



Pregnancy in heart transplant recipients – current perspectives

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Abstract: Successful pregnancy with a live birth and preserved graft function is possible in women following cardiac transplantation but requires careful assessment and planning in conjunction with the co-ordinated care of a specialist multidisciplinary team. Pregnancy poses significant risks to the mother, graft and foetus; these include the challenges of managing immunosuppression to avoid rejection whilst balancing the risks to the foetus from potentially teratogenic medication. This article aims to provide a contemporary perspective on the issues pertaining to pregnancy in heart transplant recipients; describing the pre-conception, pre-partum, intrapartum and postpartum management in this unique group of women.

Keywords: pregnancy, cardiac transplantation, heart transplant

Introduction

The first successful pregnancy in a solid organ transplant recipient was in 1958, and reported in 1963.¹ Twenty-five years later, Lowenstein described the first pregnancy in a heart transplant recipient in 1988.² Over the past 25 years the International Society for Heart and Lung Transplantation (ISHLT) has reported an increase in the percentage of female heart transplant recipients from 19.9% [1992–2003] to 25.1% [2009–2017].³ Women of child bearing age may consider starting (or expanding) their family after transplantation. Pregnancy poses significant risks to the mother, graft and foetus; these include the challenges of managing immunosuppression to avoid rejection whilst balancing the risks to the foetus from potentially teratogenic medication. Counselling regarding the implications of pregnancy is an important component of on-going clinical care. The care of a pregnant woman following cardiac transplantation should involve a multi-disciplinary team of transplant physicians, obstetricians and maternal and foetal medicine specialists to optimise maternal and foetal outcomes and minimize risk through pregnancy and the postpartum period.

Pregnancy in heart transplant recipients has been described in several case reports and small series from individual centres.^{4–8} The ISHLT has published recommendations on the management of post heart transplant patients who conceive but do not report pregnancy outcomes.

The National Transplantation Pregnancy Registry (NTPR) is the only active registry worldwide to report pregnancy outcomes.⁹ It was established in 1991 and renamed in 2016 as the Transplant Pregnancy Registry (TPR). The registry reports on the pregnancies of female recipients and male recipients who have fathered children.

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This article aims to provide a contemporary perspective on the issues pertaining to pregnancy in heart transplant recipients; describing the pre-conception, pre-partum, intra-partum and postpartum management in this unique group of women.

Pre-pregnancy

Pre-conception counselling

Pregnancy should be discussed with all women of child-bearing age prior to transplantation and counselling should continue throughout subsequent post-transplant care.¹⁰ As many pregnancies in the transplant population are unplanned (over 80% in some series)⁷ it should be emphasised that pregnancy should be planned in conjunction with both the transplant and obstetric teams. Planning will ensure that all necessary investigations are up to date and allow immunosuppression to be adjusted in a timely manner. Contraceptive options should also be discussed, along with general advice for a healthy pregnancy such as weight control, activity and folic acid supplementation.

For women with a pre-transplant diagnosis of an inherited cardiomyopathy, genetic counselling can be considered and offered if appropriate. Offspring from couples with a pre-transplant diagnosis of congenital heart disease have a varying degree of inheritance risk dependent upon the underlying lesion. Two larger series have demonstrated that for cardiac lesions such as Tetralogy of Fallot inheritance risk is in the region of 2.5%, however for some left sided lesions, such as aortic stenosis, this risk may be as high as 13–18%.^{11,12} For congenital heart disease that arises de-novo the risk of recurrence in off-spring is between 3–5%.¹³ Dedicated foetal echocardiography at 19–22 weeks' gestation is recommended if the original maternal diagnosis was congenital heart disease, but not generally performed for cardiomyopathies with postnatal onset.^{14,15} If peripartum cardiomyopathy was the maternal pathology there is data to suggest that this group of women are at a higher risk of rejection in the first 12 months following transplantation, and that they have a higher risk of re-transplantation. This has led some transplant centres to advise against pregnancy given the potential adverse outcomes.^{16,17}

Importantly, the longer term maternal prognosis, graft and maternal survival should be considered on an individual basis and sensitively discussed with a woman and her partner at the time of pre-conception counselling. Family and social considerations including the ability of

a woman's family to cope with the possibility of her becoming unwell during pregnancy, the possibility of complications including graft dysfunction whilst a child is young, and how this would impact upon the wider family must be considered. Also, sadly the impact upon a child or children, and surviving parent if a mother were to die.

Assessment of risk

Pregnancy following heart transplantation is a complex condition with risks to the mother, the graft and the foetus. The assessment of overall risk must therefore incorporate an evaluation of each separate entity. Recommendations from the ISHLT advise delaying pregnancy to at least one year post transplantation owing to the aggressive immunosuppressive regime in the first twelve months.¹⁸ Contemporary guidelines on the Management of Cardiovascular Diseases during Pregnancy from the European Society of Cardiology (ESC) include opinion in line with the ISHLT.¹⁹

Maternal assessment

The haemodynamic changes of normal pregnancy have been previously described. Adaptations in the maternal cardiovascular system begin early in the first trimester to meet the increasing demands of the mother and foetus.²⁰ Blood volume increases by approximately 45%, and cardiac output by up to 45%.²¹ Both systemic and pulmonary vascular resistance decrease and there is a 10–20% increase in maternal heart rate in the third trimester. Pregnancy also represents a hypercoagulable state due to an increase in the levels of circulating factor VII, VIII, IX, X, XII and fibrinogen,^{22,23} placing women at a higher risk of thromboembolic events. The expansion in circulating plasma volume and changes in gastrointestinal absorption lead to alterations in levels of circulating immunosuppression vital for graft function.

Provided there is normal cardiac allograft function prior to pregnancy it is generally accepted that the physiological changes of pregnancy are well tolerated. Pre-conception maternal assessment should include a full cardiac, surgical and obstetric history, and physical examination. The ISHLT recommend that a woman considering pregnancy have a full panel of cardiac screening 6 months prior to conception (**Box 1**), including an electrocardiogram (ECG), an echocardiogram and coronary angiography. Depending on individual circumstances, endomyocardial biopsy and right heart catheterisation may additionally be required.¹⁸

Box 1 Recommended (ISHLT) work-up prior to conception

- ECG and echocardiogram
- Coronary angiography (if not in the last 6 months)
- Right heart catheter and endomyocardial biopsy (if clinically indicated)
- Review of liver and renal function (including urine analysis for proteinuria)
- Review of immunosuppressive and cardiac drugs for teratogenicity
- Vaccination review: influenza, pneumococcus, hepatitis B, tetanus should be vaccinated against (no live viruses)

Note: Data from Costanzo et al.¹⁸

Abbreviations: ECG, electrocardiogram; ISHLT, International Society for Heart and Lung Transplantation.

Immunosuppression and other cardiac medication

All immunosuppressive drugs cross the placenta to enter the foetal circulation. The United States (US) Federal Drug Administration (FDA) places most immunosuppressive agents into categories B, C or D, but is now moving away from this classification system to favour of a more narrative method of drug labelling. This method will summarise the risks of treatment and provide a discussion on the supporting evidence, allowing patients and healthcare professionals to make an informed choice on drug use in pregnancy. Women may be fearful of continuing immunosuppression through pregnancy due to the possible risks to their unborn child. Meticulous counselling, emphasising the importance of immunosuppression throughout pregnancy is vital in maintaining drug compliance and reducing the likelihood of complications such as allograft rejection.

Pregnancy affects drug absorption, distribution and elimination due to the expansion of plasma volume, decreased gut motility and increase in glomerular filtration rate. Careful attention to immunosuppression level monitoring is necessary and is discussed in more detail below.²⁴

Corticosteroids (CS) are categorised in US FDA Class C and can be continued during pregnancy. There are however maternal risks from prolonged CS use in pregnancy including gestational diabetes, preterm premature rupture of membranes and peptic ulcer disease.

Antimetabolites such as mycophenolate mofetil (MMF), mycophenolic acid (MPA) and azathioprine (AZA) are placed in FDA category D. Their use in pregnancy is discouraged by the ISHLT. Maternal registry data suggests an increased risk of miscarriage, microtia and orofacial clefts alongside an increased risk of

spontaneous abortion, recently termed mycophenolate mofetil embryopathy.²⁵ Female patients post transplantation prescribed MMF/MPA and intending to conceive must be changed to an alternative immunosuppressive agent ideally six weeks prior to conception given its teratogenic effects. The European Medicines Agency has recently advised that males prescribed MMF/MPA use effective contraception when taking these agents and avoid fathering a pregnancy for 90 days after cessation of treatment.²⁶

Small studies have suggested that the placenta serves as a barrier to thiopurines and its metabolites, and that no additional thiopurine metabolism takes place in the foetus.²⁷ The risk of foetal immunosuppression and pancytopenia is low if maternal leukocyte counts are maintained in the normal range. Contemporary doses of AZA used in transplant recipients tend to be lower than a few decades ago (1–2 mg/kg, compared to >3 mg/kg) and the more recent literature indicates that there is no evidence that exposure to AZA is associated with congenital malformations, stillbirths or spontaneous abortions.^{28,29} For these reasons, if an antimetabolite drug is indicated it is preferable that AZA is used after an assessment of risk and benefit to the mother and foetus (ISHLT guidelines, class IIb, level of evidence C).^{18,30}

Calcineurin inhibitors (CNI) such as cyclosporine and tacrolimus are FDA class C and may be continued during pregnancy. In a meta-analysis of pregnancy outcome after cyclosporine therapy during pregnancy in over 400 women, cyclosporine was not found to have significant teratogenic effects. The overall prevalence of major malformations in the study group was 4.1% which did not differ significantly from the general population. An association was seen between cyclosporine and increased rates of preterm delivery however.³¹ Particularly during the second trimester of pregnancy there is a significant fall in the trough levels of these drugs and frequent (ideally weekly) monitoring of therapeutic levels is recommended.⁷

Mammalian target of rapamycin inhibitors (mTORi) such as everolimus and sirolimus have not been tested in human pregnancy but have shown an increased risk of foetal abortion in animal studies. Switching to a CNI is preferable for the duration of pregnancy.^{4,16} Table 1 summarises the classification of post transplantation immunosuppressive agents and their potential adverse foetal effects.

All patients are prescribed statin therapy after transplantation to lower cholesterol, improve 1-year survival

Table 1 Immunosuppression, FDA categories and potential adverse foetal effects

Drug	FDA category	ISHLT recommendation ¹⁸	Potential foetal adverse effects ^{4,64–72}
Corticosteroids	B	Continue	Adrenal insufficiency, thymic hyperplasia, cleft palate
Mycophenolate Mofetil	D	Stop	Spontaneous abortion, facial abnormalities, distal limb, heart, oesophagus, kidneys and nervous system abnormalities
Azathioprine	D	Risk-benefit discussion	Skeletal and visceral malformations in mice; lymphopenia, pancytopenia and severe immunosuppression reported in infants
Cyclosporine	C	Continue	Gestational diabetes, hypertension, pre-eclampsia, low birth weight
Tacrolimus	C	Continue	Increased risk of miscarriage, pre-term delivery, low birth weight, birth defects and foetal distress, Transient neonatal hyperkalaemia
Everolimus	D	Does not comment	Abortions, maternal lethality in rabbits; reduction in body weight and survival in rats. Insufficient reports to inform drug associated risk of adverse developmental outcomes in humans
Sirolimus	C	Does not comment	Reduced foetal weight and fatality in rats. No teratogenesis. Inadequate evidence in humans
Antithymocyte globulin	Not assigned	Does not comment	No animal reproductive studies
Rituximab	C	Does not comment	B cell lymphocytopenia in infants exposed in utero, increased risk of infection
Basiliximab	B	Does not comment	No adequate controlled studies in humans. No maternal toxicity, embryopathy or teratogenicity in monkeys

Notes: Category B, animal studies have not shown any risk to the foetus, no studies in humans; Category C, animal studies have shown adverse effects on the foetus, no adequate or well controlled human studies but potential benefits may warrant use in pregnancy; Category D, evidence of human foetal risk based on adverse reaction data however the potential benefits may warrant use.

Abbreviations: FDA, Food and Drug Administration; ISHLT, International Society for Heart and Lung Transplantation.

and reduce the likelihood of cardiac allograft vasculopathy (CAV).³² Statins are contraindicated in pregnancy and must be stopped when pregnancy is confirmed. Up to seventy per cent of patients post heart transplant develop hypertension (predominantly due to CNI therapy) and require anti-hypertensive treatment.³³ Dihydropyridine calcium channel blockers (CCB) and angiotensin converting enzyme inhibitors (ACEi) are often used. ACEi inhibitors are teratogenic and must be omitted during pregnancy. Amongst non-dihydropyridine calcium channel blockers verapamil is considered safe in pregnancy. Diltiazem has limited human data and is FDA category C however teratogenicity has only been shown in animal studies.³⁴ Dihydropyridine CCB can be continued.¹⁹

Risks to the graft

Cardiac allograft function, and the risk of rejection require assessment pre-pregnancy, or in the case of an unplanned pregnancy, at baseline. In the most recent era reported by the ISHLT (2010–2015) 12.7% of adult heart transplant recipients experience an episode of rejection requiring

treatment in the first year following transplantation.³ The rate of rejection generally declines over subsequent years.³⁵ The risk of graft rejection is elevated during pregnancy at around 20%,³⁶ although 40% of these episodes are mild and require no specific treatment. The Transplant Pregnancy Registry's (TPR) most recent presentation (abstract alone) reports rejection in 9% of pregnancies, and 7% within 3 months post-partum.³⁷

Further risk stratification may be considered and performed through HLA testing of the father. If the donor and the father share similar antigens (particularly if the recipient already has donor-specific antibodies to this HLA locus), then conception could provoke rejection.⁵ The woman may then be counselled regarding this additive risk. Table 2 summarises the maternal and foetal outcomes from four of the most recently published series.

Foetal risk

Maternal health during pregnancy determines overall pregnancy and foetal outcome.²⁴ Spontaneous abortion, or

Table 2 Summary of maternal and foetal outcomes in cardiac transplant recipients

Series	TPR data ³⁷ 2018	Macera et al ⁴ 2018	D'Souza et al ⁶ 2018	Bhagra et al ⁷ 2016
Number of pregnancies (number of women)*	162 (91)	17 (11)	17 (16)	22 (17)
Maternal complications (as % of pregnancies)				
Hypertension	46	0	–	14
Pre-eclampsia	23	0	12	14
Diabetes mellitus	7	0	6	0
Graft loss	3	0	0	0
Rejection	9	0	12	5
Obstetric outcomes (as % of live births)				
Live birth	68	71	76	91
Mean gestational age (weeks)	36	-	33	34
Spontaneous miscarriage	25	-	6	9
Low birth weight (<2500g)	-	45	-	45
Premature (<37 weeks)	-	33	46	45
Caesarean delivery	-	83	46	55

Note: *Some women may have had more than one pregnancy in each series.

miscarriage, is the most common complication of early pregnancy. Within the general population the risk of miscarriage is dependent upon gestational age and a variety of maternal factors, with maternal age being one of the biggest risk factors.^{38,39} Within the post cardiac transplant population, the reported risk of miscarriage is similar at around 27%.⁴⁰

Pregnant women should be monitored for seroconversion or reactivation of cytomegalovirus (CMV) owing to the potential risk of CMV viraemia in the foetus. Valgancyclovir and ganciclovir can be used to treat CMV infection, although their safety in pregnancy is not known (FDA category C).

The foetus of a mother post transplantation is also at risk of prematurity and low birth weight, along with a risk of major structural malformations of 4–5% (compared to 3% in the general population).⁴ As increasing data over time accumulates however it is becoming clear that foetal survival in the long term is good.⁴¹

Intrapartum management

General principles

Clinical review at the woman's usual transplant centre, ideally combined with obstetric assessment should occur frequently throughout pregnancy;⁴² generally every 4 weeks until 32 weeks' gestation, then fortnightly until 36 weeks, then weekly until delivery.²⁴ Box 2 summarises these recommendations. Monthly ultrasound examination of the foetus is recommended given the potential risk of complications.²⁴

At each visit blood tests including a full blood count, renal function, immunosuppression levels, urinalysis for proteinuria and urine culture should be performed, along with blood pressure monitoring and screening for diabetes. Corticosteroids can affect bone mineralisation, therefore calcium and phosphate levels should also be carefully monitored and replaced if necessary. Myelosuppressives can cause anaemia and so serum iron levels, vitamin B12 and folate should be checked and supplemented where needed. CMV Polymerase Chain Reaction (PCR) for viral levels (or alternatively IgG and IgM) and serology for toxoplasmosis should be carried out each trimester, and serology for Herpes Simplex Virus (HSV) in the last trimester. Vaginal or anal swabs are taken for Group B Streptococci in the third trimester.

Caution should be observed in prescribing additional medication or nutritional supplements for pregnant post-transplant patients as it is not uncommon for CNI

Box 2 Recommendations for monitoring during pregnancy

- Blood CNI levels should be monitored closely: ideally once a fortnight up to 36 weeks and then weekly
- Monthly urine culture
- Frequent blood pressure, urinalysis and blood sugar monitoring: surveillance for hypertension, pre-eclampsia and gestational diabetes mellitus
- Bloods including calcium and phosphate levels
- Surveillance for bacterial or viral infection (CMV, toxoplasmosis, hepatitis)
- Surveillance for rejection but fluoroscopy guided endomyocardial biopsy should be avoided; if required it should take place under echocardiographic guidance, or with lead draping
- Foetal ultrasound at 18–20 weeks' gestation to assess growth, and for congenital malformations
- Serial foetal ultrasound every 4 weeks from the 24th week to monitor growth

Note: Data from Costanzo et al,¹⁸ Vos et al²⁴ and Durst and Rampersad.⁴³

Abbreviations: CNI, Calcineurin inhibitor; CMV, Cytomegalovirus.

metabolism (and therefore levels) to be affected. Patients must be educated on this, and similarly counselled that hyperemesis gravidum requires prompt treatment as it can negatively impact upon the intake and absorption of immunosuppressive drugs.

The most frequently encountered maternal complications are hypertension, pre-eclampsia, diabetes and infection (including urinary tract infection).²⁴ There is an increased risk of venous thromboembolism and pulmonary embolism in pregnancy, although it is unknown if this is multiplicative with the increased risk in transplanted patients.⁴³

Management of maternal complications

Rejection

During pregnancy, there is the risk of acute rejection leading to graft dysfunction. Reported rates of maternal death due to graft dysfunction are low and published series suggest that 70% of recipients retain cardiac function postpartum.⁷ In the TPR registry graft loss within two years of delivery was uncommon, occurring in only 3 of 91 recipients.³⁷ An episode of rejection during or within 3 months of pregnancy, and an elevated serum creatinine during pregnancy are both associated with an increased risk of graft loss within 5 years of pregnancy.⁴² Graft surveillance is vital and regular assessment should be undertaken through physical examination, ECG and echocardiography. Right heart catheterisation and endomyocardial biopsy with appropriate shielding is not believed to pose prohibitive risk to the mother or foetus,¹⁶ nonetheless endomyocardial biopsy is not recommended on a routine basis and should only be performed under circumstances where rejection is suspected.

Hypertension and pre-eclampsia

Hypertension is more prevalent in transplant patients as a side effect of CNIs. Regular blood pressure assessment is important as hypertension can lead to foetal growth restriction and preterm delivery. Increased rates of preeclampsia have been reported in women following solid organ transplantation, with rates in post renal transplant patients greater than those post liver transplantation (27% versus 22%).^{44,45} Rates tend to be lower in women after cardiac transplantation with pre-eclampsia complicating 13.6–24% of pregnancies.^{7,46} Similar figures have been reported through the TPR.³⁶ This is higher than the pre-eclampsia rate for the general population (3.4%).⁴⁷ Higher rates of hypertension in the post solid organ transplant recipients may be a

predisposing factor.^{48,49} The American College of Obstetricians and Gynaecologists (ACOG) recommends the use of low dose aspirin prophylaxis in women at high risk for preeclampsia between 12–28 weeks' gestation (ideally before 16 weeks) and continued until delivery.⁵⁰ The guidelines do not make specific comment on solid organ transplant recipients however. Baseline blood pressure, renal and hepatic function are useful in making the diagnoses of pre-eclampsia: but undoubtedly the diagnosis is more challenging in cases where there is baseline proteinuria and hypertension. A high index of suspicion for pre-eclampsia, and consideration of the introduction of low dose aspirin in those with hypertension may be a pragmatic approach in these women. Beta blockers (aside from atenolol), hydralazine and CCB are acceptable antihypertensive options in pregnancy. ACE inhibitors and mineralocorticoid receptor antagonists should be avoided owing to the risks of teratogenicity.

Diabetes mellitus

A new diagnosis of, or deterioration in the glycaemic control of type 2 diabetes mellitus is more common following heart transplantation owing to side effects of steroids (and, to a lesser extent, tacrolimus). The most recent TPR data reports a 7% prevalence of diabetes (within a cohort of 162 pregnancies in 91 heart transplant recipients).³⁷ Screening should take place in the 24th to 28th week of pregnancy and optimal glycaemic control be maintained to reduce the risk of miscarriage. A fasting plasma glucose <90 mg/dL, postprandial glucose <120 mg/dL and HbA1c <6% is encouraged both pre pregnancy and thereafter to minimize the risk of miscarriage.⁵¹

Infection

Urinary tract infection complicated up to 11% of pregnancies in the TPR, and regular screening is important as untreated asymptomatic bacteriuria can lead to pyelonephritis. Where a positive urine culture is detected, antibiotics should be prescribed and further prophylactic treatment should be considered.

Valganciclovir and ganciclovir are used for the treatment or prevention of CMV infection in pregnancy, both are FDA category C.⁵² Aciclovir is used to prevent neonatal HSV, or treat recurrent maternal HSV. Aciclovir is FDA category B and may be used safely.⁵³

Management of delivery

The mode of delivery for pregnant heart transplant recipients is generally dictated by obstetric indications. Where cardiac allograft function remains normal, vaginal delivery is preferable. Caesarean section delivery is frequently reported in the post-transplant population at 30–60% depending on the series.^{4,7,42} The latest ESC guidelines recommend vaginal delivery with spinal/epidural anaesthesia in those with stable congestive HF and Caesarean delivery in those with advanced HF and hemodynamic instability.⁵⁴ In the presence of significant graft dysfunction a scheduled Caesarean section with a multi-disciplinary team of transplant cardiologists, maternal/foetal medicine physicians, neonatologists, obstetric and cardiac anaesthetists, and cardiac surgeons guiding decision making is advised.¹⁶ Delivery in the case of graft dysfunction should be co-ordinated in a facility where mechanical circulatory support is accessible. Prophylactic antibiotics should be prescribed in line with local guidelines for patients undergoing Caesarean section. Impairment of wound healing due to immunosuppression (especially mTORi) is a concern in those who undergo a Caesarean delivery.¹⁰

During labour, women should be monitored for cardiac dysrhythmia with telemetry. Invasive haemodynamic monitoring is not recommended except in cases of significant graft dysfunction. Epidural anaesthesia is often favoured as it is well tolerated and provides effective pain control whilst minimising the sympathetic response and fluctuations in blood pressure during labour and delivery.^{4,16} Close observation should continue through the immediate post-partum period as this is often the time of highest risk due to the rapid haemodynamic and volume shifts. Uterine involution results in auto-transfusion of approximately 300–500 mls of blood, increasing stroke volume and cardiac output.⁵⁵ Cardiac output returns to just above pre-partum levels around two to four weeks following delivery.⁵⁶

Postpartum management

Immunosuppression

The postpartum management of immunosuppression requires ideally weekly assessment of plasma trough CNI levels. It takes several weeks for the maternal haemodynamic changes of pregnancy to return to baseline. During this time, female transplant recipients remain at higher risk of complications due to fluctuations in immunosuppression

levels.⁵⁷ Levels should be monitored closely for at least a month post-partum.²⁴ Cardiac medications which were stopped for the duration of pregnancy can be reintroduced following delivery depending upon the woman's decision to breastfeed or not.

Young children have the propensity to pass infection to their parents. A mother post cardiac transplantation is at higher risk of opportunistic infection owing to immunosuppressive medication. It is important that offspring of transplant recipients receive appropriate immunisations, and that their parents observe strict hygiene measures to reduce the risks of transmission.

Breastfeeding

Breastfeeding has unique advantages to mother and baby, both nutritional and non-nutritional. There are proven benefits of breastfeeding in preterm infants and those of low birth weight. The American Academy of Paediatrics has recommended that all preterm babies receive human milk.⁵⁸ Historically heart transplant recipients have been advised against breastfeeding, owing to the passage of immunosuppressant's into, and the unknown safety profile of these drugs in breast milk. More recently however the TPR have reported a rise in the number of infants being breastfed, from a nadir of only 1% in 1994 to 36% in 2012.⁵⁹ During breastfeeding no adverse effects on infants have been reported with women receiving corticosteroids; prednisolone is considered safe as the level of drug detectable in human milk is not expected to cause any undue effects. Similarly, azathioprine, cyclosporine and tacrolimus can be continued whilst breast feeding and, as suggested by Constantinescu et al testing of blood and milk may reassure those who have continued concerns regarding the infant's exposure to these drugs.⁵⁹ Current review of the available literature cautions against breastfeeding whilst taking mycophenolic acid products (MPA), sirolimus, everolimus and belatacept due to the scarcity of clinical data.⁵⁹ Further investigation into the quantities and effects of these drugs in breast milk is necessary to enable informed decision making. Furthermore, the longer-term follow-up of breast fed infants is important in increasing our understanding of the longer-term effects of exposure to immunosuppression in human milk.

Contraception

Given that a significant proportion of pregnancies following cardiac transplantation are unplanned,⁶⁰ appropriate contraceptive counselling is key and should be started prior to

transplant assessment and continued throughout post-transplant care. There are recognised advantages and disadvantages to all methods of contraception. Individualisation is therefore crucial in underpinning compliance and limiting potential side effects. Barrier methods of contraception (for example condoms, cervical cap/diaphragm) are safe, with the advantage of having no drug interactions and can reduce the risk of transmission of infection. Barrier contraceptives are useful adjuncts when using another method of contraception but are not reliable when used in isolation.⁶¹ Contraceptive recommendations for women following heart transplantation are divided into two groups, one group of recommendations is applicable to those patients who are complicated (for example those with a history of graft failure, rejection or cardiac allograft vasculopathy), the other is for those who are uncomplicated (in the absence of the above). Uncomplicated heart transplant recipients can be safely offered a wide range of contraceptives including the combined oral contraceptive pill, the progesterone-only pill, the depot progesterone implant and the copper or progesterone IUD. The benefits of each contraceptive option are recognised to outweigh the theoretical or proven risk for this group.

For those women who complicated, combined hormonal contraceptive methods such as the combined oral contraceptive pill, contraceptive patch or vaginal ring are not considered safe. The use of emergency contraception if required has no restrictions.^{61–63}

When considering the most appropriate contraceptive method for an individual it is also helpful to take into account more general contra-indications for various methods (for instance, combined oral contraceptives are advised against in hypertensives and women over 35) along with personal preference for the recipient.

Conclusion

Successful pregnancy with a live birth and preserved graft function is possible in women following cardiac transplantation but requires careful assessment and planning in conjunction with the co-ordinated care of a specialist multidisciplinary team. Stable maternal cardiac function and no recent episodes of rejection are advised prior to pregnancy to maximise the chances of a favourable outcome, despite the inherent maternal and foetal risks. Pre-pregnancy counselling must include a discussion surrounding longer term maternal health and maternal survival. Serious complications can arise during pregnancy hence the need for frequent clinical review and close monitoring of immunosuppression and graft function. It has been suggested that pregnancy may have no impact on the longer-term survival but larger studies are now needed to confirm

these findings.⁸ Balancing the risks of immunosuppressive medication to the foetus against the risk of graft rejection remains a challenge and meticulous monitoring is vital throughout pregnancy and postpartum. Breast feeding remains controversial and further data on the safety of immunosuppression in breast milk is required to aid informed decision making. Finally, on-going registry submissions will follow the outcomes of off-spring born to transplant recipients and help address some of the remaining concerns over the longer-term health of these children.

Disclosure

The authors report no conflicts of interest in this work.

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