

## A Successful Pregnancy and Delivery after Heart Transplantation: The First Case Report from Korea

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Pregnancy following heart transplantation is a high-risk condition, requiring adequate maintenance of immunosuppressive drugs that enable proper graft function for optimal maternal and fetal outcomes. Here, we present the first case of successful child delivery in a patient who underwent heart transplantation in Korea. The 35-year-old female patient had become pregnant at 4 years after heart transplantation. The pregnancy progressed uneventfully, and the infant was healthy.

**Key Words:** Heart transplantation, Pregnancy, Delivery, Immunosuppressant

**중심 단어:** 심장이식, 임신, 출산, 면역억제제

### INTRODUCTION

Heart transplantation is a widely accepted procedure for patients with end-stage heart disease who are refractory to medical therapy. The number of women of childbearing age who have received heart transplants has risen partly due to the overall increase in heart transplantation in adults as well as increased rate of pediatric heart transplant recipients surviving to childbearing age(1). After receiving transplantation, most patients regain fertility and may consider pregnancy(2). However, pregnancy in heart transplant recipients imposes significant risks to the mother, graft, and the fetus(3). Such pregnancies carry increased risk of obstetric complications including pre-eclampsia, spontaneous abortions, low birth weight, and intrauterine growth re-

striction (IUGR)(4,5).

In South Korea, a total of 1,354 transplantations have been performed since 2000; of those, female cardiac transplant recipient population accounts for 32% of all recipients, and 38% of them are of childbearing age(6). However, there has been no reported case of successful child delivery in Korean heart transplant recipients. This may be because transplantation and immunosuppressive drugs can act as major limitations to the success of a pregnancy, the latter of which is essential for maintaining graft function and recipient survival(7). We here report the first Korean case of successful child delivery in a patient who underwent heart transplantation.

### CASE REPORT

A 35-year-old patient in the 38th week of her first pregnancy was admitted to the obstetrics clinic at Asan Medical Center due to IUGR. At the age of 26, the patient had been diagnosed with dilated cardiomyopathy; her family medical history revealed that her older brother died from sudden cardiac death before the age of 18, and that her mother also

Received May 9, 2018

Revised June 22, 2018

Accepted June 22, 2018

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suffered from dilated cardiomyopathy and received heart transplantation at our institution. The patient's exercise capacity deteriorated between the age of 30 and 31, and she began to suffer from dyspnea at rest. In May 2013, the patient received a heart allograft from a 26-year-old donor, and since then has received immunosuppressive treatment consisting of tacrolimus and mycophenolate on schedule, with no rejection episode being noted. A coronary angiogram was performed in June 2016, which showed no cardiac allograft vasculopathy. Her condition remained stable and in September 2016, she decided to have a baby if her condition allowed. Mycophenolate mofetil, which is classified as pregnancy category D by the U.S. Food and Drug Administration (FDA)(8), was discontinued. We kept her in immunosuppressed state by treating her with tacrolimus (4 mg/day) and methylprednisolone (2 mg/day). Six months later in May 2017 (4 years after heart transplantation), her urine pregnancy test was positive. Her echocardiogram revealed that her cardiac function was stable with left ventricular ejection fraction (LVEF) at 65%. The whole blood-trough target level of tacrolimus was 6 to 8 ng/mL. Based on the blood level, the dosage of tacrolimus was progressively increased to 9 mg/day from 4 mg/day before pregnancy (Table 1). During pregnancy, antenatal care was performed in a timely manner and no obstetrical complication was found. After discussion among obstetricians and cardiologist, the patient underwent cesarean section at the gestational age of 38 weeks. Her pre-pregnancy weight was 56 kg and she weighed 60 kg on the day of surgery (January 9th, 2018), and had good overall physical condition with normal circulation and respiration. Echocardiography showed hyperdynamic left ventricular (LVEF=70%). Fetal ultrasound showed signs of IUGR as previously noted, and the monitored flow in the umbilical artery was normal. The patient fasted overnight and no pre-operative

medication was administered except for the immunosuppressive agents. Tacrolimus was orally treated at 4.5 mg/12 hours until the morning of surgery. Perioperative stress-dose steroid was not given. The patient gave birth to a baby boy with a birth weight of 2,985 g. The new-born son was in good general condition with the Apgar score of 9 and without signs of growth restriction. The patient continued to receive oral tacrolimus at 4.5 mg/12 hours, and breast feeding was not allowed in order to prevent the infant from being exposed to the immunosuppressant. The patient made full recovery with no complications, and was discharged 3 days after delivery. Follow-up was carried out at 1 month, and no abnormality was found.

## DISCUSSION

In South Korea, female cardiac transplant recipient population accounts for 32% of all recipients(9), and 38% of them are of childbearing age. Our current report describes the first Korean case of a heart transplant recipient who gave birth to a healthy child. Clinical practice regarding pregnancy management in women after transplantation of vital organs is mostly based on expert recommendations, and there are no guidelines constructed on the basis of randomized controlled trials due to the small number of heart transplant recipients(2,4,5). The considerations for cardiologists providing care for female heart transplant recipients include pre-conception counseling, maternal and fetal risks during gestational period, intrapartum and post-partum care, and breast feeding. A multi-disciplinary team involving specialists in maternal medicine, cardiology, transplant medicine, anesthesiology, high-risk nursing, neonatology, psychology, and social service is recommended for taking care of such patients throughout their pregnancies and the post-partum periods(9).

**Table 1.** The immunosuppressive concentrations and doses, and cardiac function during pregnancy

|                                | Pre-pregnancy | First trimester | Second trimester | Third trimester | Post-partum |
|--------------------------------|---------------|-----------------|------------------|-----------------|-------------|
| Tacrolimus blood level (ng/mL) | 7.3           | 5.9             | 5.7              | 6               | 8.6         |
| Tacrolimus dose (mg/day)       | 5             | 6               | 9                | 9               | 3           |
| LVEF (%)                       | 65            | 60              | 64               | 70              |             |

Abbreviation: LVEF, left ventricular ejection fraction.

Most experts recommend that cardiac transplant recipients avoid pregnancy during the first year of post-transplantation(3,9) when the risk of graft rejection is greatest and immunosuppressive therapy is most aggressive. Female heart transplant recipients wishing to become pregnant must be informed of both the possible influence of immunosuppressants on fetal development and the high number of complications pertaining to pregnancy and transplantation(10,11). Such complications include arterial hypertension(12), pre-eclampsia, infections (especially viral), IUGR, and preterm birth(11-14). Unassisted discontinuation of immunosuppressive medication during pregnancy may lead to transplant rejection(15), and changes in the body's immune response associated with pregnancy may result in the development of antibodies in the human leukocyte antigen (HLA) system, which may lead to the loss of the transplanted organ(16). The International Society for Heart Lung Transplantation (ISHLT) guidelines recommend that women contemplating pregnancy should undergo full cardiac assessment 6 months prior to conception. This includes coronary angiography, echocardiography, and electrocardiography(9). Depending on the clinical circumstances, right heart catheterization and endomyocardial biopsy may also be required(9).

During pregnancy, blood volume increases significantly by an average of 40%. This increase begins in the 6th week of pregnancy and reaches a peak in the 32nd week of pregnancy. Cardiac output increases by 30% to 50% and heart rate also increases by 10 to 20 bpm. Systemic blood pressure decreases in the first and second trimesters, and is restored to pre-gestational levels at the end of pregnancy. The most evident change is elevation in end-diastolic volume(17). In transplant recipients, cardiac output is usually reduced and ventricular compliance is smaller than that in the normal ventricle, which is maintained by the high central venous pressure(18). Intracardiac pressures are normal at rest, but ventricular diastolic pressure drastically increases during physical exertion. If such changes occur in a pregnant transplant recipients, they can adversely affect the heart in terms of increase in cardiac contractility, central venous pressure, blood volume, and cardiac output(19,20). These hemodynamic changes are usually well tolerated by transplant recipients during pregnancy(21).

Most immunosuppressive agents are designated as category C by the U.S. FDA in terms of their safety for use in pregnant women(8); nevertheless, immunosuppressive agents must be administered to transplant recipients during pregnancy(15). Currently, treatment with azathioprine, tacrolimus, glucocorticoids, and cyclosporin is allowed in pregnant women(22,23), and blood levels of immunosuppressive drugs should be monitored closely and adjusted on a case-by-case basis. We recommend that the target immunosuppressive blood level should be adjusted in the same manner as the post-transplant recommendations. Careful dosing adjustments are needed because the increase in circulation plasma volume can affect the blood level of immunosuppressive drugs(24). The need for these agents during pregnancy usually increases, and various clinical situations such as anemia or concurrent therapy with agents that inhibit the enzymes of hepatic cytochromes may require further dose adjustments. However, there is currently no standard immunosuppressive protocol for pregnant transplant recipients. We have shown that through the trimesters of pregnancy, a significant increase in the total daily doses of calcineurin inhibitors (CNIs) is required to maintain a therapeutic level. Similar findings have been described in pregnant heart(2) and renal(25,26) transplant recipients. Kim et al.(27) reported that a 20% to 25% dose increase in CNIs is necessary during the gestational period. To adjust the immunosuppressive dosage based on stable blood level before pregnancy is our feasible experience. We would suggest even more frequent CNI trough levels in the first two trimesters to minimize the risk of significantly reduced levels culminating in rejection. Mycophenolate mofetil and sirolimus should be discontinued approximately 6 weeks before planned pregnancy in order to avoid the risk of fatal congenital defects(27). Statins remain contraindicated and should be stopped(28,29). After delivery, the levels of immunosuppressive drugs should be checked regularly and doses should be adjusted to maintain adequate immunosuppression.

Female patients with heart transplants have been documented to tolerate vaginal delivery, and cesarean section should only be indicated for obstetric reasons(24); in practice, however, the rate of cesarean section in female transplant recipients is high(30,31). Stress-dose steroids during

delivery have been recommended for patients on chronic maintenance steroids. The decision to give perioperative supplemental glucocorticoid should be tailored on an individual basis with special consideration given to the patients. During childbirth, cardiac output is elevated by up to 25% by uterine contractions, which cause an increase in venous return(32); therefore, strict cardiac monitoring is required. In the early post-partum period, an increase in pre-load may occur due to blood drainage from the uterus to peripheral circulation, a situation that may require medical intervention. During puerperium, cyclosporine and tacrolimus levels tend to increase, thus requiring a decrease in their daily doses(33).

There is no consensus on immunosuppressant drug levels in breast milk, but breastfeeding is generally discouraged in order to avoid the risk of passing immunosuppressive drugs, particularly cyclosporine and tacrolimus, to the baby(33). The American Society of Transplantation stated that breastfeeding need not be viewed as absolutely contraindicated(3). The International Society for Heart and Lung Transplantation guidelines note that it is uncertain whether the risks of infant drug exposure outweigh the benefits of breastfeeding, and they do not recommend that heart transplant recipients breastfeed(9).

To our knowledge, this is the first successful case of parturition by a heart transplant recipient in Korea. The successful outcome of this case can be attributed to the involvement of an interdisciplinary team as well as good cooperation by the patient.

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