

Heart transplant and pregnancy

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Heart transplantation

The first human heart transplant was performed in 1967 by Dr Christiaan Barnard at Groote Schuur Hospital in Cape Town, South Africa, following a decade of pioneering animal transplantation research work by Dr Norman Shumway at Stanford University in California, USA. The first heart transplant in Australia was performed at St Vincent's Hospital in Sydney in 1968 by Dr Harry Windsor and 40 years later, heart transplants have evolved from being experimental procedures to established medical treatments in carefully screened and selected patients with advanced heart disease.

The 2007 *Twenty-fourth Official Adult Heart Transplant Report* by the Registry of the International Society for Heart and Lung Transplantation described the primary indication for adult heart transplantation during the last three years being relatively equally divided between coronary artery disease-associated heart failure and non-coronary cardiomyopathy (41 per cent and 45 per cent respectively). Valvular heart disease (three per cent), adult congenital heart disease (three per cent) and re-transplantation (three per cent) accounted for the remaining transplants.¹

This international experience is reflected in Australia and New Zealand as reported in the *Twelfth Annual Report (1984-2007)* of the Australia and New Zealand Cardiothoracic Organ Transplant Registry, which describes the primary indications for heart transplantation being idiopathic dilated cardiomyopathy (40 per cent); ischaemic heart disease (37 per cent); peripartum cardiomyopathy (one per cent); familial cardiomyopathy (two per cent); viral cardiomyopathy and myocarditis (three per cent); congenital heart disease (five per cent); and other indications, for example, valvular heart disease and drug toxicity (12 per cent), account for the remainder of the heart transplants in Australia and New Zealand.²

The major barrier to performing more than 60 heart transplants annually in Australia and New Zealand is the shortage of donor hearts, which has not changed significantly over the last 15 to 20 years. In January 2007, 154 patients awaited heart transplantation in Australia and New Zealand and 68 patients (44.2 per cent) underwent heart transplantation, while 59 patients (38.3 per cent) remained on the cardiac transplantation waiting list at the end of the year.²

The actuarial survival values following heart transplantation in Australia and New Zealand are 87 per cent at one year, 77 per cent at five years and 61 per cent at ten years.² The common causes of death are transplant coronary artery disease (19 per cent), infection (14 per cent), acute rejection (12 per cent) and malignancies (13 per cent). Approximately 24 per cent of deaths are due to a variety of reasons, including sudden death, cardiac arrest, heart failure,

respiratory failure, renal failure and multi-organ failure.²

Within the first month after heart transplantation, graft failure (primary and non-specific) accounted for 40 per cent of deaths, followed by multi-organ failure (14 per cent) and infection (13 per cent). From one month to one year post-transplant, infection accounted for almost 33 per cent of deaths, followed by graft failure (18 per cent) and acute rejection (12 per cent). Infection represents the leading single cause of death from six months post-transplant throughout the ten years of follow-up.¹

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After five years, graft vasculopathy and late graft failure (likely due to graft vasculopathy) together accounted for 30 per cent of deaths, followed by malignancies (22 per cent) and infections (ten per cent). The causes of death that reflect the results of 'excess' immunosuppression (infection and malignancy) are as common as the causes reflecting inadequate immunosuppression (graft vasculopathy, late graft failure and acute rejection).¹

The actuarial survival in female transplant recipients aged 17 to 39 years in Australia and New Zealand is 88.8 per cent at one year, 80 per cent at five years and 64.5 per cent at ten years.² Therefore, younger female patients without serious coexisting conditions who undergo heart transplantation have a probability of almost 90 per cent of surviving the first year following heart transplantation. Almost two-thirds will survive the next ten years and are likely to have an excellent quality of life.³ It is this patient cohort who may desire pregnancy and children.

Heart transplantation and pregnancy

Pregnancy in cardiac transplant recipients involves unique circumstances not encountered in the pregnancies of recipients of other solid organ transplants. These patients must also undergo invasive surveillance for graft rejection as well as close monitoring of immunomodulation therapy, fetal surveillance, maternal risks of infection and malignancy, and the psychological stress of a high-risk pregnancy and being a heart transplant recipient.

The denervated transplanted heart adapts to up to 40 per cent gestational increases in blood volume and cardiac output, so that central venous pressure and preload increases to produce an

increased stroke volume.⁴ The transplanted heart can also increase heart rate and contractility in response to circulating catecholamines to increase cardiac output, particularly during exercise.⁴ This pregnancy-induced increased cardiac workload is usually tolerated by the transplanted heart, but may represent a risk for a pre-pregnancy dysfunctional graft.^{5,6}

Ten years ago, Löwenstein and colleagues reported the first successful pregnancy after cardiac transplantation.⁷ However, information on the course and outcome of pregnancy in heart transplant recipients is limited.⁸

Many uncertainties exist including the risks that pregnancy presents to the graft, the patient herself and the long-term risks to the fetus. It is also unclear how to best modify immunosuppressive agents or treat rejection during pregnancy, especially in light of newer agents available where pregnancy safety has not been established.

To begin to address uncertainties and define clinical practice guidelines, a consensus conference was held in Maryland, USA in 2003. The primary goals of the conference were to develop clinical practice guidelines for both transplant physicians and obstetricians, identify areas needing study, encourage the universal use of established registries and to advocate prospective observational studies.⁹ The consensus opinion is presented in Table 1.⁹

Table 1: Consensus summary

Basis on which to determine timing of pregnancy

- No rejection in the past year
- Adequate and stable graft function
- No acute infections that might impact the fetus
- Maintenance immunosuppression at stable dosing.

Special circumstances that impact on recommendations:

- Rejection within the first year
- Maternal age
- Comorbid factors that may impact pregnancy and graft function
- Established medical noncompliance.

Pregnancies outside the guidelines need to be evaluated on a case-by-case basis. In general, these considerations could be met at one year post-transplant based on individual circumstances.

Comorbid factors that may influence pregnancy outcome

- Aetiology of original disease (risk of recurrent disease, etc)
- Chronic allograft dysfunction
- Cardiovascular status and pulmonary status
- Diabetes mellitus (or history of DM)
- Hypertension
- Inherited diseases in mother and or father (genetic versus chromosomal)
- HBV, HCV, CMV
- Obesity.

Preconception counselling

- Should be introduced at least at the pre-transplant evaluation
- Should be followed up throughout the post-transplant process
- Should be offered to both the patient and her partner
- Ideally, patients should be vaccinated pre-transplant, but if not, should be vaccinated pre-pregnancy – influenza, pneumococcus, hepatitis B, tetanus
- Must discuss consequences of pre-term birth and long-term consequences of pre-term birth for both the mother and child with both prospective parents.

Obstetric management

- Management of all pregnant transplant patients should be by high-risk obstetrician (because of IUGR and pre-eclampsia) in conjunction with transplant physician
- Caesarean section indicated only for obstetric reasons
- Graft dysfunction during pregnancy warrants appropriate investigation (by biopsy if necessary)
- Immunosuppression must be maintained during pregnancy to avoid rejection
- Future studies need to address optimal selection and dosing of these agents
- Hyperemesis gravidum may lead to decreased absorption or inadequate immunosuppression.

At this point, we must balance risk of teratology against risk for acute rejection. The group agrees that at this point in time, the teratogenicity of newer immunosuppressants is not known (MMF, sirolimus).

Future research goals

- Define optimal pre-pregnancy graft function
- Define best parameters to follow for liver, heart and lung transplant recipients during pregnancy
- Define how pregnancy impacts on short and long-term graft function (study pre and post-pregnancy biopsies)
- Determine how the natural history of different diseases is affected by pregnancy
- Identify the risk factors for pre-eclampsia
- Establish whether the mother is immunosuppressed by the pregnancy
- Determine the target levels of BP control and agents
- Determine which immunosuppressives can be used most safely during pregnancy and breastfeeding
- Define optimal immunosuppression during pregnancy
- Define the long-term effects on the offspring
- Establish whether pregnancy accelerates graft coronary artery disease in heart recipients
- Clarify the effects of transplantation and immunosuppression on fertility in male and female solid organ recipients
- Collect data on the outcome of IVF in transplant recipients.

The conference also identified a number of critical questions to be resolved in order to establish evidence-based guidelines, to better understand how to advise and manage pregnant solid organ transplant patients:

Do immunosuppressive medications interfere with fertility?

Patients with end-organ failure experience hypothalamic-pituitary-gonadal dysfunction and decreased ovulation and sperm maturation. There is no data to determine if improvements in gonadal function and fertility follow transplantation of organs other than kidneys.

The consensus opinion was that there is a need to investigate whether transplant recipients have appropriate access to assisted reproduction or adoption services. Fertility is clearly restored to such a degree that careful contraceptive counselling is required before transplantation.

What constitutes appropriate and effective contraception in transplant recipients?

There is limited data on appropriate contraception following transplantation. The literature cites many theoretical complications to the hormonal approaches and the transplant community has favoured barrier methods, among the least effective of modern contraceptive approaches. Immunosuppressive agents also decrease the effectiveness of intrauterine devices and immunocompromised patients using such devices have increased risk for infection.

The conference discussed risks and benefits of oral contraceptives. Progestin-only oral contraceptives are less effective and subject to irregular bleeding, but are not associated with adverse medical consequences. While data is limited, there is no information to suggest that oestrogen/progestin is associated with adverse consequences in transplant patients when hypertension is well controlled.

The conference agreed that a discussion of post-transplant contraception should occur prior to transplantation in all transplant recipients of reproductive age. The optimal contraceptive agent/s to use after transplantation depends not only on balancing risks and benefits of each possible contraceptive method, but also on consideration of costs of contraceptive and patient's ultimate desire to conceive.

How long should one wait after transplantation to attempt conception and do risks increase if we wait too long?

The waiting period for heart transplantation has resulted in potentially leaving women with fewer childbearing years.

Information regarding timing of pregnancy for women with solid organ grafts other than renal transplants is limited and the consensus group warned against extrapolating results for renal transplant recipients to those receiving other organs. However, patients with nonrenal solid organ grafts often have renal dysfunction and this must be taken into consideration.

The consensus conference addressed timing of pregnancy and felt several individual factors should be considered including risk of acute rejection, risk of infection, concomitant therapy with dangerous medications and adequacy of graft function.

The patient who has adequate and stable graft function is at low-risk for opportunistic infections and is not taking teratogenic medications, warrants optimism. However, recent episodes of acute graft rejection or evidence of graft dysfunction indicate the need for caution.

How should pregnancy be managed in transplant recipients?

These gestations should all be considered high-risk and preferably managed by both transplant physicians and specialists in high-risk pregnancies. They require close scrutiny.

The major goals are to ensure that patients maintain graft function using appropriate immunosuppressive dosing during gestation and immediately after delivery; optimise maternal health including graft function; maintain a normal metabolic environment; minimise complications associated with pre-term birth; detect and manage hypertensive complications especially pre-eclampsia; and to ensure adequate fetal growth.

Pregnancy following heart transplant has often been discouraged but successful gestations have been recorded.^{4,7,8} There is risk of rejection, fetal growth restriction, pre-term delivery, increased hypertension, pre-eclampsia and psychological stress.

Heart transplant patients are monitored closely for rejection and require regular right ventricular biopsies that may even increase in frequency during pregnancy, exposing the fetus to radiation. Specific risk factors for adverse graft outcomes have yet to be defined and while registries have helped identify risks, large prospectively designed observational studies are needed for studying both risks and outcomes.

How should rejection be treated during pregnancy?

There is evidence to show that pregnant women do not have diminished systemic immunity and that the uterus may in fact be an 'immunoprivileged site'. While paternal cells have been found in maternal tissue, maternal regulatory T-cells appear to specifically suppress responses to these antigens and maternal responses to the allogeneic fetus are also suppressed locally at the maternal-fetal interface.

This is an important concept to emphasise, because inappropriate reduction in immunosuppression during pregnancy will lead to rejection of the transplanted organ. The consensus opinion was that steroids are safe for anti-rejection therapy, but the safety of antilymphocyte globulins and rituximab in pregnancy are unknown and intravenous immunoglobulin (IVIg) has been used fairly extensively without adverse effects.

Do immunosuppressants cross the placenta and do they appear in breast milk?

The extent to which individual immunosuppressants cross the placenta or appear in breast milk varies and depends on several factors, including maternal serum drug concentration, the concentration gradient between maternal plasma and breast milk, molecular weight, lipid solubility, protein binding and ionisation.

Cyclosporine crosses the placenta and is present in measurable quantities in the infant after delivery and there is no evidence that it is associated with teratogenicity. However, cyclosporine has more than 50 per cent risk of being associated with small for gestational age infants^{4,6}, which is exacerbated in the presence of hypertension and renal dysfunction.

Prednisone and prednisolone do not appear to be teratogenic but do increase the risk of gestational diabetes.⁴ Active metabolites of azathioprine cross the placenta, but are thought to be safe in pregnancy, while newer agents such as sirolimus and mycophenolate mofetil (MMF) have limited data on their safety in pregnancy.

Breastfeeding is still controversial and further study is required before definitive recommendations can be made.

What are the risks to the baby of a female transplant recipient?

There are several immediate and long-term risks to discuss with prospective parents prior to transplantation and certainly prior to conception.

The risk of prematurity and IUGR is very high – up to 50 per cent of infants born to transplant recipients are premature and up to 20 per cent have intrauterine growth restriction. The consequences of decreased gestational age at delivery, particularly at less than 34 weeks gestation, include neonatal death and long-term morbidities such as cerebral palsy, blindness, deafness, learning disabilities and low intelligence quotients.

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Low birth weight may be associated with increased hypertension, diabetes and coronary artery disease in adulthood. While these potential risks need to be discussed with the prospective parents, the unplanned pregnant patient needs to be aware of these risks in order to make appropriate decisions about care for a potentially disabled child.

Exposure of infants to immunosuppressive medications in utero might increase the child's risk for autoimmune disease later in life, possibly due to maternal immunosuppressive therapy interfering with fetal thymic development. Although there appear to be no obvious congenital abnormalities associated with in utero exposure to conventional immunosuppressive agents, long-term follow-up of exposed children is needed.

Current registry numbers are still too small to permit firm conclusions regarding any pattern of congenital abnormalities associated with the use of calcineurin inhibitors, azathioprine or steroids therapies, including several newer agents such as TOR inhibitors, therapeutic antibodies and antimetabolites like mycophenolate mofetil. Learning disabilities may not be obvious until children become school-age. Prospective trials are needed to report on outcomes and define the long-term consequences of immunosuppressive agents in the children of heart transplant recipient mothers.

What has been reported to the registries?

The National Transplantation Pregnancy Registry (NTPR)¹ in the United States and the Transplant Pregnancy Registry in the United Kingdom¹⁰ showed spontaneous abortion rates of about 17 per cent, a high prevalence of hypertension and an increased occurrence of pre-eclampsia in heart transplant recipient pregnancies.

There was a 46 per cent incidence of hypertension during pregnancy, 10 per cent incidence of pre-eclampsia and 21 per cent had a rejection episode during the pregnancy in heart transplant recipients.

Approximately one-third of babies born to heart transplant recipients were delivered at less than 37 weeks gestation, with a 30 to 45 per cent caesarean section rate. There was an 80 per cent incidence

of low birth weight (under 2500g)¹⁰ and over one-fifth of newborns had complications with developmental delays noted in some of the offspring because of the high rate of prematurity.¹

Should transplant patients become pregnant?

While there is data showing good outcomes⁴, there may be valid reasons to counsel against pregnancy, including the potential risks to the graft, to the mother and to the child.

However, the transplant patient may have no other option for parenthood due to restricted access to adoption services. Potential parents need to be aware of the possibility and demands of having a premature infant who survives with disability and need to consider a plan for alternative care in case of parental disability or death.

Summary

Younger female patients who undergo heart transplantation have a probability of almost 90 per cent of surviving the first year. Almost two-thirds will survive the next ten years and are likely to have an excellent quality of life and may yearn to start a family.

Current voluntary United States and United Kingdom registry data indicate that pregnancies in heart transplant recipients are associated with increases in spontaneous abortion rates, hypertension in pregnancy and pre-eclampsia. The delivered infants have an increased incidence of complications, including developmental delay, which is not surprising given the increased incidence of prematurity and low birthweight.

A consensus conference has developed clinical practice guidelines for transplant physicians and obstetricians and encouraged the universal use of established registries. The consensus conference identified a paucity of data in outcomes of children of heart transplant recipient mothers and recommended prospective trials of these children to establish the effect of immunosuppressive agents on 'in utero' and childhood development. As specific risk factors for adverse graft outcomes in pregnant heart transplant recipients have yet to be defined, the consensus conference also recommended large prospective observational studies to investigate risks and outcomes in this patient population.

While there is data showing good outcomes⁴ in pregnancies in heart transplant recipients, there may be valid reasons to counsel against pregnancy, including the potential risks to the graft, to the mother and to the child. However, the transplant patient may have no other option for parenthood due to restricted access to adoption services.

The potential parents need to be aware of the possibility of having a premature infant who survives with disability, the need to prepare for the immediate and long-term needs of the child and the demands of continued graft and maternal surveillance, as well as the need to consider a plan for alternative care in case of parental disability or death.

References

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