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Case Report

Management of pregnancy in pancreas alone transplant recipient complicated with stage-4 chronic renal insufficiency and superimposed pre-eclampsia: Case report and literature review

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ABSTRACT

Objective: With the prolonged life expectancy in solid organ transplant recipients, their quality of life and fertility desire become of particular concern. Pregnancy in pancreas-alone transplantation, although rare and complicated to manage, is not impossible anymore. We here report such a case with literature review to address this issue.

Case report: A 29-year-old, primigravida patient with underlying stage 4 chronic renal insufficiency and type 1 diabetes mellitus post pancreas-alone transplantation 5 years prior to her initial visit consulted our service. Antepartum care with intensive monitoring of blood pressure, renal function, and tacrolimus serum concentration were given. Successful maternal and fetal outcomes are presented here.

Conclusion: Child-bearing in solid organ transplantation recipients has become more promising nowadays, even for a difficult case of pancreas-alone transplant recipient complicated with chronic renal insufficiency and superimposed pre-eclampsia. Thorough antepartum counseling and cautious monitoring of maternal, fetal and graft conditions by multidisciplinary specialties are key to favorable pregnancy outcomes.

Introduction

Pregnancy in solid organ transplant recipients takes high-risk pregnancy to a new horizon, for its complexity and interplay among the maternal patient, the fetal patient and the graft. With the advent of pharmacology and quality healthcare, transplant recipients can be stabilized to restore not only longevity but also fertility. We here report a primigravida female, who received pancreas-alone transplantation and her pregnancy was further complicated with chronic renal insufficiency and superimposed pre-eclampsia. A literature review regarding the post-transplantation timing of conception, impact of immunosuppression drugs, obstetrics complications, pregnancy outcomes and breastfeeding will be discussed.

Case presentation

A 29-year-old, primigravida patient presented herself at gestational age of 11 + 6 weeks for prenatal consultation and management. She had underlying type 1 diabetes mellitus post pancreas-alone transplantation at age 24, complicated with stage 4 chronic renal insufficiency. She was on tacrolimus maintenance dose 4 mg twice daily and her graft had functioned well with HbA1c stabilized at 5.5–5.6%. The fetus was conceived naturally. When related maternal and fetal risks, such as pre-eclampsia, gestational diabetes, preterm delivery, small for gestational age, loss of graft function and worsening renal function were explained to her. She was determined to continue the pregnancy. After weighing both the maternal and fetal benefits and risks, elective preterm delivery was aimed at gestational age of 32 weeks. Fetal growth had been up to schedule and organ-targeted sonography examination at 21 + 5 weeks of gestation showed no structural anomalies. Raising blood pressure began in mid-second trimester and oral labetalol 200 mg twice daily were given since 24 + 4 weeks of gestation. However, her blood pressure gradually rose to 170–180/100–110 mmHg at 30 + 1 weeks. The already impaired renal function deteriorated gradually paralleling the worsening blood pressure (Fig. 1). She was then admitted at gestation age of 30 + 1 weeks for intensive blood pressure control with increased labetalol dosage up to 200 mg every 6 h, continuous fetal monitoring, and corticosteroids fetal lung maturation. Cesarean section at gestational age of 31 + 2 weeks was performed due to poor fetal

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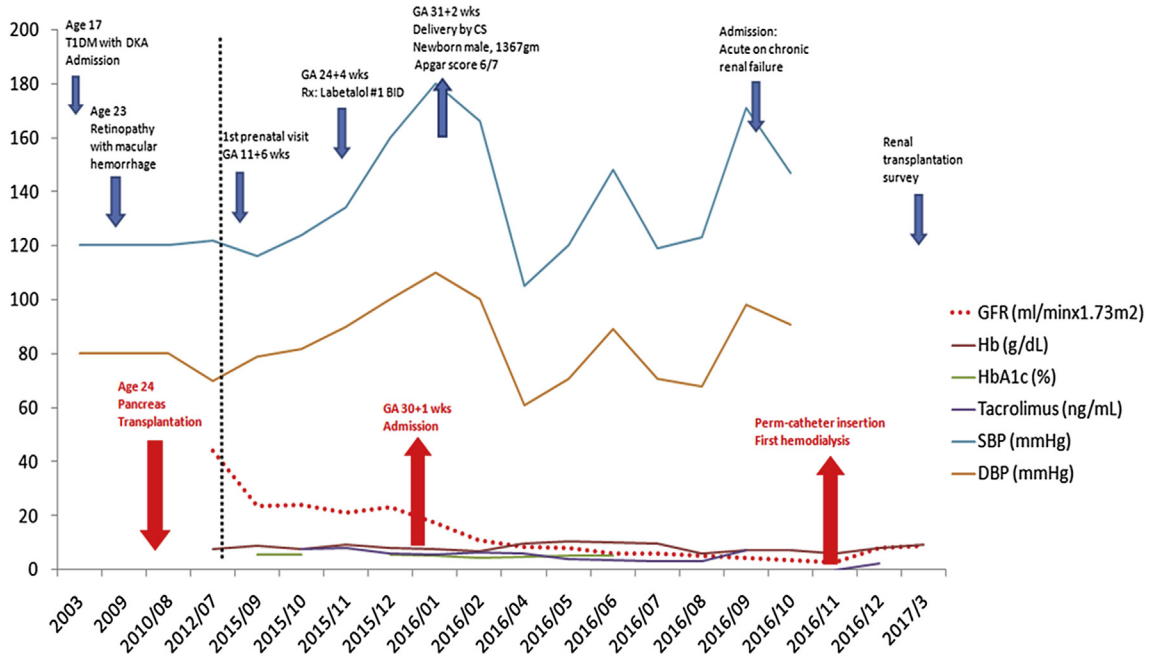

Fig. 1. Clinical course of the patient in terms of systolic blood pressure (SBP), diastolic blood pressure (DBP), glomerular filtration rate (GFR), hemoglobin (Hb), HbA1c, tacrolimus serum concentration ante-, intra- and postpartum.

heart beat variability and poor blood pressure control. The male newborn weighted 1367 g with the first and fifth Apgar score 7 and 9 respectively. The newborn was fully breastfed. No congenital anomaly or developmental defects were observed. However, a decline of glomerular filtration rate at the time of delivery (26 ml/min–12 ml/min) was noted. Further deterioration of renal function was found 10 months postpartum. Her glomerular filtration reached nadir at 2.61 ml/min in November 2016, when regular hemodialysis was initiated. As of the date of article submission, the patient has been relatively stable and her child thrived.

Discussion

Pregnancy in solid organ transplant recipients is not only feasible but becoming commonplace nowadays. National Transplantation in Pregnancy Registry (NTPR) [1], founded in 1991, totaled 2609 pregnancies in 1461 female solid organ recipients in North America as of December 2015. Largest pool of data came from kidney transplants (1005 recipients), which were analyzed in most publications. Pregnancy after pancreas-alone transplantation is rare, accounting for only 5 patients, 9 pregnancies, 2 surrogate pregnancies and 7 live births without noted birth defects in the published literature (Table 1). With our case added to the statistics, there are 10 biological pregnancies, 4 were spontaneously aborted at early gestation. Among those that were able to maintain pregnancy after second trimester, 2 delivered at full term, 2 preterm, and all children survived. Only one graft loss at 5 months postpartum was reported. Although no solid conclusion could yet be drawn from this limited number of case reports, it appears that pregnancy in pancreas-alone transplant recipients results in extreme outcomes: either early spontaneous abortion or favorable live births without serious complications. Graft loss is possible but uncommon.

According to the American College of Obstetricians and Gynecologists (ACOG)'s recommendation issued in 2008 for pregnancy after solid organ transplantation, it is advised to secure graft function and treat original disease at least 1 year before conception when immunosuppressant serum level stabilizes and opportunistic infection rates are reduced to optimize pregnancy outcome [2]. Maintenance immunosuppressant therapeutic level should be monitored closely, for it can be altered by increased volume of distribution, increased glomerular filtration rate, decreased albumin levels, increased body fat and slowed gastrointestinal motility in pregnancy physiology [3]. Most immunosuppressive drugs are classified as C or D, but studies have shown that tacrolimus, prednisolone, azathioprine and cyclosporin do not result in more congenital anomalies (4–5%) than the background population (3–5%) at steady therapeutic level [3]. Its concentration in breast milk is negligible for feeding as shown in the study by Armenti et al. [4]. The benefits of breastfeeding, thus, reasonably outweigh its unidentified adverse effects and should be encouraged. On the contrary, an identified orofacial abnormalities and microtia with mycophenolate mofetil exposure warranted its discontinuation at least 6 weeks before conception [1,3].

In our case, the patient's graft function was maintained optimal with tacrolimus use throughout her preconception, pregnancy and breastfeeding periods, with its therapeutic level monitored and adjusted by the Nephrologist. It is noteworthy that tacrolimus is indispensable here to maintain good graft function, but the drug is also notorious for its nephrotoxicity. Although the underlying mechanism and genetic basis of the phenomenon are still under investigation, the association between tacrolimus use and chronic renal function deterioration is well documented [6]. This partially explains the worsened renal function in our patient. Furthermore, pregnancy itself is a risk factor to damage glomerular filtration performance in chronic renal insufficiency patients, especially at advanced stages. This concept is well presented by Alkhunaizi A et al. in their review article in 2015, where precautions of progressive underlying renal dysfunction, worsening proteinuria, hypertension, pre-eclampsia, intrauterine growth restriction and preterm delivery were given for pregnancy in advanced chronic renal insufficiency [7]. Interestingly, the authors devoted a section discussing the role of aspirin as the prophylactic therapy for pre-eclampsia in this particular population. They concluded that there was no sufficient evidence to support similar efficacy in this specific

Table 1
Reported cases of pregnancy in pancreas-alone transplant recipients.

Case report	Parity	At birth	Outcome	Comment
Patient 1	Pregnancy 1	39 weeks	Live	
	Pregnancy 2	39 weeks	Live	
Patient 2	2 pregnancy	X	Spontaneous abortion	
	Surrogate pregnancy 1	38 weeks	Twins (1 miscarriage at 8 weeks, 1 live birth at 38 weeks)	
	Surrogate pregnancy 2	38 weeks	Live	
Patient 3	Pregnancy 1	X	Spontaneous abortion	
	Pregnancy 2	Not reported	Live	Graft loss 5 months postpartum
	Pregnancy 3	Not reported	Live	
Patient 4	Pregnancy 1	5 weeks	Spontaneous abortion	
Patient 5	Pregnancy 1	28 weeks	Vaginal delivery, male, 1023 g	
Current case	Pregnancy 1	31 + 2 weeks	Cesarean section, male, 1367 g	

All 8 children: no birth defects reported.
All except for one remaining recipients report adequate pancreas function.

subgroup of women with advanced renal dysfunction. Aspirin could also worsen renal performance and the underlying platelet dysfunction, augmenting the patient's bleeding risks. Our decision of not prescribing aspirin at early gestation is thus justified. Overall speaking, tacrolimus nephrotoxicity and pregnancy in advanced chronic disease are two plausible explanations to our patient's renal function downfall, apart from the natural disease course of her underlying diabetic nephropathy.

Obstetrics complications associated with solid organ transplantation are well documented in reported literature, with the best-known for pre-eclampsia, gestation diabetes, preterm delivery and low birth body weight [5]. Complications experienced by our patient were consistent with those reported in literature, and further perplexed with stage 4 renal insufficiency, presenting with raising blood pressure and deteriorating glomerular filtration rate. Intensive blood pressure control, fetal monitoring, proper timing of delivery and avoidance of nephrotoxicity medications become crucial to optimize both maternal and fetal outcomes. Indeed, our fetal patient, although preterm, is in relatively good condition without structural anomalies or functional disabilities. He has grown and matured up to schedule. This could be partially attributed to the timely administration of corticosteroids prenatally for fetal lung maturation according to the recommendation made by ACOG in 2016 [8].

In summary, pregnancy in solid organ transplantation recipients is becoming more promising nowadays. In the present case, a pancreas-alone transplantation recipient has conceived naturally and successfully gave birth to a preterm but healthy baby after securing her pancreas graft function for 5 years. The graft has endured well throughout the pregnancy, as reflected by her stable HbA1c level. Tacrolimus is essential in maintaining graft function without increased teratogenic effects compared to background population, as evidenced in both reported documentation and our case. Prenatal corticosteroids administration for fetal maturation is also indispensable to optimize fetal prognosis. The only fall back is the patient's deteriorating renal function, which is postulated to be due to tacrolimus nephrotoxicity, pregnancy in advanced chronic renal insufficiency and the natural course of her diabetic nephropathy. This case also reaffirms the concept that thorough antepartum counseling and cautious monitoring of maternal, fetal and graft conditions by multidisciplinary specialties are keys to favorable pregnancy outcomes.

Conflict of interest statement

No conflict of interest.

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