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Successful Term Pregnancy in an Intestine-Pancreas Transplant Recipient With Chronic Graft Dysfunction and Parenteral Nutrition Dependence: A Case Report

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Abstract

Pregnancy after solid organ transplantation is becoming more common, with the largest recorded numbers in renal and liver transplant recipients. Intestinal transplantation is relatively new compared to other solid organs, and reports of successful pregnancy are far less frequent. All pregnancies reported to date in intestinal transplant recipients have been in women with stable graft function. The case reported here involves the first reported successful term pregnancy in an intestine-pancreas transplant recipient with chronic graft dysfunction and dependence on both transplant immunosuppression and parenteral nutrition (PN) at the time of conception. Pregnancy was unplanned and unexpected in the setting of chronic illness and menstrual irregularities, discovered incidentally on abdominal ultrasound at approximately 18 weeks' gestation. Rapamune was held, tacrolimus continued, and PN adjusted to maintain consistent weight gain. A healthy female infant was delivered vaginally at term. Medical complications during pregnancy included anemia and need for tunneled catheter replacements. Ascites and edema were improved from baseline, with recurrence of large volume ascites shortly after delivery. Successful pregnancy is possible in the setting of transplant immunosuppression, chronic intestinal graft dysfunction, and long-term PN requirement, but close monitoring is required to ensure the health of mother and child.

Intestinal transplantation is rapidly becoming more established as a treatment modality for intestinal failure with life-threatening complications, such as loss of vascular access or intestinal failure-associated liver disease. As more patients are surviving and regaining reproductive function, it is critical to recognize the options for female patients and the care required for successful pregnancy in this unique population. Successful term pregnancy has been reported in 6 intestinal transplant recipients, all with stable graft function [1–4]. The case reported here describes a patient who lost a majority of her small bowel from superior

mesenteric artery injury during resection of a desmoid tumor. She was the recipient of a heterotopic en-bloc intestine and pancreas transplant with preservation of the remaining native pancreas. She had a complex post-transplant course, with chronic rejection necessitating long-term parenteral nutrition (PN). In the setting of chronic graft dysfunction and home PN use, she carried a pregnancy to term and delivered a healthy infant. Information gained from management of this pregnancy is critical for understanding the approach needed to care for this unique patient population and the counseling required from consideration of conception to birth.

CASE DESCRIPTION

A Hispanic female with no significant past medical history and 2 healthy children presented to an outside facility at age 23 with progressive abdominal fullness. An 8 × 6 cm mid-abdominal mass was discovered on imaging. Surgical resection involved part of the duodenum, head of the pancreas, and the mesentery with its blood supply. She became unstable over the next 48 hours and on surgical exploration was found to have ischemia and necrosis of the entire small bowel and right colon, requiring subtotal enterectomy. Tumor pathology revealed a low-grade gastrointestinal stromal tumor (GIST), spindle cell type. She was started on parenteral nutrition (PN) and referred to our center for intestinal transplant evaluation in the setting of nonreconstructible gastrointestinal tract. Her first tunneled catheter was placed and she was discharged on PN after completion of transplant evaluation.

Seven months after her initial presentation, she received an en bloc intestine and pancreas transplant. Liver biopsy at the time of transplant showed 90% macro and microvesicular steatosis without fibrosis or inflammation. She was discharged 2 months post-transplant on full enteral feeds and on warfarin for partial thrombosis of the mesenteric vein. Ostomy was taken down 5 months post-transplant. For the first 3 years post-transplant, she had stable graft function on tacrolimus and sirolimus. She was on an all-enteral regimen with no central line and was able to return to work part time.

At age 26, going into the fourth post-transplant year, she had a period of variable compliance with her medication regimen, mainly due to social stressors and separation from her husband. Endoscopy 6 months later revealed multiple ulcerations in the graft and she was treated with a 7-day methylprednisolone pulse and taper. She was discharged on full enteral feeds. She remained stable on an enteral regimen for 9 months.

At age 27 and age 28, she presented with intrauterine pregnancies at 8 and 14 weeks despite efforts to avoid pregnancy and use of contraception. She chose to terminate both pregnancies after extensive counseling regarding the risks, history of variable graft function, and potential exposure to teratogenic medications and infections, including cytomegalovirus viremia around the time of the first pregnancy. She experienced steady decline in graft function over the next several years. Multiple episodes of biopsy-proven rejection and loss of mucosal architecture on imaging were treated with methylprednisolone pulse, infliximab, and OKT3. She was restarted on enteral diet, but due to poor absorption, a central line was placed and she was started on PN. Over the next 3 months, she developed ascites and edema,

slightly responsive to dilation of a vascular anastomosis to her graft. She had her third central line placed due to infection, subsequently removed due to dysfunction.

At age 30, she was again treated with a methylprednisolone pulse, then anti-thymocyte globulin 10 mg/kg for moderate acute cellular rejection. A new tunneled central line was placed and retransplant evaluation was completed. She had multiple infectious complications and had 2 additional central line placements over the next year. She was relisted for intestine and pancreas transplant due to chronic graft dysfunction, with wait list time extended due to highly sensitized status, with multiple positive donor specific antibodies. She was treated with high-dose IVIG. Plasmapheresis was not an option due to progressively limited vascular access. She remained dependent on PN due to chronic rejection/graft dysfunction for a majority of her calories. She had intermittent problems with ascites due to compromise of mesenteric venous flow.

At age 33, she was admitted for ascites and an upper GI bleed. Liver biopsy showed >60% steatosis and patchy obliteration of the central vein branches. She was then listed for a liver inclusive graft due to progressive intestinal failure-associated liver disease. At age 34, she complained of worsening ascites at a routine clinic visit. Ultrasound was ordered for further assessment, which revealed an intrauterine pregnancy at approximately 18 weeks. This was unexpected as she reported condom use, typically had irregular menses, and did not have any symptoms of pregnancy. At this time, she was on PN and was taking tacrolimus and sirolimus. PN included complete caloric support compressed to 12 hours overnight, with daily lipids. Other medications at the time included fluconazole, ferrous sulfate, furosemide, enoxaparin, Co-trimoxazole, vitamin C, and ergocalciferol. Extensive counseling was provided from the transplant team and high-risk obstetrics. She chose to proceed with this pregnancy. She was placed on internal hold for liver/intestine/pancreas transplant. Sirolimus was held when the pregnancy was discovered and tacrolimus was continued in an effort to prevent acute on chronic rejection and for maintenance of the pancreas graft. PN volume and calories were titrated up to allow for appropriate weight gain. As PN multivitamin only contained 600 µg folic acid, a prenatal vitamin regimen was started, although absorption was in doubt due to continued graft dysfunction. The tunneled catheter was replaced twice during pregnancy. She was admitted at 20 weeks for fever and at 27 weeks for symptomatic anemia, requiring packed red blood cells, followed by outpatient intravenous iron infusions.

She had regular prenatal care once pregnancy was discovered. Ultrasounds revealed a normally developing female fetus. Oral glucose tolerance test was normal and glucose levels were normal without insulin despite increase in PN dextrose over the course of the pregnancy, indicating stable function of the pancreas graft. Weight gain was sluggish at first but picked up appropriately closer to term. A ventral hernia became more prominent closer to term. Oral intake decreased, stools remained loose with stable volume. She required increasing furosemide dosing closer to term for lower extremity edema.

A healthy female infant was delivered at term (39 1/7 weeks) by normal spontaneous vaginal delivery without complications. Apgar scores were 5 and 9. Thick meconium was noted. Birth weight was 3090 g. She required a 3-day hospital stay for delivery. Breastfeeding was considered briefly, then decided by the delivering physician to be too

high risk for mother and baby. PN was slowly titrated back down to baseline volume and calories after delivery. Sirolimus was restarted several weeks after delivery. She developed a *Pseudomonas* infection at her CVC exit site, which recurred 3 times despite IV antibiotics. She developed large volume ascites, requiring paracentesis with drainage of 6 L of fluid.

Three months postpartum, at age 35, she was doing well with no significant reaccumulation of ascites. She was within 2 pounds of her base weight. Major complaints were hair loss and emesis of old food. Nuclear medicine gastric emptying study revealed severe gastroparesis with 6% emptying at 90 minutes, and she was started on metoclopramide. The tunneled catheter was again replaced due to exposed cuff and persistent exit site infection. She remained on internal hold for transplant pending full recovery from pregnancy. The infant continued to do well, with no signs of health or developmental problems.

DISCUSSION

Pregnancy after solid organ transplantation has become more common, with most of the available data focused on recipients of renal or liver grafts. The first pregnancy in a renal transplant recipient was reported in 1958, and in a liver transplant recipient in 1978 [5,6]. Thousands of pregnancies have been reported since, in recipients of renal, liver, cardiac, lung, and pancreas transplants, allowing for collection of registry data and assessment of risks [7]. The National Transplantation Pregnancy Registry (NTPR) was developed in 1991 to determine trends and outcomes, and as of 2010, had data on 2000 U.S. pregnancy outcomes [8]. Based on registry data, 71% to 76% of pregnancies in renal transplant recipients and 50% to 86% in other organ recipients result in a live birth. The rate of birth defects is similar to that in the general population, except in the case of mycophenolate exposure (23% risk) [8]. Children have been followed for up to 20 years without any alarming trends in development or overall health [8].

End stage organ disease typically leads to impaired fertility. As seen with the case presented here, this should not be assumed even in the setting of menstrual irregularities, and counseling should be provided both pre- and post-transplant. Planned pregnancy should be considered 1 to 2 years post-transplant, with stable graft function on reduced immunosuppression, stable blood pressure, and absence of infectious complications [9]. Hypertension and renal dysfunction are common after solid organ transplant, and these conditions are commonly associated with complications of pregnancy [10]. The risks of pre-eclampsia, preterm delivery, and intrauterine growth restriction are elevated in this population [11,12]. In a large case-control study of liver transplant recipients in the U.S., there was a 2-fold increase in risk of antepartum admission for liver transplant patients, and 17% of these admissions were for hepatic complications [13]. As demonstrated by the case presented here, anemia is one of the most common reasons for antepartum admission and should be closely monitored [14,15]. Rates of acute rejection and graft loss for liver transplant patients during and closely following pregnancy were not significantly different compared to the general transplant population [16]. Cesarean section and obstetric/perinatal complications are more common in transplant patients, requiring a multidisciplinary approach to prenatal care and counseling [8].

Intestinal transplantation is relatively new compared with other solid organ transplantation, and reports of successful pregnancy are rare to date (Table 1). Pregnancy after intestinal transplantation was first reported in 2006, in a 23-year-old woman who had undergone liver transplant for biliary atresia at age 2.5 years, followed by small bowel herniation, intestinal failure, and intestinal transplant 11 years later. She delivered a healthy term infant while in her early 20s, during a period of stable graft function on tacrolimus [3]. Two additional cases were reported in 2012. The first described a 26-year-old woman who had extensive bowel resection following gastric bypass surgery, due to internal herniation that occurred during a pregnancy at 20 weeks gestation, resulting in pregnancy loss [1]. She underwent successful isolated intestinal transplant and had stable graft function when she presented with an unplanned pregnancy at 13 weeks gestation. Immunosuppression at the time was with prednisone and tacrolimus. Pregnancy complications included elevated creatinine and anemia. Graft function remained stable and labor was induced at 39 weeks, leading to delivery of a healthy female infant. She had an episode of rejection 3 months after delivery treated with polyclonal antithymocyte globulin with restoration of normal graft function [1]. The second described a woman with en-bloc intestine, liver, and pancreas transplant in childhood due to intestinal pseudo-obstruction and intestinal failure-associated liver disease [4]. At age 19, and 12 years post-transplant, she presented with an unplanned pregnancy at about 8 weeks' gestation. She had stable graft function at the time, maintained on tacrolimus, sirolimus, and prednisolone. Graft function was maintained throughout pregnancy. She had a spontaneous vaginal delivery of a healthy infant at 39 weeks, and sirolimus was held briefly after delivery to allow for wound healing [4]. The center reporting the first pregnancy has since reported 3 additional successful near-term/term births in intestinal transplant patients with stable graft function [2]. The common factor linking these cases, despite the fact that at least 2 were documented as unplanned, is that the patients all had adequate and stable graft function. This is a consensus criterion for timing of a planned pregnancy after solid organ transplantation [7]. The case presented here is unique in that the patient had chronic dysfunction of the intestinal graft, requiring relisting for a liver inclusive graft. She was dependent on both transplant immunosuppression and long-term PN, with associated liver disease, at the time the pregnancy was discovered. Management of the pregnancy required a multidisciplinary approach, with contributions from high risk obstetrics, transplant surgery, gastroenterology, and hematology.

The need for post-transplant immunosuppression presents a challenge in the pregnant patient. All commonly used immunosuppressant medications cross the placenta [17]. Safety data are limited in pregnancy since properly controlled trials cannot be completed in a pregnant population. The patient presented here was on a regimen of tacrolimus and sirolimus at the time pregnancy was discovered. Sirolimus was stopped when pregnancy was discovered, but the fetus was exposed for about half the term gestational period before the medication was stopped. Maintaining an intestinal graft on tacrolimus monotherapy is not typically possible, but was deemed acceptable in the setting of chronic graft dysfunction to minimize potential risk to the fetus, and was restarted once she recovered from delivery. Tacrolimus concentrates in the placenta and can reach 3 times maternal levels, but levels in the fetal circulation are less than half maternal levels [18]. Mouse studies suggest a risk of abnormal fetal growth and development, but outcomes seen in humans do not suggest an

increased risk of malformations [19,20]. In a study of 100 pregnancies on tacrolimus, there was no increased risk of malformations compared to the general population and no specific patterns were identified [21]. Information on sirolimus is less readily available, but animal studies have suggested risk of decreased fetal weight and delayed skeletal ossification. In combination with cyclosporin, there was an increased risk of fetal death [22]. Successful pregnancy after early exposure to sirolimus has been reported in case reports, including in the intestinal transplant population, as detailed above [4]. Infants exposed to immunosuppressive medication in general may have a transient immune dysregulation, which self resolves but may impact response to vaccinations [23]. Tacrolimus does pass into breast milk [24], but blood levels in breastfeeding infants are generally undetectable and the estimated dose ingested by the infant is 0.32% of the maternal dose [25]. In the current case, the patient expressed interest in breastfeeding but was discouraged by her obstetrician and ultimately exclusively formula fed her infant.

The case presented here is unique in that the patient, in addition to transplant immunosuppression, required long-term PN for chronic intestinal graft dysfunction. Use of PN during pregnancy is well-reported in the short term. It is considered safe and effective for treatment of conditions related to pregnancy, such as hyperemesis gravidarum [26,27]. Pregnancy in the setting of long-term PN, while more infrequently reported, is considered safe without evidence of increased PN-associated complication rates [28]. Two pregnancies were reported in the same patient with chronic intestinal pseudo-obstruction (CIPO), with the first occurring after 6 years on PN [26,28]. At the time of the first pregnancy, this patient was 30 years old and receiving PN 5 nights a week, indicating some enteral absorption. The pregnancy was without complications with adequate maternal weight gain and normal fetal growth, and the infant was delivered at 36 weeks. PN was increased from 5 to 7 days per week during the period of breastfeeding [26]. Twenty months after delivery, the same woman became pregnant again, and delivered a healthy infant at term without any complications related to PN [28]. A successful pregnancy was more recently reported in a woman who had been on PN since infancy for chronic intestinal pseudo-obstruction, a total of 24 years at the time of conception. She required emergency cesarean delivery at 33 weeks for fetal distress, but the baby had normal Apgar scores and did well. Nutritional support was increased during pregnancy and weight gain was appropriate [29].

Maternal nutritional status is critical during pregnancy to ensure the health of the developing fetus. In a patient with intestinal graft dysfunction and questionable absorption, it is critical to ensure adequate weight gain and regular multidisciplinary follow-up. Estimated needs during pregnancy are about 300 kcal/day and 30 g/day protein over basal requirements [27]. Requirements for essential fatty acids also increase during pregnancy, to ensure proper brain development in the fetus [30]. Regular daily infusions of vitamins and minerals should be included in the parenteral formulation throughout pregnancy. High dextrose infusions and changes in glucose tolerance during pregnancy may necessitate addition of insulin [29]. Anemia during pregnancy is associated with lower birth weight [31], and in the setting of iron deficiency, intravenous replacement should be considered when absorption is questionable.

As intestinal transplant becomes more common, and survival increases, it is critical to understand the options for successful pregnancy and the potential risks to the mother. Pregnancy is possible in the setting of transplant immunosuppression and chronic PN for intestinal graft dysfunction. The patient described here did well over the course of her pregnancy, with ascites under better control than in the periods immediately before conception and after delivery. Major issues were anemia and central access complications. She was able to deliver vaginally despite multiple abdominal surgeries and ventral hernias in the pelvic region. She did not have any significant changes in graft function during pregnancy, although PO intake did decrease, and the pancreatic graft remained stable on tacrolimus monotherapy, with no insulin needs despite increase in dextrose infusion. Ideally pregnancy would be timed for periods of stable graft function, but in the case of unexpected conception, it is critical that patients are counseled on the risks and followed closely by a multidisciplinary team to ensure the optimal health of the mother and child.

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Table 1

Reported Successful Pregnancies in Intestinal Transplant Recipients

Reference	Age	Graft type	Years post-ITx	Immunosuppression	Outcome
Kosmach-Park 2006 [3]	23 y	Isolated intestine	11 y	Tacrolimus	Healthy term female, NSVD
Srivastava 2012 [4]	19 y	Intestine, liver, pancreas	12 y	Tacrolimus, Sirolimus, Prednisolone	Healthy term male, NSVD
Gomez-Lobo 2012 [1]	26 y	Isolated intestine	~3 y	Tacrolimus, Prednisone	Healthy term female, induced
Kosmach-Park 2013 [2], n = 3	26–30 y	Not reported	3–14 y	Tacrolimus (n = 3), Prednisone (n = 1)	35–39 w.k. all healthy, cesarean × 3