Successful Pregnancy in a Kidney Transplant Recipient With Chronic Hepatitis B Virus Infection

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Overall success rate of pregnancies in kidney transplant recipients is higher than 90% if pregnancy goes beyond the 1st trimester. Risks to mother include hypertension, preeclampsia, infections, and worsening proteinuria, and those to the fetus are prematurity, intrauterine growth retardation, and low birth weight. Hepatitis B infection is associated with progressive liver disease and diminished survival in kidney transplant recipients. A 32-year-old woman had undergone living unrelated donor kidney transplant. Two years after transplantation, she presented with live gestation of 6 weeks. She was also found positive for hepatitis B surface antigen and extracellular antigen. Liver enzymes were normal and ultrasonography findings were normal. Cyclosporine dose was reduced and lamivudine was started. She was monitored closely until 33 weeks, when she gave birth to a healthy female baby through spontaneous vaginal delivery. The newborn received vaccination and immunoglobulins for hepatitis B virus. Mother's kidney allograft function remained stable throughout pregnancy.

INTRODUCTION

The quality of life, longevity, and general functioning of patients with a kidney transplant are significantly better than those on dialysis awaiting a transplant.[1,2] Fertility is one of the physiologic functions that improve after kidney transplantation, due to improvement in gonadal physiology.[3,4] While successful outcome of pregnancy is possible in kidney transplant recipients with a well-functioning graft,[5] these pregnancies are generally high risk and are associated with a higher risk of pregnancy associated complications such as hypertension and preeclampsia.[4] Exposure to hepatitis B virus (HBV) during dialysis is a major concern, especially among patients planning to undergo a kidney transplant. Pregnant women suffering from HBV infection are at risk for having both maternal as well as fetal complications, including the chances of transmitting the infection to their babies.

We report an interesting case of a pregnancy in a 32-year-old kidney transplant recipient complicated by chronic HBV infection during the course of gestation.

CASE REPORT

A 32-years-old woman with chronic kidney disease of unknown etiology (small kidneys) progressed to end-stage renal disease and underwent living unrelated kidney transplant at another center. She had an episode of acute cellular rejection 6 months after her transplant, which was managed with intravenous steroids. She also suffered from recurrent urinary tract infections. She had developed chronic allograft nephropathy with a baseline serum creatinine of 2.5 mg/dL. Before transplant, her hepatitis B surface antigen (HBsAg), hepatitis C antibody, and hepatitis B surface antibody were all negative. At that time,

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she was vaccinated against HBV, but she did not achieve an adequate antibody response.

Two years after her transplant, she presented to the transplant clinic with gestational amenorrhea of 6 weeks duration. There had been no history of jaundice in the past. Her physical examination was unremarkable except for marked obesity and mild pallor. Her blood pressure was within normal limits. Her ultrasonography examination revealed a gestational sac of 6 weeks. On routine antenatal screening at the 10th week of pregnancy, HBsAg was found to be reactive. Her liver function tests showed aspartate aminotransferase of 15 IU/L; alanine aminotransferase, 31 IU/L; direct bilirubin, 0.1 mg/dL; and alkaline phosphatase, 58 U/L. Her prothrombin time was 11.7 seconds against a control of 12 seconds and her serum albumin was 3.9 g/dL. Her hepatitis B extracellular antigen (HBeAg) was reactive with hepatitis B viral load (HBV DNA) of 40 000 000 copies per milliliter. Her hepatitis D antibody was reactive, but hepatitis D virus DNA was undetectable. Findings of abdominal ultrasonography were within normal limits. She was diagnosed to have chronic hepatitis B infection (CHB) along with past exposure to hepatitis D. She was started on lamivudine, 25 mg/d (dose adjusted according to creatinine clearance), which she tolerated well.

Her liver function tests remained stable throughout the course of pregnancy. Due to poor compliance, her HBV DNA and HBeAg could not be checked again while she was pregnant. Her serum creatinine increased from an average prepregnancy level of 2.3 mg/dL to an average level of 2.7 mg/dL during pregnancy. Her 24-hour urine studies showed a creatinine clearance of 23 mL/min and protein excretion of 284 mg. Serial ultrasonography confirmed a low-lying placenta (previa type II), while fetal growth appeared to be satisfactory with cephalic presentation.

Considering the pregnancy, cyclosporine was reduced from the prepregnancy dose of 100mg, twice a day, to 75 mg, twice a day. Other immunosuppressive drugs including azathioprine, 75mg/d, and prednisolone, 10 mg/d, were continued in the same dose. Methyldopa was added for better blood pressure control. She was also started on prophylactic antibiotics in light of her history of recurrent urinary tract infections. Close monitoring was carried out with monthly follow-ups of clinical parameters, along with liver and kidney function tests and regular obstetric reviews until the successful conclusion of pregnancy.

At 33 weeks of gestation, she had a spontaneous normal vaginal delivery after an episode of antepartum hemorrhage. The female baby weighed 2080 g and remained stable postnatal with an APGAR score of 9 at 5 minutes. Precautions were taken to avoid transmission of HBV to the neonate, including administration of hepatitis B immunoglobulin and hepatitis B vaccine at birth. The baby received both active and passive immunization within 12 hours of delivery, and later completed the 3 doses HBV vaccination schedule. The baby was found to be HBsAg negative. The mother was advised against breast feeding and future pregnancies. The patient was later switched to entecavir 3 months after delivery. Her HBV DNA levels continued to fall progressively and on her latest follow-up in July 2011, it was below detection level (less than 50 copies per milliliter) with an alanine aminotransferase level of 15 IU/L.

DISCUSSION

A successful pregnancy in a kidney transplant recipient can be predicted by the preconception graft function and time interval between transplant and conception.[6] Ideally, transplant recipients should wait at least 2 years posttransplantation before planning a pregnancy.[7] The American Society of Transplantation Consensus Opinion has recommended that pregnancy can be safely planned in a patient with a well-functioning graft, defined as serum creatinine less than 1.5mg/dL, protein excretion less than 500mg/24h, and absence of teratogenic medications, as well as stable doses of immunosuppressants at maintenance level.[8] Graft function may worsen during pregnancy due to preeclampsia, acute rejection, allograft obstruction, and urinary tract infections.[9] Studies have shown that pregnancy does not appear to cause major effects on graft outcome if the function is stable prior to pregnancy.[10-12]

In kidney transplant recipients, the principal risks to the fetus are prematurity, preterm labor, intrauterine growth retardation (IUGR), and low birth weight.[11,13] Up to 40% of babies delivered by kidney transplant recipients suffer from IUGR.[14,15] Mean gestational age at delivery in this population is reported to be 34 weeks, with maternal blood

pressure and graft functions predicting the risk of prematurity.[10,11,16] Furthermore, prematurity and associated complications are important issues encountered in babies born to patients suffering from acute or chronic forms of HBV infection during pregnancy.[17]

In our case, the time interval between kidney transplant and pregnancy was almost 2 years, but her baseline serum creatinine was greater than 2mg/dL. Despite having chronic graft dysfunction, her pregnancy ran an uncomplicated course with good control of blood pressure and only slight worsening of graft function. Although our patient had multiple risk factors for premature birth and IUGR, including kidney transplantation, moderate graft dysfunction, and CHB infection, yet her pregnancy ended up with good maternal as well as fetal outcomes. She delivered at 33 weeks of gestation and the baby was healthy and did not suffer from IUGR.

In Pakistan, the reported prevalence of HBV infection in pregnant women is 5.9 ± 5.0%.[18] The prevalence of HBsAg positivity among asymptomatic pregnant women in North India is 1.1%, with 71% having high HBV DNA levels.[19] These women may have a high risk of transmitting infection to their newborns. The American College of Obstetrics and Gynecology and the American Association for the Study of Liver Diseases guidelines suggest that HBsAg-positive mothers should be evaluated and managed early without delaying it to the postpartum period.[20] Majority of HBsAg positive patients will do well during pregnancy, with exception of a few who may develop significant liver disease and complications such as cholestasis, flare of HBV infection, and hepatic failure.[21-23] Women suffering from HBV infection who have higher viral loads are more likely to transmit HBV to their babies.[24] Thirty five percent to 50% of all CHB carriers are believed to be infected through vertical transmission.[25] There is a greater risk of vertical transmission if the infection is acquired late in pregnancy or early postpartum.[26,27] Up to 60% of pregnant women who acquire acute HBV infection close to delivery transmit HBV to their infants.[26] A positive HBeAg test in pregnant mothers has been found to predict an even higher vertical transmission risk.[28] Hence, the treatment goal for CHB in pregnancy is to achieve stabilization of liver function in mothers

and prevent HBV infection in newborns.[29]

How to treat CHB during pregnancy is an important issue. Interferon is contraindicated in pregnant women due to its potential ability to inhibit cell proliferation. Hence, it has been recommended for individuals under treatment with interferon to avoid pregnancy at least till 6 months after discontinuation of interferon.[29] One year treatment with nucleos(t)ide analogues in nucleoside-naive patients with HBeAg-negative CHB, results in high rates of undetectable levels of HBV DNA (51% to 93%) and normalization of alanine aminotransferase levels (62% to 78%), but low rates of HBsAg loss (<1%).[30] However, extending treatment with tenofovir to 4 to 5 years could maintain viral suppression in 83% of patients. Virus resistance to nucleos(t)ide analogues ranged from zero to 27% after 1 year of therapy to zero to 80% after 5 years of therapy with the lowest resistance rate of zero by tenofovir.[30]

Currently, tenofovir (category B in pregnancy) or entecavir (category C in pregnancy) are the preferred antiviral therapy for HBV infection during pregnancy, because of minimal chance of developing viral strains resistant to therapy and better efficacy.[23,31,32] Moreover, it is recommended that patients who are on immunosuppressive therapy be on antiviral therapy even if they are inactive carrier as there is a high risk of reactivation of HBV, which may lead to liver failure and death in 80% to 100% of patients.[33,34]

Occult HBV infection is a condition which has been reported in up to 58% patients on regular dialysis.[35] Many of occult HBV patients remain negative for all HBV markers except HBV DNA. However, up to 50 % and 35% of them could be positive for hepatitis B core antibody and hepatitis B surface antibody, respectively.[35,36] Hence, occult HBV is relatively common in high-risk cases, including patients on hemodialysis, those receiving immunosuppressive therapy, and HIV-infected patients. Therefore, the risk of HBV transmission is high in these groups and screening of high-risk groups is recommended.[36]

Our patient was HBsAg negative before her transplant and it was found to be reactive during her pregnancy after kidney transplant. It is likely that she might have acquired the infection from the donor (whose HBV status was not known) or sometime later in the early posttransplant period.

Moreover, possibility of underlying occult HBV and its reactivation after transplant could not be ruled out. Once found to have CHB, she needed antiviral therapy for her own disease as well as to reduce the risk of perinatal transmission. We used lamivudine in renal adjusted doses as our patient was post kidney transplant, with a creatinine clearance of 27 mL/min in the setting of pregnancy and on immunosuppressive therapy. Tenofovir was not used because it was not an approved drug for HBV infection in 2008, while lamivudine was preferred over entecavir due to good safety data in pregnancy, and also because its dose could be adjusted safely for graft dysfunction. Although she was advised to start antiviral therapy earlier in the second trimester, she happened to be relatively poorly compliant and was lost to follow-up. We could not get serial HBV DNA levels done (to monitor the viral activity) and that was again due to issues with compliance to investigations and treatment.

Generally, in transplant recipients, vaginal delivery is recommended, with caesarean section only preformed for routine obstetric indications.[11] Although there is no consensus on mode of delivery in hepatitis B-infected mothers, some data suggests caesarean section may reduce vertical transmission.[37,38] However, this is not protective in the absence of active and passive vaccination by hepatitis B immunoglobulin at birth.[39] This combination is effective in preventing mother-to-child transmission of HBV in 95% of the cases. While breast feeding is discouraged in patients taking immunosuppressive medications, it poses no additional risk of transmission in HBV-carrier mothers with proper immunoprophylaxis of the infant.[40,41]

In the presented case, the odds of conceiving and carrying out a pregnancy were low at the onset due to poor graft function. Presence of CHB infection in this pregnant immunocompromised woman made it even more complicated and difficult to manage. However, with intense and close monitoring, adjustment of immunosuppression, timely use of lamivudine, and a multidisciplinary team effort between obstetrics, hepatology, and nephrology services resulted in a successful outcome. Four years later this patient still had stable graft and liver function and has a healthy 4-year old daughter who was negative for HBV.

CONFLICT OF INTEREST

None declared.

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