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Successful Pregnancy in a Kidney-Pancreas Transplanted Patient on LifeCycle Pharma Tacrolimus (LCPT)-Based Immunosuppression

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Patient: Female, 25-year-old
Final Diagnosis: Type 1 diabetes mellitus
Symptoms: No symptoms
Medication: —
Clinical Procedure: Immunosuppression
Specialty: Metabolic Disorders and Diabetics

Objective: Unusual clinical course

Background: There has been, to our knowledge, no reports on LifeCycle Pharma tacrolimus (LCPT) taken during pregnancy after simultaneous pancreas-kidney transplantation (SPK). Here, we report a 25-year-old female SPK recipient who gave birth to a healthy infant in posttransplant month 32. We analyzed the long-term graft function, obstetric/neonatal course, LCPT dosage, tacrolimus (TAC) levels, concomitant medication, and complications.

Case Report: Her medical history consisted of type 1 diabetes with chronic nephropathy, arterial hypertension, and atypical haemolytic uremic syndrome with critical deterioration of her general condition requiring clinically indicated early termination of her first pregnancy prior to SPK. SPK was performed according to surgical standards. The immunosuppressive prophylaxis consisted of thymoglobulin, mycophenolate mofetil, standard TAC formulation, and steroids. Due to rapid TAC metabolism, the patient was converted from a standard TAC formulation to LCPT in the first month posttransplant. Her long-term immunosuppression, including the obstetric and peripartal course, consisted of LCPT, prednisolone, and azathioprine. She was normotensive without antihypertensive medication and maintained excellent function of both grafts during the observation period of 48 months post-transplant. All (mostly infectious) complications were reversible, especially temporary polyoma viremia within normal renal function, and 2 episodes of urosepsis. No relapse of her pretransplant episode of atypical haemolytic uremic syndrome occurred posttransplant. Her child is in good health at the age of 12 months without any malformations.

Conclusions: This case suggests that pregnancy after SPK under LCPT is feasible. Further studies are needed to expand the empirical knowledge surrounding tacrolimus.

Keywords: Pregnancy • Pancreas Transplantation • Kidney Transplantation • Tacrolimus

Full-text PDF: <https://www.amjcaserep.com/abstract/index/idArt/937386>



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Background

LifeCycle Pharma tacrolimus (LCPT), with a delayed absorption profile, is an established pharmaceutical for immunosuppression after kidney transplantation. It has suitable bioavailability in tacrolimus (TAC) fast-metabolizing patients, and is reported to be safe and effective for immunosuppressive prophylaxis following pancreas transplantation [1,2].

In addition to reports on successful pregnancy following simultaneous pancreas-kidney transplantation (SPK), we also thought it worthy to describe our experience with pregnancy under LCPT therapy [3-12].

Case Report

A 25-year-old type 1 diabetic woman with comorbidities of substituted hypothyroidism, recovered hepatitis C, and arterial hypertension, underwent SPK at our center. She suffered from atypical hemolytic uremic syndrome (aHUS) in the first weeks of her first pregnancy prior to SPK. An extensive aHUS workup, including genetics of the complement system, revealed only a low titer of anti-factor H antibodies. A kidney biopsy identified progressive diabetic glomerulosclerosis but no thrombotic microangiopathy. With deteriorating kidney function and uncontrolled hypertension, her pregnancy was terminated in gestational week 10 for medical reasons, followed by prompt remission of aHUS and improvement of her condition. She was dependent on dialysis for 6 months prior to SPK.

The patient underwent SPK at our center. She received the organs of a 10-year-old male donor with HLA mismatches 1-1-2. The old ischemia time (hours) for pancreas/kidney was 10: 26/08: 47, respectively. Surgery was performed according to standard techniques with an exocrine pancreatic drainage by duodenojejunostomy (Figure 1). Immunosuppression included thymoglobulin 4 mg/kg, mycophenolate mofetil (MMF) 2 g, steroids tapered to 2.5 mg, prolonged-release TAC with targeted trough level 12-14 ng/mL in the first month, 6-8 ng/mL in months 6-8, 4-7 ng/mL thereafter. Antimicrobial prophylaxis included piperacillin-tazobactam, micafungin, trimethoprim-sulfamethoxazole, valganciclovir, co-medication pantoprazole and bisoprolol for temporary tachycardia, levothyroxine, and low molecular weight heparin.

As a therapeutic TAC level was not reached until day 10 (8.1 ng/mL), despite consistent dose increases in the standard prolonged-release TAC formulation, to a maximal dose of 0.25 mg/kg, she was identified as a TAC fast metabolizer as defined by a concentration/dose ratio <1.05 (0.34). After conversion to LCPT at day 11, the TAC level increased to 15.5 ng/mL at day 13. Analysis of a genetic variation of cytochrome P450 3A5 causing TAC fast metabolism was not performed for logistic reasons.



Figure 1. Radiologic followup after combined kidney-pancreas transplantation. Computed tomography prior to pregnancy showing the functional and well-perfused pancreas (marked with a black asterisk) and kidney grafts (marked with black pound sign).

All posttransplant complications were reversible. An incident of bleeding at the pancreaticoduodenojejunostomy at day 1 was controlled by a new anastomosis of the duodenojejunostomy. A clinically suspected pancreatic rejection from increased pancreatic enzymes at day 6 was reversed with 1.5 g methylprednisolone. The incidence of acute cystitis was probably caused by temporary hypohydration. The details are described as follows:

At month 1, bacteriuria with *Klebsiella* was successfully treated with amoxicillin plus ciprofloxacin. This infection was subsequently followed by bacteriuria with *Citrobacter*, which was reversed by fosfomycin. At month 4, uriculture revealed infection with *E. coli*, and this was successfully treated with piperacillin-tazobactam. At month 15, bacteriuria with *Proteus* was reversed by ceftriaxone. At month 27, urosepsis with *E. coli* was successfully treated with piperacillin-tazobactam. At month 28, urosepsis with *E. coli* was reversed by ceftriaxone.

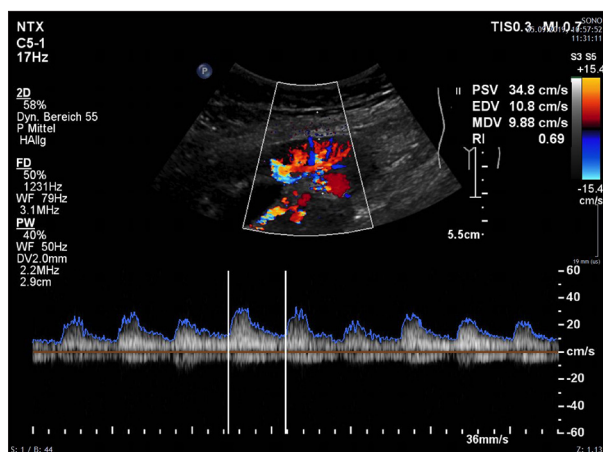


Figure 2. Radiologic followup after combined kidney-pancreas transplantation with successful pregnancy. Doppler ultrasound of the kidney graft at gestational week 16 indicating good perfusion.



Figure 3. Radiologic followup after combined kidney-pancreas transplantation with successful pregnancy. Ultrasound of the intrauterine embryo at gestational week 16; white arrow indicates embryonal head inside the womb.

At month 40, uricure with *E. coli* was successfully treated with trimethoprim-sulfamethoxazole. An acute case of bronchitis occurred at month 7. LCPT was temporarily discontinued during 2 episodes of urosepsis. Recurrent tonsillitis was reversed by tonsillectomy at month 21. The pre-transplant arterial hypertension resolved. Following elevated TAC levels (maximal 24 ng/mL) due to temporary diarrhea, polyoma viremia occurred from months 8-15 within a context of stable renal function, followed by PCR negativity after LCPT dose reduction with a stable trough level of 4-7 ng/mL with normal digestion.

Respecting her wish to conceive, she was converted from MMF 1.5 g daily to azathioprine 1.0 mg/kg at month 14 to avoid

potential teratogenicity. Following conception in posttransplant month 23 she experienced an uncomplicated obstetric course with stable graft function, with maintenance of therapeutic TAC levels based on an LCPT dosage ranging from 0.05-0.07 mg/kg, co-medicated with levothyroxine and oral iron prophylaxis. No aHUS occurred. Ultrasound findings from gestational week 16 are shown in **Figures 2 and 3**, respectively.

Caesarean section was indicated due to preterm birth at gestational week 36+4 which was defined by the completed 36th week following the last menstruation, plus 4 days. In spite of the late preterm phase prior to the calculated birth date, caesarean section was favored due to the advantage of the elective operative delivery being performed by a competent team who respected the anatomy of the renal and pancreatic graft.

The urological infectious history of the immunosuppressed patient was considered in making the decision to favor sterile operative conditions during caesarean section. The planned operative birth also included the advantage of the reservation of a postpartal bed at the neonatal ward for an adequate observation in case of a probable respiratory distress of the newborn baby.

Caesarean section was performed at month 32 posttransplantation. The patient gave birth to a healthy son with a weight of 2630 g, length 47 cm, and Apgar score 9/10/10, who underwent respiratory adjustment for 1 day and antibiotic prophylaxis. He was discharged in good health and breastfed by his mother. A measurement of the concentration of LCPT and its metabolites in the patient's human milk was not performed for logistic reasons.

The maternal peripartal dosage of LCPT was kept at 0.07 mg/kg resulting in a prepartum TAC level of 4.3 ng/mL, combined with prednisolone 2.5 mg, and azathioprine 1.0 mg/kg. Prepartum/postpartum serum creatinine was 0.9 mg/dL each, blood glucose was 85/91 mg/dL, and HbA1c was 30/37 mmol/mol.

At posttransplant month 48, the patient was healthy, with excellent graft function. Her serum creatinine was at 0.9 mg/dL, blood glucose at 87 mg/dL, HbA1c at 35 mmol/mol, and she was immunosuppressed with LCPT at 0.07 mg/kg, resulting in a TAC level of 7.7 ng/mL and MMF of 1000 mg following reconversion intending no subsequent pregnancy; prednisolone was 2.5 mg and levothyroxine 50 µg was administered as a co-medication.

Her son's size fell within percentiles 97% to 92%, with a length of 82 cm and weight of 12 kg at month 12 without any malformations. The child's psychomotor development was normal.

Discussion

According to the National Transplantation Pregnancy Registry, the reported incidence of 3.9% of pregnancies and birth after SPK is relatively small in comparison to pregnancies after single kidney or liver transplantation [11].

Despite many reports in the literature about the immunosuppressive efficacy of ordinary tacrolimus during pregnancy and its safety for the mother, the transplanted organ, and the fetus, no detailed reports focusing on pregnancy and birth under LCPT after organ transplantation were found by literature research to date [1-11]. LCPT is a modified form of tacrolimus with a more controlled extended release with high bioavailability, which allows for a reduction in the daily dose [1,2]. Our case report aims to extend adequate experiences under this particularly bioavailable TAC formulation, also respecting reported challenging courses of pregnancies after SPK and the demand of improving knowledge about immunosuppressive drugs during pregnancy [12,13].

In the presented case, it was demonstrated that the use of LCPT was safe. The patient gave birth to a healthy infant and maintained stable peripartum kidney-pancreas function without a relapse of her pretransplant episode of aHUS. Her LCPT-based long-term immunosuppression indicated fast TAC metabolism. The treatment was well tolerated and all complications were reversible, resulting in excellent long-term kidney-pancreas function and good health at month 48.

This positive single-case experience is encouraging for the application of LCPT, with its higher bioavailability permitting dose reduction in women intending pregnancy after organ transplantation [1,2]. Standard TAC has already been repeatedly

published and recommended over the last 2 decades as being safe in posttransplant pregnancies, preferably combined with azathioprine or steroids, to avoid the potential teratogenicity of MMF and mTOR-inhibitors [3-5,8]. In previous experiences at our own center with births after SPK, all patients were on TAC plus azathioprine with balanced dosages individualized by obtaining both therapeutic levels under TAC and normal blood cell counts under azathioprine. In light of this experience, we would favor this type of tailored immunosuppression, using LCPT combined with azathioprine or steroids [9].

In addition to enlarging the knowledge on LCPT, future studies including the measurement of its concentration and metabolites in human milk would be of interest.

Conclusions

Women using LCPT may become pregnant. The use of this formulation of TAC is safe for the patient, the transplanted organs, and the child. Further studies are needed to expand the empirical knowledge surrounding TAC.

Clinical Trial Notation

Ethics Committee of the Medical University of Innsbruck, Austria. Registration number: 1305/2021.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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