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LETTER TO THE EDITORS

Successful management of six pregnancies resulting in live births after simultaneous pancreas kidney transplantation: a single-center experience

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Apart from improving quality of life and long-term cardiovascular function, a successful simultaneous kidney pancreas transplantation (SPK) also contributes to restoration of fertility in female patients [1–4].

In contrast to multiple reported successful births following kidney transplantation, only few registry analyses and case reports regarding childbirth after SPK have been published to date [5–8].

We report on our single-center experience regarding the obstetric, maternal, and graft outcome in total six successful deliveries in four female SPK patients:

Of total 442 SPKs performed between 1979 and 2011, 166 (37.6%) were in females. Four of them (mean age of 32 at transplant) became pregnant for the first time at mean 55 months post-transplant and two of them again at mean 97 months. No *in vitro* fertilization was performed (Table 1).

Transplantation was performed according to standard techniques: The kidney was implanted into the left side (vascular anastomosis to the common/external iliac vessels), the pancreas through transperitoneal access with arterial anastomosis to the recipient common iliac artery and venous anastomosis to the external iliac vein, and in one patient each to the V. cava inferior and the V. mesenterica superior. The exocrine pancreas was drained by either duodenojejunostomy (three patients) or duodenocystostomy (one patient).

Secondary diabetic complications included one case of severe proliferative retinopathy with bilateral amaurosis, one case of successful laser coagulation controlled by split lamp, one severe peripheral angiopathy requiring amputation of one toe, and one asymptomatic noncritical coronary artery stenosis.

Maintenance immunosuppression consisted of tacrolimus and mycophenolate mofetil (MMF) after induction therapy with antithymocyte globulin. Steroids were discontinued during the first post-transplant year. In one patient, sirolimus was administered on a study protocol. In all prospectively planned pregnancies, immunosuppression was adapted preconception by converting MMF/sirolimus to azathioprine following reports of MMF being associated with a higher incidence of spontaneous abortion and congenital malformation in contrast to azathioprine being favorable in deliveries after kidney transplantation [1]. Tacrolimus (mean level 5.9 ng/ml) and azathioprine 1.0 mg/kg (rounded according to pills of 50 mg) remained unmodified during pregnancy.

All kidney and pancreas grafts were at stable function prior to conception (Table 1).

Three patients had no history of pregnancy, miscarriage or abortion, and one patient had one early abortion each before and post-transplant. Study data were recorded in an electronic database. Permission for analysis was given by the local ethics board. Statistics were performed using SPSS 15.0 IBM Deutschland GmbH, Ehningen, Germany.

Cesarean section was performed in all pregnancies at mean gestational week 32.8. Concerning pediatric course, all six babies were born without any congenital malformation corresponding to the report by Bar *et al.* [9], who found no statistically significant differences in neonatal malformations when comparing babies from untransplanted mothers and from renal-transplanted mothers. Our study group had a low birth weight (mean 1851 g) in coincidence with lower gestational age (according to the reports by Coscia *et al.*); two babies required respiratory support without subsequent pulmonary disorder or hypoxic damage ([8], Table 1). No gynecological complications in maternal course were observed.

Three women remained physically stable without deterioration of blood pressure, peripheral angiopathy, or retinopathy. No severe urinary tract infection or other bacterial/serious viral infection occurred, probably due to the relatively low-dosed immunosuppression, exact attention to hygiene standards and controlled fluid balances avoiding cystitis. The patient with a graft pancreaticocystostomy developed leukocyturia (within sterile bacterial

Table 1. Clinical characteristics of patients and children.

	All SPK $n = 442$	Delivery $n = 4$	Females <40 years $n = 91$	*P* value vs. all	*P* value vs. female <40 years
Age at transplant	41.5 (±9.3)	32.5 (±3.3)	32.1 (±5.0)	0.056	0.89
BMI at transplant kg/m^2	23.3 (±3.1)	22.8 (±0.6)	23.55 (±3.4)	0.79	0.71
Donor age	30.1 (±10.8)	28.7 (±12.2)	28.0 (±10.5)	0.80	0.89
HLA MM					
A and B	2.8 (±0.9)	2.3 (±1.0)	2.7 (±0.9)	0.23	0.37
DR	1.5 (±0.6)	1.8 (±0.5)	1.5 (±1.6)	0.34	0.33
DM1	96.8%	100%	100%	0.71	1.0
5-year graft survival (%)					
Pancreas	74.7	75.0	74.1	0.59	0.56
Kidney	87.5	75.0	89.5	0.34	0.51

	Patient 1		Patient 2	Patient 3	Patient 4	
Age at delivery	36	39	40	36	36	39
Prior to conception						
Creatinine (mg/dl)	1.2	1.0	0.8	0.9	2.4	2.6
Fasting glucose (mg/dl)	77	94	93	91	100	91
HbA1c (%)	5.3	5.5	5.9	not noted	4.9	5.5
C peptide (ng/l)	3.1	2.7	2.2	2.2	4.6	nn
TAC (ng/l)	4.3	4.1	6.0	7.4	8.0	nn
Antihypertensive drugs (*n*)	0	0	1	2	0	0
Delivery						
Cesarean section	Yes	Yes	Yes	Yes	Yes	Yes
Delivery (preg. week)	36	30	33	28	35	35
Birth weight (g)	2042	2019	1730	870	2060	2390
6 months postpartum						
Creatinine (mg/dl)	1.0	0.9	0.9	Dialysis	2.2	4.4
Fasting glucose (mg/dl)	95	93	69	Insulin requirement	90	87
HbA1c (%)	5.2	5.4	5.4	nn	5.2	5.3
C peptide (ng/l)	3.0	3.0	2.2	nn	nn	nn
TAC (ng/l)	8.9	5.6	5.7	nn	nn	4.5

Values expressed as mean (standard deviation) and number or %, where appropriate.
SPK, simultaneous pancreas kidney transplantation; DM1, Diabetes mellitus type I; y, year; f, females; vs, versus; BMI, body mass index; MM, mismatch; TAC, tacrolimus; n, number; nn, not noted; g, gram.

cultures), apparently due to chemical cystitis to the exocrine pancreas drainage. One case of mild nausea in the early gestational period was observed.

No patient breast-fed her infant in keeping with the gynecological recommendation that transport of traces of tacrolimus by breast milk be avoided.

In one patient, the maternal course was complicated: The 36-year-old woman with obesity, arterial hypertension, and asymptomatic coronary heart disease developed preeclampsia in gestational week 28, requiring urgent Cesarean section. The early postpartum course was complicated by CMV pneumonia and myocardial infarction, which were successfully treated. An immediate coronary angiography-proven critical stenosis was successfully revascularized by stent implantation. The lesson to be learned from this case is the importance of especially cautious, more frequent preconception cardiac monitoring in even young SPK patients planning pregnancy, in addition to standard post-transplant controls including ECG and echocardiography.

Analysis of the transplant course showed that no ureteral obstruction was observed in our patients at the frequent ultrasound controls, probably related to the transperitoneally positioned (retroperitonealized) kidney. In four pregnancies (in three patients), kidney and pancreas function remained stable without any oscillations until postpartum month 6 (Table 1).

In two patients, graft function deteriorated:

1. In the (above mentioned) 36-year-old patient, immediate postpartum renal dysfunction was suspected as a probable acute rejection episode, treated by pulsed steroids and followed by graft loss at day 18 postpartum. The renal biopsy showed interstitial fibrosis and tubular atrophy, but no acute rejection. Immunosuppression was minimized because of the CMV pneumonia. The pancreas graft was lost in the first month postpartum.

2. A 38-year-old woman with an uncomplicated first delivery had a strong desire for a second child despite medical warnings based on her elevated preconception serum creatinine >2.5 mg/dl. Serum creatinine increased to >4.4. mg/dl at postpartum month 6; the graft was lost in the second year with stable pancreas function. This experience confirms the recommendation that preconception serum creatinine levels be low to maintain stable renal function during pregnancy [1].

Our study group showed no acute puerperal rejection, probably due to the >20-month stable preconception graft function. This observation corresponds well with the probable allograft tolerance proposed by Ma *et al.* [10] in pregnant women, who are a complex chimera in maternal, fetal, and donor cell populations.

Concluding our data and published reports, we consider the risk of pregnancy in SPK patients to be elevated but manageable with very cautious gynecological, pediatric, cardiac, and transplant monitoring.

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