predictive values for preeclampsia have not been evaluated in the transplanted population so far.

Four patients (15.4%) developed reversible gestational diabetes, an incidence similar to that encountered in the general population, which suggests that transplanted pancreas have sufficient functional reserve to meet the increased insulin demand associated with pregnancy [32].

Survival of kidney and pancreas grafts 1 year postconception were, respectively, 96% and 100% (Fig. 3a and b), similar to what observed in the control cohort of women transplanted with SPK over the same period in France but who did not carry a pregnancy (Fig. 3a and b). Despite the long interval between transplantation to conception (38.3 $\pm$ 25 months) and the stable preconception kidney function, two kidney acute rejections occurred during SPK pregnancies. These rejection episodes are described in the literature as being the consequence of the decrease of immunosuppressive drug trough levels resulting from the increased maternal blood volume [33]. We, however, did not observe significant reduction in tacrolimus trough levels during SPK pregnancies, probably due to the close monitoring of the drug level.

Increase in maternal blood volume is normally associated with a reduction in serum creatinine levels [34]. Serum creatinine remained stable in all pregnant women (data not shown), suggesting that renal graft function may worsen during pregnancy in diabetic patients of a SPK. This hypothesis is supported by the significantly decrease in eGFR at 1 year postdelivery, and the progressive increase in proteinuria during pregnancy, which persisted after delivery. These worrying findings were, however, not reported in previous studies [5,35,36] and we did not observe any deleterious impact of pregnancy on pancreas graft function. No SPK patient resumed insulin 1 year after delivery and the markers of pancreas graft endocrine function remained stable compared to baseline levels throughout follow-up (Fig. 3e and f).

Considering the risk for developing DSA after a pregnancy, only three patients from our cohort developed DSA during or after their pregnancy. For patient #4 who was diagnosed with acute antibody-mediated rejection at 5 months, one can consider that DSA appearance is related to her pregnancy and low immunosuppressive trough levels. For the remaining two patients, the long interval between pregnancy and DSA appearance does not support a direct role for pregnancy in DSA appearance.

Our study has several limitations: First, its design precluded the analysis of the fertility and the risk for early spontaneous abortion for SPK women; second its retrospective nature could have generated biases. In particular, it shall be noted that in order to deal with the potential immortal time bias when comparing graft outcomes of pregnant and nonpregnant SPK recipients, we artificially started the clock in nonpregnant recipients at the observed median time to pregnancy (Fig. 3a and f). Despite these limits, the description of maternal, fetal, and graft outcomes of one of the largest cohorts of pregnancies in SPK recipients still provides useful data for counseling of patients. Based on these data, we conclude that pregnancy in SPK recipients with stable graft functions is feasible but remains at high risk. Planning is key to allow a personalized multidisciplinary monitoring, which represents the most straightforward approach to optimize maternal, fetal, and graft outcomes.

Authorship

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Conflicts of interest

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