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ORIGINAL ARTICLE

# Pregnancy Following Heart Transplantation: A Single Centre Case Series and Review of the Literature

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**Background** Maternal and fetal outcomes of pregnancy amongst cardiac transplant recipients are limited in the current literature.

**Methods** We describe five pregnancies in three cardiac transplant recipients managed between a tertiary centre for obstetric medicine and an associated state-wide transplant centre between 2014-2018, and provide a narrative review of the literature.

**Results** Pre-conception counselling was undertaken. There were no recent rejection episodes and all women demonstrated good baseline cardiac function. Median maternal age was 27 years (range 23-38 yrs.). Median time from transplantation to pregnancy was 5 years (range 2-14 yrs.). All women were managed with modified immunosuppressant regimens and multidisciplinary care. Cardiac function, tacrolimus levels and renal function were closely monitored with frequent monitoring for common complications of pregnancy. There were no maternal or fetal deaths. There was no evidence of graft rejection and no deterioration in cardiac function. Tacrolimus doses were increased to maintain therapeutic targets. Gestational diabetes occurred in three women and cholestasis of pregnancy occurred in one. Each infant was delivered by vaginal delivery. One mother had postpartum haemorrhage in both pregnancies. Pre-eclampsia did not occur. Median gestation at delivery was 37 weeks (range $35^{+4}$-$40^{+5}$ days) with two preterm deliveries. One (1) infant was born with low birth weight. One (1) infant had jaundice requiring phototherapy. All infants were breastfed.

**Conclusion** Pregnancy in transplant recipients confers risk to the mother and fetus. Pre-conception counselling, immunosuppressant tailoring and regular monitoring are paramount to avoid rejection and possible teratogenic complications. Favourable pregnancy outcomes are achievable with specialist multidisciplinary care.

**Keywords** Heart transplantation • Pregnancy • Cardiac disease in pregnancy • Women's cardiovascular health

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# Introduction

Contemplating a pregnancy following cardiac transplantation can be a daunting but desirable prospect for women. It is often discouraged by treating physicians due to concerns regarding significant risks to the mother and the fetus, however successful pregnancy outcomes have been reported. The first report of a pregnancy in a cardiac transplant recipient with good outcomes for both the mother and infant was described in Argentina in 1988 [1].

Globally, with growing collective experience in long-term management and improved long-term survival there is now a greater expectation of longevity in female transplant recipients of reproductive age [2].

Reports of maternal and fetal outcomes of pregnancy amongst women who are cardiac transplant recipients are relatively limited in the current literature (Table 1). These consist primarily of observational studies of small cohorts from a variety of geographical and health care settings and clinical recommendations are largely base on expert opinion [3]. Because of the limited literature, optimal management is largely based on consensus with regard to pre-conception counselling, management of immunosuppression, surveillance of graft function and frequency of review during and following pregnancy. Despite this, the overwhelming consensus from the published reports is that for the majority of patients, successful pregnancy is achievable.

The International Society of Heart and Lung Transplantation (ISHLT) advise that pregnancy management should be individualised based on the clinical status of the mother and function of the allograft. Avoidance of pregnancy in the first year following cardiac transplantation is recommended as this is the period of highest risk of rejection in the recipient and consequently most intense immunosuppression, with an associated increased risk of teratogenicity in the developing fetus [4].

The American National Transplantation in Pregnancy Registry (NTPR) has advised that both positive and negative pregnancy outcomes in transplant recipients be made readily available to health care providers to assist in optimising the care of individual patients following transplant [5].

The aim of this paper is to provide insight into the 'pregnancy journey' of patients in a single state within the Australian health care setting; from pre-conception to post-partum follow-up. Our goal is to assist clinicians to risk stratify and provide management recommendations to cardiac transplant recipients in order to improve maternal and fetal outcomes. We describe, in detail, a series of patients managed collaboratively between a tertiary centre for obstetric medicine and an associated state-wide cardiac transplant centre together with a brief narrative review of the relevant literature.

# Methods

This is an observational case series of all pregnancies in heart transplant recipients whose pregnancy care and deliveries were managed in Queensland, Australia, at a single centre for obstetrics, maternal medicine and cardiology. All patients known to be heart transplant recipients and referred for antenatal care were invited to participate in this study. All patients were managed by a single state-wide cardiac transplantation centre according to standard practice before pregnancy. All data was derived from a retrospective review of available medical records from each pregnancy. Medical records from the time of transplantation or referral to the adult cardiac transplantation service, through pre-conception counselling, pregnancy and on to post-partum follow-up in both tertiary centres where the women were managed were reviewed.

Data collection for maternal and fetal outcomes was approved by the local Ethics Committee [RBWH HREC/10/QRBW/400] prior to data collection and all patients provided written, informed consent.

# Case Series

We describe the outcome of five pregnancies in three patients between 2014 and 2018. A summary of the baseline characteristics of all three women including their age and indication for cardiac transplantation are outlined in Table 2.

## Patient 1

Patient 1 underwent orthotopic heart transplantation in 2002 when she was 13 years of age for restrictive cardiomyopathy. Histology of the explanted heart demonstrated histological features of hypertrophic cardiomyopathy. Initial post-transplant immunosuppression included cyclosporin, however the first endo-myocardial biopsy following transplantation demonstrated acute allograft rejection, therefore immunosuppression was changed to tacrolimus 3 mg twice daily and sirolimus 2 mg daily. Sirolimus was subsequently changed to azathioprine 50 mg prior to conception. There were no further episodes of rejection. The patient had two episodes of *Mycoplasma pneumoniae* infection in the years following cardiac transplantation, the latter episode was complicated by *Clostridium difficile* infection following a prolonged course of antibiotic therapy for pneumonia and this precipitated a first presentation of reactive arthritis, which was later successfully controlled with infliximab infusions. Systemic hypertension was also present prior to pregnancy.

### Patient 1, pregnancy

Patient 1 conceived in 2016, 14 years following cardiac transplantation. The pregnancy was planned, and formal pre-conception counselling occurred both at the transplant centre with transplant coordinator and consultant cardiologist involvement and subsequently at the multi-disciplinary obstetric cardiology clinic. Pregnancy was uncomplicated other than an early, uncomplicated urinary tract infection which was managed with oral antibiotic therapy. The patient was reviewed every 4 months in the cardiology outpatient setting following her expression of plans to conceive, then

**Table 1** Characteristics and outcomes of pregnancy following cardiac transplantation in the published literature.

| Publication | Number of Pregnancies | Mean Maternal Age (yr) | Transplant to Conception Interval (yr) | Immunosuppression | Maternal Complications during Pregnancy | Fetal Outcomes | Mode of Delivery |
|---|---|---|---|---|---|---|---|
| Punnoose et al. 2020 [10] | 157 | 27 | 7 | CNI (20% exposed to mycophenolate mofetil during pregnancy) | No maternal deaths<br>Gestational hypertension (46%)<br>Pre-eclampsia (23%)<br>Rejection (9%) | Livebirths (69%)<br>Prematurity (41%)<br>Low birth weight (37%) | N/A |
| Macera et al. 2018 [12] | 17 | 33 | 5.6 | CNI (+ prednisolone in 92%) | No maternal deaths<br>1 patient with uncontrolled (pre-existing) hypertension at 28 wk leading to emergency delivery | Livebirths (71%)<br>Premature (33%)<br>Low birth weight (45%) | Caesarean delivery (83%) |
| Dagher et al. 2018 [27] | 18 | 26 | 10.1 | CNI (+ prednisolone and/or azathioprine in 50%) | No maternal deaths<br>Gestational hypertension (39%)<br>Pre-eclampsia (15%) | Live births (72%)<br>Prematurity (54%)<br>Low birth weight (33%) | Caesarean section (39%) |
| D'Souza et al. 2017 [25] | 17 | 28 | 7.3 | CNI/azathioprine/ corticosteroids<br>Sirolimus was used in 2 patients and discontinued in 1 patient in early pregnancy.<br>Mycophenolate mofetil was used in 3 patients but ceased early in pregnancy | No maternal deaths<br>Gestational diabetes (6%)<br>Pre-eclampsia (12%)<br>Rejection (12%) | Livebirths (81%)<br>Premature (46%)<br>Low birth weight (15%) | Caesarean delivery (46%) |
| Bhagra et al. 2016 [26] | 22 | 25 | 8.2 | CNI/azathioprine/ corticosteroids | No maternal deaths during pregnancy (1 death in the immediate postpartum period from tonic PPH)<br>Gestational hypertension (14%)<br>Pre-eclampsia (14%)<br>Rejection (5%) | Livebirths (91%)<br>Prematurity (45%)<br>Low birth weight (45%) | Caesarean delivery (55%) |
| Moritz and Constantinescu 2016 [29] | 147 | N/A | 6.9 | CNI (+ azathioprine in 51%, 33% exposed to MPA, 8.8% exposed to sirolimus) | No maternal deaths<br>Gestational hypertension (45%)<br>Pre-eclampsia (24%)<br>Rejection (10%) | Livebirths (66%)<br>Prematurity (43%)<br>Low birth weight (40%) | Caesarean section (45%) |
| Miniero et al. 2004 [28] | 10 | 29 | 6.9 | Cyclosporine A (75%)<br>Cyclosporine A and azathioprine (25%) | No maternal deaths<br>No pre-eclampsia, gestational hypertension or rejection | Livebirths (80%)<br>Prematurity (25%) | Caesarean section (100%) |

**Table 1 (continued).**

| Publication | Number of Pregnancies | Mean Maternal Age (yr) | Transplant to Conception Interval (yr) | Immunosuppression | Maternal Complications during Pregnancy | Fetal Outcomes | Mode of Delivery |
|---|---|---|---|---|---|---|---|
| Shen et al. 1997 [24] | 35 | N/A | 2.5 | CNI/azathioprine/ corticosteroids | No maternal deaths Gestational hypertension (41%) Pre-eclampsia (24%) Rejection (29%) | Livebirths (89%) Prematurity (35%) Low birth weight (19%) | Caesarean section (34%) |

Abbreviations: CNI, calcineurin inhibitor; PPH, postpartum haemorrhage.

approximately monthly initially during her pregnancy until the final month of pregnancy where she was reviewed weekly prior to delivery.

Patient 1 delivered a healthy male infant weighing 3,322 g by induction of labour and vaginal delivery with episiotomy at 37 weeks gestation. The pregnancy, delivery and details of infant nutrition are outlined in Table 3. Following pregnancy, the immunosuppressant regimen was changed to mycophenolate mofetil 2 mg twice daily in combination with tacrolimus (7 mg of the extended release preparation once daily). After routine postpartum care, patient 1 returned to follow-up at the transplant centre 1 week following delivery at which time both she and her son were well.

## Patient 2

Patient 2 was diagnosed with chemotherapy-induced cardiomyopathy. Despite optimal pharmacotherapy and implantable cardiac device therapy (biventricular cardiac resynchronisation therapy and primary prevention defibrillator) ongoing deterioration in left ventricular function with worsening symptoms and signs of chronic heart failure were observed and the patient underwent orthotopic heart transplantation in 2011. The patient had been diagnosed with acute lymphocytic leukaemia as a child and had received curative chemotherapy including anthracycline drugs in 1989. In the context of severe left ventricular dysfunction, the patient had transient neurological symptoms in 2001 attributed to a transient ischaemic attack and was initially commenced on warfarin. This was discontinued prior to cardiac transplantation but the patient remained on aspirin 100 mg, which is normal protocol following heart transplantation, in addition to her immunosuppression during pregnancy. There were no episodes of rejection following cardiac transplantation. The patient did have an episode of cytomegalovirus gastritis in 2012 which was successfully treated. Medical co-morbidities include asthma, eczema and obesity. Patient 2 has had two pregnancies.

### Patient 2, pregnancy 1

The first pregnancy was planned from 2014. Maintenance immunosuppression was changed from tacrolimus and mycophenolate mofetil to tacrolimus 2 mg twice daily and azathioprine 75 mg once daily. The patient conceived in 2015. During pregnancy the dose of azathioprine remained unchanged but the dose of tacrolimus was increased in the second trimester to 6 mg in the morning and 7 mg in the evening in order to maintain usual therapeutic drug levels. Spontaneous and prolonged rupture of membranes occurred, requiring antibiotic therapy with subsequent induction of labour at 40 weeks and 5 days gestation. A healthy female infant was born by vaginal delivery. The immediate post-partum phase was complicated by post-partum haemorrhage secondary to an atonic uterus with 3.6 litres blood loss requiring two units of red blood cells to be transfused. There was no haemodynamic instability associated with the high volume of blood loss.

### Patient 2, pregnancy 2

Patient 2 conceived for the second time in 2017 whilst taking tacrolimus 5 mg twice daily and azathioprine 75 mg daily for immunosuppression. This second pregnancy was complicated by gestational diabetes which was adequately controlled with subcutaneous insulin therapy. The patient delivered a healthy, female infant by spontaneous vaginal delivery at 39 weeks and 2 days gestation. This was again complicated by a 3.1 litre post-partum haemorrhage secondary to retained placental products which required two units of packed red blood cells to be transfused but again there was no significant haemodynamic instability or long-term sequelae. The patient also required a subsequent re-admission to hospital with endometritis requiring aspiration curettage for retained products of conception in the early post-partum period. Following her second pregnancy, the patient's immunosuppression was readjusted to include mycophenolate once again, with azathioprine being discontinued and mycophenolate being recommenced at 720 mg twice daily. The tacrolimus dose was reduced to 3 mg twice daily. The details of the pregnancies, deliveries and infant nutrition in Patient 2 are outlined in Table 3.

## Patient 3

Patient 3 underwent cardiac transplantation in 2012 aged 21 years following fulminant myocarditis with severe left and right ventricular systolic dysfunction which did not improve.

**Table 2** **Patient characteristics.**

| Patient Characteristics | Patient 1 | Patient 2 | Patient 3 |
|---|---|---|---|
| Age at cardiac transplantation (yr) | 13 | 32 | 21 |
| Reasons for cardiac transplantation | Restrictive cardiomyopathy with features of hypertrophic cardiomyopathy | Chemotherapy-induced dilated cardiomyopathy | Fulminant myocarditis induced dilated cardiomyopathy |
| Left ventricular ejection fraction (%) pre-pregnancy | >55 | >55 | >55 |
| Duration between transplant and first pregnancy (yr) | 14 | 4 | 2 |
| Age at pregnancy (yr) | 27 | 36 (1st pregnancy)<br>38 (2nd pregnancy) | 23 (1st pregnancy)<br>26 (2nd pregnancy) |
| Body mass index | 22 | 32 | 31 |
| Co-morbidities | Systemic hypertension<br>Reactive arthritis | Asthma<br>Eczema<br>Obesity<br>Transient ischaemic attack | Obesity<br>Benign intracranial hypertension<br>Red cell aplasia |
| Immunosuppressant regimen prior to pre-conception counselling | Tacrolimus<br>Sirolimus | Tacrolimus<br>Mycophenolate | Tacrolimus<br>Mycophenolate<br>Prednisolone |
| Immunosuppressant agents used during pregnancy | Tacrolimus<br>Azathioprine | Tacrolimus<br>Azathioprine | Tacrolimus<br>Azathioprine<br>Prednisolone |

This was further complicated by recurrent ventricular fibrillation and cardiac arrests. Thus, the patient went on to insertion of a left ventricular assist device (LVAD) as a bridge to transplant. An infection with *Candida parapsilosis* led to accelerated transplantation. There were no episodes of graft rejection following cardiac transplantation. Relevant co-morbidities prior to pregnancy included chronic iron deficiency anaemia) and benign intracranial hypertension (treated with acetazolamide). Patient 3 had two pregnancies.

**Patient 3, pregnancy 1**

Patient 3 expressed a desire for pregnancy in early 2014, and this was discussed in the cardiology outpatient clinic at the cardiac transplant centre. She was referred to the obstetric medicine and cardiology clinic for pre-conception counselling. Immunosuppression was changed from tacrolimus (extended release preparation) 3 mg, prednisolone 10 mg and mycophenolate mofetil 1.5 g twice daily to tacrolimus and azathioprine 75 mg; the prednisolone was continued. The patient conceived in mid-2014.

Early pregnancy was complicated by hyperemesis gravidarum requiring hospitalisation for 10 days. Vaginal delivery followed induction of labour at 36 weeks and 2 days gestation due to the development of cholestasis of pregnancy. A healthy male infant weighing 2,690 g was born. During pregnancy the patient was reviewed in the outpatient clinic at monthly intervals until the final weeks of pregnancy when weekly reviews were arranged. Tacrolimus dosing was temporarily increased in stages during pregnancy from 3 mg to 8 mg of the extended release preparation to maintain usual therapeutic drug levels, with prednisolone and azathioprine doses remaining constant.

**Patient 3, pregnancy 2**

Patient 3 conceived again in 2017. Azathioprine was continued after the first pregnancy, as a second pregnancy was desired. Hyperemesis gravidarum recurred in early pregnancy, but the pregnancy was otherwise uncomplicated. Patient 3 delivered a second infant, with low birth weight at delivery, weighing 2,236 g at 35 weeks and 4 days gestation. The details of the pregnancies, deliveries and infant nutrition are outlined in Table 3. Following delivery, it was noted that the patient had an abnormally persistent phase of post-partum vaginal bleeding requiring further investigation. After routine post-partum care the patient remained otherwise well with unlimited exercise tolerance and normal left ventricular systolic function. Following this second pregnancy azathioprine was discontinued and sirolimus was recommenced.

# Discussion

Survival with good quality of life after cardiac transplantation is increasing. As a result, many cardiac transplant recipients wish to experience parenthood. For clinicians caring for such patients, there are limited guidelines outlining optimal management during pregnancy. From the published literature that is available, mainly small

**Table 3 Pregnancy outcomes.**

| | Patient 1 | Patient 2: 1st Pregnancy | Patient 2: 2nd Pregnancy | Patient 3: 1st Pregnancy | Patient 3: 2nd Pregnancy |
|---|---|---|---|---|---|
| Pre-conception counselling | Yes | Yes | Yes | Yes | Yes |
| Gestation at delivery (wk) | 37 | 40 +5 d | 39 +2 d | 36 +2 d | 35 +4 d |
| Mode of delivery | Induction of labour with vaginal delivery and episiotomy | Spontaneous rupture of membrane, induction of labour and vaginal delivery | Spontaneous vaginal delivery | Spontaneous vaginal delivery | Spontaneous vaginal delivery |
| APGAR score of baby | 9+9 | 9+9 | 9+9 | 9+9 | 9+9 |
| Birth weight of baby (g) | 3,322 | 3,850 | 3,236 | 2,690 | 2,236 |
| Complications | Nil | Post-partum haemorrhage | Gestational diabetes, post-partum haemorrhage, endometritis | Hyperemesis gravidarum, cholestasis of pregnancy | Hyperemesis gravidarum |
| Total blood loss (mL) | 250 | 3,600 | 3,100 | 180 | 250 |
| Left ventricular function at the end of pregnancy | >55% | >55% | >55% | >55% | >55% |
| Infant nutrition | Breastfed | Breastfed | Breastfed | Breastfed | Breastfed |

observational studies, most pregnancies in cardiac transplant recipients have favourable short to medium term outcomes following pregnancy.

A recent survey of cardiac transplant providers (the majority of which were cardiologists) in the United States of America, found that over one third of practitioners believe pregnancy to be contraindicated post cardiac transplantation for all women. Less than half of the providers reported having an institutional policy outlining the management of patients with pregnancy post cardiac transplantation [6].

Generally, the consensus appears to be that the main reasons to advise avoidance of pregnancy are: poor concordance with medical therapy or poor engagement with medical services, left ventricular systolic dysfunction, allograft vasculopathy, prior episodes of rejection, the presence of donor specific antibodies and previous peripartum cardiomyopathy (leading to the initial transplantation) [3]. Advanced maternal age and significant co-morbid conditions are also deterrents.

The American Society of Transplantation consensus summary recommends that prior to consideration of pregnancy in transplant recipients there should have been a significant period of at least 12 months without evidence of rejection, stable and satisfactory graft function and a stable immunosuppression regimen [7]. In addition, the ISHLT suggests that a thorough assessment with electrocardiograph (ECG), echocardiography and consideration of further more invasive investigations such as coronary angiography, right heart catheterisation and myocardial biopsy where indicated to assess that the patient and graft are in optimum condition prior to pregnancy [4].

Importantly, none of the small observational studies to date have looked at quality of life as an outcome in their analyses of pregnancy following cardiac transplantation. Motherhood is a prominent life goal for many women. A significant proportion wish to accept the potential risks to their own health and longevity, as well as the possibility of transmission of inheritable cardiac conditions (in specific conditions) to their offspring, in order to experience the challenges and rewards of pregnancy and motherhood.

## Pre-Conception Counselling

Counselling on reproductive decisions after cardiac transplantation is an extremely important aspect of patients' post-transplant care. Timely pre-conception counselling in patients who express a desire to have a baby is a priority during each consultation to optimise timing of pregnancy; the aim being to avoid pregnancy in the context of graft dysfunction, cardiac decompensation in the mother and an increased risk of teratogenic complications in the fetus. Pre-conception counselling also includes appropriate contraception advice which should be tailored to the individual. At our institution, as part of the Hospital Heart Transplant Education program, contraception counselling is provided to all patients of reproductive age. Generally, for heart transplant recipients who are well and avoiding pregnancy; any form of reliable contraception is acceptable as any theoretical risks are outweighed by the potential benefits. However, in complex heart transplant recipients with prior allograft vasculopathy,

graft failure or rejection, the combined hormonal contraceptive pill is not considered safe [8].

It is important to discuss the statistics surrounding survival after cardiac transplantation and potential adverse consequences during pregnancy so that patients embarking on pregnancy post cardiac transplant are making a fully informed decision with an awareness of the potential implications. This discussion should include the possibility that even following successful pregnancy and delivery of a healthy infant, that the mother may have shortened life expectancy as a consequence of her cardiac transplant. It is advisable to encourage the patient to undertake preconception counselling with their partner. In instances where the patient has a history of an inheritable cardiac condition, genetic testing and counselling should be undertaken.

In our case series, all five pregnancies were planned and each woman was thoroughly counselled prior to pregnancy regarding the potential risks and complications of pregnancy to the mother and the fetus. Although pre-conception counselling and planned pregnancy is the desired approach, studies have shown that almost half of pregnancies in cardiac transplant recipients are unplanned [9].

## Maternal and Fetal Outcomes

In our case series, the median maternal age at pregnancy was 27 years (range 23–38 years). This is consistent with the mean maternal age at pregnancy in two recent publications of pregnancy outcomes after cardiac transplantation of 27 years (±5.6 years) [10] and 28 years [11]. The median time from cardiac transplantation to pregnancy was 5 years (range 2–14 years) in our series which again was comparable to the published literature [10,11]. The most common reasons for cardiac transplantation in women who later became pregnant were congenital heart disease, viral myocarditis and idiopathic dilated cardiomyopathy [10,11].

Gestational diabetes mellitus occurred in three out of five pregnancies in our series and cholestasis occurred in one patient. Pre-eclampsia did not occur. During pregnancy, the multidisciplinary team should regularly monitor for common complications such as pregnancy induced hypertension, gestational diabetes, and pre-eclampsia.

In our case series all pregnancies progressed to live births. No prior miscarriages were reported. On review of the wider literature it appears that spontaneous miscarriage in cardiac transplant recipients usually occurs with a similar rate to that of the general pregnant population [10,12,13].

All infants in our study were well at birth (Appearance, Pulse, Grimace, Activity, and Respiration [APGAR] scores of 9+9). The mode of delivery for all five pregnancies was vaginal delivery. This possibly contrasts with one previous large series where 42% women underwent caesarean section [10]. Obstetric guidelines for patients after solid organ transplantation recommend that caesarean delivery should only occur if obstetric indications are present and should be avoided if possible [14].

Median gestation at delivery was 37 weeks (range $35^{+4}$-$40^{+5}$ weeks) with two mothers delivering preterm. The mean birth weight of the babies born in our case series was 3,067 g (range 2,236–3,850 g). In the multicentre study from North America, 41% of infants were preterm and approximately one third of infants born to cardiac transplant recipient mothers were born with low birth weight (<2,500 g) [10]. This is comparable to the general population of women with structural heart disease where preterm delivery and infantile low birth weight are two of the most commonly observed adverse neonatal outcomes of pregnancy [15]. One (1) infant in our case series had jaundice requiring phototherapy. Both pregnancies in one mother were complicated by post-partum haemorrhage and there was one case of endometritis following retained placental products.

The recent systematic review and meta-analysis of observational studies in patients after thoracic transplant stated that mortality in pregnancy is very low, and significantly lower in patients with cardiac transplantation compared to lung transplantation [11]. Although mortality during pregnancy is low there is a significant risk of morbidity during pregnancy in cardiac transplant recipients. The systematic review and meta-analysis did highlight an observed high rate of mortality for heart transplant recipients in the years following pregnancy. It is currently not clear whether this is a reflection of the shortened lifespan of heart transplant recipients generally or whether pregnancy itself contributes to increased mortality in the years following delivery [11]. These risks need to be carefully considered by the patient and weighed against their desire for pregnancy. The ISHLT report a median survival of 10.8 years following cardiac transplantation [4]. However, data from the ISHLT registry represents a wide range of patients who likely represent a more complex cohort than those patients well enough post-transplant to have a successful pregnancy. The Australian and New Zealand Cardiothoracic Organ Transplant Registry (ANZCOTR) report a median survival post-transplant of approximately 15 years from 1984 to 2018 [2].

The main explanations provided for maternal deaths during or following pregnancy in cardiac transplant recipients include non-adherence with immunosuppressant therapies, allograft vasculopathy and chronic graft failure [11]. For the vast majority of patients, however, graft function remains stable during and after pregnancy and this has been demonstrated at 9 years of follow-up [10].

## Regular Multidisciplinary Care

As with all women with cardiac disease in pregnancy, multidisciplinary care of pregnant women with prior cardiac transplantation provides the best chance of a successful pregnancy outcome [16]. In our case series, each patient's pregnancy was carefully managed throughout pregnancy with coordinated care provided by obstetric cardiology, maternal medicine, cardiac transplant and obstetric teams who regularly reviewed the patients with discussion of their progress in multidisciplinary meetings. The women were

also reviewed by the obstetric and cardiac pharmacy team preconception and throughout pregnancy, with monitoring of immunosuppressant drug levels.

Patients were routinely assessed for the development of common pregnancy complications such as gestational diabetes, hypertension and pre-eclampsia. Echocardiography was performed pre-conception, routinely monitored during each trimester and re-assessed postpartum (within 42 days) to assess for any deterioration in left ventricular systolic function as assessed by LVEF. If there had been a deterioration in echocardiographic appearances or change in symptoms, then more frequent echocardiographic surveillance would have been arranged. No deterioration in LVEF was noted in any of the women during or following pregnancy.

There is a paucity of data regarding the echocardiographic 'normal values' in pregnant women therefore interpretation of echocardiographic findings which differ from the values expected in adult females can be challenging.

## Immunosuppression

Immunosuppressant agents cross the placenta with the potential for adverse effects on the fetus. The pharmacokinetics of many immunosuppressant therapies are altered in pregnancy and require close surveillance and monitoring of levels where possible throughout pregnancy and the puerperium. Pre-conception counselling allows early review and alteration of immunosuppressant regimens to minimise teratogenic effects to the fetus and transplant rejection in the mother. The evidence suggests that the most commonly utilised immunosuppressant agents during pregnancy in cardiac transplant recipients are calcineurin inhibitors (CNIs) (tacrolimus and cyclosporine) combined with azathioprine. Over half of the patients in the meta-analysis were managed with steroids at some stage of their pregnancy [11]. In the recent multicentre registry from North America, 99% of patients were taking a CNI during pregnancy and 46% were also on azathioprine [10].

Tacrolimus and cyclosporine are considered safe in pregnancy though the pharmacokinetics change with advancing pregnancy (whole blood concentrations decrease however unbound concentrations increase) which can affect the interpretation of therapeutic blood levels. Tacrolimus is the most recent immunosuppressant to be used in pregnancy post cardiac transplant. The macrolide antibiotic was used for the first time in 1989 and exerts its immunosuppressant effect by inhibition of T-lymphocyte activation [17]. The main adverse effects of tacrolimus are dose-related nephrotoxicity and the development of glucose intolerance. In view of this, renal function and blood glucose levels require close monitoring. Azathioprine is a pro-drug which exerts its immunosuppressant effect via active metabolites of 6-mercaptopurine. It does cross the placenta however the majority of the drug is metabolised to inactive thiouric acid in the fetus [18]. It has been associated with bone marrow suppression and intrauterine growth restriction in the fetus in case reports of maternal use in renal transplant recipients. Some of these adverse effects may be dose related or attributed to underlying maternal morbidity [19,20]. There is some evidence to suggest that adjusting the azathioprine dosing to maintain normal cell counts in the mother in turn normalises cell counts in the infant at birth [21]. Prednisolone is known to cross the placenta, but the majority is metabolised by placental enzymes and does not reach the fetus. It is not associated with adverse effects in pregnancy and there is considerable experience in the use of prednisolone in multiple clinical contexts. Mycophenolate should be avoided in pregnancy given higher incidence of teratogenicity and spontaneous miscarriage of up to 27% and 49%, respectively. It should therefore be discontinued for at least 6 weeks prior to conception or when pregnancy is being contemplated [12]. Substituting azathioprine in place of mycophenolate is carried out solely to avoid teratogenicity to the fetus. Mycophenolate is internationally recognised as the preferred second immunosuppressive agent (after CNIs) in heart transplant recipients generally.

In our case series, all patients were temporarily managed with modified immunosuppressant regimens during pregnancy which included tacrolimus and azathioprine. Tacrolimus levels and renal function were closely monitored. Each patient had an increase in their tacrolimus dose during pregnancy due to falling drug levels in pregnancy. There were no clinical episodes of graft rejection during any of the pregnancies in our case series and endomyocardial biopsy was not performed in any of the pregnancies. In a previous meta-analysis, graft rejection was reported to occur in 11% of women during pregnancy, with the majority of cases being low grade, without major adverse consequences and responding well to modified immunosuppression and pulsed steroid therapy if required [11]. There was no significant deterioration from baseline renal function with pregnancy in our study as assessed by serum creatinine and glomerular filtration rate values.

## Breast Feeding

All five of the infants in our case series were breastfed. A significant proportion of transplant recipients' health care providers believe breastfeeding to be contraindicated post-transplantation [6]. Tacrolimus is present in the breast milk of lactating mothers receiving this immunosuppressant. The concentrations reaching the infant from breastfeeding are low (<0.5% of the weight-adjusted maternal dose). Azathioprine is rapidly metabolised to 6-mercaptoprine which is present in breast milk. However, it is then inactive until further metabolised to 6-TGN (thioguanine nucleotide), which is present only in red blood cells. Guidance on breastfeeding whilst taking immunosuppressive drugs varies. There is some literature supporting expressing breast milk and discarding for the first 4 hours after an azathioprine dose or avoiding breastfeeding over this time to minimise the exposure to the breast-feeding infant [22]. There is limited long-term outcomes data from infants exposed to breast milk from mothers taking immunosuppressant agents. There are

**Table 4 Recommendations for management of pregnancy in cardiac transplant recipients.**

| | |
|---|---|
| Preconception counselling | This is essential in all patients. Counselling should be undertaken by collaboration between the transplant team and members of the pregnancy heart team who will be responsible for care during pregnancy |
| Care during pregnancy | At an expert centre for pregnancy and cardiac disease. It is expected that usual care delivered by the transplant team will continue throughout |
| Minimum frequency of cardiac review | Monthly – Which can be a combination of review by the transplant team and pregnancy heart team |
| Minimum cardiac investigations prior to pregnancy | Echocardiography should have been performed within 6 mo of conception. Functional capacity should also be investigated as part of preconception care either by cardiopulmonary exercise testing or stress echocardiography. In patients more than 5 yr after transplant consideration should be given to exclude graft vasculopathy |
| Minimum cardiac investigations during pregnancy | As a minimum transthoracic echocardiography should be performed each trimester and within 6 wk post-partum. Additional echocardiography may be required for a change in clinical status or after a significant alteration in immunosuppressive therapy |
| Screening for hypertensive disorders of pregnancy and gestational diabetes | According to usual obstetric guidelines. However, an early glucose tolerance test (first trimester) is advised. Additionally, quantification of baseline presence of proteinuria with a urinary protein-creatinine ration early in pregnancy assists in subsequent diagnosis of pre-eclampsia. Blood pressure should be documented at all clinical encounters |
| Location of delivery | At an expert centre for pregnancy and cardiac disease. |
| Mode of delivery | According to obstetric indications. There is no evidence to support routine Caesarean section and vaginal delivery is preferred |
| Breast feeding | Individualised but feasible in most patients |

theoretical risks of growth restriction, immunosuppression and carcinogenesis, however, this has to be discussed and balanced against the perceived benefits of breastfeeding and the decision should be individualised. We have found the Drugs and Lactation Database (LactMed) to be a useful resource to review known or potential neonatal risks for women wishing to breastfeed post-partum [23].

## Limitations

This is a small case series of five pregnancies in three women from a single obstetric cardiology service. The follow-up of the women and their offspring in this study is relatively short. Future publications documenting clinicians' experiences of pregnancy in women following cardiac transplantation including short and long-term outcomes would provide valuable insight and will potentially improve outcomes for women and their offspring. A detailed description of the pharmacology of individual and combination immunosuppressive drugs as they relate to pregnancy and breastfeeding was considered beyond the scope of this paper. Readers are directed to existing data sources in order to formulate individualised management strategies for patients.

# Conclusions

Advances in cardiac transplantation continue to improve survival for patients. Successful pregnancy in cardiac transplant recipients is attainable. Pregnancy in this group of patients is associated with some increased risk of complications and, rarely, maternal mortality, which is higher than that in the general population. However, in the majority of cases reported in the literature, successful pregnancy and delivery of a healthy infant is the most likely outcome when care is taken to plan and monitor preconception, throughout pregnancy and in the early post-partum period. In this series, we report generally favourable outcomes of five pregnancies in three transplant recipients at a single Australian centre. All women in our series were compliant with immunosuppression and clinic attendance and engaged with the obstetric, obstetric medicine and cardiology services. Prior to pregnancy there were no recent rejection episodes, good baseline cardiac function and no history of peripartum cardiomyopathy. The literature, although limited, is consistent in the observation that coordinated care prior to pregnancy, ongoing multidisciplinary management and monitoring during and post pregnancy increases the chance of successful outcomes (See Table 4).

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# Competing Interest Statement

The authors declare no conflict of interest relevant to this manuscript.

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