Successful pregnancy and delivery after simultaneous islet-kidney transplantation

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Abstract

Allogeneic islet of Langerhans transplantation is a recognized beta-cell replacement therapy for patients affected by type 1 diabetes mellitus. Type 1 diabetes mellitus is a condition associated with an increased risk of adverse outcomes for pregnant women and fetuses. We report the case of a 29-year-old woman with type 1 diabetes mellitus, who underwent successful allogeneic islet transplantation with simultaneous kidney transplantation. She achieved durable insulin independence after two islet infusions. Pregnancy was desired and planned 2 years after last islet infusion. Multidisciplinary monitoring of pregnancy was carried out and immunosuppressive regimen was adapted. Euglycemia was maintained throughout pregnancy without the need for exogenous insulin. After an uneventful pregnancy, she delivered on term an otherwise healthy male child with imperforate anus that was immediately surgically corrected. In conclusion, allogeneic islet transplantation is a suitable treatment for women of childbearing age with complicated type 1 diabetes mellitus, allowing physiologic glycemic control during pregnancy with a low risk of [...]
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Successful pregnancy and delivery after simultaneous islet-kidney transplantation

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Abbreviations

AIT: allogeneic islet of Langerhans transplantation

T1DM: type 1 diabetes mellitus

LVEF: left ventricular ejection fraction

IS: immunosuppressive

SIK: simultaneous islet-kidney transplantation

SPK: simultaneous pancreas-kidney

IEQ: islet equivalents

ABSTRACT

Allogeneic islet of Langerhans transplantation is a recognized beta-cell replacement therapy for patients affected by type 1 diabetes mellitus. Type 1 diabetes mellitus is a condition associated with an increased risk of adverse outcomes for pregnant women and fetuses.

We report the case of a 29 year-old woman with type 1 diabetes mellitus, who underwent successful allogeneic islet transplantation with simultaneous kidney transplantation. She achieved durable insulin independence after two islet infusions. Pregnancy was desired and planned 2 years after last islet infusion. Multidisciplinary monitoring of pregnancy was carried out and immunosuppressive regimen was adapted. Euglycemia was maintained throughout pregnancy without the need for exogenous insulin. After an uneventful pregnancy,
she delivered on term an otherwise healthy male child with imperforate anus that was immediately surgically corrected.

In conclusion, allogeneic islet transplantation is a suitable treatment for women of childbearing age with complicated type 1 diabetes mellitus, allowing physiologic glycemic control during pregnancy with a low risk of graft loss. This target can only be achieved by a tight multidisciplinary follow-up, including immunosuppressive therapy adaptation and adequate diabetes and obstetrical monitoring.

INTRODUCTION

Allogeneic islet of Langerhans transplantation (AIT) is a recognized treatment for complicated T1DM in adult patients. Many clinical trials have shown that this treatment can allow, at least for some years, insulin independence and other benefits such as better quality of life and improved control of diabetes complications (1). T1DM is a condition associated with an increased risk of adverse outcomes for pregnant women and fetuses (2). Fetal and neonatal death, preterm delivery, congenital malformation and maternal mortality are related to high levels of HbA1c in early and late pregnancy (2,3). For this reason, a strict glycemic control during pregnancy is crucial to optimize maternal and fetal outcomes (4). This target can be achieved by multiple insulin injections or with continuous insulin infusion by subcutaneous pumps. These methods are not always sufficient to ensure glycemic control during pregnancy and are associated with a high risk of severe hypoglycemia (5).

We report the case of a simultaneous islet-kidney graft recipient, who retained excellent glycemic control during and after pregnancy.
CASE REPORT

A 29-year-old Caucasian woman (height 164 cm; weight 62 kg; body mass index 23.1 kg/m²) with a 23-year history of T1DM and diabetic end-stage nephropathy (GFR 13 ml/min) was referred to our institution. Autoantibodies (IA-2, GAD65, ICA) were all negative. Her medical history also included diabetic retinopathy and idiopathic congestive cardiomyopathy with a 35% left ventricular ejection fraction (LVEF). At the time of admission, diabetes was treated by a basal/bolus subcutaneous insulin scheme (total dose: 33 IU, i.e. 0.53 IU/kg/day). Glycemic control was mediocre, as witnessed by HbA1c of 8.7%, with hypoglycemia unawareness. Because of the complication risks associated with her cardiopathy, it was decided to list the patient for simultaneous islet-kidney transplantation (SIK), rather than simultaneous pancreas-kidney (SPK). She received a kidney transplant after 18 months waiting time. The islet preparation (234,000 islet equivalents (IEQ) from the same donor) was injected intra-portal by a percutaneous approach under radiological guidance 2 days later. No procedure-related complication occurred and postoperative recovery was uneventful. She received a steroid-free immunosuppressive (IS) regimen, with thymoglobulin induction (6 mg/kg iv total dose) and tacrolimus/sirolimus maintenance (target trough levels: tacrolimus 3-5 ng/ml, sirolimus 10-15 ng/ml).

Kidney graft function was immediate. This first islet infusion significantly improved glycemic control (Figure 1) with a reduction of 64% of daily insulin doses (12 UI/day). Interestingly, cardiomyopathy was corrected after kidney transplantation and she recovered a normal LVEF. A second islet infusion was performed 11 months later. A total of 389,241 IEQ was infused. She received re-induction with daclizumab (1 mg/kg iv, 5 doses) and was kept on the same maintenance IS.

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Insulin was slowly weaned and she became fully insulin-independent 6 months after the second islet infusion (Figure 1), at which time she first expressed a wish to become pregnant. It was agreed with the patient to wait 2 years after the second islet infusion before allowing the pregnancy project. The IS treatment was adapted at that time, with a switch to high-dose tacrolimus (7-10 ng/ml) and azathioprine (75 mg qd).

She became pregnant 35 and 24 months after the first and second AIT respectively.

During pregnancy, she was followed by a multidisciplinary team, including specialists in obstetrics, diabetology and transplantation medicine. Fasting blood glucose, C-peptide, HbA1c and fructosamine levels were closely monitored. She remained off insulin and euglycemic throughout pregnancy. Fructosamine and HbA1c levels remained normal and even progressively decreased over the course of pregnancy. No obstetrical complication occurred. Caesarian section was performed at week 37 because of a worsening renal function. A healthy male baby (Apgar 8/10/10, length 49cm, weight 3200g) was delivered. The child was born with imperforate anus that was immediately corrected surgically.

After delivery, the IS treatment was modified again with a switch from azathioprine to mycophenolate mofetil, 1 g bid. The patient remained fully insulin-independent up to 16 months after delivery. At this point (HbA1c 6.5%; fructosamine 434 µmol/L; fasting blood glucose 7.7 mmol/l), she began requiring small doses of exogenous insulin again in order to maintain euglycemia. This was felt as a loss in her quality of life and she expressed the wish to have an additional islet graft. Since a retransplant would imply a minimal procedure-related risk only, she was relisted and retransplanted 29 months after delivery (2 infusions). She has been insulin-free ever since more than 6 years after islet re-infusion.

Figure 1 summarizes long term endocrine function after AIT.
DISCUSSION

T1DM increases the risk of adverse outcomes for pregnant women and fetuses, even despite optimized insulin therapy (2-7). The higher incidence of perinatal mortality, preterm delivery, congenital malformation, macrosomia, pre-eclampsia and maternal mortality are well known and are increased by poor glycemic control. (8)

SPK is currently the best therapeutic option for young adults with T1DM and terminal renal failure. Compared to AIT, whole pancreas transplantation achieves more durable euglycemia and insulin-independence at the cost of a highest morbidity rate.

Conduction of a successful and uneventful pregnancy in a pancreatic transplant recipient is a challenging endeavor because of the threats posed by diabetes itself, and in particular hyperglycemia, and by immunosuppression and its potential toxicities.

Pregnancy, in itself, is considered a “diabetogenic condition”, in which hormonal changes are associated at their worst to gestational diabetes. On the other hand, there is an adaptation to hormonal changes, in order to adjust β-cell function to the new metabolic condition, with an increased insulin secretion by the effect of pregnancy hormones, such as placental lactogen, prolactin and growth hormone (9). In rodent models, and possibly in humans, β-cells mass is even able to expand during pregnancy for this purpose (10,11).

IS drugs are also a challenging part of pregnancy management in pancreatic transplant recipients. Several IS drugs are considered as diabetogenic, such as corticosteroids, but also calcineurin inhibitors and mostly tacrolimus at higher doses. Teratogenicity issues exist for mycophenolate and m-TOR inhibitors and their use during pregnancy is contraindicated (12).

Thanks to strategies to switch contraindicated IS drugs to accepted ones, no significant increase of fetal malformation has been reported in pregnancies in transplant recipients (13).

As reported by a national Transplantation Pregnancy Registry (13) and a national French survey study (14), abortion, small size and prematurity are still the greatest concern for the
newborn in case of pregnancies in SPK recipients, whereas gestational hypertension (53.8%), infections (50%) and graft loss (4%) are the most common complications for the mother.

While pregnancy in whole pancreas transplant recipient has been investigated in retrospective studies, only one case of pregnancy in a solitary AIT recipient has been reported. (15)

In this study, we describe a case of successful pregnancy in a SIK recipient with T1DM and end-stage kidney failure. We observed an optimal glycaemic control throughout pregnancy, without the need for exogenous insulin. We even observed a slight increase in basal C-peptide levels from the 24th week of pregnancy with a peak at delivery. A similar C-peptide trend can be observed during the pregnancy period in the AIT recipient described by Schrive et al (15) as well as in healthy women (16). This might be the result of the higher metabolic demand observed in pregnancy. Despite that, the HOMA-IR index never was significant for pathologic insulin resistance. It could also be speculated that a slight enhancement of β-cell function was seen in the last 4 months of pregnancy. In particular, we noticed a progressive decrease of fructosamine levels indicating that the quality of glycaemic control was at least maintained. This could be explained by an increased sensitivity of β-cells to glucose stimulation, which is one of the adaptive changes occurring in pancreatic islets during normal pregnancy (9). Therefore, transplanted islets seem to be as sensitive to hormonal changes occurring in pregnancy, as normal pancreatic islets. From another standpoint, it can be considered that pregnancy is a period of mild allogenic tolerance (17). The increased levels of circulating steroids during this particular period of life are known for their anti-inflammatory and immunomodulatory effects (17,18). For this reason, we propose that a more favorable immunological environment, with reduced immune inflammatory insults, may impact on islet graft function during pregnancy.
As is usually the case in islet transplant recipients, we have no definite explanation for the partial loss of islet graft function experienced by our patient 16 months after delivery. In particular, no immune cause was identified, since the patient developed neither allo-, nor auto-antibodies. The relationship between the pregnancy, the changes in IS regimen and the subsequent functional alterations is unclear, especially in view of the long time lag between these events. Results of metabolic tests (arginine stimulation test, OGTT) performed 2 months before the start of pregnancy and 2 months after delivery were essentially identical (data not shown).

In conclusion, AIT is a suitable treatment for women of childbearing age with complicated T1DM, allowing a physiologic glycemic control during pregnancy with a low risk of graft loss. This target can only be achieved by a tight multidisciplinary follow-up, including IS therapy adaptation and adequate diabetes and obstetrical monitoring.

DISCLOSURE
The authors of this manuscript have no conflicts of interest to disclose as described by the American Journal of Transplantation.

FIGURE LEGENDS

Figure 1: Long term endocrine function after SPK:

On the right axis, HbA1c (%) is represented as black histograms and fasting blood glucose (mmol/L) as grey histograms. On the left axis, fasting C-peptide (pmol/l) is represented as open squares and fructosamine (µmol/l) is represented as open triangles. Daily insulin requirements (U/day) and HOMA-IR values are indicated below the graph. The red area shows the time of pregnancy.

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REFERENCES


TABLE 1

Characteristics of recipient, donors and islet preparations. (n.a. = not applicable)

<table>
<thead>
<tr>
<th>ABO</th>
<th>Recipient</th>
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<th>Donor B</th>
<th>Donor C</th>
<th>Donor D</th>
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<td>28</td>
<td>29</td>
<td>29</td>
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<td>Islet equivalents (IEQ)</td>
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<td>389.241</td>
<td>308.375</td>
<td>326.041</td>
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<td>Total islet infused/kg body weight (IEQ/kg)</td>
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<td>3.777</td>
<td>6.278</td>
<td>4.973</td>
<td>5.258</td>
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![Graph](image-url)