

Two successful pregnancies after a simultaneous kidney and pancreas transplantation for type 1 diabetes mellitus-complicated nephropathy

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Background: Simultaneous kidney and pancreas transplantation (SKPT) is the treatment of choice for patients with type 1 diabetes mellitus and end-stage renal disease. A successful transplantation result in improved functional status, health-related quality of life and reproductive health. The most significant factors for successful outcomes for mother and child are stable pre-pregnancy transplant function tests and absence of immunosuppressive therapy. Pregnancy after transplantation is a high-risk condition; it should be carefully considered, planned, and monitored by a multidisciplinary health care team. **Case presentation:** We describe a case report of a 40 years old woman, how had two successful pregnancies after a simultaneous kidney and pancreas transplantation. Her pregnancy course was uneventful until 34 weeks of gestation when she had pre-eclampsia in the first pregnancy and PPRM in the second pregnancy. **Conclusion:** Scientific data about simultaneous kidney and pancreas transplantation are yet limited, so it is difficult to build guidelines in this clinical condition. We describe in literature the first case of two successful pregnancy after SKPT. Both babies had a low birth weight in coincidence with lower gestational age and in the first pregnancy, the mother developed preeclampsia.

Keywords

Diabetes; Preeclampsia; Pregnancy; Transplant

1. Introduction

The number of women in reproductive age and children, which undergo to transplantation of solid organ increases each year, and pregnancy after transplantation is increasingly common. The improvement of transplantation techniques and immunosuppressive drugs gave the opportunity to girls with organ transplants to reach childbearing age and become pregnant [1, 2].

Today in scientific literature, there are not enough evidences, represented by randomized trials or prospective studies about pregnancy after transplantation. The current information available are from voluntary register, the bigger is the American National Transplantation Pregnancy Registry (NTPR), and smaller register which is represented by

the European Dialysis and Transplant Association Registry and the United Kingdom Transplant Pregnancy Registry. In 2016 the US based National Transplantation Pregnancy Registry (NTPR) expanded to include participation worldwide and was renamed the Transplant Pregnancy Registry International (TPR).

Although pregnancy has been most commonly described after kidney transplantation, pregnancies between simultaneous kidney and pancreas transplantation include only 81 pregnancies reported by the TPR in 2017 [3].

Ovarian insufficiency is the direct consequence of kidney failure and it can be solved only after the kidney transplant, when the graft works normally. There is normalization of the main metabolic endocrine abnormalities and restoration of normal hormone levels, reflecting on the resetting of the hypothalamic-hypophysis-ovary axis, leading to a significant improvement of the fertility.

At the time of transplantation woman with wish of pregnancy should be counseled regarding the reproductive aspects at the time of transplantation. Pre-conception plan is extremely important and should be organized between the obstetrician and the transplant team.

Patient should defer conception, with adequate contraception. Pregnancy should be postponed until the general clinical conditions about renal and pancreas functions are stabilized as much as possible, and there is a lower risk of rapid onset of acute post-transplant events.

The optimal pregnancy outcomes are associated to normal systolic blood pressure values and regular serum creatinine. Optimal glycemic control in the pre-conception period and through the first trimester may reduce the risk of congenital anomalies and miscarriage. Vaccinations should be given in pre-conception period.

Pregnant women, who received a transplant, have a higher risk to be affected by hypertension, preeclampsia, and infections, and there is a higher possibility of preterm delivery due to fetal anomalies and low weight, and to have a

preterm maternal indication of induction of labor, such as preeclampsia and preterm premature rupture of the membranes.

The opportunity to suppress the maternal immune system has immediately improved the pregnancy outcomes after transplantation. An important aspect to consider is to establish a balance between the risk of acute rejection and the teratogenic effects of immunosuppressive drugs. Currently available data indicate that risks related to the use of immunosuppressive drugs are relatively low. According to NTPR data, the prevalence of neonatal malformations is 5% similar to their prevalence in the general population, about 3% [4, 5]. The FDA has differentiated the medications into five categories according to the teratogenic risk: A remote possibility; B no evident risk in human; C a risk in human could not be ruled out; D evident risk in humans; X contraindicated. If we consider all the drugs, most of the immunosuppressive medications are classified into Group C, not considering azathioprine and mycophenolate mofetil, which are located in the Group D. The adverse effects of immunosuppressive drugs are different (miscarriage, congenital malformations, neurological and immunological developmental problems in the newborn, behavioral disturbances in the unborn child), but the real assessment of the risks involved is difficult to evaluate [4]. Transplanted women can give birth at term with spontaneous delivery unless complications appear, cesarean section is reserved for obstetric indications only.

2. Case presentation

We followed in our hospital a pregnant woman of 40-years-old after simultaneous kidney and pancreas transplantation. At 10 years old she was affected by type 1 diabetes mellitus, which was well treated by insulin for about 10 years. When the patient was 23 years-old she had a diabetic retinopathy, so it was decided to do a surgical treatment by laser photocoagulation. She evolved to an end-stage renal disease related to diabetic nephropathy, so she started having hemodialysis. In 2012, at the age of 34, she was treated by simultaneous kidney and pancreas transplantation from a brain-dead donor. The transplanted pancreas was sited in the intraperitoneal cavity in right iliac fossa, and the renal graft was sited in the extra-peritoneal cavity in left iliac fossa. This simultaneous kidney and pancreas transplantation allows her to avoid dialysis and insulin therapy. She received immunosuppression therapy with mycophenolate.

One year after surgery, the patient would like to get pregnant. At that time she was taking mycophenolate, her blood pressure was regular by medical pharmacological treatment, she had no proteinuria and both grafts were functionally normal. She had two miscarriages 2 year after transplantation.

At 38 years old, she conceived spontaneously 4 year after simultaneous kidney and pancreas transplantation. The follow-up appointments in pregnancy were performed at the high-risk pregnancy outpatient clinic of the Obstetric Department of the ARNAS Garibaldi Nesima Hospital in Cata-

nia. The transplant team as well her nephrologist, endocrinologist, and the obstetrician closely followed her progress through the pregnancy.

When the patient was pregnant the following medication were administrated: tacrolimus (1.2 mg every day), metildopa (1500 mg every day), nifedipina (60 mg every day). Furthermore, aspirin at the dose of 100 mg/day, prednisone (5 mg/day), and iron were prescribed. Pre-gestational blood screening were normal.

At the beginning her blood pressure in the first and second trimester of pregnancy was 120/70 mmHg with therapy and no proteins in the urine test. Blood glucose monitoring, fasting blood glucose and serial glycosylated hemoglobin (HbA1c) levels were in the normal range through pregnancy. Insulin treatment was not required at any stage before, during, or after pregnancy. As weight gain in pregnancy, she took only 6 kg.

The pregnancy was regular until 32 weeks when ultrasound examination showed fetal growth in a normal range, with abdomen circumference at 15^o centile for gestational age. Her clinical appointments have been set every week until 34 weeks gestation when she had lower limb edemas, proteinuria (3 gr/24 h) and hypertension (160/100) not controlled with pharmacological therapy, configuring a condition of pre-eclampsia. This situation led to the decision to perform a cesarean section (CS). She delivered at 34 weeks and 5 days of gestation a 1740 g healthy infant by cesarean section for pre-eclampsia. APGAR score was 7 and 8 at five and ten minutes, respectively. The physical examination and blood test of the baby showed a healthy baby, without any malformations or immunosuppressive compromise. Cesarean section was performed with a Pfannenstiel and a transverse incision of the lower uterine segment. The postpartum was regular, the hospital stay was three days and then she was discharged.

After two years she had another normal pregnancy, by natural conception. She conceived spontaneously at 40 years old. The medications were the same of the first pregnancy and the blood tests were normal. All the vital parameters (blood pressure, pulse and temperature) were normal, and also the urinary test demonstrated no proteins in the urine. Blood glucose monitoring, fasting blood glucose and serial glycosylated hemoglobin (HbA1c) levels were in the normal range through pregnancy. Insulin treatment was not required at any stage before, during, or after pregnancy.

At 30 weeks of gestation the blood test show an increase of creatinine (1.34), amylase and lipase and proteinuria (0.79 g/24 h). The pregnancy was regular and the clinical follow up was performed every week; ultrasound examination showed fetal abdomen circumference at 40^o centile for gestational age. She had a preterm premature rupture of the membranes at 33 weeks and 3 days of gestation. She delivered an 1860 gr healthy infant by cesarean section due to a non-reassuring cardiotocography at 33⁺⁴ weeks of gestation. APGAR score was 8 and 8 at five and ten minutes, respectively. The new-

born was in a good condition and had no medical problems. Cesarean section was performed in the same way of the first surgery. The postpartum course was uneventful.

3. Discussion

Simultaneous kidney and pancreas transplantation is the treatment of choice for patients with type 1 diabetes mellitus and end-stage renal disease. The advantage of simultaneous kidney and pancreas transplantation is represented by the reduction of the complications of diabetes mellitus [6]. Successful transplantation result in improved functional status, health-related quality of life and reproductive health [1]. Scientific data about simultaneous kidney and pancreas transplantation are yet limited [7], so it is difficult to build guidelines in this clinical condition.

Pregnancy considerations vary depending on the organ transplanted, but the most significant factors for successful outcomes for mother and child are stable before pregnancy transplant function, avoidance of immunosuppressive therapy, and close follow-up during pregnancy and postpartum. The authors agree that pregnancy after transplantation represents a high-risk condition; it should be carefully planned and monitored by a multidisciplinary health care team [3].

We describe in literature the only case of two successful deliveries after SKPT. Both babies had a low birth weight in coincidence with lower gestational age and in the first pregnancy, the mother developed preeclampsia (according to the reports by Coscia *et al.* [3]). Evaluating the NTPR database, our case report was normal and the pregnancy was well managed considering the fact that there was a previous SPK transplantation.

Author contributions

EP and CE conceived the project of this work and designed the experiments. EP and FR made the clinical activity, following the patients in their appointments. FAG and SC wrote the paper. GE was the clinical and scientific coordinator of the study.

Ethics approval and consent to participate

All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Comitato Etico Catania 2 (2020/CECT2).

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Conflict of interest

The authors declare no conflict of interest.

References

- [1] Rao S, Ghanta M, Moritz MJ, Constantinescu S. Long-term functional recovery, quality of life, and pregnancy after solid organ transplantation. *Medical Clinics of North America*. 2016; 100: 613–629.
- [2] Mastrobattista JM, Gomez-Lobo V; Society for Maternal-Fetal Medicine. Pregnancy after solid organ transplantation. *Obstetrics and Gynecology*. 2008; 112: 919–932.
- [3] Coscia LA, Constantinescu S, Armenti DP, Moritz MJ. The 25th Anniversary of the national transplantation pregnancy registry. *Clinical Transplants*. 2015; 31: 57–68.
- [4] McKay DB, Josephson MA. Pregnancy in recipients of solid organs-effects on mother and child. *The New England Journal of Medicine*. 2006; 354: 1281–1293.
- [5] Stratta P, Canavese C, Giacchino F, Mesiano P, Quaglia M, Rossetti M. Pregnancy in kidney transplantation: satisfactory outcomes and harsh realities. *Journal of Nephrology*. 2003; 16: 792–806.
- [6] Koyama S, Tomimatsu T, Kanagawa T, Daimon E, Kimura T, Kuroda A, *et al.* Successful pregnancy after simultaneous pancreas-kidney transplantation from a brain-dead donor: the first case report in Japan. *The Journal of Obstetrics and Gynaecology Research*. 2011; 37: 1711–1716.
- [7] Hortu I, Arı SA, Akdemir A, Koroglu OA, Yılmaz M, Toz H, *et al.* Perinatal outcomes of renal transplant pregnancies: a 22-year experience at a single tertiary referral center. *The Journal of Maternal-Fetal & Neonatal Medicine*. 2020; 33: 3028–3034.