Successful Pregnancy and Delivery in a Heart Transplantation Recipient

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Summary

For 6 years after heart transplantation, a 23-year old female recipient had been treated with immunosuppressants including tacrolimus and mycophenolate mofetil (MMF), without any major rejection or graft dysfunction. She unexpectedly became pregnant for the first time, and we converted MMF to azathioprine (AZA), but she soon experienced a spontaneous abortion. After careful counseling under the continuation of AZA, she became pregnant again 3 months after the abortion. We closely monitored the concentration of immunosuppressive agents, cardiac function, fetal condition, and serological assay including human leukocyte antigen (HLA) sensitization, and she eventually delivered a normal male infant at 38 weeks gestation without any complications. AZA was converted to MMF soon after the delivery. There have been no complications in either the patient or infant after the delivery.

Because pregnancy itself involves a risk of cardiac graft rejection in the recipient as well as fetal complications, it is important to educate HTx recipients about planned pregnancy and to conduct careful follow-up after pregnancy. (Int Heart J 2016; 57: 383-385)

Key words: Immunosuppressive agents, Graft rejection

Recent advances in heart transplantation (HTx) treatment including surgical techniques and immunosuppressive agents have improved the long-term prognosis of HTx patients. The survival rates at 1 and 5-years worldwide have been reported as 85% and 69%, respectively,1 and the survival rate is even better in Japan.2 Consequently, the chance of pregnancy after heart transplantation is increasing in young female recipients. Although there are a few reports from overseas of pregnancy after HTx,3 no definite guidelines exist concerning its management. In Japan, successful pregnancy after HTx has never been reported. We here report the first case of a successful pregnancy and delivery in a Japanese HTx recipient.

Case Report

A 23-year old female with dilated cardiomyopathy had received HTx in the United States 7 years previously. The post-HTx procedure was uneventful with the standard immunosuppressive therapy consisting of tacrolimus (TCR), mycophenolate mofetil (MMF), and low dose prednisolone.

Despite receiving detailed instructions concerning planned pregnancy, she unexpectedly became pregnant for the first time one year earlier and was then diagnosed as 7 weeks gestation. We immediately converted MMF to azathioprine (AZA) (100 mg/day), but she experienced a genital hemorrhage a few days later and subsequently suffered a spontaneous abortion.

Because she desired to conceive again after careful counseling, we continued AZA instead of MMF. Because the blood concentration of AZA (6-thioguanine nucleotides; 6-TGN) was low (94 pmol/8×108 RBC) soon after administration, we raised the dose to 150 mg/day. The concentration of 6-TGN was 234 pmol/8×108 RBC 3 weeks later so we continued with the same dose (Figure).

She became pregnant again 3 months later. Echocardiography revealed normal left ventricular function and there was no evidence of human leukocyte antigen (HLA) sensitization. She had been carefully followed-up as an outpatient by a multidisciplinary team that included cardiologists, obstetricians, and transplant coordinators. Routine blood tests and echocardiography revealed no abnormalities and abdominal ultrasonography showed no complications like fetal growth re-
Due to proteinuria of 1.3 g/day at 37 weeks gestation, she was admitted to our department. Echocardiography on admission revealed normal cardiac function and her immunosuppressive agents consisted of TCR and 150 mg/day of AZA. The trough concentration of TCR was maintained around 3-6 ng/mL. At 38 weeks 4 days gestation, rupture of the membrane was observed and epidural anesthesia was performed to reduce cardiac stress. She delivered a normal male infant (3122 g, APGAR score 4/8) transvaginally without any major complications.

No severe graft dysfunction or infection was observed during the puerperal period and she was discharged 5 days later. Soon after delivery, AZA was switched to MMF (750 mg/day). Considering the translocation of these drugs to milk, bottle-feeding was continued. One month later we performed a routine catheter study. Cardiac function and intra-cardiac pressure were normal and endomyocardial biopsy (EMB) showed only mild cellular rejection with International Society for Heart and Lung Transplantation (ISHLT) grade 1R. She and her child experienced no major complications afterwards.

**DISCUSSION**

The management of pregnancy after HTx is challenging and should be monitored carefully by a multidisciplinary team. Because the number of young females among HTx recipients at a reproductive age is increasing, appropriate management strategies for the pregnancy after HTx should be developed. After the first report of a pregnancy in a post-HTx patient in 1988, some case reports have been published, although various matters remain unknown about the management and outcome of the pregnancy among HTx recipients.

In the case of pregnancy after HTx, there could be multiple complications including acute graft rejection and fetal complications. The US National Transplantation Pregnancy Registry in 2009 reported that HTx recipients experienced higher acute graft rejection (21%) compared with other solid organ transplant recipients. Although most of them were mild and required no specific treatment, some presented with severe rejection accompanied by graft loss. Ginwalla, et al reported a case of severe cardiac allograft vasculopathy and graft loss because of pregnancy-related HLA sensitization. In cases of past spontaneous abortion like our case, the risk of HLA sensitization elevates, and such patients should be monitored closely for cardiac graft rejection. Therefore, we should educate HTx recipients that pregnancy itself may enhance their own risk of cardiac dysfunction.

How should we construct an immunosuppressant strategy in case of pregnancy? Calcineurin inhibitors (CNI) and prednisolone are allowed in pregnant HTx recipients from the viewpoint of the lower risk of teratogenicity and fetal toxicity (FDA pregnancy category C).

In contrast, MMF is classified as FDA pregnancy category D, and should be discontinued during pregnancy, because MMF enhances the risk of teratogenicity, especially in the first trimester. Though there are many risk factors for the development of spontaneous abortion including smoking/drinking during pregnancy, and endocrine disorder or coagulation disorder...
(eg, anti-phospholipid antibody syndrome; APS) in the mother, no such factors were observed in the present patient. We concluded the primary reason for the abortion was the MMF.

ISHLT guidelines recommend the use of AZA in place of MMF during pregnancy as class IIb, since the safety of AZA in infants has not been established. We switched MMF to AZA, and continued CNI and AZA therapy taking into consideration the risk of rejection reaction. With regard to the concentration of TCR, the ISHLT guideline recommends maintaining its range between 5-10 ng/mL 6 months after HTx. However, there is no definite recommendation about the target range of the concentration of AZA (usually measured as its active metabolites; 6-TGN) among HTx recipients because of its volatility. Generally, its target concentration for clinically significant immunosuppressive effect without a major adverse event is reported to be about 230-400 pmol/8×10^6 RBC, so we aimed at this range.

Everolimus, one of the mammalian targets of rapamycin (mTOR) inhibitors, may be another agent to be administered during pregnancy. Although everolimus is classified as FDA pregnancy category D and there are no appropriate studies about its use in pregnancy, a study reported it can be used during pregnancy if at a low-dose. Everolimus is a promising drug for preventing renal dysfunction and cytomegalovirus infection in HTx recipients with maintaining a low rejection risk. However, it should be discontinued when a cesarean section is planned because of its delayed wound healing.

In HTx female recipients, the incidence of spontaneous abortion is reported to be 15-20%, which is higher than that of non-transplantation mothers, partially because of the teratogenicity induced by immunosuppressive agents. These immunosuppressive agents should be used on the basis of the balance between the risk to the mother and the fetus. Furthermore, newborn children have a higher risk of infection and sometimes cause transmission to an immunocompromised mother. Appropriate vaccination of both the mother and child in the postpartum period is also essential in order to prevent infection.

Because catheter study and EMB cannot be performed during pregnancy, it is important to evaluate graft function appropriately in advance. Though there is no definite guideline, it is preferable that no evidence of rejection (ISHLT grade 0) is observed before pregnancy.

To the best of our knowledge, this is the first case of successful pregnancy and delivery in a post-HTx recipient in Japan. Preconception counseling, appropriate evaluation of graft function, and monitoring of immunosuppressive agents and the fetus are necessary in HTx recipients who are pregnant or may become pregnant.

REFERENCES