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Islet Graft Function Is Preserved After Pregnancy in Patients With Previous Total Pancreatectomy With Islet Autotransplant

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To the Editor:

Total pancreatectomy with islet autotransplantation (TPIAT) has been used as a treatment for carefully selected patients with chronic and acute relapsing pancreatitis since it was first performed in 1977. This procedure allows removal of the diseased pancreas while maintaining endogenous insulin production through engraftment of islet cells in the liver after infusion into the portal vein.^{1,2} At the authors' institution, approximately one third of patients are insulin independent at 3 years postoperatively.¹ Of the remaining two thirds, half have partial graft function whereas half are insulin dependent. Women comprise over 70% of our institution's TPIAT population. Further-more, this procedure has been applied in the pediatric population as well, notably for patients with hereditary pancreatitis. Given these patient demographics, the implications of TPIAT for future reproductive health are critically important to elucidate. Apart from 2 case reports describing successful pregnancy after islet autotransplant, no literature is available to guide practice and to counsel patients.^{3,4}

To examine the effect of pregnancy on the islet graft function of women who had previously undergone TPIAT, we conducted a retrospective review of our patients with completed pregnancies. We hypothesized that, although pregnancy would temporarily stress graft function and increase insulin needs, there would be no sustained impact on islet graft function. A control group was selected from our female TPIAT patients without pregnancies who were of childbearing age at the time of transplant. The controls were matched to women reporting pregnancies by year of transplant, islet yield, and class of body mass index at transplant. The primary endpoints were the glycemic outcomes representative of islet graft

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function: (1) glycosylated hemoglobin (HbA1c), (2) insulin use (units/d), and (3) graft function classification. Case-control comparisons used Mantel-Haenszel tests with case-control groupings as strata or mixed linear models with case-control grouping as the random effect.

Five patients were identified, representing 7 pregnancies with 1 woman having completed 3 pregnancies. Time from transplant to conception was a median 21 months (interquartile range [IQR], 8–163). As anticipated, during pregnancy, 4 (80%) of the 5 patients did have an increased exogenous insulin requirement. Placental hormones, namely, human placental lactogen and placental growth hormone, in addition to progesterone, prolactin, and cortisol contribute to increased insulin resistance and decreased insulin sensitivity.⁵ At the time of last follow-up, however, the cases and controls did not differ significantly in the primary outcomes of HbA1c (mean $\pm$ standard error, 6.8 ± 0.87 vs 6.4 ± 0.62 , respectively; $P = 0.68$), insulin use (16.6 units ± 9.6 vs 12.6 units ± 7.6 , $P = 0.64$), or graft function categorized as failed, partial, or full function ($P = 0.82$) (Table 1). Four of the 5 women were partially or fully insulin dependent before the first pregnancy; only 2 were insulin dependent at the last follow-up.

Besides graft function, there are additional considerations for pregnancies after TPIAT, as the challenges of glycemic control during pregnancy in women with pregestational diabetes mellitus (PDM) can have significant maternal and fetal implications. Our cesarean delivery rate of 57% ($n = 4$) fits within the previously reported range (39%–84%) for women with PDM, and we also observed a high rate of preterm labor (71%).^{6,7} Although preeclampsia and gestational hypertension occur at higher rates in the PDM population and contribute to increased preterm delivery rates, none of our patients had documented preeclampsia or gestational hypertension, and the median gestational age at birth was 36 weeks (IQR, 35.5–38.0).⁸

The incidence of fetal macrosomia (>4000 g) is also increased in PDM. This can contribute to birth trauma for both the infant (eg, brachial plexus injuries, fractures) and mother (eg, perineal tears). Macrosomia did not occur in our study population where the median infant birth weight was 2800 g (IQR, 2325–3254). One potential contributor to the lack of macrosomia in our patient population may be the presence of exocrine insufficiency after pancreatotomy, leading to nutritional deficiencies.⁹ Also, placental dysfunction and vasculopathy in PDM mothers can actually lead to fetal growth restriction; however, this was not seen in our study cohort.¹⁰ In addition, the frequency of congenital anomalies in infants born to PDM mothers is 3% to 4%, compared with 6% to 12% in the normal population.⁵ In our study, 1 (1.4%) of 7 pregnancies involved an infant with a congenital malformation (sacroccygeal teratoma).

This case series provides an important perspective on pregnancy after TPIAT with a few key findings. Long-term graft function was comparable between patients with a pregnancy after TPIAT and their matched controls, supporting the conclusion that pregnancy did not have a negative impact on graft function in women with a history of TPIAT. Although our sample size is small, the results of this study provide an important foundation for the understanding

of pregnancy after TPIAT that will aid patient counseling and provide a basis for further investigation.

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TABLE 1.
Comparison of Baseline Characteristics and Analysis of Primary Endpoints of Cases and Controls

	Case (n = 5)	Control (n = 14)	P
Age at transplant, mean $\pm$ SE, y	24.8 $\pm$ 2.8	28.4 $\pm$ 2.0	0.21
BMI at transplant, mean $\pm$ SE, kg/m ²	22.0 $\pm$ 1.5	22.6 $\pm$ 1.0	0.75
Islet yield, mean $\pm$ SE, IEQ/kg	4474 $\pm$ 1065	433 $\pm$ 1054	0.55
HbA1c, mean $\pm$ SE	6.8 $\pm$ 0.87	6.4 $\pm$ 0.62	0.68
Time to follow-up, mean $\pm$ SE, mo	77 $\pm$ 16.7	41 $\pm$ 2.3	0.045
Insulin, mean $\pm$ SE, units/d	16.6 $\pm$ 9.6	12.6 $\pm$ 7.6	0.64
Current insulin use, n (%)	2 (40)	5 (36)	0.23
Time to follow-up, mean $\pm$ SE, mo	78 $\pm$ 18.2	39 $\pm$ 13.4	0.051
Graft function *			0.82
Failed, n (%)	1 (20)	3(21)	
Partial, n (%)	1 (20)	8 (57)	
Full, n (%)	3 (60)	3(21)	
Time to follow-up, mean $\pm$ SE, mo	75 $\pm$ 18.1	41 $\pm$ 12.6	0.10

* Failed, no endogenous insulin production as determined by a meal-stimulated C-peptide response 0.6 ng/mL or, in the absence of C-peptide data, the requirement of basal-bolus insulin; partial, some endogenous insulin production but exogenous insulin supplementation required; full, independent of exogenous insulin requirements.

SE indicates standard error; BMI, body mass index; IEQ, islet equivalent.