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CASE REPORT

# Kidney transplantation during a twin pregnancy. Case report and review of the literature

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**Abstract** Kidney transplant in a pregnant woman is exceptional, with only six cases being reported. Pregnancy was not known at the time of the transplant in five of these cases. We report the case of a 26-year-old woman who was diagnosed as carrying a twin pregnancy 4 months after starting hemodialysis. In order to improve the survival chances for the twins, she underwent an orthotopic renal transplant from a living donor at 20 weeks of gestation. The allograft functioned immediately and 4 weeks passed without incident. At the 26th week of gestation, the patient had a precipitous labor, delivering two male babies with no malformations, weighing 755 and 890 g, who died due to respiratory failure. The allograft worked normally afterwards. Sixteen months later, the patient delivered a normal 37 weeks' gestation baby. The renal graft continued working normally for the next 20 years, after which signs of chronic allograft nephropathy developed. Azathioprine was replaced with mycophenolate mofetil. At the last evaluation, 23 years after transplant, the patient's serum creatinine was 2.9 mg/dl and her estimated glomerular filtration rate (eGFR) was 22 ml/min/1.73 $m^2$. This unique case demonstrates that it is possible to perform an orthotopic kidney transplant in a 20-week twin-gestation, with a long graft survival time.

**Keywords** Pregnancy, multiple · Kidney transplantation · Allogeneic transplantation · Cyclosporine · Azathioprine · Mycophenolate mofetil

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## Introduction

The probability of pregnancy in a patient on hemodialysis (HD) is low, given the marked reduction in the fertility of women with kidney failure. However, pregnancy occurs in approximately 1 % of patients undergoing dialysis, usually within the first several years of starting the procedure. Although 42 % of women receiving HD who are of childbearing age continue menstruating, many of their cycles are likely anovulatory [1]. The diagnosis of pregnancy in HD patients is often difficult, because levels of beta-human chorionic gonadotropin (b-hCG) are usually elevated in women receiving dialysis; therefore, when pregnancy is suspected, ultrasonography should be performed. Pregnancy is generally not advisable for patients on HD, as the fetal outcome is poor. Only 23–55 % of pregnancies result in live infants; of these, 85 % are born premature and 28 % are born small for gestational age [2, 3]. Maternal morbidity is also high, and arterial hypertension worsens in more than 80 % of pregnant women on dialysis, sometimes even resulting in maternal deaths [2, 4]. The management of a pregnant patient on HD includes the increase in the frequency and duration of dialysis sessions, up to 6 days per week, attempting to keep the blood urea nitrogen

(BUN) below 50 mg/dl, which may avoid polyhydramnios, control hypertension, and improve the mother's nutritional status [2, 3, 5]. It has also been recommended to use erythropoietin and to place the patient on a kidney transplant (KTx) list, given that successful KTx markedly improves fetal prognosis [2]. This last recommendation is based only on six case reports [6–12]. In five of these, pregnancy was not known at the time of KTx and in the other case, it was suspected [10].

This communication, to the best of our knowledge, is the first KTx performed intentionally on a woman carrying a confirmed pregnancy, as well as the first performed on a patient bearing a twin pregnancy, and in an orthotopic position.

## Case report

A woman who had mesangiocapillary glomerulonephritis diagnosed when she was 6 years old had a pregnancy at age 20 years, which was terminated by cesarean section; the newborn was healthy and followed a normal development. At age 26 years, the patient developed a uremic syndrome (BUN 169 mg/dl, serum creatinine 17 mg/dl). She had not had a medical checkup during the intervening 6 years. The patient started HD in August, 1987.

In October, 1987, she was evaluated by an obstetrician because of menometrorrhagia and severe anemia (hematocrit 13 %), with a normal gynecological examination. The upper gastrointestinal endoscopy showed mild antral gastritis and a bone marrow smear revealed erythroblastic hyperplasia with slight dyserythropoiesis. Ferrous sulphate, folic acid, and vitamins were prescribed.

Four months after the initiation of HD, due to a menstrual delay of 2 weeks associated with vomiting, her physician requested a pregnancy test, which was positive. It was thought that the pregnancy had little chance to succeed and miscarriage was expected soon. The patient continued on HD, 4.5 h per session, three times a week, using methyldopa for hypertension. Because of progressive anemia (hematocrit 12 %), she received 6 units of red blood cells.

One month after diagnosing the pregnancy, an ultrasound revealed an approximately 10 weeks' gestation of two fetuses. Ultrasound was repeated after 5 weeks, confirming two active fetuses, with a posterior placenta and normal amniotic fluid. The gestational age was estimated to be 17 weeks.

Her sister, with whom she had no HLA mismatches, offered to donate a kidney to save the twins, and the patient accepted. The case was presented to the ethics committee of the hospital, which authorized the KTx, considering that it was ethically irreproachable to try to save the twins, who had little probability of survival if the mother remained on dialysis. At the time, there was only one published report of a KTx on a patient who was already pregnant (at 12 weeks' gestation), which had a good outcome for both the mother and the child.

On March 17 1988, at the 18th week of gestation, she was admitted to the obstetric unit in order to prepare her for kidney transplantation. She was anemic (hematocrit 16 %, hemoglobin 5.5 g/dl) and malnourished (body mass index [BMI] 19 kg/m$^2$, serum albumin 3.2 g/dl). She remained on hemodialysis for 4.5 h each session and her BUN ranged from 60 to 86 mg/dl. At the 19th gestational week, the sonography showed both twins in shoulder presentation, their biparietal diameters (BPD) were 46 and 47 mm, abdominal circumferences 45 and 46 mm, femur lengths 28 and 28 mm, tibias 24 and 25 mm, and radiuses 25 and 25 mm. The placenta was biamniotic, in the posterior position, and there was moderate polyhydramnios. It was concluded that fetal development was adequate. Fenoterol was used to avoid uterine contractions.

The patient was given three whole blood transfusions from her sister, along with 100 mg of azathioprine (AZA), at intervals of 15 days each, to reduce the possibility of rejection of the graft during the pregnancy, given the high titer of antibodies against lymphocyte panel.

At 20 weeks of gestation (March 29, 1988), after administrating 150 mg progesterone and 1 g of methylprednisolone (MPDN), an orthotopic KTx was performed on the left flank, since the size of the abdomen did not allow localizing the kidney in the usual position. The renal artery of the graft was anastomosed to the aorta, at the origin of its own renal artery; the renal vein of the graft was anastomosed to the renal vein of the patient and the renal pelvis of the graft to the renal pelvis of the recipient. A nephrostomy was left for protection. General anesthesia with halothane and epidural anesthesia with bupivacaine was used. The reactive antibodies against a panel of lymphocytes was 45 % in the days previous to the surgery and the cross-match between the donor and the recipient was negative. Immunosuppression was continued with 100 mg of AZA with the addition of 60 mg of prednisone (PDN), antibiotic prophylaxis with cefazolin, and antihypertensive therapy with hydralazine and methyldopa. The graft started to function immediately and azotemia decreased rapidly. On the sixth post-transplant day, the patient's BUN was 14.5 mg/dl and her serum creatinine was 1.1 mg/dl. One day after transplant, uterine contractions developed, which were controlled with fenoterol. On the fifth day post-KTx, jaundice was noted, associated with pruritus and slight elevation of aminotransferases, which were attributed to a cholestasis associated to methyldopa, which was withdrawn. In the following days, the hepatic disorder disappeared. On the sixth day post-KTx, an ultrasound showed

both fetuses in good condition and discrete polyhydramnios. Oral fenoterol to avoid uterine contractions and weekly progesterone (150 mg) was used. Twelve days after transplantation, ultrasound showed normal fetal movements. One fetus was in cephalic and the other in breech presentation. Their measurements at that moment were: BPD 56 and 58 mm, femur length 38 and 39 mm, and abdominal circumference 65 and 65 mm. The gestational age was estimated to be 22 + 5 weeks. At the 30th day after transplantation, a new ultrasound revealed increased amniotic fluid and live fetuses. The BPDs were 64 and 64 mm, femur length 43 and 43 mm, abdominal circumference 70 and 64 mm, and there were two amniotic sacs. The gestational age was estimated to be 25 + 3 weeks. It was stated that one of the fetuses had reduced its abdominal circumference.

The patient remained hospitalized without complications and 1 month after transplant, she was authorized to visit her home for a weekend. She returned 2 days later in labor, which could not be stopped. At 32 days post-transplant and at 25 and 5/7 weeks of gestation, the patient delivered vaginally two males babies of birth weight 890 and 755 g who had an Apgar test of 1 after one min and 6 after 5 min. The first twin was born by cephalic delivery and the second by incomplete breech delivery. Their lengths were 35 and 32 cm; both had a cranial circumference of 25 cm. The twins were both intubated and connected to oxygen. They were not ventilated because, at that moment, there were no available mechanical ventilators at the neonatology unit. Both infants died 4 h later due to respiratory failure. The amniotic fluid contained meconium, indicating the presence of fetal distress. In the following days, the patient developed endometritis, which responded to antibiotics. She was discharged 43 days post-KTx with normal kidney function (serum creatinine 0.60 mg/dl, creatinine clearance 115 ml/min/1.73 $m^2$).

Seven months after the KTx, and while undergoing treatment with AZA 125 mg, PDN 10 mg, and nitrendipine 20 mg daily, a new pregnancy was diagnosed. Sixteen months post-KTx, she gave birth by cesarean section to a healthy baby of 37 weeks' gestation who weighed 3,240 g. One year later, she underwent tubal ligation by laparoscopy.

In the first 5 years after KTx, the allograft functioned normally (serum creatinine 0.9 mg/dl, estimated glomerular filtration rate ([GFR] by Cockcroft–Gault 136 ml/min); the only intercurrent conditions were one episode of lower urinary tract infection and shingles. Ten years after KTx, her renal function was adequate (serum creatinine 1.37 mg/dl, eGFR 68 ml/min), and the only complication was a duodenal ulcer that was treated with ranitidine. Twenty years after transplantation, proteinuria was detected (1,452 mg/24 h) and the graft function began to deteriorate slowly (serum creatinine 2.6 mg/dl, eGFR 31 ml/min), which was attributed to a chronic allograft nephropathy. It was decided not to perform a renal biopsy, but, instead, to change AZA to mycophenolate mofetil (MMF) 1,250 mg/day; this was associated with the stabilization of kidney function. In the most recent visit, 23 years after KTx, the patient's serum creatinine was 2.9 mg/dl and her eGFR was 22 ml/min.

## Discussion

The first KTx on a pregnant woman was performed in 1979 [8]. To date, six transplants have been performed during pregnancy and published in the literature: five of them during undiagnosed pregnancies and one in which there was suspicion of pregnancy prior to transplantation [6–12]. Four women were nulliparous at the time of transplantation, two were second transplants, and three were performed using live donors. The age of the recipients ranged from 18 to 36 years, and time spent on dialysis ranged from 5 months to several years. Three of the six pregnancies were discovered by accident during routine ultrasound assessment of the kidney graft and one studying a painful abdominal mass. Pregnancy diagnosis was made between day 5 and 100 after kidney transplant. Gestational age at the time of transplant varied from 10 to 13 weeks. Vaginal delivery was performed in four births and cesarean section in two. All the newborns were premature, with weights ranging from 870 to 2,948 g. Four of them presented perinatal complications, secondary to prematurity (hyperbilirubinemia, respiratory distress due to hyaline membrane disease, and gastroesophageal reflux).

Three newborns presented congenital malformations. One of them was exposed to MMF and tacrolimus since the 6th week, presenting finger and nail hypoplasia and bilateral shortening of the fifth fingers. There is one previous communication in humans of this malformation with the use of MMF, being categorized as C drug during pregnancy, so it is possible to think that MMF may have had a causal role in the defects observed [13]. In animal teratogenicity assays, head and eye malformations as well as diaphragmatic hernias have been described [14–16]. In humans, microtia, auditory canal atresia, cleft lip and palate, micrognathia, hypertelorism, diaphragmatic hernia, and ocular coloboma are related to MMF use [13, 16]. Digital malformations have been related to alcohol and phenytoin use during pregnancy in humans and nifedipine in animals; nevertheless, this patient had not received any of them. Tacrolimus is considered to be a safe drug to use during pregnancy, without presenting any increase in malformation rate with its use. There are no digital defects related with this drug [17–19]. Another infant had two

**Table 1** Characteristics of the seven women who underwent kidney transplantation during pregnancy

| Year of transplant and authors | Age of recipient (years) and previous pregnancies | ESRD etiology | Time on dialysis | Donor | Pregnancy diagnosis | Diagnosis of pregnancy | Gestational age at KTx | Immunosuppression |
|---|---|---|---|---|---|---|---|---|
| 1979 Burleson et al. [8] | 18, nulliparous | Congenital renal abnormalities | 5 months | Live | 1 week after KTx | Accidentally during ultrasound of kidney graft | 11–13 weeks | Azathioprine and prednisone |
| 1984 Solá et al. [11] | 23, nulliparous | Nephronophthisis | 2 years | Deceased | 12 days after KTx | Accidentally during ultrasound of kidney graft | 11–12 weeks | Azathioprine and prednisone |
| 1985 Davis et al. [7] | 36, multiparous | Chronic pyelonephritis | Several years | Deceased | 1 month after KTx | Ultrasound due to painful mass in lower abdomen | 12 weeks | Azathioprine, cyclosporine, and prednisone |
| 1994 Miller et al. [10] | 31, nulliparous | Lupus nephritis | One year, previous KTx | Deceased | Suspected before KTx | Ultrasound due to slight increase in b-hCG | 10 days | Antithymocyte globulin, azathioprine, cyclosporine, and prednisone |
| 1996 Pérgola et al. [9] | 33, multiparous | Unknown | One year, previous KTx | Live | 100 days after KTx | Ultrasound due to absence of menses and weight gain | 6–7 weeks | Tacrolimus, mycophenolate mofetil, and prednisone |
| 2005 Hold et al. [6] | 23, nulliparous | Unknown | Approaching hemodialysis, GFR 15 ml/min | Live | 5 days after KTx | Accidentally during ultrasound of kidney graft | 12 weeks | Cyclosporine and prednisone |
| 1988 Vega et al. | 26, multiparous | Mesangiocapillary glomerulonephritis | 4 months | Live | Before KTx | In dialysis | 20 weeks | Azathioprine and prednisone |

*KTx* kidney transplant, *ESRD* end-stage renal disease

**Table 2** Maternal, infant, graft complications and outcome

| Year of transplant and authors | Maternal complications after KTx | KTx complications | Site of allografting | Type of delivery and gestation age | Gender, weight, and outcome | Infant's complications | Birth defects | Graft outcome |
|---|---|---|---|---|---|---|---|---|
| 1979 Burleson et al. [8] | Uterine cramps | Acute cellular rejection, DGF, hypertension | Right iliac fossa | Spontaneous vaginal, 34–35 weeks | Female, 1,870 g, alive | Prematurity, mild hyaline membrane disease, hyperbilirubinemia | Hypothyroidism secondary to a lingual thyroid, atrial septal defect | Stable renal function during 2.5 years of follow-up |
| 1984 Solá et al. [11] | Hypertension | Two acute rejection episodes | Heterotopic | Cesarean section, 34 weeks | Male, 1,490 g, alive | Prematurity, esophageal reflux | Pyeloureteral junction stenosis | Stable renal function after the last acute rejection episode |
| 1985 Davis et al. [7] | Abdominal cramps, abruptio placentae | DGF, presumed acute rejection | Right iliac fossa | Cesarean section, 28 weeks | Female, 870 g, alive | Prematurity, hyaline membrane disease, hyperbilirubinemia, patent ductus arteriosus, adrenocortical suppression secondary to exogenously steroids | None | She was discharged on dialysis but graft function improved after |
| 1994 Miller et al. [10] | Hypertension | CMV reactivation | Unknown | Spontaneous vaginal, 38 weeks | Male, 2,640 g, alive | None | None | Stable renal function in the 1 year follow-up |
| 1996 Pérgola et al. [9] | Gestational diabetes, obesity, pancytopenia, pre-eclampsia | Graft dysfunction and proteinuria. Renal biopsy: focal foot process fusion | Unknown | Induced, 34 and 3/7 weeks | Female, 2,250 g, alive | Apnea and bradycardia with feeds, requirement of oxygen supplementation, hyperbilirubinemia | Hypoplastic fingers and toenails, shortened fifth fingers bilaterally, aberrant blood vessel between trachea and esophagus | Stable kidney function in the 1 year follow-up |
| 2005 Hold et al. [6] | None | None | Unknown | Induced, 37 weeks | Male, 2,948, alive | None | None | Discharged with normal graft function |
| 1988 Vega et al. | Uterine cramps, cholestasis, premature delivery | None | Orthotopic (left side) | Spontaneous vaginal, 26 weeks | Male 890 g, died. Male 755 g, died | Prematurity, respiratory distress | None | Allograft functioning for 23 years |

*KTx* kidney transplant, *DGF* delayed graft function, *CMV* cytomegalovirus infection

development defects: lingual thyroid and interatrial septum defect, and the third infant a pyeloureteral junction stenosis. It is unlikely that the immunosuppression had a role in the defects of the two infants because transplantation was performed between weeks 11 and 13, knowing that organogenesis is almost completed at week 12 [8, 11, 12]. Uremic milieu of both patients may have participated in the occurrence of malformations. All the infants resulting from these six transplants during pregnancy survived. Maternal complications more frequently observed after kidney transplantation were hypertension and acute cellular rejection. Four patients received azathioprine, three cyclosporine, and one patient tacrolimus and MMF. Only one case was induced with antithymocyte globulin (ATG), during a second transplant. The most relevant data of these six case reports are shown in Tables 1 and 2.

Current recommendations suggest that women who undergo any type of organ transplant wait at least 18–24 months after surgery to become pregnant. This allows the graft time to stabilize its function and immunosuppression to achieve appropriate maintenance levels [20].

This clinical case shows that is possible to perform an orthotopic KTx during a twin pregnancy at 20 weeks of gestation, allowing it to continue for almost 6 weeks and obtaining neonates with a weight that, today, 23 years later, with the available technology, would have had a high probability of survival. This case also demonstrates that it is possible to have a long survival time for a kidney allograft with immunosuppression using AZA and corticoids, in spite of higher titers of antibodies against a panel of lymphocytes when the KTx is performed with a live donor during pregnancy, after performing donor-specific transfusions. It is also possible that the natural immunosuppression induced by pregnancy had an influence in the long survival time of the kidney graft in this patient.

It is not our intention to recommend a kidney transplant in pregnant women on dialysis. We just wanted to communicate an experience of almost a quarter century ago, when we performed a kidney transplant in a woman carrying a twin pregnancy because, at that time, it seemed to be the best alternative in order to result in viable twins.

During the 1980s, conception of a dialysis patient had only a 20 % chance of success. Severe transfusion-dependent anemia, polyhydramnios (due to fetal osmotic diuresis induced by elevated placental BUN), elevated risk of premature rupture of membranes of a twin pregnancy, hypertension, and acute extracellular volume changes and hypotension during dialysis sessions with compromised utero-placental circulation made it extremely difficult for the pregnancy to achieve viable fetuses [21]. This lead to the acceptance of the patient's sister's proposition of donating a kidney with the intention to try to save the twins. Successful transplantation would help to avoid the uremic milieu surrounding the twins' development, correct the anemia, and avoid hemodynamic events during dialysis.

Several transplant specialists were gathered in a meeting to discuss the risks of performing an orthotopic transplant on a malnourished, anemic, and hypersensitized pregnant patient against the potential benefits of a successful transplant. The decision to proceed with the transplantation was the choice of the group. Today, with the knowledge that dialysis six times a week in an attempt to be sure of reaching 20 h/week or nocturnal dialysis, to keep BUN levels less than 50 mg/dl with blood pressure tightly controlled with ultrafiltration and medications, fetal monitoring during dialysis, and the judicious use of erythropoietin, it is possible to increase baby survival up to 75–80 % in pregnant women on dialysis [1–3, 22]. We certainly would not decide to perform a kidney transplant as the first choice.

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