TRANSPLANT INTERNATIONAL

Transplant International ISSN 0934-0874

CASE REPORT

Graft function 1 year after pregnancy in an islet-transplanted patient

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Keywords
glucocorticoids, islet transplantation, pregnancy, type 1 diabetes.

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Conflicts of interest
The authors of this manuscript declare no conflict of interests.

Received: 23 January 2015
Revision requested: 19 February 2015
Accepted: 20 April 2015
Published online: 11 May 2015

doi:10.1111/tri.12596

Summary

Pancreatic islet transplantation is a treatment option for patients with type 1 diabetes (T1D), but pregnancy has generally not been advised for women after receiving an islet allograft. We hereby describe what is to our knowledge the first successful pregnancy and persistent graft function in a woman 4 years after her initial islet transplantation. A 37-year-old woman with brittle type 1 diabetes was transplanted with two separate islet graft infusions, eventually becoming insulin independent. Ten months after her second transplantation, her immunosuppression was switched from tacrolimus and sirolimus to tacrolimus, azathioprine, and prednisolone, due to her wish to become pregnant. She became pregnant one year later, and after 38 weeks of uncomplicated pregnancy, she gave birth to a healthy child by C-section. The current report suggests that pregnancy and childbirth can be accomplished after islet transplantation without loss of islet graft function.

Introduction

Islet transplantation is now a clinical treatment option for type 1 diabetes (T1D) [1]. Significant improvement in graft survival was accomplished due to the introduction of a glucocorticoid-free immunosuppressive regimen as described in the Edmonton protocol in 2000 [2,3]. The protocol relied on the combination of sirolimus, low-dose tacrolimus, and daclizumab as maintenance immunosuppression. All these, and most other immunosuppressive drugs used in transplantation, are classified as 'fetal risk cannot be ruled out' or 'evidence of fetal risk' by the US Food and Drug Administration. Yet, an increasing experience with pregnancies after solid organ transplantation has been showing encouraging outcomes [4].

Pregnancy is in itself a diabetogenic condition with hyperglycemia occurring in 1 – 22% of all pregnant women and could potentially pose an increased strain on the graft in patients with an islet allograft [5,6]. However, experience from combined pancreas–kidney transplantation does not show elevation in pregnancy-related diabetes [4]. Although there exists reports of successful pregnancy after autologous islet transplantation in a patient with chronic pancreatitis, and one in a patient whom had undergone pancreatectomy

due to a solid pseudo papillary neoplasm, there has to our knowledge been no report of a successful pregnancy after allogenic islet transplantation [7,8]. Here, we report on a successful pregnancy with preserved islet graft function after allogenic transplantation due to T1D.

Case history

A 37-year-old woman underwent islet transplantation due to brittle T1D. She was diagnosed T1D when she was 8 years old and experienced unawareness to hypoglycemic episodes and highly variable blood sugar levels throughout her disease span. She was hospitalized several times due to ketoacidosis in her late twenties. After this, she was offered treatment with an insulin pump, but she refused this in favor of a strict insulin regimen and close glucose monitoring. During the years before her transplantation, she was living alone and experienced weekly episodes of hypoglycemia in spite measuring her blood glucose levels more than 15 times each day. At the time of transplantation, she had been diagnosed with mild nonproliferative retinopathy and early stage neuropathy. She was taking insulin at a mean total dose of 0.58 units/kg/day and her glycated hemoglobin A1c (HbA1c) varied the year before her transplantation between 8.0 and 8.4%. She scored 6 on Clarke score for hypoglycemia unawareness [9].

After a thorough physical and psychological evaluation, she was found eligible for islet transplantation and underwent the procedure at Oslo University Hospital receiving 5990 islet equivalent (IEQ)/kg obtained from a 34-year-old donor. Islets purity was 47% and the stimulation index (SI) 9.7. The islets were isolated at the Nordic Network for Islet Transplantation facility at Uppsala University, Sweden, according to previously described methods [10]. The patient was enrolled into the Clinical Islet Transplantation Consortium study-01 (ClinicalTrials.gov Identifier: NCT00789308) and was randomized to the treatment group given low molecular weight dextran sulphate (LMW-DS) instead of conventional heparin [11].

Induction therapy was achieved by antithymocyte globulin (ATG) 1.5 mg/kg (Thymoglobuline, Genzyme, Naarden, Netherlands) and etanercept 50 mg (Enbrel, Pfizer, Kent, Great Britain) prior to the transplantation, and then ATG 1.5 mg/kg and 25 mg etanercept for three more days. As maintenance immunosuppression, she was given tacrolimus (target 5–8 μg/l) (Prograf, Astellas, Kastrup, Denmark) and mycophenolate mofetil (MMF) 33 mg/kg (CellCept, Roche, Welwyn Garden City, Great Britain). However, due to drug-related side effects, MMF was changed to sirolimus (Rapamune, Pfizer) (target 10 ng/ml) 1 week after transplantation, and the tacrolimus target was changed to 8-9 μl/L. After transplantation, there was a

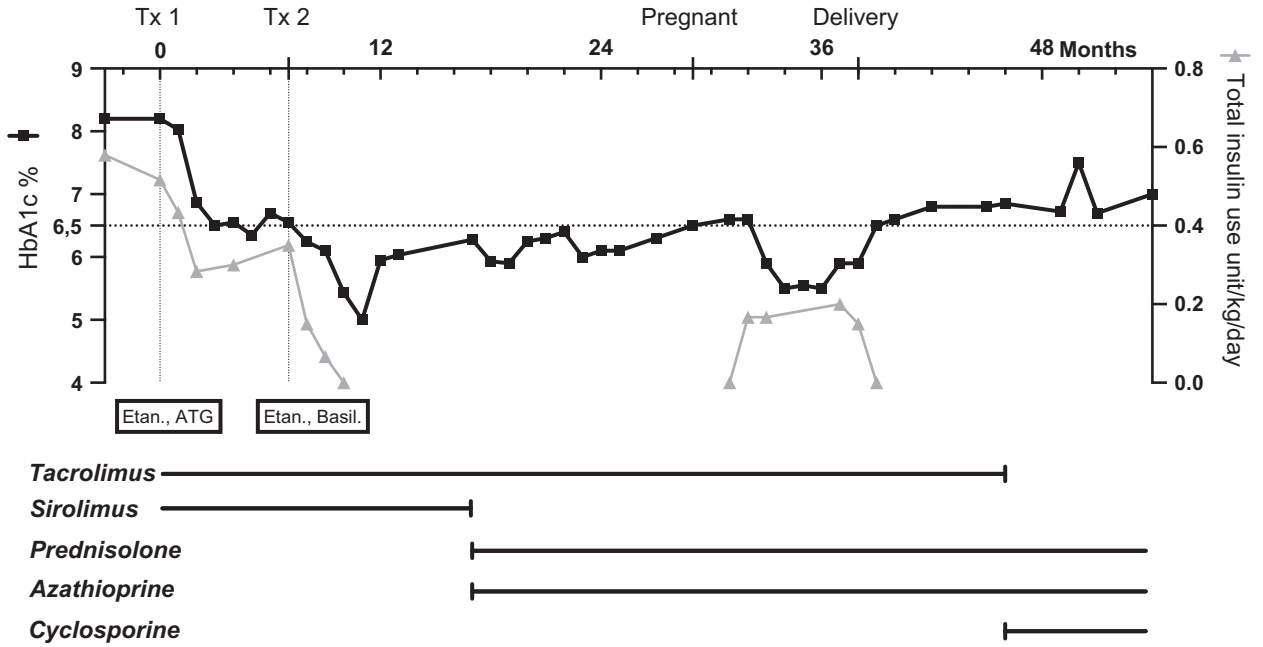

Figure 1 Hb1Ac (black square) and total insulin use unit/kg/day (gray triangle) plotted against time. Transplantations 1 and 2 (Tx 1, 2), time for pregnancy and delivery is noted. Medication administered as induction therapy prior to transplantation is noted (Etan., etanercept; ATG, antithymocyte globulin; Basil., basiliximab). Maintenance immunosuppressive drug therapy with timeline plotted under the graph. Dotted horizontal line at HbA1c 6.5%.

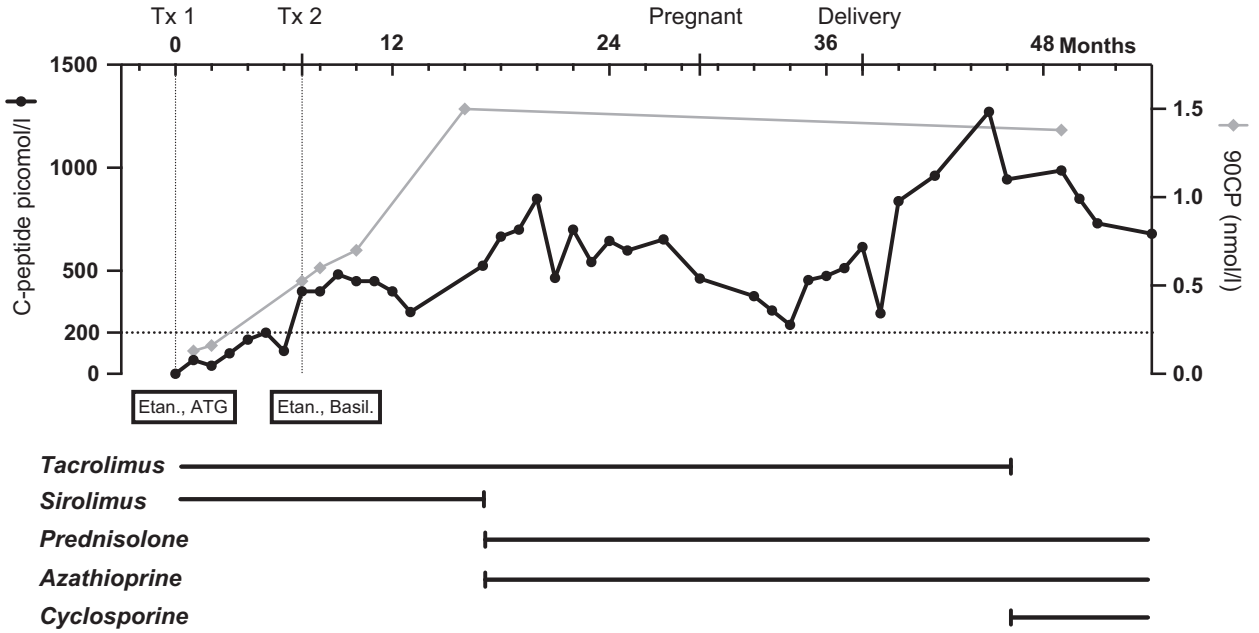

Figure 2 Graft function as measured by fasting plasma C-peptide (black circle) and 90-min stimulated C-peptide (90CP) after mixed meal test (gray square) plotted against time. Transplantations 1 and 2 (Tx 1, 2), time for pregnancy and delivery is noted. Medication administered as induction therapy prior to transplantation is noted (Etan., etanercept; ATG, antithymocyte globulin; Basil., basiliximab). Maintenance immunosuppressive drug therapy with timeline plotted under the graph. Dotted horizontal line at C-peptide 200 picomol/l.

decrease in HbA1c and insulin requirement, as seen in Fig. 1. Fasting plasma C-peptide was detectable, but less than 200 picomol/l. Stimulated C-peptide at 90 min after mixed meal tolerance test (90CP) ranged between 100 and 300 picomol/l, as seen in Fig. 2.

Six months after her first transplantation, the patient received a second islet infusion with 9055 IEQ/kg to reach insulin independence. The cells were obtained from a 63-year-old donor, the purity of the preparation was 55% and SI 6.7. Due to possible drug-related side effect of ATG during her first transplantation, etanercept was now combined with basiliximab (Simulect, Novartis, West Sussex, Great Britain) 20 mg twice, four days apart. Similar to her first transplantation, she also this time received LMW-DS infusion instead of heparin. Insulin independence was achieved 3 months after the second transplantation with fasting C-peptide levels of 400-500 picomol/l.

Ten months after her second islet transplantation, she expressed a wish to become pregnant, accepting the risk that a change in her medication and the pregnancy itself might pose a threat to the graft. Due to the unknown teratogenic potential of sirolimus, it was replaced with azathioprine (Imurel, Aspen Pharma Trading Ltd., Dublin, Ireland), initially 75 mg daily then increased to 100 mg once daily, and prednisolone (Takeda Nycomed, Asker, Norway), initially 10 mg daily then reduced to 5 mg once daily after two months [12,13]. Twenty-nine months after her initial transplantation, she became pregnant and underwent an uncomplicated pregnancy, giving birth to a 3400 g healthy child by C-section at gestational week 38. Sirolimus-free immunosuppression was maintained after delivery due to breastfeeding. Forty-six months after her initial transplantation, 8 months postpartum, tacrolimus was changed to cyclosporine (Sandimmun Neoral, Novartis) 100 mg twice daily due to hair loss.

Since her second transplantation, she has remained insulin free, with the exception of the last 6 months of her pregnancy. Although only borderline HbA1c of 6.6% was measured, she was prescribed 4 IU of the long-acting insulin glargine (Lantus, Sanofi-Aventis, Frankfurt am Main, Germany) in addition to 2 IU of the short-acting insulin aspart (Novorapid, Novo Nordisk, Bagsværd, Denmark) in relation to meals in order to minimize the risk of any hyperglycemic events during pregnancy. At the time of writing, 54 months after her initial transplantation and 16 months postpartum, she has preserved graft function by fasting C-peptide and 90CP, a HbA1c of 7.0% without the use of exogenous insulin, and she no longer experience any hypoglycemic episodes.

Discussion

We here describe the first successful pregnancy after allogenic islet transplantation in the setting of type 1 diabe-

tes. Apparently, the graft has tolerated the pregnancy, as she is insulin independent after delivery. Her retinopathy was controlled 16 months after delivery and showed no progression of disease. Pregnancy and immunosuppression are both potentially diabetogenic conditions, but data from pancreas–kidney transplantation do not show an increased risk of pregnancy-related diabetes [4]. Despite this, she was given low doses of insulin during the last 6 months of her pregnancy to protect both the graft and the fetus from any potential hyperglycemic events. Hyperglycemia during conception and pregnancy is associated with fetal malformations, maternal, and prenatal complications [14,15]. This patient had major difficulties controlling her blood glucose prior to the transplantations, while she remained euglycemic without need of insulin after the treatments. One could argue that islet transplantation in this case reduced the risk related to the pregnancy posed by poorly regulated blood glucose levels in a brittle diabetic patient. After delivery, an increase in both C-peptide and HbA1c has been noted, which may be related to the withdrawal of insulin injections. After an initial rise, the drop in C-peptide corresponds to her switch from tacrolimus to cyclosporine. Recently, she has also been experiencing a CMV infection, corresponding to the peak in HbA1c in month 50 after the first transplantation.

We have also studied the graft function over time after the switch to an immunosuppressive regimen containing low dose prednisolone, a glucocorticoid. Although glucocorticoids have mainly been avoided in the transplantation setting since the Edmonton protocol, there are studies showing that glucocorticoids have a favorable effect on islet survival in culture [16,17]. Tacrolimus is also known to have potential chronic toxic effects upon beta cells, but is considered safe in low doses after islet transplantation [18]. In this case, pregnancy happened less than two years after the initial transplantation, limiting the long-term graft exposure to tacrolimus prior to the pregnancy. Interestingly, we observed that an increased dose of tacrolimus during the last trimester was necessary to reach the desired blood levels.

In summary, we here describe a successful pregnancy after islet transplantation. Although graft function is maintained more than 1 year postpartum, the long-term effects remain to be seen.

Authorship

SWS: analyzed the data and wrote the manuscript. HS, AF and TGJ: participated in the research design and reviewed/edited the manuscript. AS, KKJ, GH, AF and TGJ: treated and followed up the patient. OK: supplied the islets and contributed to the scientific discussion. All authors have reviewed the manuscript and agreed on its contents.

Funding

This work was supported by the Department of Transplant Medicine at Oslo University Hospital Rikshospitalet and grants from Helse Soer-Oest.

Acknowledgements

The authors are grateful to all members at the human islet facility at Uppsala University and the Nordic Network for Islet Transplantation.

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