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Management of Pregnancy in the Post-Cardiac Transplant Patient

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Abstract

Over the past 10 years, heart transplantation survival has increased among transplant recipients. Because of improved outcomes in both congenital and adult transplant recipients, the number of male and female patients of childbearing age who desire pregnancy has also increased within this population. While there have been many successful pregnancies in post-cardiac transplant patients reported in the literature, long-term outcome data is limited. Decisions regarding the optimal timing and management of pregnancy in male and female post-cardiac transplant patients are challenging and should be coordinated by a multidisciplinary team of healthcare providers. Pregnant patients will need to be counseled and monitored carefully for complications including rejection, graft dysfunction, and infection. This review focuses on preconception counseling for both male and female cardiac transplant recipients. The maternal and fetal risks during pregnancy and the postpartum period, including risks to the fetus fathered by a male cardiac transplant recipient will be reviewed. It also provides a brief summary of our own transplant experience and recommendations for overall management of pregnancy in the post-cardiac transplant recipient.

Introduction

The first pregnancy and delivery post-solid organ transplant occurred in 1958 in a renal transplant recipient.^{1, 2} In 1988, the first pregnancy in a post-cardiac transplant patient was reported in a female patient with a history of a dilated cardiomyopathy who conceived less than 2 years post-transplant.^{1, 3, 4} Since then, data published in case reports along with outcomes data from the National Transplantation Pregnancy Registry (NTPR) have demonstrated many successful pregnancies in solid organ transplant recipients including in cardiac transplant patients.^{3, 5–11}

Worldwide, female patients represent approximately 20% of overall cardiac transplants.¹² Between 2006–2012, 25% of female cardiac transplant patients were between the ages of

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18–39 years old and were of childbearing age.¹² Females are also part of the growing population of surviving congenital cardiac transplant recipients. As this population ages, the number of female patients of childbearing age who desire pregnancy will also increase. As a result, healthcare providers should be familiar with the maternal and fetal risks associated with pregnancy in general, including risks to the fetus fathered by a male cardiac transplant recipient, as well as understanding the unique management challenges during pregnancy that arise while caring for a cardiac transplant recipient. These include assessment of graft function, rejection, immunosuppressive medications, and infection. Integration of this information by healthcare providers as part of a multidisciplinary care plan is essential in order to provide the patient an adequate assessment of overall risk and appropriate care throughout pregnancy and the postpartum period.

Preconception Counseling & Baseline Risk Assessment

Ideally, preconception counseling should begin in all patients during their pre-transplant evaluation and throughout their post-transplant care.¹³ Pre-transplant, pregnancy is contraindicated in women with stage D heart failure due to the increase in the overall metabolic needs and increased hemodynamic load associated with pregnancy. Both women with stage D heart failure and those with advanced mechanical support devices such as left ventricular assist devices should be strongly counseled on birth control. Females with mechanical support devices are able to conceive and have had successful pregnancies. Two patients who conceived and delivered on mechanical support have previously been reported.^{14, 15} In contrast, male patients with severe heart failure frequently are impotent but implantation of mechanical support devices and subsequent cardiac transplantation can often ameliorate this problem and these patients require genetic counseling for those with inherited cardiomyopathies.

In a cardiac transplant recipient, natural conception is a safe option. In vitro fertilization is also another option that has been successful in post-cardiac transplant patients.¹⁶ The International Society of Heart and Lung Transplantation (ISHLT) 2010 guidelines recommend the involvement of a multidisciplinary team of healthcare providers from transplant cardiology, maternal and fetal medicine, neonatology, psychology, genetics, and social services.¹⁷ If possible, the management plan should be coordinated at the cardiac transplant facility with the involvement of other members of the multidisciplinary team.

Preconception counseling should include assessment of overall risk to both mother and fetus. The patient should be counseled on the risk of pregnancy-specifically on the risk of acute rejection, graft dysfunction, infection, and the possible teratogenic effects of immunosuppressive medications. For female cardiac transplant recipients who consider pregnancy, the risk of allograft rejection during conception should be discussed. At our center, prior to conception, we request that fathers undergo human leukocyte antigen (HLA) testing. If the female cardiac transplant recipient's donor and the father share the same antigen, and particularly if the recipient already has donor specific antibodies to this HLA locus, then conception could provoke allograft rejection and the patient is counseled about the heightened risk to her graft.¹⁸ For male cardiac transplant recipients, there is no need for HLA testing in the mother.

The underlying etiology of the initial heart disease leading to transplant must be considered since certain transplant patients may require more detailed preconception counseling. A mother's pre-transplant diagnosis, especially of congenital heart disease or genetic disorders, can affect a child's outcome as well. Children of mothers with a pre-transplant diagnosis of congenital heart disease have up to a 10% risk of congenital heart disease.^{4, 19} As such, early fetal screening for congenital heart disease may be warranted in this population. Likewise, children born to mothers with a pre-transplant genetic condition are also at a higher risk for developing the same genetic disease.^{4, 20, 21} As such, transplant recipients need to be counseled on the risks of possible transmission of the disease to their unborn child. In our own transplant experience, a female patient with carnitine deficiency who subsequently underwent cardiac transplant at our center gave birth to twins with the same genetic condition. We recommend early referral and consultation with a genetic counselor in females with pre-transplant genetic conditions ideally prior to pregnancy.

It is unknown if female patients with a pre-transplant diagnosis of postpartum cardiomyopathy are at increased risk of recurrence of postpartum cardiomyopathy in the transplanted organ. These patients appear to be at increased risk of rejection within the first year post-transplant and overall graft survival is shorter with an increased risk of re-transplantation.²² Our policy has been to advise against pregnancy for patients with prior postpartum cardiomyopathy.

Timing of Pregnancy

If a female cardiac transplant recipient chooses to conceive then the patient is counseled to delay pregnancy until at least 1 year post-cardiac transplant and to expect more intense surveillance of graft function as the risk of rejection during pregnancy may be increased. If there is a high risk of rejection or baseline graft dysfunction is not adequate, pregnancy should be discouraged or delayed until these risks can be minimized. While the ISHLT guidelines recommend that pregnancy should not be attempted less than 1 year post-cardiac transplant, several case reports have reported successful outcomes with varying time intervals from transplantation, some even as early as 3 months.^{10, 23}

Cardiac Assessment prior to Conception

Baseline electrocardiogram and graft function should be assessed preconception since a successful pregnancy is most likely to occur in a cardiac transplant recipient with normal graft function and no evidence of rejection.^{8, 10} If clinically indicated, dobutamine stress echocardiography or left and right heart catheterization with subsequent endomyocardial biopsy should be performed prior to pregnancy. If there is significant baseline graft dysfunction which would preclude a successful outcome, pregnancy should be discouraged.¹⁷ The hemodynamic changes associated with pregnancy, including an increase in cardiac output by as much as 30%, anemia, and volume expansion, are generally well-tolerated in the post-cardiac transplant patient as long as there is adequate graft function.^{5, 8, 10, 24}

Review of potential teratogenic immunosuppressive or other medications must be performed with a plan to alter these medications prior to pregnancy. Immunosuppressive medication

levels must be closely monitored. For example, cyclosporine metabolism is often increased during pregnancy.^{10, 25} As such cyclosporine dose may need to be increased during pregnancy and subsequently decreased post-delivery.^{10, 25} Mycophenolate mofetil has been shown to be teratogenic and counseling must be provided to all woman of childbearing age using this agent. Teratogenic effects associated with this drug are discussed in detail later in this chapter.

Ideally, vaccination history prior to cardiac transplantation should be up-to-date. However, in the post-cardiac transplant patient who wishes to become pregnant, immunizations should be reviewed. The patient should receive vaccinations against influenza, pneumococcus, hepatitis B, and tetanus.^{4, 13} However, live viruses should not be administered to any post-cardiac transplant patient since vaccination of an immunosuppressed patient with an attenuated live virus may result in systemic sepsis or even death.¹⁰

Risk of Spontaneous Abortion & Risk of Rejection

If pregnancy occurs, the risk of spontaneous abortion in the pregnant post-cardiac transplant patient is approximately 15–20%.¹⁰ Some authors report a higher percentage of spontaneous abortion associated with use of immunosuppressive medication.⁶ Mothers with a transplanted male spouse should also be counseled about this risk since immunosuppressive medications can cause a decrease in spermatogenesis, sperm viability, and an increase in spermatogenic abnormalities.^{26–30} As such, there is a concern that these spermatogenic abnormalities may cause an increase in genetic defects in the fetus leading to an increase in spontaneous abortions in the non-transplanted mother.

With regards to graft rejection, some authors have reported a higher risk in pregnancy. Among patients registered in the NTPR, rejection episodes were observed in 21% of patients. At least 40% of these reported rejections were mild and required no treatment.^{18, 20} The performance of right heart catheterization and endomyocardial biopsy during pregnancy with appropriate patient and fetus lead shielding during fluoroscopy or via echocardiography guidance appears safe and has been reported by some centers.^{7, 9, 10, 31, 32}

Currently, there is no consensus regarding the routine monitoring of HLA antibodies during pregnancy in a cardiac transplant recipient. However, this may be warranted in a patient with a spontaneous miscarriage post-transplant since de novo HLA sensitization post-pregnancy with subsequent graft failure has been reported.¹⁸ Rejection episodes have also been reported in patients after therapeutic abortion.¹⁰ It is our recommendation that patients who have a spontaneous or therapeutic abortion should be closely monitored for rejection.

Maternal & Fetal Complications During Pregnancy

a) Maternal Complications

Hypertension is the most common maternal complication in the pregnant post-cardiac transplant patient^{18, 33} and can lead to fetal growth restriction and preterm delivery.³² Once a patient is pregnant, frequent blood pressure assessments along with baseline renal and liver function tests should be obtained.¹⁷ Similar to the general population of pregnant women, the pregnant cardiac transplant patient should also be monitored for gestational diabetes,

pre-eclampsia, and eclampsia. Screening for asymptomatic urinary tract infections with routine urine culture is warranted since infections are the second most frequent maternal complication in the pregnant post-cardiac transplant patient¹⁰ and was reported in up to 11% of pregnancies in the NTPR data.³³

The pregnant post-cardiac transplant patient is also at risk for hyperemesis gravidum. This poses a particular problem in the cardiac transplant recipient since immunosuppressive medications may not be properly absorbed, placing the patient at increased risk of rejection. Immunosuppressive medication levels should be closely monitored and adjusted in patients with hyperemesis gravidum.^{10, 13}

Venous thromboembolism and pulmonary embolism are known risks in pregnant women throughout the pregnancy and postpartum period.^{34, 35} Cardiac transplant patients also have an elevated risk of thromboembolic disease.³⁶ It is unknown if the pregnant cardiac transplant patient is at an even higher risk compared to a pregnant healthy female patient. Clinical suspicion should remain high among healthcare providers taking care of the pregnant cardiac transplant recipient who presents with excessive shortness of breath. If thromboembolic disease is confirmed, appropriate anticoagulation that is safe to use in pregnancy should be initiated.

b) Fetal Complications During Pregnancy

It is well known that maternal health during pregnancy determines overall pregnancy and fetal outcomes. Hypertension, pre-eclampsia, and eclampsia increase the risks of fetal growth restriction, low birth weight, and preterm delivery. As the majority of cardiac transplant recipients develop hypertension from treatment with calcineurin inhibitors, it is not surprising that some authors have reported a higher rate of fetal preterm delivery and low birth weight among infants born to cardiac transplant recipients.^{32, 33, 37} Later on in life, these children are also at increased risk of noncommunicable diseases such as cardiovascular disease and diabetes.³⁸

As mentioned previously, prior to planned pregnancy, healthcare providers must review and counsel the patient regarding possible teratogenic medications, including immunosuppressive agents. All of the transplant immunosuppressive medications enter fetal circulation.²⁵ However, data regarding the pharmacokinetics and pharmacodynamics of immunosuppressive drugs and risk of fetal malformations is limited and has mainly been reported in observational studies and case series.^{33, 39–46} With regards to immunosuppression, both calcineurin inhibitors (CNI) and corticosteroids (CS) are classified as United States Food and Drug Administration (FDA) category C agents and can be continued.¹⁷ Of note, some authors have reported a risk of fetal growth retardation, low birth weight, and fetal immunosuppression especially with use of certain CNIs especially cyclosporine.^{10, 31, 37, 40, 44, 47} However, follow-up and long-term outcome studies have been limited and not consistently reported in studies.³⁷ The mammalian target of rapamycin (mTOR) inhibitors, everolimus and sirolimus, have not been tested in human pregnancy but in animal studies there is an increased risk of fetal abortions.⁴⁸ As these agents have been associated with poor wound healing,⁴⁹ if a cardiac transplant recipient is anticipated to require caesarian section then discontinuation of the mTOR inhibitor and transition to a

calcineurin inhibitor would be indicated. The antimetabolite, mycophenolate mofetil (MMF) is classified as a FDA category D agent and must be discontinued¹⁷ since case reports of fetal malformations with MMF have been reported.^{39,45} Azathioprine (AZA) has been used as a substitute for MMF therapy, however AZA is also a FDA category D agent. Data regarding risk of fetal malformation with AZA has been mixed.^{10,25,50} While the decision to use AZA as an alternative immunosuppressive agent should be based on the risk and benefits to both mother and fetus,¹⁷ avoidance of both agents is now recommended in the pregnant post-cardiac transplant recipient.¹⁷ Table 1 lists the common immunosuppressive medications and classes used in post-cardiac transplant care, the corresponding FDA pregnancy category, and the ISHLT 2010 guidelines regarding safety of use in pregnancy.

Maternal Complications During Delivery and the Postpartum Period

Decisions regarding mode of delivery in the pregnant post-cardiac transplant patient do not differ when compared to the general population. Risks and benefits are determined by the risk to the mother and fetus. There is a slight increased risk of infection with Cesarean section in patients on immunosuppressive medications⁴ and as such this should be taken into account while prepping a patient for delivery. From a cardiovascular perspective, use of prophylactic antibiotics should be in accordance with the 2008 ACC/AHA guidelines.⁵¹ While the routine use of prophylactic antibiotics is not recommended, transplanted patients who have had prior episodes of infective endocarditis in the graft, significant valvulopathy in the transplanted graft, or who have residual patches from prior cardiothoracic surgeries will need prophylactic antibiotics.⁵¹ Additionally, patients should be closely monitored for arrhythmias via continuous electrocardiogram.⁴ Invasive hemodynamic monitoring via Swan-Ganz catheter is not routinely recommended but may be warranted if significant rejection with graft dysfunction has occurred during the course of the pregnancy. If significant graft dysfunction has occurred which would place the mother and fetus at risk during vaginal delivery, we recommend a scheduled Cesarean section coordinated with a multidisciplinary team of specialists from transplant cardiology, maternal fetal medicine, neonatology, and cardiothoracic surgery at a facility where mechanical support is available if needed in the event of cardiogenic shock during delivery. While the most recent ISHLT guidelines do not address the type of anesthesia that should be used for delivery, some authors recommend the use of epidural anesthesia since it is well tolerated and provides effective pain control while minimizing the pain-induced sympathetic response.^{4,52}

Because of the hemodynamic changes and volume shifts that occur immediately post-delivery, the cardiac transplant patient is at highest risk during the immediate postpartum period.⁴ Similar to the shifts that occur during pregnancy, these postpartum hemodynamic changes and volume shifts are tolerated in a patient with normal graft function. Postpartum patients are also at risk of thromboembolism.³⁴ In one study, postpartum women who were hospitalized were at increased risk of venous thromboembolism and this risk lasted up to 1 month after hospitalization.⁵³

Risk of Infection from Newborn Child to Mother During the Postpartum Period

While the arrival of a newborn child is a joyous occasion for parents, it presents a particular challenge in the immunosuppressed patient with regards to an increased risk of infection. Newborns and young children have a higher susceptibility to infections which are often readily passed to caretakers within the household. Maintaining an appropriate vaccination schedule postpartum for both mother and child will be essential in decreasing risk of overall infection. Likewise, frequent and thorough hand washing after changing diapers is also recommended to prevent the risk of fecal-oral transmission from child to mother. Per the Infectious Disease Society of America (IDSA) 2013 guidelines, immunocompetent individuals including children and adults who live in a household with immunocompromised patients can safely receive inactivated vaccines based on the CDC-ACIP recommended vaccination schedule.⁵⁴ If live vaccines must be administered to the child, the transplant recipient should minimize contact including diaper changes (for children receiving rotavirus) while other household members assume the role of care provider. The length of time in which contact should be minimized varies by level of immunosuppression. For example, the IDSA guidelines recommend highly immunocompromised patients should avoid changing diapers for 4 weeks after a child is vaccinated against rotavirus.⁵⁴ Table 2 lists the different vaccination types and the Centers for Disease Control and Prevention recommended age for administration of the first vaccination dose in immunocompetent children. The transplant recipient should discuss the type of vaccination administered with the child's pediatrician during the postpartum period. Special attention should be made to those that are live vaccinations and which can be substituted with inactivated vaccinations such as the influenza and polio vaccines.

Breastfeeding and Management of Immunosuppressive Medications

During the postpartum period, levels of immunosuppressive medications should be checked regularly and doses adjusted to maintain adequate immunosuppression. In particular, patients on cyclosporine who may have had their dose increased during pregnancy due to the increase in metabolism observed during this period, may need to have their dose reduced postpartum.²⁵ All immunosuppressive medications are secreted through breast milk.²⁵ The long-term effects of immunosuppressive drug exposure on infants are unknown. As such, the ISHLT recommends against breastfeeding.¹⁷

Post-Delivery Contraception

Post-delivery, cardiac transplant patients may request or be offered contraception by their healthcare providers. Both barrier methods and combination hormonal contraception are acceptable methods of contraception in cardiac transplant patients. Prior to the use of combination hormonal contraception, patients will need to be screened for risk factors for a hypercoagulable state, hypertension, severe cardiac allograft vasculopathy, active liver disease, and estrogen-sensitive cancers.¹⁷ Both intrauterine devices (IUD) and depot-medroxyprogesterone acetate are contraindicated in cardiac transplant recipients due to increased risk of pelvic inflammatory disease with use of the IUD and decreased bone

density which has been associated with the long-term use of depo-medroxyprogesterone acetate.¹⁷

The Columbia Transplant Experience

At our transplant center, <1% of our adult cardiac transplant patients have had successful deliveries since the inception of the program in 1987. Because many of our young transplant recipients have had congenital heart disease or genetic cardiomyopathies as a pre-transplant diagnosis, a large number of our patients have elected not to have children or to adopt rather than risk transmission of genetic abnormalities. Of those who have elected to proceed with conception and pregnancy post-transplant, 3 have been woman and 10 have been men. The children born to the male recipients have all been healthy. Two of the 3 women bore children with the same pre-transplant diagnosis i.e. hypertrophic cardiomyopathy in one and carnitine deficiency in the other.

Summary

Preconception counseling in the post-cardiac transplant patient should ideally occur prior to initial transplant and readdressed by caretakers throughout the post-transplant period. In patients who wish to proceed with pregnancy, early involvement of a multidisciplinary team of specialists from transplant cardiology, maternal fetal medicine, neonatology, psychology, and social services is encouraged in order to provide patients with a complete assessment of risks and benefits of planned pregnancy and formation of a multidisciplinary care plan. Graft function and risk of rejection should be assessed at baseline. Immunosuppressive medication levels must be monitored closely and doses adjusted since medication levels may vary greatly due to the hemodynamic and volume changes that occur during pregnancy and in the postpartum period. The post-cardiac transplant patient is at a higher risk of complications both during pregnancy and in the postpartum period. Risks include hypertension, pre-eclampsia, eclampsia, infection, gestational diabetes, and thromboembolic disease, all of which can lead to adverse maternal, fetal, and neonatal outcomes. Postpartum contraception appears safe however breastfeeding is discouraged since the long-term effects of exposure to immunosuppressive medications on an infant are unknown. While there are many challenges in the management of the pregnant post-cardiac transplant patient, successful pregnancy outcomes can be readily achieved.

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Table 1

Immunosuppressive Agents, US FDA Pregnancy Category, and ISHLT 2010 Guideline Recommendations on the Use of Immunosuppressive Agents in Pregnancy

Medication & Class	FDA Pregnancy Category[*]	ISHLT 2010 Guidelines Recommendations
<i>Corticosteroids</i>		Can be continued in pregnancy, Level of Evidence C
Methylprednisolone	C	
Prednisolone	C	
Prednisone	D	
<i>Calcineurin inhibitors</i>		Can be continued in pregnancy, Level of Evidence C
Cyclosporine	C	
Tacrolimus	C	
<i>Mammalian target of rapamycin (mTOR) inhibitors[#]</i>		Concerns regarding wound healing; should be discontinued if Cesarean Section is planned
Everolimus	Low dose C High Dose D	
Sirolimus	C	
<i>Antimetabolites</i>		Should be discontinued in pregnancy, Level of Evidence C
Azathioprine	D	
Mycophenolate Mofetil	D	

^{*} FDA Pregnancy Category information as reported in Micromedex 2.0 ©

FDA Pregnancy Category C Definition: Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

FDA Pregnancy Category D Definition: There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

[#] Whether mTOR inhibitors can be continued in pregnancy is not specifically addressed in the ISHLT 2010 guidelines.

Table 2

Vaccination Type and Recommended Age of First Dose Administration in Immunocompetent Children

<u>Vaccination</u>	<u>Type</u>	<u>Recommended Age of First Dose Administration in Immunocompetent Children (Centers for Disease Control and Prevention)</u>
Diphtheria, tetanus, and acellular pertussis (DTaP)	Inactivated Bacterial	1 month
<i>Haemophilus influenzae</i> type b	Inactivated Bacterial	1 month
Hepatitis A	Inactivated Viral	12 months
Hepatitis B	Inactivated Viral	Birth
Human papillomavirus (HPV2)	Inactivated Viral	11–12 years old
Inactivated Poliovirus (IPV)	Inactivated Viral	1 month
Oral Poliovirus (OPV) *	Live viral	n/a
Influenza (IIV)	Inactivated Viral	6–23 months, annual vaccination
Influenza (LAIV): FluMist	Live attenuated viral	Age 2–18 years old, annual vaccination
Measles, mumps, rubella (MMR)	Live attenuated viral	12 months
Meningococcal (MCV4; MPSV4)	Inactivated Bacterial	11–12 years old
Pneumococcal conjugate (PCV13)	Inactivated Bacterial	1 month
Rotavirus	Live viral	1 month
Tetanus, diphtheria, and acellular pertussis (Tdap)	Inactivated Bacterial	11–12 years old
Varicella (VAR)	Live viral	12 months

* Not available in the United States but used in other countries

Source: <http://www.cdc.gov/vaccines/about/terms/USVaccines.html> (last accessed December 25, 2013) and <http://www.cdc.gov/vaccines/schedules/easy-to-read/child.html> (last accessed December 25, 2013)