Pregnancy After Combined Pancreas-Kidney Transplantation

GUNNAR TYDÉN, CHRISTINA BRATTSTRÖM, ULLA BJÖRKMAN, RÜDIGER LANDGRAF, JÜRG BALTZER, GÜNTHER HILLEBRAND, WALTER LAND, ROY CALNE, I. GABRIELLE M. BRONS, JEAN-PAUL SQUIFFLET, JOELLY GHYSEN, AND GUY P.J. ALEXANDRE

Four successful cases of pregnancy after combined pancreas-kidney transplantation at four different centers are summarized. The techniques used for the pancreas transplantations were duct obstruction in one patient and enteric exocrine diversion in two patients; in all three patients the insulin delivery was to the systemic circulation. In one patient exocrine diversion was to the stomach and the vascular anastomosis to the splenic vessels, thus accomplishing portal insulin delivery. Immunosuppression consisted of cyclosporin and prednisolone in two patients; cyclosporin alone in one patient; and cyclosporin, azathioprine, and prednisolone in one patient. In all a cesarean section was performed, due to deteriorating renal function in two patients, a fall in fetal growth in one patient, and fear of inducing pancreas-graft pancreatitis during normal delivery in one patient. In all four women, perfect metabolic control was retained throughout the pregnancy, and despite the proximity of the pancreas graft to the growing uterus in three of the women, the pancreas grafts did not suffer any damage during the pregnancy. However, in one patient the pancreas graft was lost in acute rejection after delivery. This pancreas had functioned normally for 3 yr before this occasion. Of the offspring, one was completely normal, one had a bilateral cataract, and two were small for date. The latter two subsequently showed normal growth development. At follow-up at 3, 5, 7, and 28 mo, all kidney grafts and three of the pancreas grafts remained functional. We conclude that after combined pancreas-kidney transplantation, successful conception and pregnancy can be obtained. Despite reduced islet mass (segmental grafts), normal metabolic control can be retained throughout the pregnancy. However, the risks of complications related to kidney- or pancreas-graft function are considerable and must be emphasized in each case in which pregnancy is considered. *Diabetes* 38 (Suppl. 1): 43–45, 1989

From the Departments of Transplantation Surgery and Gynecology and Obstetrics, Karolinska Institute, Huddinge Hospital, Stockholm, Sweden; the Departments of Internal Medicine "Innenstadt," Gynecology and Obstetrics, and the Division of Transplant Surgery, Klinikum Grosshadern, University of Munich, Federal Republic of Germany; the Department of Surgery, Addenbrooke's Hospital, University of Cambridge, Cambridge, England, United Kingdom; and the Departments of Surgery and Gynecology and Obstetrics, Catholique University of Louvain, Brussels, Belgium.

Address correspondence and reprint requests to Gunnar Tydén, MD, Department of Transplantation Surgery, Huddinge Hospital, S-141 86 Huddinge, Sweden.

Successful conception and pregnancy in uremic women is extremely rare. However, after kidney transplantation, fertility is restored, and despite immunosuppression with cyclosporin and steroids, numerous successful pregnancies in transplanted women have been achieved (1). In diabetic women with end-stage nephropathy, kidney transplantation restores renal function, but the metabolic abnormalities of diabetes prevail, thereby drastically reducing the chances of a successful pregnancy (2). However, after a combined pancreas-kidney transplantation, the chances of a successful pregnancy are increased, although the pregnancy itself imposes a formidable challenge to the endocrine capacity of the pancreas graft. Nevertheless, after the first report on the successful outcome of a pregnancy in a recipient of pancreas-kidney transplantation (3), another three cases have accumulated, and the outcome of these four cases is summarized herein.

MATERIALS AND METHODS

Relevant patient data and immunosuppressive therapy at the time of conception are given in Table 1. The individual data are summarized in the following case reports.

Case 1 (Munich). In August 1983, a 32-yr-old woman who had suffered insulin-dependent diabetes mellitus (IDDM) since age 9 yr was subjected to pancreas-kidney transplantation due to end-stage diabetic nephropathy. The pancreas graft was placed in the right iliac fossa with vascular anastomosis to the iliac vessels, and the exocrine secretion of the pancreas graft was obstructed by the injection of

TABLE 1
Patient data and immunosuppressive therapy at time of conception

Case	Patient age at conception (yr)	Diabetes duration (yr)	Time from pancreatic transplantation to conception (mo)	Immunosuppression (mg/day)		
				CsA	Aza	Pred
Munich	33	24	16	300		
Cambridge	24	17	27	400		9
Brussels	29	23	10	220	50	7.5
Stockholm	30	21	27	220		10

CsA, cyclosporin A; Aza, azathioprine; Pred, prednisolone.

prolamine into the ductal system. The kidney graft was placed in the opposite iliac fossa (4). She became pregnant 16 mo posttransplantation, when cyclosporin was administered at 300 mg/day. Despite weight gain during pregnancy, the total dose of cyclosporin was not modified.

Case 2 (Cambridge). A 22-yr-old female with IDDM from age 7 yr received a paratopic segmental pancreas and simultaneously a kidney allograft from the same donor in May 1984. The pancreas graft vessels were anastomosed to the splenic vessels, and the exocrine secretion of the graft was diverted to the stomach by an anastomosis between the pancreatic duct and the ventricular mucosa (5). The postoperative course was uneventful, and her maintenance immunosuppression was 400 mg/day cyclosporin and 9 mg/day prednisolone. She became pregnant in September 1986, 27 mo posttransplantation.

Case 3 (Brussels). A 22-yr-old woman with IDDM from age 6 yr was subjected to a cadaveric kidney transplantation for end-stage renal failure in 1980. The graft was lost in chronic rejection in 1984, and in January 1986 at age 28 yr, she underwent a combined pancreas-kidney transplantation. The pancreas graft was placed intraperitoneally with vascular anastomosis to the left iliac vessels, and the cut end of the pancreas graft was anastomosed to a jejunal Roux-en-Y loop to accomplish enteric exocrine diversion. The kidney graft was placed in the right iliac fossa in a standard fashion. Postoperative immunosuppression consisted of rabbit antithymocyte globulin, cyclosporin, azathioprine, and prednisolone, and the maintenance dose at the time of conception (November 1986, 10 mo posttransplantation) was 220 mg/day cyclosporin, 50 mg/day azathioprine, and 10 mg/day Deltacortril (Pfizer, New York). The dosages of cyclosporin and azathioprine were maintained throughout the pregnancy, but the dosage of Deltacortril was reduced to 7.5 mg/day.

Case 4 (Stockholm). A 27-yr-old woman with IDDM from age 9 yr was subjected to a kidney-pancreas transplantation in October 1984. The segmental pancreas graft was placed intraperitoneally with vascular anastomoses to the right common iliac artery and the vena cava. The cut end of the graft was anastomosed to a jejunal Roux-en-Y loop to accomplish enteric exocrine drainage (6). The kidney graft was placed in the left iliac fossa in a standard fashion. The patient suffered an acute kidney-graft rejection within 14 days, and the graft was removed. However, the pancreas graft was retained with normal function, and the patient resumed maintenance hemodialysis. She received a second kidney graft in May 1986, and at the time of conception 10 mo later, the immunosuppressive therapy consisted of 220 mg/day cyclosporin and 10 mg/day prednisolone. This treatment was not altered during the pregnancy.

RESULTS

The function of the kidney and pancreas grafts at delivery and the outcome of the pregnancies are summarized in Table 2. All patients remained normoglycemic throughout pregnancy, and repeated measurements of glycosylated hemoglobin and oral glucose tolerance tests were normal. In two cases (Munich and Brussels), evidence of kidney-graft dysfunction was detected in the 34th and 33rd wk, respectively, and a cesarean section was therefore performed at 35 and 37 wk of gestation, respectively. In the Cambridge case, there was no sign of kidney-graft dysfunction, but the antenatal monitoring showed a fall in fetal growth at 33 wk gestation as seen by ultrasound scans, and on the grounds of a further fall in fetal growth at the beginning of the 35th wk, an elective cesarean section was undertaken. In the Stockholm case a cesarean section was performed because of fear of inducing pancreas-graft pancreatitis during normal delivery. Two of the children (Stockholm and Cambridge) were small for date, but both children subsequently showed normal growth development. One child had a bilateral cataract (Munich), and surgical lens extraction was undertaken 5 wk after birth. No other fetal abnormalities

TABLE 2
Kidney- and pancreas-graft function at delivery and outcome of pregnancy

Case	Serum creatinine (μM)	Oral glucose tolerance (2-h blood glucose; <8 mM*)	HbA_{1c} (%; <5.0*)	Gestational age at cesarean section (wk)	Outcome
Munich	180	6.1	5.0	35	Bilateral cataract
Cambridge	172	8	4.9	35	Small for date
Brussels	125	7.8	3.9	37	Normal
Stockholm	116	7.1	4.8	36	Small for date

HbA_{1c}, glycosylated hemoglobin.
*Reference value.

were found. At follow-up at 3, 5, 7, and 28 mo, all kidney grafts and three of the pancreas grafts remained functional. One patient (Stockholm) suffered from an acute pancreas-graft rejection postdelivery, and the pancreas graft was removed 2.5 mo postdelivery.

DISCUSSION

After pancreas-kidney transplantation in IDDM patients with end-stage diabetic nephropathy, the metabolic abnormalities caused by chronic renal failure and diabetes mellitus are abolished, thereby facilitating normal conception and pregnancy. Nevertheless, pregnancy in these patients imposes an enormous stress on both the kidney and pancreas graft. Even in normal healthy women, there is a 5–10% risk of developing proteinuria and hypertension near term, and the corresponding figure for nondiabetic kidney-graft recipients may be 40% (7). The risk of developing gestational diabetes in nondiabetic women resulting from increased insulin resistance during the 3rd trimester of pregnancy has been reported to be in the range of 0.15–12.3%, depending on the diagnostic criteria used. In patients subjected to segmental pancreas grafting, this risk is probably much greater, because a segmental pancreas graft contains only 50% of the normal islet mass, and steroids and cyclosporin may exert diabetogenic effects (8). The finding of normal glycemic control throughout pregnancy in our patients is therefore very encouraging. It also seems that equally good metabolic control was obtained regardless of the technique used for the pancreas transplantation (systemic or portal insulin delivery; destroyed or preserved exocrine function). In two of the patients, worsening proteinuria necessitated preterm cesarean sections. This figure seems to correspond to the 40% risk of deteriorating kidney-graft function reported in nondiabetic kidney-graft recipients (7). Two of the babies were small for date, also a figure corresponding to that found in nondiabetic kidney-graft recipients (9). In patients in whom the pancreatic grafts were placed in the pelvis close to the uterus, it was feared that the growing uterus might, by compressing the graft, induce pancreatitis. Indeed, graft pancreatitis with ensuing loss of graft function after pelvic examination has been reported (10). However, no episodes of graft pancreatitis were encountered in these four patients. However, in all these patients a cesarean section was performed, and the effects of vaginal delivery on a pancreas graft placed in the pelvis remains unknown. A somewhat discouraging experience was that of an acute pancreas-graft rejection postdelivery in one of the patients. Analysis of this patient's serum showed no signs of immunization against the child, and there was no evidence of withdrawal of immunosuppression postdelivery. Theoretically, the termination of pregnancy and its natural immunosuppressive stage should be followed by an increased risk of rejection, and indeed an increased incidence of kidney-graft rejection postdelivery has been reported (11).

This study clearly shows that successful conception and pregnancy can be obtained in diabetic patients who have been subjected to pancreas-kidney transplantation and that good metabolic control can be maintained throughout the pregnancy. This is in contrast to diabetic kidney-graft recipients, in whom pregnancy is rare. However, the risks of complications related to the original disease, such as retinopathy and angiopathy, and to deterioration of kidney- or pancreas-graft function are considerable and must be emphasized in each case in which pregnancy is considered.

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