

CONSENSUS STATEMENT

# Reproductive health after thoracic transplantation: An ISHLT expert consensus statement



Michelle M. Kittleson, MD, PhD (Chair),<sup>a</sup> Ersilia M. DeFilippis, MD (Co-Chair),<sup>b</sup> Catriona J. Bhagra, MRCP, MD,<sup>c</sup> Jillian P. Casale, PharmD,<sup>d</sup> Matthew Cauldwell, MD,<sup>e</sup> Lisa A. Coscia, RN, BSN, CCTC,<sup>f</sup> Rohan D'Souza, MD,<sup>g</sup> Nicole Gaffney, MD,<sup>h,i</sup> Vicky Gerovasili, MD,<sup>j</sup> Patricia Ging, MSc,<sup>k</sup> Kristin Horsley, PhD,<sup>l</sup> Francesca Macera, MD,<sup>m,n</sup> Joan M. Mastrobattista, MD,<sup>o</sup> Miranda A. Paraskeva, MD,<sup>h,i</sup> Lynn R. Punnoose, MD,<sup>p</sup> Kismet D. Rasmusson, DNP, FNP,<sup>q</sup> Quitterie Reynaud, MD, PhD,<sup>r</sup> Heather J. Ross, MD,<sup>s,t,u</sup> Mitesh V. Thakrar, MD,<sup>v</sup> and Mary Norine Walsh, MD<sup>w</sup>

*From the <sup>a</sup>Department of Cardiology, Smidt Heart Institute, Cedars-Sinai Medical Center, Los Angeles, California; <sup>b</sup>Division of Cardiology, New York Presbyterian-Columbia University Irving Medical Center, New York, New York; <sup>c</sup>Department of Cardiology, Cambridge University and Royal Papworth NHS Foundation Trusts, Cambridge, UK; <sup>d</sup>Department of Pharmacy Services, University of Maryland Medical Center, Baltimore, Maryland; <sup>e</sup>Department of Obstetrics, Maternal Medicine Service, St George's Hospital, London, UK; <sup>f</sup>Transplant Pregnancy Registry International, Gift of Life Institute, Philadelphia, Pennsylvania; <sup>g</sup>Division of Maternal and Fetal Medicine, Department of Obstetrics and Gynecology, McMaster University, Hamilton, Ontario, Canada; <sup>h</sup>Lung Transplant Service, Alfred Hospital, Melbourne, Australia; <sup>i</sup>Department of Medicine, Central Clinical School, Monash University, Melbourne, Australia; <sup>j</sup>Heart and Lung Institute, Imperial College, London, UK; <sup>k</sup>Department of Pharmacy, Mater Misericordiae University Hospital, Dublin, Ireland; <sup>l</sup>Department of Obstetrics and Gynecology, McMaster University, Hamilton, Ontario, Canada; <sup>m</sup>De Gasperis Cardio Center and Transplant Center, Niguarda Hospital, Milan, Italy; <sup>n</sup>Dept of Cardiology, Cliniques Universitaires de Bruxelles - Hôpital Erasme, Brussels, Belgium; <sup>o</sup>Department of Obstetrics & Gynecology, Division of Maternal-Fetal Medicine, Baylor College of Medicine Houston, Texas; <sup>p</sup>Vanderbilt Heart and Vascular Institute, Vanderbilt University Medical Center, Nashville, Tennessee; <sup>q</sup>Intermountain Medical Center Heart Institute, Salt Lake City, Utah; <sup>r</sup>Cystic Fibrosis Adult Referral Care Centre, Department of Internal Medicine, Hospices civils de Lyon, Pierre Bénite, France; <sup>s</sup>Peter Munk Cardiac Centre of the University Health Network, Toronto, Ontario, Canada; <sup>t</sup>Ted Rogers Centre for Heart Research, Toronto, Ontario, Canada; <sup>u</sup>University of Toronto, Toronto, Ontario, Canada; <sup>v</sup>Department of Medicine, Division of Respiriology, University of Calgary, Calgary, Alberta, Canada; and the <sup>w</sup>St. Vincent Heart Center, Indianapolis, Indiana.*

Reprint requests: Michelle M. Kittleson, MD, PhD, 8670 Wilshire Boulevard 2nd floor, Los Angeles, CA 90211. Telephone: 310-248-8300. Fax: 310-248-8333. E-mail address: [Michelle.kittleson@cshs.org](mailto:Michelle.kittleson@cshs.org)

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Pregnancy after thoracic organ transplantation is feasible for select individuals but requires multidisciplinary subspecialty care. Key components for a successful pregnancy after lung or heart transplantation include preconception and contraceptive planning, thorough risk stratification, optimization of maternal comorbidities and fetal health through careful monitoring, and open communication with shared decision-making. The goal of this consensus statement is to summarize the current evidence and provide guidance surrounding preconception counseling, patient risk assessment, medical management, maternal and fetal outcomes, obstetric management, and pharmacologic considerations.

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With surgical and immunosuppressive advances in thoracic organ transplantation over the past 3 decades and attendant improved long-term outcomes, post-transplant pregnancy is an achievable goal for many lung transplant (LT) and heart transplant (HT) recipients.<sup>1</sup> The keys to successful post-transplant pregnancy are preconception and contraceptive planning, appropriate patient risk assessment with comprehensive risk stratification, and optimization of maternal comorbidities and fetal health through careful monitoring.<sup>2</sup> The goal to optimize outcomes in pregnant LT and HT recipients aligns well with the increasing contemporary emphasis on strategies to reduce maternal mortality worldwide.<sup>3,4</sup>

The purpose of this statement is to summarize the current evidence and provide guidance surrounding preconception counseling, patient risk assessment, and medical management, maternal and fetal outcomes, obstetric management, and pharmacologic considerations. This consensus statement represents the current state of knowledge and expertise in the field of pregnancy after thoracic organ transplantation.

## Methods

This consensus document was developed in accordance with the International Society of Heart and Lung Transplantation (ISHLT) Standards and Guidelines committee document development policies. The consensus committee members were selected to represent the diversity and multidisciplinary nature of the society and were approved by the ISHLT Standards and Guidelines committee. Each member contributed to the literature searches, developed content, reviewed the final consensus statements, and approved the final manuscript.

Literature searches performed in mid-2021 reviewed all pertinent articles, focusing on newer peer-reviewed research. The guidance reflects expert synthesis of the current literature. In the absence of a strong evidentiary base regarding best practices for the reproductive health in thoracic transplantation, this document was written as a summation of the current literature with accompanying expert opinion, rather than guidelines written with specific levels of evidence. Recommendations were iteratively discussed by the full writing group in a series of virtual consensus meetings and correspondence until a majority of group members agreed on the text and qualifying remarks, akin to the process of similar ISHLT consensus statements.<sup>5–7</sup> The proposed statements herein represent consensus recommendations.

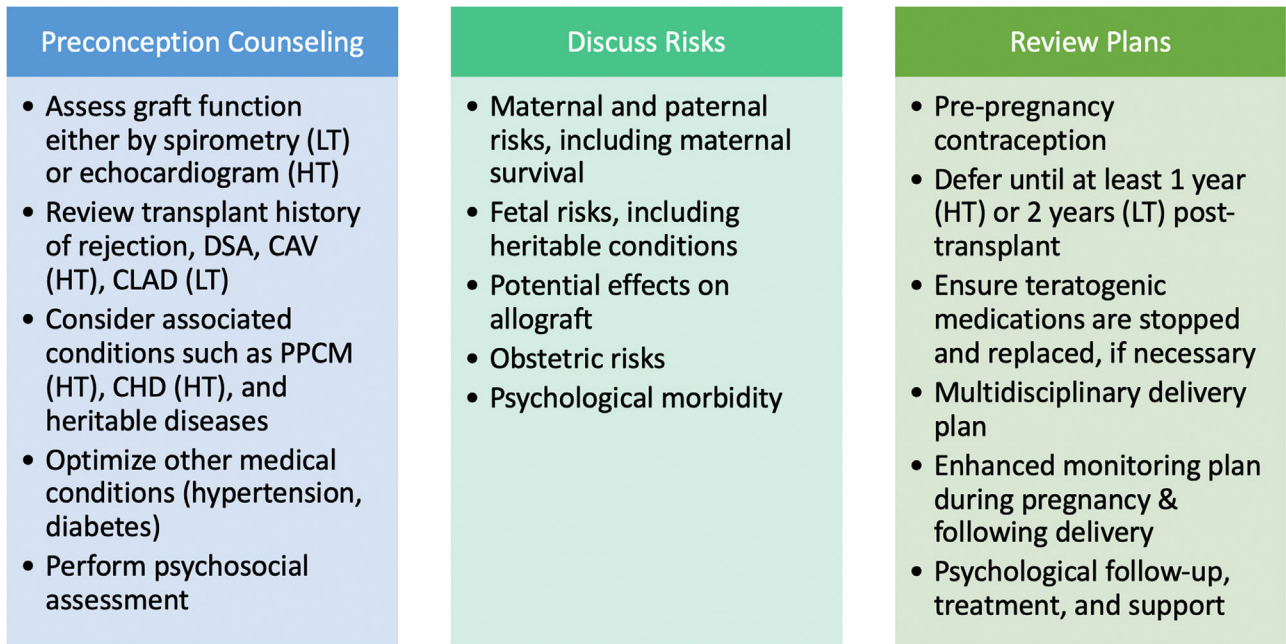
## Preconception counseling

Achieving optimal pregnancy outcomes in LT and HT recipients requires a comprehensive and coordinated multidisciplinary team approach that begins before conception.<sup>8</sup> Preconception counseling for all individuals of childbearing age encompasses pregnancy intention, contraception, timing of conception after transplant, maternal risks including those unique to transplant recipients, fetal risks, and psychosocial support for optimal shared decision-making.<sup>9,10</sup> Whenever possible, counseling and shared decision-making should be facilitated in an experienced transplant center with a multidisciplinary expert team.

Unfortunately, about half of pregnancies in HT recipients<sup>11,12</sup> and LT recipients<sup>13,14</sup> are unplanned, demonstrating a significant opportunity for education both pre- and post-transplantation regarding contraception and transition to medications that are safe during pregnancy.<sup>11,12</sup> Because of the potential risks involved with pregnancy after LT or HT, these discussions should ideally include both the patient and partner and begin during the pre-transplant evaluation. Revisiting these discussions annually throughout the post-transplant period allows recipients opportunities to re-assess their decisions. Pre-pregnancy planning allows for the adjustment of medications to those with a safety profile compatible with pregnancy, time to optimize comorbidities, and the opportunity to consider genetic counseling for potentially heritable pre-transplant diagnoses. The latter may be especially important in those with proven or suspected genetic cardiomyopathies or lung disease (e.g., cystic fibrosis [CF]).<sup>15</sup>

Figure 1 summarizes the key components of preconception counseling. Figure 2 provides a patient-focused summary of important concepts for patients to discuss with their treating clinicians. A major component of preconception counseling is a frank discussion of how transplant status influences maternal and fetal risks during pregnancy.

Generally, pregnancy is considered relatively safe in transplant recipients if there is adequate and stable graft function, no episodes of allograft rejection in the prior year, no maternal infections that may impact upon the fetus, and stable dosing of maintenance non-teratogenic immunosuppression.<sup>16</sup> However, there are issues unique to LT and HT regarding contraindications to pregnancy and maternal and fetal risks. These considerations are described in detail in Sections IV and V, respectively. This section will focus on other aspects of preconception counseling including



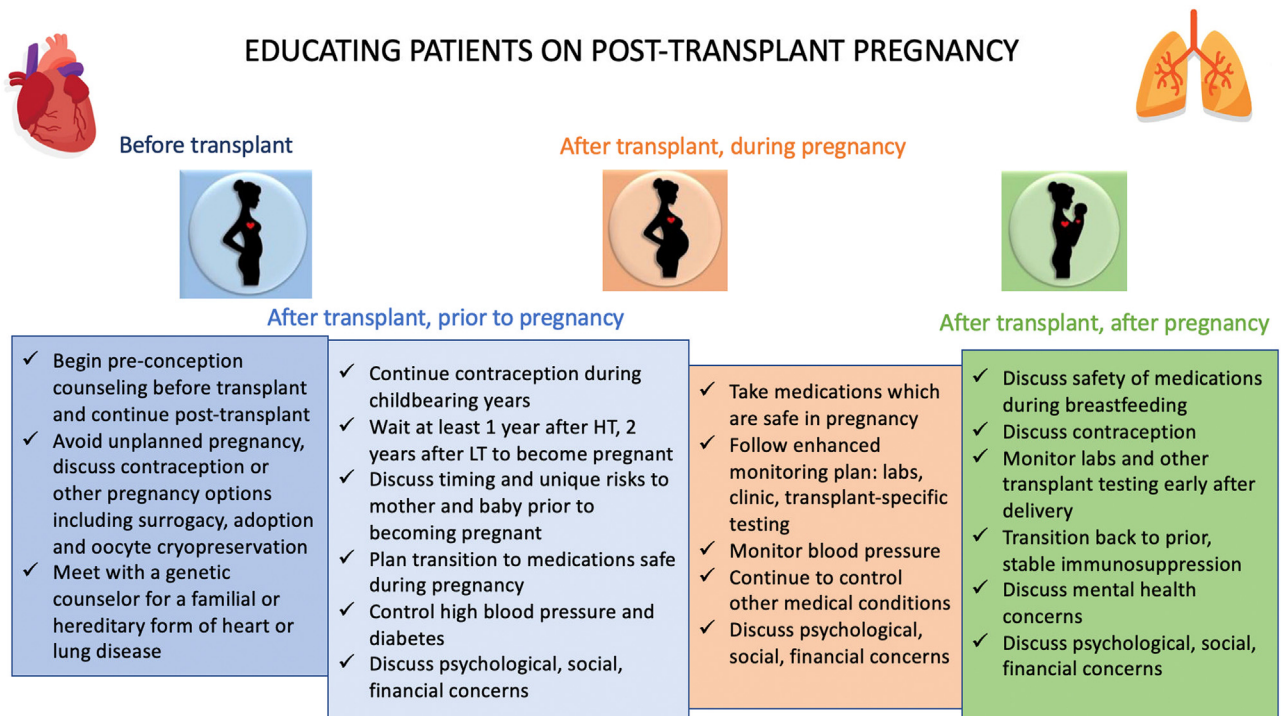
**Figure 1** Approach to preconception counseling in lung and heart transplant recipients. CAV, cardiac allograft vasculopathy; CHD, congenital heart disease; CLAD, chronic lung allograft dysfunction; DSA, donor-specific antibodies; HT, heart transplant; LT, lung transplant; PPCM, peripartum cardiomyopathy.

contraception, assisted reproductive technology (ART), psychosocial risks, and the importance of shared decision-making.

**Contraception**

As any disruption to the hypothalamic-gonadal axis is usually restored within 2-6 months following transplant,

effective contraception should be recommended immediately.<sup>17</sup> This is particularly relevant as nearly half of pregnancies in HT recipients<sup>11,12</sup> and LT recipients<sup>13,14</sup> are unplanned, with the risk of inadvertent fetal exposure to the teratogenic effects of immunosuppressive agents such as mycophenolate mofetil and other potential teratogens such as statins, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs).<sup>18</sup> Thus, there is



**Figure 2** Educating patients on post-transplant pregnancy. HT, heart transplant; LT, lung transplant.

**Table 1** Summary of Contraceptive Options in Transplant Recipients

Type of contraception	Consensus recommendations	Use in transplant recipients taking mycophenolate products	Safe in breastfeeding	Notes
Intrauterine devices (hormonal and non-hormonal)	Preferred method for long-term contraception	Acceptable as sole method of contraception	Yes	<ul style="list-style-type: none"> <li>• Long-term, highly effective</li> <li>• Immunosuppression is not a contraindication</li> <li>• Lack of drug-drug interactions</li> <li>• Straightforward removal for reversal</li> </ul>
Progesterone depot injection	Not recommended for long-term (i.e., > 2 years) contraception due to risk of decreased bone mineral density	Use with barrier method	Yes	<ul style="list-style-type: none"> <li>• Highly effective</li> <li>• Delayed return to fertility after cessation</li> <li>• Decreased bone mineral density</li> <li>• Weight gain</li> </ul>
Progesterone subdermal implant	Acceptable method of long-term contraception	Use with barrier method	Yes	<ul style="list-style-type: none"> <li>• Long-term, highly effective</li> <li>• Rapid return of fertility once removed</li> </ul>
Combined hormonal contraceptives (pills, vaginal ring, transdermal patch)	Not recommended as sole method of contraception given contraindications and drug interactions	Use with barrier method	May reduce milk production	<ul style="list-style-type: none"> <li>• Screen for hypercoagulable states before the initiation of combination hormonal contraception</li> <li>• Avoid in patient with transplant-related coronary artery disease or hypertension</li> <li>• Contraindicated in patients with a history of stroke, increased risk of thrombosis, liver disease, and estrogen-sensitive malignancies</li> <li>• Subject to drug interactions that may reduce contraception efficacy</li> <li>• Due to the inhibition of the cytochrome P450 3A4 pathway seen with these drugs, monitoring blood levels of immunosuppressive medications is required after initiation</li> <li>• Avoid early postpartum due to risk of thrombosis</li> <li>• Efficacy strongly dependent on consistent timing of administration due to short half-life</li> </ul>
Progestin-only pills	Not routinely recommended given effectiveness diminishes with nonadherence	Use with barrier method	Yes	<ul style="list-style-type: none"> <li>• Avoid early postpartum due to risk of thrombosis</li> <li>• Efficacy strongly dependent on consistent timing of administration due to short half-life</li> </ul>
Barrier methods (condoms, sponge, diaphragm, cervical cap with or without spermicide)	Not recommended as sole contraception	Use with another method	Yes	<ul style="list-style-type: none"> <li>• Should be used in combination with non-IUD hormonal methods for prevention of pregnancy</li> <li>• Should be used in combination with any another form of contraception for protection against sexually transmitted diseases</li> </ul>

Barrier methods are recommended for use with progesterone implant or depot injection based on the Mycophenolate Risk Evaluation and Mitigation Strategies (REMS) program (<https://www.mycophenolaterems.com>).

an opportunity for education both pre- and post-transplant regarding contraception. [Table 1](#) provides a detailed summary of contraceptive options; the most commonly used options are discussed below.

Intrauterine devices (copper-containing IUD and levonorgestrel-releasing IUD) offer long term, highly effective, reversible contraception.<sup>10,19,20</sup> Immunosuppression is not a contraindication to IUD use,<sup>21,22</sup> though the United States Centers for Disease Control (CDC) notes that the risks of IUD implantation may outweigh the benefits in those transplant recipients with graft failure, rejection, or cardiac allograft vasculopathy (CAV).<sup>23</sup> Similarly, the 2022 Guideline for the Care of the Heart Transplant Recipient notes that IUDs are not generally recommended for HT recipients with complications.<sup>24</sup> However, IUDs are considered the only acceptable sole method of contraception in transplant recipients taking mycophenolate mofetil. The reasons why IUDs are considered preferable to other forms of birth control in transplant recipients are their low failure rate, ability to remain in place for several years, lack of required daily adherence for effectiveness, lack of drug-drug interactions, and straightforward removal to reverse contraception.

Depo-medroxyprogesterone acetate administered every 3 months is a highly effective form of contraception, but it is associated with delayed return to fertility after cessation and decreased bone mineral density and weight gain,<sup>25</sup> which may be significant in transplant recipients who are also exposed to long-term corticosteroid therapy.<sup>26</sup> Thus, depo-medroxyprogesterone acetate is not routinely recommended as a long-term contraceptive option.<sup>24</sup>

Use of combined hormonal contraceptives should be considered carefully in patients with CAV or hypertension, and their use is contraindicated in patients with an increased risk of thrombosis, liver disease, or estrogen-sensitive malignancies.<sup>10</sup> Combined hormonal contraceptives portend increased risk in patients with prior myocardial infarction, stroke or deep venous thrombosis, hypertension, migraine with aura, and liver disease.<sup>26</sup> In addition, the ISHLT guidelines recommend transplant recipients be screened for hypercoagulable states before the initiation of combination hormonal contraception.<sup>24</sup> Furthermore, due to the inhibition of the cytochrome P450 3A4 pathway with these drugs, additional monitoring of immunosuppression blood levels is required after initiation. Progestin-only pills are not routinely recommended as their efficacy is strongly dependent on consistent timing of administration due to the short half-life, and thus the effectiveness will diminish with nonadherence.

Barrier methods are not recommended as a sole method of contraception, given their relatively high failure rates. They should be used, in combination with another reliable form of birth control, for protection against sexually transmitted infection when indicated.

Sterilization of the recipient or partner may be considered for those who desire permanent forms of contraception. Failure rates are low, however, female sterilization such as tubal ligation does carry some surgical and anesthetic risk that should be accounted for depending on the individual risk profile. Male sterilization with vasectomy alternatively may be considered as a less invasive

approach.<sup>27</sup> However, it is important to note that there is a failure rate of 1-2 per 1000 men,<sup>28</sup> and couples should be advised that an analysis of a semen specimen after vasectomy is required to confirm success before the use of alternative contraception is abandoned.<sup>29</sup>

It is important to note that endometrial ablation, which may be performed as a treatment for menorrhagia, is not a form of contraception. In fact, pregnancy post endometrial ablation may result in high rates of maternal and fetal complications.<sup>30</sup> Thus, individuals who desire pregnancy should not undergo this procedure and those who do should be counselled to use reliable contraception until menopause.

## Assisted reproductive technology

A survey of 1090 solid organ transplant recipients in the Transplant Pregnancy Registry International (TPRI) revealed that 22% of women experienced difficulty achieving pregnancy.<sup>11</sup> For such patients, and for those transplant recipients for whom pregnancy portends prohibitive risk and is not recommended, the options of surrogacy, adoption and oocyte preservation may be considered. For other patients, ART may be an option.

Although experience is limited, ART may be an option for select transplant recipients. However, the decision to proceed with ART should follow multidisciplinary discussions with the transplant physician and reproductive endocrinologist in the context of shared-decision making and account for graft function and comorbidities. Of note, the risk of thromboembolism is low with ART, 0.6% in a large registry,<sup>31</sup> which is reassuring when considering ART for HT and LT recipients without risk factors for or prior history of thromboembolism.

Multiple gestations can result from fertility treatments and may put transplant patients at further risk for hypertension and pre-eclampsia.<sup>12–14,32–35</sup> Therefore, the American Society of Reproductive Medicine recommends single embryo transfer at the blastocyst stage, which allows for high implantation rates but with a lower risk of multiple pregnancies.<sup>36</sup>

Controlled ovarian stimulation may cause increased vascular fluid shifts,<sup>37</sup> which should be tolerated in transplant recipients with normal graft function. However, patients should be closely monitored for ovarian hyperstimulation syndrome (OHSS), a potentially life-threatening complication of controlled ovarian stimulation. OHSS may result in ascites, electrolyte imbalances and pro-thrombotic state as a result of third-spacing fluid accumulation and increased vascular permeability.<sup>38</sup> OHSS has been associated with arrhythmias, pericardial effusion and adult respiratory distress syndrome in certain cases.

## Psychosocial risks and evaluation

### *Psychosocial risks*

Psychological and social circumstances are important to consider across the transplant care continuum, as there is a

high prevalence of anxiety and depression among transplant recipients.<sup>39</sup> In LT recipients, major depression is observed in 30%, panic disorder in 15%, post-traumatic stress disorder in 15%, and generalized anxiety disorder in 4% of recipients.<sup>40</sup> Similarly, in HT recipients, depression is observed in 21.6%, anxiety in 11.1%, adjustment disorder in 11%, and post-traumatic stress disorder in 13.5% of recipients.<sup>41</sup> Compared with male HT recipients, depression is more common in women (50% vs 23.6%),<sup>42</sup> and tends to persist over time.<sup>41–44</sup> Pre- and post-transplant depression is associated with an increased risk of mortality after heart, lung, and other solid-organ transplantation.<sup>39,45–48</sup>

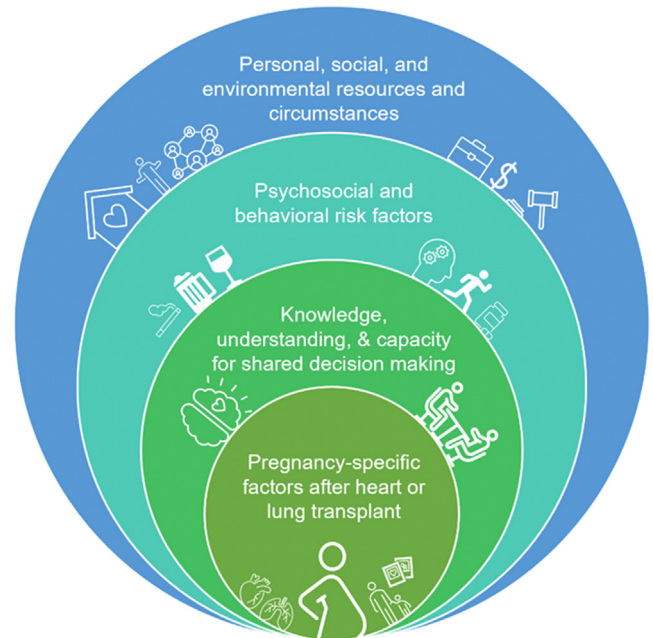
In addition, both the antenatal and postpartum periods are vulnerable times for the onset or exacerbation of psychological morbidity in non-transplant recipients, with up to 15% and 20% of pregnant individuals reporting clinically significant symptoms of depression and anxiety, respectively.<sup>49,50</sup> Medical complications such as hypertensive disorders of pregnancy, gestational diabetes, and infection are among the most potent predictors of psychological conditions including postpartum depression, anxiety, and post-traumatic stress disorder.<sup>51–55</sup>

Thus, pregnant transplant recipients are an especially vulnerable group for several reasons: (1) both transplant status and pregnancy place these patients at high risk for anxiety and depression, (2) psychopathology post-transplant portends worse outcomes, and (3) the medical complications of pregnancy which are associated with adverse psychological outcomes are the most common encountered by transplant recipients.<sup>56</sup> As a result, pregnant transplant recipients warrant careful psychosocial evaluation.

### Psychosocial evaluation

Psychosocial evaluation is recognized as an essential component of both transplant and pregnancy care. In 2018, the American College of Obstetricians and Gynecologists (ACOG) recommended screening for depression and anxiety at least once during pregnancy and again at the comprehensive 6-week postpartum visit with referral to a mental health professional for follow-up and treatment when necessary.<sup>57</sup> Also in 2018, the ISHLT published consensus recommendations for the psychosocial evaluation of adult cardiothoracic transplant candidates and candidates for long-term mechanical circulatory support.<sup>58</sup> These recommendations focus on the importance of evaluating treatment adherence and health behaviors, mental health history, substance use history, cognitive status, knowledge of current treatment options, coping with illness, and social support.

Within the context of preconception counseling, the psychosocial evaluation should cover the core components outlined in the 2018 ISHLT consensus recommendations,<sup>58</sup> with additional assessment of circumstances unique to pregnancy such as a personal or family history of postpartum mood or anxiety disorders as well as other mental health conditions (e.g., bipolar disorder, schizophrenia, personality disorders). As summarized in [Figure 3](#) and adapted for pregnancy post-transplantation, these domains can include: (1) factors specific to patients' personal, social, and



**Figure 3** Components of a comprehensive psychosocial evaluation. Psychosocial evaluation is a key part of both transplant and pregnancy care. Important components of a comprehensive psychosocial evaluation include 1) factors specific to patients' personal, social, and environmental resources and circumstances, 2) psychosocial risk factors for poor pregnancy outcomes, including treatment and medication adherence, health behaviors, mental health, and substance use history, 3) factors related to patient's knowledge, understanding, cognitive abilities, and capacity to engage in shared decision-making during preconception and pregnancy, and 4) factors specific to heart and lung transplant recipients who may be contemplating pregnancy, including lifespan, need for re-transplantation, and the impact of adverse outcomes.

environmental resources and circumstances, (2) psychosocial risk factors for poor pregnancy outcomes, including treatment and medication adherence, health behaviors, mental health, and substance use history, (3) factors related to patient's knowledge, understanding, cognitive abilities, and capacity to engage in shared decision-making during preconception and pregnancy, and (4) factors specific to LT and HT recipients who may be contemplating pregnancy, including lifespan, candidacy for re-transplantation, and the impact of adverse outcomes (e.g., hospitalizations, rejection, graft failure, or death) on the life of an unborn child, or other offspring of a transplant recipient.<sup>58</sup>

Routine psychological screening using validated tools (e.g., Edinburgh Postnatal Depression Scale<sup>59</sup> and Generalized Anxiety Disorder-7)<sup>60</sup> should be integrated into psychosocial assessment and follow-up including evidence-based psychological interventions, when required, across the continuum of transplant care. Psychological follow-up can be complemented by consultation with psychiatry for additional assessment and psychotropic medication initiation and management depending on individual needs. Other healthcare professionals who offer more specialized services can be incorporated on a case-by case basis including social work, occupational therapy, physical therapy,

chronic pain specialists, and specialists in the treatment of eating or substance use disorders. Community resources for patients, partners, and families can also be identified to enhance social support.

More research is needed on how to best assess and counsel LT and HT recipients regarding the unique psychological and social risks associated with pregnancy. Whether the integration of screening, comprehensive psychosocial assessments, and follow-up with psychological treatment and targeted functional support leads to more favorable patient, partner, family, or medical outcomes remains an opportunity for future research.

### **Shared decision-making**

A critical component of transplant care is shared decision-making, a model of patient-clinician communication that promotes the integration of patient values and preferences with discussion of potential risks, benefits, and harms to inform treatment decisions.<sup>61,62</sup> Shared decision-making is especially important given the unique physical and psychological complexities faced by transplant recipients and their families.<sup>44,63–68</sup> Key components of communication in shared decision-making are trust, understanding patient values, goals, and preferences, and continued discussion of evolving choices as new situations arise.<sup>69</sup>

Ideally, shared decision-making about contraception and risks associated with pregnancy after LT or HT will occur pre-transplant, regularly during post-transplant follow-up, and before conception. If pregnancy is unplanned or undesired, counseling on maternal and fetal risks associated with pregnancy continuation is necessary, particularly if pregnancy is medically contraindicated.

Shared decision-making is a central feature of care for transplant recipients in general, and specifically for individuals of reproductive age. Clinicians and patients should work toward patient-centered care that factors in individual and family values, goals, and preferences.<sup>69</sup>

### **Fatherhood after transplantation**

The reproductive health of the non-gestational parent should also be considered. Some issues are common to both the pregnant individual and the non-gestational parent, including the impact of post-transplant life expectancy on parenthood and the role of potentially inheritable conditions, which are covered in detail in Sections IV and V.

A specific issue for the non-gestational parent would be the potential teratogenicity of immunosuppression. Fortunately, offspring fathered by kidney, kidney-pancreas, liver, and heart transplant recipients on mycophenolate at the time of conception do not have a higher incidence of adverse outcomes of pregnancy, congenital malformations, or other adverse neonatal outcomes and thus mycophenolate avoidance is not necessary for the non-gestational parent.<sup>70–72</sup> Similar reassuring findings have been noted with corticosteroids, calcineurin inhibitors, and azathioprine,

though sirolimus may cause lower sperm counts, dysmotility, and reduced spontaneous pregnancy rates.<sup>73</sup>

### **Consensus Statements on Preconception Counseling and Shared Decision-Making**

- Preconception counseling of individuals of childbearing age should: (1) ideally occur as part of the pretransplant evaluation process, (2) be repeated at least annually after transplant during childbearing years, and (3) include a discussion of optimal contraception, timing of pregnancy, contraindications to pregnancy, and maternal and fetal risks, including those unique to transplant recipients such as psychosocial aspects of family planning in the context of a disorder with limited life-expectancy.
- Intrauterine devices (IUD) are the preferred long-term contraception option for many patients after transplantation given their low failure rate, ability to be in place for several years, lack of required daily adherence for effectiveness, lack of drug-drug interactions, and straightforward removal to reverse contraception.
- Experience with the use of assisted reproductive technology is limited in transplant recipients but may be considered on an individualized basis in collaboration with a reproductive endocrinologist, recognizing the risk of multiple gestations and ovarian hyperstimulation syndrome.
- Pregnant transplant recipients are at high risk for anxiety and depression so psychosocial evaluation and support is an essential part of the preconception, antepartum, and postpartum process.
- Issues surrounding pregnancy planning and contraception should be approached using a shared decision-making model.

### **Experience with pregnancy in other solid organ transplants**

There is far more experience with pregnancy in recipients of abdominal organ transplants (kidney or liver), compared with thoracic organ transplant recipients. As kidney transplants are the most commonly performed, the largest cohort of pregnancy outcomes is from such recipients. The first reported pregnancy after solid organ transplantation occurred in 1958 in a woman who had received a kidney transplant from her identical twin sister 2 years prior.<sup>74</sup> The issues faced by clinicians during that pregnancy were considerably different to that of contemporary practice, since the recipient was not on immunosuppression and the treating clinicians were more concerned about the impact of the gravid uterus on the function of the transplanted kidney. Most of the subsequent experience regarding pregnancy after abdominal organ transplant comes from case reports, center studies, meta-analyses, and registry data.<sup>75–84</sup> These studies have laid the groundwork for guidelines and recommendations surrounding pregnancy after thoracic transplantation.

## Guidelines for pregnancy in abdominal organ transplant recipients

The first guidelines regarding preconception counseling and peri-pregnancy management were written for kidney transplant recipients, updated over time, and extrapolated to solid-organ transplant recipients, more broadly.<sup>16,85,86</sup> Common themes of these pregnancy guidelines include the necessity of stable graft function, well-controlled comorbidities, absence of acute infection, and safety of immunosuppressive agents in pregnancy.

Other common themes derived from experience in kidney transplant recipients are delaying pregnancy until after the first transplant year and avoiding unplanned pregnancies. These recommendations stem from several studies which have demonstrated that transplant recipients who undergo pregnancy within 1 year of transplantation have a higher risk of rejection, graft loss, and non-viable fetal outcomes,<sup>81,87</sup> and that unplanned pregnancies result in more rejection and are associated with a greater risk of graft loss within the subsequent 2 years.<sup>88</sup>

## Outcomes of pregnancy in abdominal organ transplant recipients

The TPRI, formerly the National Transplantation Pregnancy Registry (NTPR), was established in 1991 by Dr. Vincent Armenti to study the outcomes of pregnancy after transplantation. The TPRI has continuously enrolled transplant recipients since that time and now has documentation of over 3,500 pregnancies. With international recipients added in 2016, it is the largest repository of pregnancy outcomes in transplant recipients.

### Maternal outcomes

The most frequent complications reported during pregnancy after kidney transplant are hypertension and preeclampsia, reported at an incidence of 24% to 48% and 21% to 29%, respectively (Table 2).<sup>75</sup> Rejection occurred in 3% to 9.4% of recipients; yet, at a mean follow-up of 14 years, 67% report adequate graft function.<sup>75</sup> In another meta-analysis, transplant recipients who had a pregnancy had no difference in kidney graft survival over time, though factors associated with graft loss were pre-pregnancy proteinuria, hypertension, and elevated serum creatinine.<sup>77</sup>

Liver transplant recipients experience similar complications (Table 2). Liver recipients have an incidence of hypertension of 18% to 21% and preeclampsia of 13% to 21%.<sup>80</sup> Rejection is uncommon in pregnant liver transplant recipients, occurring in 5%.<sup>80</sup> Data are lacking regarding transplant outcomes in pregnant vs non-pregnant liver recipients.

### Fetal outcomes

There is a high prevalence of reported cesarean deliveries for both kidney and liver recipients, at 51% to 62.6%<sup>75</sup> to

42.4% to 43%,<sup>80</sup> respectively. There is also a high incidence of prematurity and low birthweight offspring in kidney transplant and liver transplant recipients. Preterm delivery occurred in 37% to 43.1% of kidney transplant<sup>75</sup> and 26% to 27.8% of liver transplant<sup>80</sup> recipients. Despite this, however, overall long-term health and development of the offspring of kidney and liver recipients does not appear adversely affected.<sup>92–94</sup>

## Kidney vs liver transplant recipients

Compared with kidney transplant recipients, liver transplant recipients appear to have a lower incidence of pregnancy-related hypertension and preeclampsia and lower rates of preterm birth and cesarean delivery. The reasons for these differences are not clear but may be related to the differences in immunosuppressive regimens and incidence of hypertension in liver vs kidney transplant recipients; further research is needed.

## Summary

As a community, the experience with pregnancy after abdominal organ transplant has provided much of the framework for the general approach to pregnancy in thoracic transplant recipients. However, there are some important differences. The hemodynamic changes that occur during pregnancy may directly impact upon, or be influenced, by graft function in thoracic organ transplant recipients, which is not the case in abdominal transplantation.<sup>95</sup> Additionally, rates of rejection are higher in thoracic transplant recipients and hence, higher levels of immunosuppression are required.<sup>15,96–98</sup> Special considerations during pregnancy for LT and HT recipients will be discussed in the next 2 sections.

## Risk assessment, management, and outcomes of pregnancy after lung transplantation

In 1996, the first successful pregnancy in a LT recipient was reported.<sup>99</sup> Since then, an increasing number of pregnancies in this cohort have been described.<sup>13,14,100</sup> As noted in Section I, preconception counseling should include individualized discussion of timing of conception, alternative pathways to parenthood, and maternal and fetal risks (see Figure 1). As outlined in Section II, this counseling should be introduced during pre-transplant evaluation and should be followed up throughout the post-transplant process. See Figure 2 for key factors that clinicians should discuss with their patients.

### Timing of pregnancy

The relative infrequency of pregnancy following LT compared with other solid organ transplants makes establishing definite recommendations regarding the timing of pregnancy difficult. Generally, LT recipients should be advised to wait 1–2 years after LT transplant before becoming



**Table 2** Pregnancy Outcomes in Abdominal Transplant Recipients

	Kidney transplant recipients		Liver transplant recipients		Non-transplant Pregnancies
	TPRI <sup>89</sup>	Shah et al <sup>90</sup> (pooled data)	TPRI <sup>89</sup>	Marson et al <sup>80</sup> (pooled data)	US National Vital Statistics <sup>91</sup>
Recipients	1251	4174	363	1073	-
Pregnancies	2233	6712	716	1496	-
Live births	75%	72.9%	72%	85.6%	59%
Miscarriage	19%	15.4%	23%	7.8%	16%
Hypertension	48%	24.1%	21%	18.2%	-
	(drug-treated)	(pregnancy-induced)			
Preeclampsia	29%	21.5%	21%	12.8%	3.8%
Gestational diabetes	8%	5.7%	8%	7.0%	3.9%
Rejection*	3%	9.4%	5%	NR	-
Mean gestational age at delivery, weeks	35.8	34.9	36.7	37.1	-
Mean birth weight	2555 g	2470 g	2772 g	2783 g	3400 g
Preterm delivery	37%	43.1%	26%	27.8%	26%
Cesarean delivery	51%	62.6%			32%

Abbreviations: NR, not reported; TPRI, transplant pregnancy registry international.

\*TPRI included all types of rejection while Shah included acute rejection only.

pregnant.<sup>17</sup> Although guidelines for recipients of other solid organ transplants recommend a wait of 12 months, the higher rates of allograft rejection and more aggressive immunosuppression utilized following lung transplantation<sup>101</sup> support the need for a longer post-transplant period of stability before pregnancy.

Timing should allow opportunity for genetic counseling (in those with CF and other heritable conditions) if desired; appropriate consideration of risks (including those related to drugs and infections such as cytomegalovirus [CMV]); alterations to immunosuppression, and initiation of preconception vitamins.

## Patient risk assessment

Figure 4 illustrates some of the factors to consider when assessing the risk of pregnancy in LT recipients. Pregnancy should not be recommended for those with evidence of progressive, chronic lung allograft dysfunction (CLAD) or for those who have not re-established lung function stability after an episode of acute rejection. Other important contraindications include medication nonadherence, uncontrolled comorbidities such as diabetes or hypertension, severe chronic kidney disease (eGFR < 30 ml/min/1.73 m<sup>2</sup>), or the presence of donor-specific antibodies (DSA) for which necessary adjustments in immunosuppression might increase the risk of rejection.

Consideration must also be given to the risk of infection and its treatment. Primary CMV infection or reactivation in the transplant recipient can have potentially devastating consequences to both mother and fetus. Pregnancy should be delayed until viral prophylaxis is complete and alternate strategies of prophylaxis and treatment, including the use of CMV hyperimmune globulin, should be considered in those at risk.<sup>102,103</sup>

Almost half of all LT recipients of reproductive age have CF as their underlying diagnosis.<sup>15</sup> This presents specific challenges including an increased risk of diabetes, malabsorption of fat-soluble vitamins and gastric stasis, gastroesophageal reflux, and gastroparesis which are likely to be worsened during pregnancy. Those with CF should be continued on their nutritional supplements with special care taken to ensure that adequate nutritional intake occurs and no vitamin deficiencies develop. Folic acid supplementation (4-5 g daily) is recommended for all pregnant transplant recipients to prevent neural tube defects, with consideration of other fat-soluble vitamin replacement in those with CF. However, supplementation with vitamin A should not exceed 10,000 IU daily due to the risk of cranial neural crest defects.<sup>104</sup> Ideally, supplementation should begin before attempts to conceive or when pregnancy is confirmed.

It is important to recognize the limited survival of LT recipients, with a median 6.7 years, extending to 8.9 years in patients who survive the first year.<sup>15</sup> Long-term causes of death include chronic lung allograft dysfunction (CLAD), infection, and graft failure.<sup>15</sup> Counseling regarding life expectancy after LT may impact upon the shared decision-making process of pregnancy planning.

## Graft function

### Baseline assessment of graft function

Pre- and post-bronchodilator spirometry should be measured in anticipation of planned pregnancy to establish stability, capacity to carry a pregnancy to term, and to provide a baseline to allow monitoring for potential pregnancy-related deterioration. The list of recommended exams, with rationale and impact of results is shown in Table 3.<sup>16,24</sup>

## FACTORS TO BE CONSIDERED IN RISK ASSESSMENT FOR PREGNANCY AFTER LUNG TRANSPLANT

### MATERNAL CO-MORBIDITIES

- Maternal age
- Years since transplant
- Hypertension
- Diabetes
- Chronic Kidney Disease
- Prior obstetric complications (preeclampsia, preterm delivery)
- Original lung diagnosis (cystic fibrosis)

### PATERNAL FACTORS

- Heritable conditions

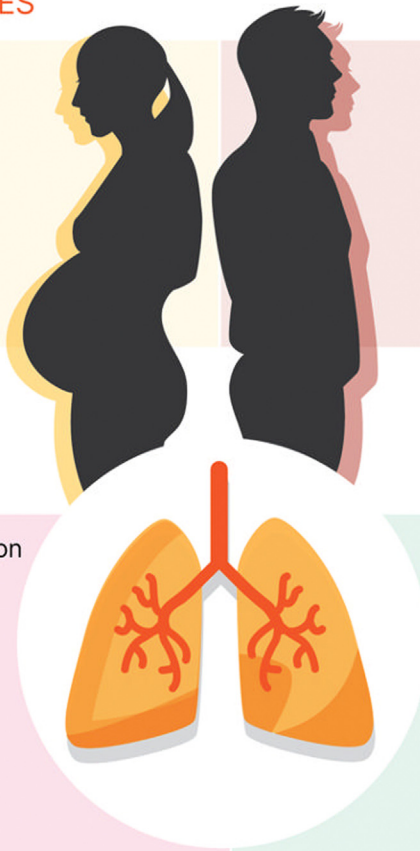
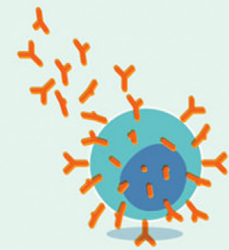
### PHARMACOLOGICAL CONSIDERATIONS

- Changes to immunosuppression
- Altered drug levels
- Cessation of statin therapy, ACE inhibitors
- Malabsorption of fat-soluble vitamins in patients with CF



### POST-TRANSPLANT SPECIFIC FACTORS

- Chronic lung allograft dysfunction
- Prior rejection
- Donor-specific antibodies
- Infection



**Figure 4** Factors to be considered in risk assessment for pregnancy after lung transplant. CF, cystic fibrosis; ACE, angiotensin-converting enzyme.

Routine imaging is not indicated; however, the availability of a contemporary baseline chest X-ray may be useful for comparison in the event of clinical decompensation.

Microbiological surveillance with bronchoscopy in those unable to provide sputum specimens, especially in those with recurrent infection with organisms of concern, should be considered. Transbronchial biopsy need only be performed if specific concerns exist. Depending on the patient's risk, measurement of the DSA profile may be considered to enable accurate future comparison.

### Surveillance of graft function

Spirometry remains the mainstay of screening of lung allograft function during pregnancy and should be undertaken monthly throughout pregnancy (Table 4). Physiological changes associated with pregnancy lead to a 20% decrease in functional residual capacity and associated increase in

tidal volume and minute ventilation.<sup>105</sup> Respiratory rate, forced expiratory volume (FEV<sub>1</sub>) and forced vital capacity (FVC) however, remain unchanged.<sup>105</sup> As evidence in LT recipients indicates that spirometric measures (FEV<sub>1</sub> and FVC) remain stable, any changes (in particular, in FEV<sub>1</sub>) should be investigated as would be done in non-pregnant LT recipients, rather than being attributed to pregnancy itself.<sup>14</sup>

Evaluation of a decline in spirometry should include bronchoscopy to assess for infection and/or rejection. Bronchoscopies have been safely performed in pregnant LT recipients.<sup>106</sup> Procedural sedation during bronchoscopy is safe in this patient population, though may be best administered by physicians trained in obstetrical anesthesia.<sup>107</sup> Antibody-mediated rejection (AMR) following pregnancy has been described in other solid organ transplant recipients<sup>108,109</sup> and when acute rejection is diagnosed, timely and appropriate treatment is indicated.

**Table 3** Recommended Baseline Assessment of Clinical Status and Graft Function in Lung Transplant and Heart Transplant Recipients Desiring Pregnancy

Assessment	Impact on management or outcome	Contraindications to planned pregnancy
History	<ul style="list-style-type: none"> <li>Genetic conditions may trigger the need for genetic counseling (Heart: ARVC, HCM, CHD, familial CM); special considerations for patients with pre-transplant diagnosis of PPCM</li> <li>Lung: Patients with CF require special attention to nutrition status</li> <li>Social history</li> </ul>	<ul style="list-style-type: none"> <li>Less than 1 year post-transplant (heart) or 1-2 years post-transplant (lung)</li> <li>Nonadherence</li> </ul>
Clinical examination	<ul style="list-style-type: none"> <li>Arterial hypertension is associated with higher risk of preeclampsia</li> </ul>	<ul style="list-style-type: none"> <li>Symptomatic graft dysfunction</li> <li>Uncontrolled hypertension</li> </ul>
Laboratory assessment: comprehensive metabolic panel, Hgb A1c, urinalysis	<ul style="list-style-type: none"> <li>Pre-pregnancy DM, renal dysfunction and proteinuria are associated with higher risk of preeclampsia</li> <li>DM requires close monitoring to lessen risk for macrosomia and shoulder dystocia</li> </ul>	<ul style="list-style-type: none"> <li>Poorly controlled diabetes</li> <li>Severe renal dysfunction (creatinine &gt;2.5 mg/dl, eGFR &lt; 30 ml/min/1.73m<sup>2</sup>, or dialysis)</li> <li>Significant proteinuria</li> </ul>
Anti-HLA antibodies	<ul style="list-style-type: none"> <li>Pregnancy could trigger alloimmunization</li> <li>Sensitized patients have a worse long-term outcome</li> </ul>	<ul style="list-style-type: none"> <li>Donor-specific antibodies</li> </ul>
Immunosuppressive levels	<ul style="list-style-type: none"> <li>Trough levels of immunosuppression should be stable before pregnancy, to minimize the risk of rejection</li> <li>Close monitoring of immunosuppression levels is recommended</li> </ul>	<ul style="list-style-type: none"> <li>Inability to maintain therapeutic levels of maintenance immunosuppression with CNI</li> <li>Inability to stop mycophenolate products</li> </ul>
Serology and PCR for CMV	<ul style="list-style-type: none"> <li>Primary CMV infection and, to a lesser extent, CMV reactivation are associated with the risk of fetal CMV disease</li> <li>CMV seronegative patients should be advised to take additional precautions</li> </ul>	<ul style="list-style-type: none"> <li>CMV infection within the past year</li> </ul>
Standard assessment of graft function <ul style="list-style-type: none"> <li>Lung transplant: pre- and post-bronchodilator spirometry</li> <li>Heart transplant: echocardiogram</li> </ul>	<ul style="list-style-type: none"> <li>Graft dysfunction is associated with high risk of complications during pregnancy and a worse long-term outcome</li> <li>Lung transplant: spirometry to establish stability, capacity to carry a pregnancy to term, and to provide a baseline to allow monitoring for potential pregnancy-related deterioration</li> </ul>	<ul style="list-style-type: none"> <li>Lung transplant: Abnormal PFTs after an episode of acute rejection, evidence of CLAD</li> <li>Heart transplant: Reduced EF (&lt; 30%), severe valvular disease (stenotic lesions)</li> </ul>
In-depth assessment of the graft function (if clinically indicated) <ul style="list-style-type: none"> <li>Lung transplant: bronchoscopy/biopsy</li> <li>Heart transplant: RHC/biopsy, coronary angiogram</li> </ul>	<ul style="list-style-type: none"> <li>Rejection may recur during pregnancy or after delivery and portends increased risk</li> <li>Lung transplant: microbiological surveillance with bronchoscopy in those unable to provide sputum specimens, especially if there is concern for recurrent infection with organisms; decline in spirometry should prompt bronchoscopy to evaluate for infection or rejection</li> <li>Heart transplant: CAV portends increased risk</li> </ul>	<ul style="list-style-type: none"> <li>Lung transplant: rejection in the past year, history of AMR or CLAD</li> <li>Heart transplant: cellular rejection in the past year, any history of AMR, CAV Grade 2 or greater</li> <li>Active infection</li> </ul>

Abbreviations: AMR, antibody-mediated rejection; ARVC, arrhythmogenic right ventricular cardiomyopathy; CAV, cardiac allograft vasculopathy; CHD, congenital heart disease; CF, cystic fibrosis; CLAD, chronic lung allograft dysfunction; CMV, cytomegalovirus; DM, diabetes mellitus; EF, ejection fraction; HCM, hypertrophic cardiomyopathy; PFTs, pulmonary function tests; PPCM, peripartum cardiomyopathy; RHC, right heart catheterization.

**Table 4** Timetable of Periodic Assessment During Pregnancy in Lung Transplant and Heart Transplant Recipients

Exam	Timing	Notes
<b>Graft function and rejection</b>		
• Physical examination, vital parameters	Every 4 weeks	24h-monitoring of BP if hypertension is suspected
• 12-lead EKG	Every 4 weeks	EMB (preferably echo-guided) if rejection is suspected
• Spirometry (Lung)	Every 4 weeks	Bronchoscopy if decline in lung function by spirometry
• Echocardiography (Heart)	At least every trimester and ideally every 1-2 months until 24 <sup>th</sup> week and then every 4 weeks until delivery.	EMB (preferably echo-guided) if rejection is suspected
<b>Hypertensive disorders</b>		
• Renal function, liver function, blood cells count	Every 4 weeks	Increase in eGFR is expected. Monitoring liver enzymes and platelet count if HELLP syndrome is suspected
• Urinalysis	Every 4 weeks	Check for proteinuria
Diabetes mellitus		
• Fasting plasma glucose	Every 4 weeks	Additional therapy if increase in steroid dose is needed
• Glucose challenge test	Between 24-28 weeks	May be performed earlier in patients at risk for diabetes
Immunosuppression		
• Circulating levels	Every 4 weeks until 32 <sup>nd</sup> week; every 2 weeks until 36 <sup>th</sup> week; weekly until delivery and the first month after delivery	Additional therapeutic drug monitoring in the first two trimesters may be suggested, following daily dose adaptation, as needed
• HLA-specific antibodies	1-3 months after delivery	Earlier testing of HLA-specific Ab if acute rejection during pregnancy
<b>Infections</b>		
• Complete blood count, CRP	Every 4 weeks	
• PCR for CMV genome	Every 4 weeks	
• Urine culture	Every 4 weeks	
• Serology for Toxoplasma (in seronegative patients), HSV, hepatitis	Third trimester (36 0/7 - 37 6/7 weeks of gestation)	
• Vaginal swab culture for Streptococci B	Third trimester (36 0/7 - 37 6/7 weeks of gestation)	
<b>Fetal growth</b>		
• Echo assessment of fetal well-being	Routine dating ultrasound between 8-9 weeks of gestation when available Nuchal translucency scan between 11-14 weeks gestation when available Early (transabdominal or transvaginal) anatomy scan between 11 -16 weeks of gestation when available Every 2 months until 24 <sup>th</sup> week; every 4 weeks until delivery	In diabetic patients: - consider closer monitoring of fetal growth from 28 <sup>th</sup> week - weekly monitoring from 32 <sup>nd</sup> week

Abbreviations: BP, blood pressure; CMV, cytomegalovirus; CNI, calcineurin-inhibitors; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; EMB, endomyocardial biopsy; HELLP, hemolysis, elevated liver enzymes, low platelets; HLA, human leukocyte antigen; HSV, herpes-simplex virus; PCR, polymerase chain reaction.

**Table 5** Summary of Maternal and Fetal Outcomes in Lung Transplant Recipients Across Contemporary Published Series, with > 10 Reported Pregnancies

Series (year)	TPRI (2019) <sup>11</sup>	Bry et al (2019) <sup>113</sup>	Thakrar et al (2014) <sup>114</sup>
Number of pregnancies (number of women)	50 (37)	39 (35) <sup>a</sup>	14 (14) <sup>a</sup>
Unplanned pregnancies, n (%)	30 (60)	16 (41)	5 (36)
Mean time from transplant (years)	4.2±3.1	5.3±3.7	6.4 (range: 2.2-11.6)
Mean age at transplant (years)	26	23±5	Not reported
Mean age at pregnancy (years)	Not reported	28±5	31.4
FEV <sub>1</sub> pre-pregnancy, (% predicted)	Not reported	83 ± 25	Not reported
Maternal complications (as % of pregnancies)			
Hypertension, n (%)	30 (60)	Before pregnancy: 18 (51) During pregnancy: 17 (59) Gestational HTN: 3 (10)	Not reported
Preeclampsia, n (%)	7 (13)	1 (3)	2 (14)
Diabetes mellitus, n (%)	15 (30)	Before pregnancy: 19 (51) During pregnancy: 18 (55) Gestational diabetes: 2(6)	Before pregnancy: 4(29) Gestational diabetes: 1 (7)
Renal failure, n (%)	Not reported	Before pregnancy: 21 (58) During pregnancy: 19 (61) New during pregnancy: 1 (3)	Before pregnancy: 7 (50)
Infection, n (%)	Not reported	8 (24)	3 (21) within 6 months of delivery
Decrease in FEV <sub>1</sub> % predicted > 5%, n (%)	Not reported	14 (36)	Not reported
Graft loss (within 2 years of delivery/termination), n (%)	3 (6)	2 (5)	1 (7)
Rejection (%)	7 (14)	Before pregnancy: 15 (39) During pregnancy: 0 (0) After pregnancy: 13 (33)	Within 6 months of pregnancy: 1 (7)
Maternal Death during Pregnancy, n (%)	0	1 (3)	0
Maternal death, n (%)	11 (29)		6 (43; time post pregnancy not reported)
Mean time from pregnancy to maternal death (years)	Not reported	4.6 ± 6.5	Not reported
Obstetric and Fetal outcomes (as % of pregnancies except as noted)			
Live birth, n (%)	30 (60)	26 (67)	8 (42)
Mean gestational age at delivery (weeks)	34±5	36±5	Not reported
Fertility treatments used, n (%)	Not reported	7 (18)	3 (21)
Cesarean delivery, n (% of live births)	24 (47)	12 (46)	Not reported
Miscarriage, n (%)	15 (29)	7 (18)	6 (32)
Ectopic pregnancies, n (%)	1 (2)	Not reported	1 (7)
Terminations, n (%)	5 (10)	5 (11)	2 (14%) (including ectopic pregnancy)
Low birth weight (<2500g), n (%)	32 (64)	12 (46)	Not reported
Preterm (<37 weeks), n(%)	25 (50)	11 (42)	Not reported
Congenital malformations, n (% of live births)	2 (4) <sup>b</sup>	n/a	n/a

Abbreviations: FEV<sub>1</sub>, forced expiratory volume in 1 second; TPRI, transplant pregnancy registry international.

Mean values or N (%) are reported.

<sup>a</sup>Includes lung and heart-lung transplant recipients.

<sup>b</sup>One child with hypospadias and arteriovenous malformation; one child with atrial and ventricular septal defects.

## Maternal and fetal outcomes

### Maternal outcomes

Table 5 summarizes existing data, albeit limited, regarding outcomes in pregnant LT recipients. There is a risk of acute rejection and graft loss during pregnancy.<sup>11,13,14,110</sup> Rates of acute rejection have been reported as ranging from 0 to 33%,<sup>11,13,14,110</sup> with CF recipients in 1 series demonstrating a higher incidence of acute rejection when compared to LT

recipients with other underlying diseases (25% vs 11%).<sup>111</sup> Heart-lung transplant recipients may have similar to slightly higher rates of rejection during pregnancy than heart-alone recipients (11% vs 9.4%).<sup>112</sup>

The risk to allograft function continues into the postpartum period. In a large cohort of pregnant lung and heart-lung transplant recipients, 40% of the cohort had an absolute FEV<sub>1</sub> decline of >5% and 29% with an absolute FEV<sub>1</sub> decline of >10% at 12 months post pregnancy.<sup>13</sup> Other series have observed postpartum CLAD in almost 30% of

LT recipients<sup>13,14</sup> and another reported a 40% incidence in decline in lung function and death due to CLAD within 3 years of delivery.<sup>100</sup> While the mechanisms leading to decline in allograft function and/or CLAD are unclear, the potential instability of immunosuppression levels due to the sudden disappearance of the placenta, decrease in circulating progesterone levels, and sudden modification of volume distribution may contribute.<sup>1</sup>

Maternal mortality during pregnancy is rare in LT recipients and reported overall at 1.7%, though this is still magnitudes greater than the maternal mortality rate in nontransplant recipients.<sup>110</sup> However, post-pregnancy mortality after LT increases over time to 43% over the next of 3-7 years<sup>14</sup> in 1 series and 29% died over 9 years in another.<sup>11</sup> Strikingly, the mean age of the child at the time of maternal death was 7.4 years.<sup>11</sup> Information regarding these outcomes may impact the shared decision-making process of pregnancy planning.

### Fetal outcomes

The rate of live birth is 42% to 67% in pregnant LT recipients with a relatively high rate of miscarriage of 18% to 32% (Table 5).<sup>11,17,34,110</sup> Cesarean delivery is common, occurring in up to 47% of LT recipients.<sup>56</sup> Preterm delivery and low birth weight are also common, with 1 case series showing 50% of deliveries occurring before 37 weeks,<sup>11</sup> and 64% of neonates having a mean birth weight of <2500g.<sup>11</sup>

Despite the theoretical risk of in utero exposure to immunosuppressants, no specific patterns of birth defects in offspring have been reported in LT recipients.<sup>35</sup> However, congenital anomalies have been reported in 5% of offspring of LT recipients,<sup>11,110</sup> which appears comparable to the 3.8% of congenital anomalies reported in a series of 1000 consecutive healthy pregnancies at a tertiary care center.<sup>116</sup>

### Breastfeeding considerations

Breastfeeding while receiving immunosuppressive medication is discussed in more detail in Section VIII. Theoretically, there may be challenges with breastmilk production after LT as the bilateral thoracotomies associated with transplant surgery have the potential to disrupt the neurovascular supply of the breast tissue. As such, breastfeeding should be considered on a case-by-case basis and early lactation support from an experienced lactation consultant sought if the pregnant transplant recipient plans to breastfeed.

### Consensus statements on risk assessment, management, and outcomes of pregnancy after lung transplantation

- Lung transplant recipients should wait 1-2 years post lung transplant before pursuing pregnancy. Before planned conception, recipients should have stable lung function (without chronic allograft lung dysfunction or

donor-specific antibodies), no evidence of rejection in the preceding 12 months, stable doses of maintenance immunosuppression safe in pregnancy, and no acute infection.

- Non-adherence with medical therapy, poorly controlled hypertension, diabetes, and renal dysfunction (eGFR < 30 ml/min/1.73 m<sup>2</sup>) are considered contraindications to pregnancy.
- Pregnant lung transplant recipients with cystic fibrosis require special attention to specific co-morbidities including gastroesophageal reflux and nutritional supplementation.
- Clinical evaluation and spirometry should occur at least monthly during pregnancy in lung transplant recipients; any changes in spirometric measures, and in particular FEV1, should be investigated as would be done in a non-pregnant lung transplant recipient, rather than being attributed to pregnancy itself.
- The risk of chronic lung allograft dysfunction remains high in the postpartum period.

### Risk assessment, management, and outcomes of pregnancy after heart transplantation

The first pregnancy in a HT recipient was described in 1988.<sup>116</sup> As the proportion of female transplant recipients have increased from 21.3% in 1992-2000 to 28.1% in 2010-2018,<sup>96</sup> there have been increasing reports of successful pregnancies in this population. Worldwide, in the eras spanning 1992-2000, 2001-2009 and 2010-2018; 2509, 3142 and 3578 women of child-bearing age (15 - 45 years) have undergone HT, respectively, with a median survival of 15.2 years.<sup>117</sup> The current median survival conditional to surviving the first year after HT is 14.8 years for women and 13.6 years for men, with 86% survival at 1 year.<sup>118</sup> Given the significant number of young transplant recipients who may be considering pregnancy, an understanding of the appropriate timing and contraindications is essential.

### Timing of pregnancy

The risk of allograft rejection is highest, and the immunosuppression regimen most aggressive, in the first 6-12 months after transplantation; hence the 2022 ISHLT guidelines for post-transplant care advise that pregnancy should not be attempted within the first year.<sup>24</sup> Similarly, the American Society of Transplantation recommends that transplant recipients considering pregnancy should have stable graft function with no rejection in the past 12 months, no active infection, and a stable immunosuppression regimen to maximize the chance of a favorable outcome.<sup>16</sup>

### Patient risk assessment

Figure 5 illustrates some of the factors requiring consideration when assessing the risk of pregnancy in HT recipients. The estimation of the risk of pregnancy for any given

## FACTORS TO BE CONSIDERED IN RISK ASSESSMENT FOR PREGNANCY AFTER CARDIAC TRANSPLANT

### MATERNAL CO-MORBIDITIES

- Maternal age
- Years since transplant
- Hypertension
- Diabetes
- Chronic Kidney Disease
- Prior obstetric complications (preeclampsia, preterm delivery)
- Original cardiac diagnosis (PPCM, inheritable DCM, CHD)

### PATERNAL FACTORS

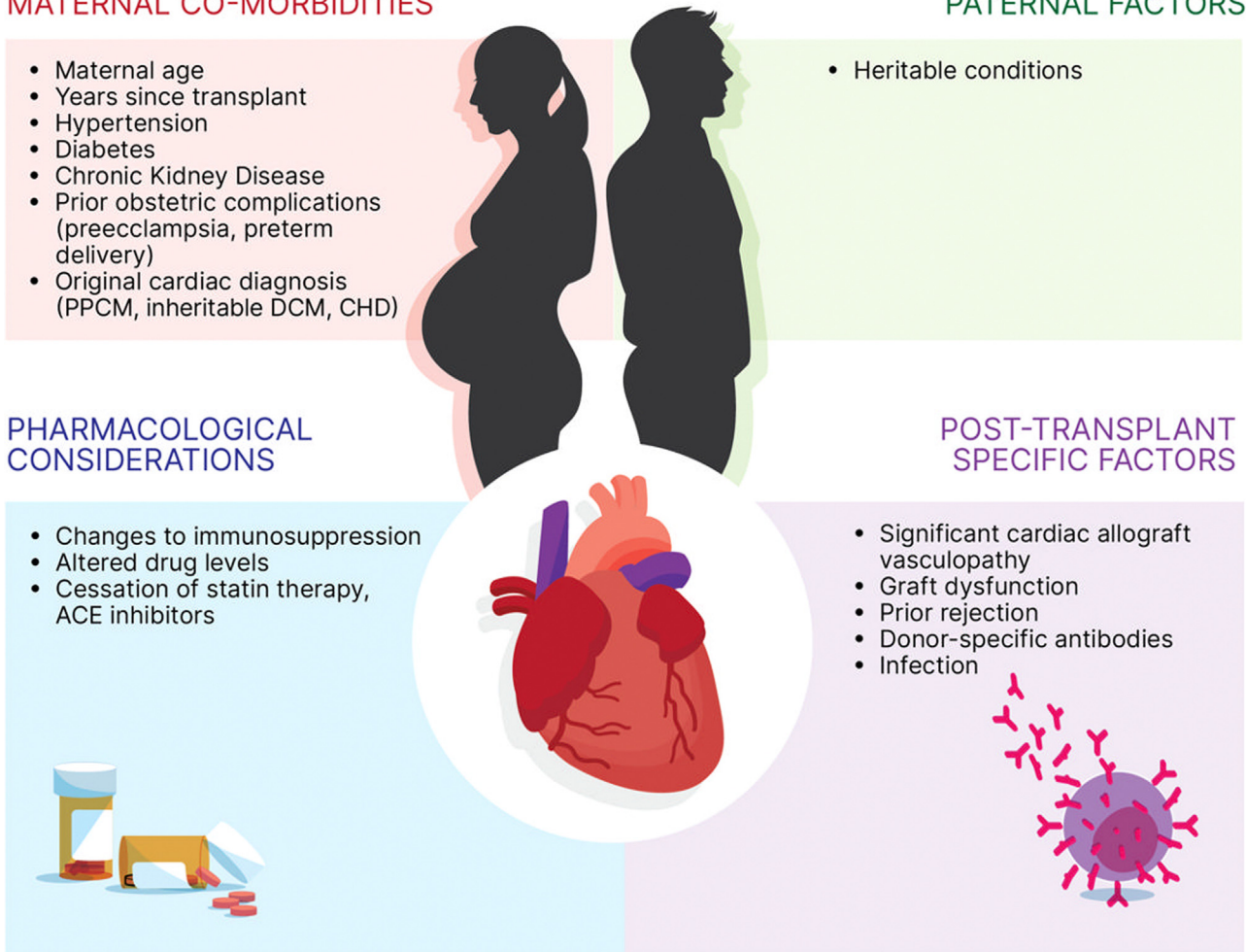
- Heritable conditions

### PHARMACOLOGICAL CONSIDERATIONS

- Changes to immunosuppression
- Altered drug levels
- Cessation of statin therapy, ACE inhibitors

### POST-TRANSPLANT SPECIFIC FACTORS

- Significant cardiac allograft vasculopathy
- Graft dysfunction
- Prior rejection
- Donor-specific antibodies
- Infection



**Figure 5** Factors to be considered in risk assessment for pregnancy after heart transplantation. ACE, angiotensin-converting enzyme; CHD, congenital heart disease; DCM, dilated cardiomyopathy; PPCM, peripartum cardiomyopathy.

individual post-transplantation is complex. Due to the lack of data and unique patient factors to be considered, no risk calculator specific to transplantation currently exists.

There are some conditions under which pregnancy in a HT recipient is considered very high risk or contraindicated; these include poor graft function (LVEF <30%) which falls into the modified World Health Organization (mWHO) classification IV of maternal risk as prohibitive (LVEF 30% to 45% is mWHO classification II to III as intermediate risk),<sup>119</sup> non-adherence with immunosuppression or other important medical therapy, significant CAV, active infection, and poorly controlled hypertension, diabetes or renal dysfunction (eGFR < 30 ml/min/1.73 m<sup>2</sup>).<sup>1,24,95</sup> Prior rejection is a concern. While treated acute cellular rejection more than 1 year before pregnancy may be a relative contraindication, any history of AMR or DSA should be considered a stronger contraindication to pregnancy given risk of sensitization from the fetus. When adverse consequences to the cardiac allograft such as left ventricular dysfunction, valvular disease, or arrhythmias

are present, the risk of long-term cardiovascular complications may be identified by using risk prediction tools such as the CARPREG II (Canadian Cardiac Disease in Pregnancy) risk score.<sup>9,120–122</sup>

In addition to these risks, the importance of co-morbidities must be emphasized. In an ISHLT registry analysis of women of childbearing age, the presence of DM and/or severe kidney dysfunction (sCKD) strongly impacted survival: DM vs no-DM: median survival 8.9 vs 14.7 years ( $p < 0.0001$ ); sCKD vs no-sCKD: median survival 10.8 vs 14.5 years ( $p < 0.0001$ ); and DM plus CKD vs none: median survival 2.5 years vs 14.9 years ( $p < 0.0001$ ).<sup>117</sup> The impact of these comorbidities on maternal survival, and on the decision to proceed or not with pregnancy should be discussed with patients. Additional maternal comorbidities which may increase the risk of pregnancy from a general cardiovascular perspective include advanced maternal age, obesity and significant prior pregnancy-related cardiac or obstetric complications.

The presence of CAV negatively affects survival,<sup>96</sup> hence even early-stage CAV requires aggressive treatment with statins and mammalian target of rapamycin (mTOR) inhibitors. However, safety of these agents has not been established during pregnancy, and discontinuation may potentially expose the patient to the risk of further CAV progression as another possible risk of pregnancy.<sup>123</sup> While significant CAV (Grade 2 or higher) may be considered a contraindication to pregnancy, those with milder CAV may consider pregnancy and in this situation, warrant ongoing therapy for CAV. In patients with known CAV, the fetal risks of potential exposure to statins and mTOR inhibitors during pregnancy should be weighed against the risks of worsening graft function. If statin and mTOR inhibitor use is continued during pregnancy, the lowest effective dose should be used to minimize fetal exposure.

Finally, a discussion regarding post-transplant life expectancy may impact decisions surrounding pregnancy planning. The median survival for HT recipients is 12.5 years extending to 14.8 years in those surviving the first year.<sup>124</sup> Median survival for women is higher than men (12.2 years vs 11.4 respectively) and leading causes of death are graft failure (mainly related to CAV), CMV infection, and multi-system organ failure.<sup>124</sup>

These considerations emphasize the complexity of pre-conception counseling, and a comprehensive approach is advised. Parenthood, however, is a deeply personal choice, and some may choose to try to conceive despite an individualized risk assessment.

## Underlying maternal cardiac conditions

### *Peripartum cardiomyopathy*

Peripartum cardiomyopathy (PPCM) remains a relatively rare, but potentially significant cause of heart failure in women of childbearing age. In the United Network for Organ Sharing (UNOS) database, PPCM is the fourth leading indication for heart transplantation in women<sup>125</sup> and 10% to 23% of women with PPCM require transplantation as definitive treatment.<sup>126–128</sup>

It is important to recognize that HT recipients with a pre-transplant diagnosis of PPCM are at higher risk for poor outcomes compared with those without PPCM. HT recipients with PPCM have higher rates of allograft rejection through the first 12 months, reduced graft half-life (8.2 years vs 10.2 years), and higher rates of re-transplantation (6.6% vs 2.1%).<sup>125</sup> The mechanisms implicated in this remain poorly understood but may be related to a higher degree of pre-transplant antibody sensitization.<sup>129</sup>

These findings have been confirmed in an analysis of ISHLT registry data: in a group of 535 women aged 15–45 years transplanted for PPCM between 2000 and 2017, the median survival was 9.1 years, compared with a median survival of 15.2 years those with congenital heart disease and 15.5 years in the remaining female HT recipients with other indications for transplantation.<sup>117</sup>

It has been suggested that women with previous PPCM may have an increased risk of peripartum recurrence in a subsequent pregnancy although there are currently no published data to support this. Non-adherence was a significant contributor to cause of death in this group,<sup>125</sup> reinforcing the need for patients to be fully informed on risk and engaged in their long-term care.

### Congenital heart disease

Offspring of patients transplanted for congenital heart disease (CHD) have a varying degree of inheritance risk dependent upon the underlying lesion. For CHD that arises de novo, the risk of recurrence in infants is approximately 3% to 7%<sup>1,10,130</sup> though varies significantly based on the specific lesion. The inheritance risk of Tetralogy of Fallot, for example, is around 2.5% while that of aortic stenosis may be as high as 13% to 18%.<sup>131,132</sup>

### Heritable cardiomyopathies

For HT recipients with a suspected or known genetic cardiomyopathy, pre-pregnancy genetic counseling should be performed. For those with an established genetic basis for their cardiomyopathy, preimplantation genetic testing of embryos may be offered.<sup>37</sup> Preimplantation genetic testing may be particularly helpful in cases of inherited cardiac diseases associated with premature or sudden death. Use of preimplantation genetic testing has been reported in families with hereditary transthyretin-related amyloidosis, familial dilated cardiomyopathies, hypertrophic cardiomyopathy, and other genetic cardiomyopathies.<sup>133–136</sup>

## Surveillance

### *Baseline evaluation of graft function and risk-assessment*

If not completed as part of usual post-transplant surveillance within the previous 6 months, echocardiogram should be performed for a diagnostic assessment of graft function with more detailed assessment for rejection and CAV depending on the patient's history and clinical status.<sup>24,137</sup> Laboratory assessment should include immunosuppression levels, complete blood count, assessment of liver and renal function, urinalysis to assess for proteinuria, and screening for infection (urinary, CMV).<sup>137</sup> For patients with documented DSA, human leukocyte antigen (HLA) testing of the potential father may give insight into the risk of rejection if both the donor and father have similar antigens, though this is not routinely performed.<sup>109</sup> The list of recommended exams, with rationale and impact of results is shown in [Table 3](#).<sup>16,24</sup>

### *Surveillance of rejection*

Pregnancy can proceed successfully in many HT recipients, provided timely preconception risk-assessment and



management (Table 3) and close monitoring of graft function and comorbidities during and after pregnancy (Table 4). Echocardiography is recommended at least every trimester and ideally every 1-2 months until 24 weeks of gestation and then monthly until delivery.

Non-invasive screening for rejection, through gene expression profiling (GEP) and donor-derived cell-free DNA (dd-cfDNA) testing, are useful tools in monitoring for acute rejection.<sup>138,139</sup> However, dd-cfDNA testing will detect fetal DNA and thus, cannot be reliably used in pregnancy.

Pregnancy also represents a unique immunologic challenge, known to promote sensitization toward fetal HLA-antigens,<sup>140</sup> thus possibly increasing the risk of AMR and CAV. Therefore, the immunologic status should be assessed before and early after pregnancy. Some reports suggest that the partners of HT patients may be typed for HLA-antigens before conception, due to the increased risk of AMR should they express the same HLA-antigens of the donor,<sup>109</sup> though this is not considered a standard practice.

### **Diagnosis and treatment of acute rejection**

Endomyocardial biopsy for cause should be performed when acute rejection is suspected (clinical assessment, echocardiography, genetic testing). An echocardiographic-guided procedure is preferred, otherwise fluoroscopy should be done with lead draping of the abdomen.<sup>24</sup>

Recommended regimens for the treatment of acute cellular rejection during pregnancy include high-dose corticosteroids; however, due to the relative insulin-resistance induced by pregnancy, closer glucose monitoring is recommended if steroids are used. The safety of other agents for treatment of rejection, such as anti-thymocyte globulin, in pregnancy has not been established and should be used with utmost caution.

### **Maternal and Fetal Outcomes**

As noted in Section II, a key component of preconception counseling is an explanation of the maternal and fetal pregnancy outcomes. Table 6 provides a summary of the key maternal and fetal outcomes in HT recipients across a review of the largest series in the literature.

#### **Maternal outcomes**

HT rejection is uncommon during pregnancy but occurs more frequently after delivery. Rejection rates in the peripartum period range from 5% to 12% and episodes are most commonly low grade without significant hemodynamic compromise.<sup>2,11,12,32,33,141</sup> Episodes can often be treated with adjustments to baseline immunosuppression and may be related to both activation of maternal alloreactive T-cells and subtherapeutic exposure to immunosuppressive drugs, the latter being secondary to changes in

circulating blood volume, intestinal motility, and renal function.<sup>2,33</sup>

However, rejection in HT recipients may also occur after delivery, noted in 7% of patients within 3 months after delivery.<sup>12</sup> The cause for rejection may be due to variable immunosuppressant levels due to increased blood volume as well as HLA antigen-sharing between fetus and donor.<sup>10,110</sup>

The association between pregnancy and the development of CAV is not clear. In 157 pregnancies in 97 HT recipients, 2 individuals developed CAV after pregnancy, leading to listing for re-transplantation, and 5 had CAV or myocardial infarction listed as the cause of death.<sup>12</sup>

In a large series of HT recipients, mortality during pregnancy was low at 0.5%.<sup>110</sup> However, the longer-term survival of HT recipients after pregnancy warrants consideration. In 1 analysis, 33% of HT recipients who experienced pregnancy died with the median time after first pregnancy to death of 8.9 years with an average survival of 9.4 years.<sup>12</sup> In other series, post-pregnancy mortality in HT recipients ranges from 10.8% over 3-7 years follow-up<sup>110</sup> to 33% with 8.7 years of follow-up.<sup>11</sup> Notably, the mean age of the child at the time of maternal death was 10.8 years.<sup>11</sup>

These real-world data reinforce the importance of thorough preconception counseling for the recipient and partner, ensuring the couple contemplating a pregnancy are aware of longer-term outcomes.

#### **Fetal outcomes**

The rate of miscarriage in HT recipients ranges can be as high as 25%<sup>35,110</sup> compared to 16% in non-transplant pregnancies.<sup>4</sup> However, several contemporary published series have shown that with careful intrapartum management, pregnancy in HT recipients can be successful with a reported live birth rate between 69% to 91%.<sup>2,11,12,32,33,110,141</sup> Cesarean delivery occurs commonly in HT recipients with a frequency reported of 39% to 83%.<sup>11,34,56</sup>

Nonetheless, about half of infants in published series were delivered preterm, before 37 weeks' gestation, and 35% to 40% were low birth weight (<2500g).<sup>2,11,12,32,33,110,141</sup> About 20% of infants born to HT recipients are admitted to neonatal intensive care units<sup>110</sup> and 6.5% to 9% have congenital anomalies.<sup>11,110</sup> Data are limited regarding detailed longer-term follow up of offspring of HT recipients.

### **Consensus statements on risk assessment, management, and outcomes of pregnancy after heart transplantation**

- Heart transplant recipients should wait at least 1 year post heart transplant before pursuing pregnancy. Before planned conception, recipients should have stable heart function (LVEF > 45% without significant allograft vasculopathy or donor-specific antibodies), no rejection in the past 12 months, stable doses of maintenance

**Table 6** Summary of Maternal and Fetal Outcomes in Heart Transplant Recipients Across Contemporary Published Series, With > 10 Reported Pregnancies

Series (year)	Punnoose et al. (2020) <sup>12</sup> (includes TPRI data (2019) <sup>11</sup> )	Macera et al. (2018) <sup>2</sup>	D'Souza et al. (2018) <sup>141</sup>	Dagher et al. (2018) <sup>32</sup>	Bhagra et al (2016) <sup>33</sup>
Number of pregnancies (number of women)	157 (91)	17 (11)	17 (16)	18 (8)	22 (17)
Unplanned pregnancies, n (%)	59 (46)	Not reported	Not reported	10 (56)	18 (82)
Mean time from transplant (years)	7 ± 6	5.6	7.3 ± 4	8.2 (2.6 - 24.6)	8.2 ± 5.2
Mean age at transplant (years)	20 ± 8	Not reported	Not reported	16.0 (6.2-26.6)	Not reported
Mean age at pregnancy (years)	27 ± 5.6	33	28 ± 5.8	25.5 (17.6 - 33.3)	25.3 ± 5.8
LVEF (%) pre-pregnancy	Not reported	All with normal graft function but no LVEF reported	All with normal graft function but LVEF not reported	61 (55-65)	All with normal graft function, no LVEF reported
Maternal complications (as % of pregnancies)					
Hypertension, n (%)	Before pregnancy: 65 (42) During pregnancy: 72 (46)	Before pregnancy: 5 (45) During pregnancy: 1 (6)	-	Before pregnancy: 2 (25) During pregnancy: 5 (39)	Before pregnancy: 5 (36) During pregnancy: 3 (14)
Preeclampsia, n (%)	27 (23)	0 (0)	2 (12)	2 (15)	13 (4)
Diabetes mellitus, n (%)	Before pregnancy: 7 (5) During pregnancy: 11 (7)	0 (0)	During pregnancy: 1 (6)	Before pregnancy: 1 (13) During pregnancy: 2 (15)	0 (0)
Renal failure, n (%)	Not reported	Not reported	4 (24)	Not reported	Not reported
Infection, n (%)	22 (14)	0 (0)	2 (12)	3 (23)	Not reported
Graft loss (within 2 years of delivery/termination), n (%)	2 (2)	0	0	0 (0)	0
Rejection, n (%)	14 (9)	0 (0)	2 (12)	0 (0)	1 (5)
Maternal Death during Pregnancy, n (%)	0	0 (0)	0 (0)	0 (0)	1 (during immediate postpartum period from postpartum hemorrhage)
Maternal death, n (%)	30 (33)	3 (27)	2 (12)	3 (38)	4 (24)
Mean time from pregnancy to maternal death (years)	9.4 (0.5 - 26)	11	At 10 and 18 months after delivery (attributed to rejection from nonadherence with immunosuppression)	3.9 (2.6-5.4)	Not reported
Obstetric and Fetal outcomes (as % of pregnancies except as noted)					
Live birth, n (%)	111 (69)	12 (71)	14 (81)	13 (72)	20 (91)
Mean gestational age at delivery (weeks)	36	36.5	Not reported	35	34 ± 4
Fertility treatments used, n (%)	Not reported	Not reported	Not reported	Not reported	1 (5)

*(continued on next page)*

**Table 6 (Continued)**

Series (year)	Punnoose et al. (2020) <sup>12</sup> (includes TPRI data (2019) <sup>11</sup> )	Macara et al. (2018) <sup>2</sup>	D'Souza et al. (2018) <sup>141</sup>	Dagher et al. (2018) <sup>32</sup>	Bhagra et al. (2016) <sup>33</sup>
Cesarean delivery, n (% of live births)	45 (42)	10 (83)	8 (46)	5 (39)	11 (55)
Miscarriage, n (%)	41 (25)	3 (18)	1 (6)	3 (17)	2 (9)
Ectopic pregnancies, n (%)	2 (1)	Not reported	Not reported	Not reported	Not reported
Terminations, n (%)	7 (4)	2 (12)	2 (12)	2 (11)	0 (0)
Low birth weight (<2500g), n (%)	41 (37)	4 (36)	Not reported	6 (46)	9 (45)
Preterm (<37 weeks), n (%)	45 (41)	4 (36)	6 (46)	7 (54)	9 (45)
Congenital malformations, n (% of live births)	9 (8) <sup>a</sup>	Not reported	2 (14%) <sup>b</sup>	1 (8) <sup>c</sup>	0

Abbreviations: LVEF, left ventricular ejection fraction; TPRI, transplant pregnancy registry international.

<sup>a</sup>Duodenal atresia, tetralogy of Fallot, laryngomalacia, facial deformities, facial hypoplasia of the cerebellum, hypospadias, cystic hygroma, pectus excavatum, lip and tongue tie, and long QT syndrome.

<sup>b</sup>Frontonasal dysplasia, bilateral radial ray anomalies with oligodactyly.

<sup>c</sup>Only fetal cardiac malformations noted; perimembranous ventricular septal defect.

immunosuppression safe in pregnancy, and no acute infection.

- Non-adherence with medical therapy, poorly controlled hypertension, diabetes, and renal dysfunction (eGFR < 30 ml/min/1.73 m<sup>2</sup>) are considered contraindications to pregnancy.
- The pre-transplant diagnosis may have an impact of the risk for pregnancy: (1) those with PPCM have worse post-transplant outcomes compared to those without PPCM, (2) there is a risk of recurrence of congenital heart disease (CHD) in offspring of those with CHD, and (3) heritable cardiomyopathies may be passed on to the fetus.
- Clinical evaluation and echocardiography form the cornerstone of rejection surveillance; echocardiogram should be performed at least every trimester but ideally every 1-2 months until 24 weeks of gestation and then monthly until delivery. Noninvasive assessment of rejection with donor-derived cell-free DNA cannot be used as current assays cannot distinguish fetal from donor DNA.

## Management of comorbid conditions during pregnancy

While there are considerations regarding patient risk assessment, contraindications, and graft assessment and surveillance that are unique to HT or LT recipients, the management of comorbidities including hypertension, diabetes, and infections is similar and discussed below.

### Diabetes

Pregnancy can exacerbate pregestational diabetes and lead to gestational diabetes with significant impacts on both the fetus and pregnant individual.<sup>142</sup> Pregestational diabetes, both type 1 and type 2, is associated with congenital anomalies and both pregestational and gestational diabetes are associated with fetal growth abnormalities, fetal growth restriction and macrosomia, and fetal demise if glycemic control is poor.<sup>143</sup> Infants of diabetic individuals are at increased risk of congenital heart disease, including isolated ventricular septal defects, transposition of the great arteries, and aortic stenosis.<sup>144</sup>

Pregestational diabetes is common in both LT and HT recipients. Over 20% of LT recipients have diabetes;<sup>145</sup> the prevalence is even higher among those with CF.<sup>146</sup> In HT recipients, 21% develop diabetes within 5 years of transplant.<sup>147</sup> Gestational diabetes occurs in up to 16% of LT recipients<sup>110</sup> and up to 11% of HT recipients have pregestational and gestational diabetes.<sup>2,12,33</sup> This is not surprising, as pregnancy is physiologically associated with insulin resistance, mediated by progesterone, cortisol, and prolactin. Furthermore, compensatory increases in insulin production may be impaired in transplant recipients, due to predisposing factors and diabetogenic effects of calcineurin inhibitors and steroids.<sup>148</sup>

Consistent with ACOG recommendations, screening for gestational DM should be performed at 24-28 weeks in pregnant LT and HT recipients, potentially earlier in those with an increased risk for diabetes.<sup>149,150</sup> Treatment of DM during pregnancy should occur in consultation with a maternal-fetal-medicine specialist or an endocrinologist. ACOG recommends a pre-pregnancy HgbA1c level less than 6%, as at this level the fetal malformation rate is close to that of a normal pregnancy (2%-3%).<sup>56</sup> Non-pharmacological strategies for management of diabetes include daily exercise, diet, and self-monitoring of blood glucose. The cornerstones of pharmacological measures are insulin or metformin; other oral agents such as sulfonylureas, GLP-1 receptor agonists or SGLT-2 inhibitors are not recommended due to a lack of safety data. Optimal glycemic control is essential in early pregnancy to reduce the risk of miscarriage and other potential harm to the fetus. In fact, diabetic control improves both maternal and fetal outcomes, with reduced risk of maternal hypertensive disorders and fetal macrosomia with potential associated obstetric trauma such as shoulder dystocia.<sup>151</sup>

## Hypertension

Hypertension is common in LT recipients, occurring in 51.5% of patients at 1 year and 54.6% of patients at 5 years post-transplant.<sup>145</sup> In HT recipients, hypertension is even more common, with a prevalence of 72% at 1 year and 92% at 5 years after HT.<sup>152</sup> The pathophysiological mechanisms of post-transplant hypertension are related to systemic and renal vasoconstriction resulting from calcineurin inhibitors as well as cardiac denervation in HT recipients. Cardiac denervation results in the inability to suppress the renin-angiotensin aldosterone system (RAAS), thus leading to sodium and water retention which may be exacerbated by corticosteroids.

The expansion of circulating volume and hemodilution occurring during pregnancy can further enhance the development of hypertension.<sup>17,153</sup> Physiologic pregnancy is usually associated with estrogen-promoted peripheral vasodilation and increase in creatinine clearance, which may partially counterbalance this process.<sup>154</sup> However, hypertension during pregnancy is commonly diagnosed post-transplant in 41% to 60% of LT recipients and 25% to 48% of HT recipients.<sup>11,110</sup> Baseline hypertension in transplant recipients results in an increased risk of preeclampsia, observed in 8% to 13% of LT recipients and 17% to 29% of HT recipients (described further in Section IX),<sup>11,110</sup> and preterm delivery.<sup>155</sup>

To manage hypertension in these patients, one must consider the cardiovascular adaptation to hemodynamic changes related to pregnancy, as well as the pharmacological interactions between anti-hypertensive drugs and immunosuppression.<sup>24,119,156-158</sup> Meticulous control of blood pressure is advisable; generally nifedipine, amlodipine, labetalol, hydralazine, and methyldopa can be used safely in pregnancy. Specific pharmacologic considerations

for management of hypertension in pregnancy in transplant recipients are addressed in Section VIII.

## Infections

Infections, especially those of the urinary tract and respiratory tract, can be more common in pregnancy and should be actively screened for and treated.<sup>17</sup> CMV infection is of particular concern in pregnant transplant recipients. Primary CMV infection and reactivation are common after transplantation, and during pregnancy there are additional concerns about the risk of congenital CMV disease in the fetus, a potentially serious condition associated with intellectual disability, microcephaly, and visual or hearing loss.<sup>159</sup> The risk of transmission of CMV to the fetus could be as high as 40%<sup>159,160</sup> during primary infection, while for reactivation the risk is lower.<sup>161</sup>

As CMV carries a significant risk to the fetus<sup>102</sup> as well as to the transplant recipient, pregnant transplant recipients should be tested monthly for CMV viremia during pregnancy. Patients who are CMV-seronegative at the time of pregnancy should be advised to adopt specific behaviors to minimize the risk of primary infection. As CMV is often transmitted through the care of young children, regular hand washing, particularly after changing diapers, is recommended to decrease the spread of infection and may reduce exposure to CMV.<sup>162</sup>

Maternal primary infection should be treated to reduce the risk of vertical transmission, especially in the first trimester. No established treatments are available for congenital CMV. Some studies have explored the role of CMV hyperimmune globulin in reducing the rate of fetal abnormalities at birth but showed conflicting results and raised concerns about safety.<sup>163,164</sup> Others showed promising results with high-dose valacyclovir,<sup>165</sup> but further studies are needed.

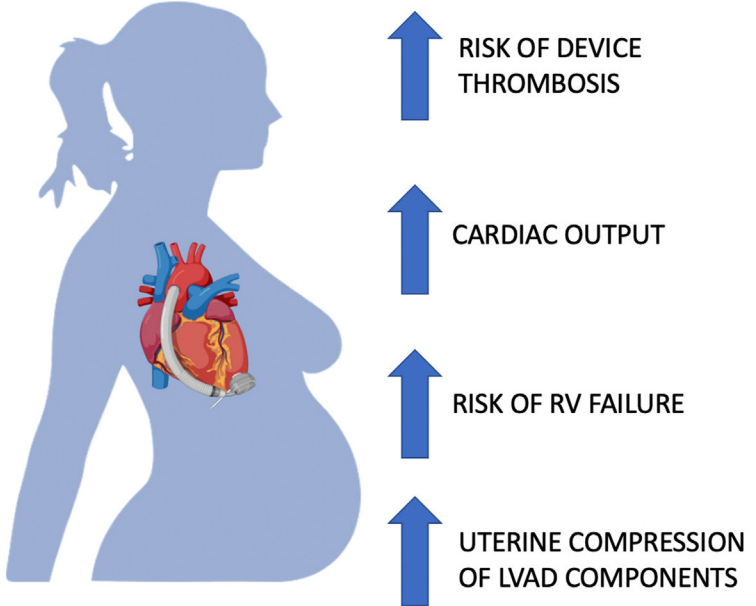
## Other issues

Gastroesophageal reflux is reported in 40% to 85% of non-transplant recipients during pregnancy with an increasing prevalence of symptoms from first to third trimester;<sup>166</sup> there are potential significant implications in transplant recipients. Gastroesophageal reflux, in combination with nausea and possible hyperemesis, could impact the absorption of immunosuppressive agents and other medications. Aggressive and early treatment is recommended with anti-reflux medications and antiemetics.

## Consensus statements for management of comorbid conditions during pregnancy

- Pregnant lung transplant and heart transplant recipients should be screened for gestational diabetes at 24-28 weeks of gestation.
- Treatment of diabetes during pregnancy in transplant recipients, in conjunction with consultation with endocrinology or maternal-fetal-medicine, requires non-

Clinical Evaluation	Frequency of Assessment
Physical Exam: <ul style="list-style-type: none"> <li>Blood Pressure measurement with Doppler</li> <li>LVAD interrogation</li> <li>Driveline assessment</li> <li>Psychosocial evaluation</li> </ul>	Every 2 weeks
Echocardiography	In first trimester; every 4 weeks in second and third trimester
Laboratory testing (including INR or anti-Xa levels)	Every 2 weeks



**Figure 6** Pregnancy in patients on LVAD support. LVAD, left ventricular assist device.

pharmacological strategies (daily exercise, diet, self-monitoring of blood glucose) and pharmacological measures (insulin or metformin as cornerstone treatments; other oral agents such as sulfonylureas, GLP-1 receptor agonists, and SGLT-2 inhibitors are not recommended due to lack of safety data).

- Hypertension is common in pregnant transplant recipients and should be managed to reduce the risk of preeclampsia and preterm delivery; nifedipine, amlodipine, labetalol, hydralazine, and methyldopa can be used safely during pregnancy.
- As CMV infection poses risks to the fetus, transplant recipients should be periodically tested for CMV viremia and CMV-seronegative patients advised to adopt specific behaviors to minimize the risk of primary infection.

### Pregnancy while on LVAD support

Since 2008, over 18,000 patients with advanced heart failure have undergone implantation of continuous flow left ventricular assist devices (LVAD).<sup>167</sup> Among the almost 4000 women in this population, median survival time is 48.6 months, and most are implanted as a bridge to transplant strategy. Nonetheless, pregnancy is uncommonly reported in patients with LVADs<sup>168–173</sup> likely due to 2 factors. First, only 7% of women with LVADs are of reproductive age.<sup>167</sup> Second, LVAD support is considered a contraindication to pregnancy given risks of hemodynamic compromise and challenges of anticoagulation management. However, as unplanned pregnancies can occur, this section will outline the unique challenges of managing pregnancy in LVAD patients (Figure 6).

### Discussion of termination

Given the potential risks of pregnancy in patients with LVADs, a shared decision-making discussion regarding termination is appropriate to optimize the health of the pregnant patient since LVAD support is considered a contraindication to pregnancy. However, it is important to recognize that not all pregnant individuals will choose this medically recommended option, and thus pregnancy considerations are discussed in detail below.

Surgical therapeutic abortion is recommended over medical abortion to minimize bleeding, though complications including sepsis and hemorrhage may occur.<sup>174</sup> Seventy-five percent of obstetric/gynecologic procedures in LVAD patients require perioperative blood transfusions.<sup>175</sup> Therefore, vitamin K antagonists must be stopped and bridging anticoagulation with an unfractionated heparin infusion must be held before surgery. Aspirin may be continued as it appears safe in most non-cardiac surgeries.<sup>176</sup>

Prophylactic antibiotics, often doxycycline and metronidazole, should be prescribed to reduce the risk of endometritis and sepsis. An LVAD team member should be present to monitor LVAD parameters during the procedure. An arterial line may be required for continuous blood pressure monitoring, and attention must be paid to volume status. Further details regarding choice of procedure and periprocedural monitoring are reviewed in Section IX and counseling regarding reliable contraception is reviewed in Section II.

### Hemodynamic considerations during pregnancy

LVAD support causes hemodynamic and metabolic derangements to the circulatory system, which in turn may affect pregnancy outcomes. Only a few case reports

describe pregnancy while on LVAD support,<sup>168–173</sup> but these reports offer insight on adjusting LVAD parameters to account for the hemodynamic changes including increased cardiac output and changes in afterload.

Throughout pregnancy, cardiac output increases by up to 45% in a non-linear fashion, reaching its peak in the early third trimester; this physiological adaptation is due to a combination of increases in heart rate and stroke volume.<sup>177</sup> In LVAD-supported patients, the need for increased cardiac output presents unique challenges. On the one hand, the failing left ventricle is unable to augment stroke volume, requiring an increase in pump speed through pregnancy to maintain adequate cardiac output.<sup>168,170,171</sup> However, these progressive increments in LVAD output could precipitate right ventricular failure, particularly in the third trimester and at the time of delivery when additional blood volume returns to the maternal circulation from the utero-placental system. Therefore, throughout the third trimester and at the time of delivery, careful attention to right ventricular function and volume shifts is essential with judicious use of diuretics and inotropic support, if required.<sup>168</sup>

Furthermore, patients with cardiovascular disease have a higher risk of pregnancy-induced hypertension and preeclampsia.<sup>178</sup> LVADs are sensitive to such increases in afterload which may result in decreased pump flow, left ventricular dilation, and worsening mitral regurgitation.<sup>179</sup> Similarly, active labor and vaginal delivery are associated with a rise in filling pressures and vascular resistance, increasing the risk of acute hemodynamic impairment. Additionally, progressive elevation of the diaphragm in pregnant individuals can cause displacement of the left ventricle,<sup>177</sup> with the potential for possible malposition and rotation of device components and potential driveline infection.

### Thrombosis risk and management of anticoagulation

Pregnancy increases the risk of LVAD pump thrombosis due to several factors. First, women have been reported to have higher rates of pump thrombosis compared to men.<sup>167</sup> Second, clotting factors increase, and Protein S levels decrease over the gestational course, making pregnancy itself a hypercoagulable state.<sup>177</sup> Third, as extrapolated from experience with anticoagulation for mechanical heart valves in pregnancy, all anticoagulant strategies present unique maternal and fetal risks, and demonstrate variable efficacy.<sup>180</sup>

The recommended anticoagulation strategy should be based on careful discussion of the maternal and fetal risk profile, along with patient preference. As thrombosis risk profiles vary by device,<sup>181</sup> low-intensity anticoagulation and aspirin discontinuation may be feasible in patients with HeartMate III LVAD.<sup>182</sup> In the absence of robust evidence in the LVAD population, guideline recommendations for the management of pregnant patients with prosthetic mechanical valves prove instructive:<sup>180</sup>

- a) vitamin K antagonists are contraindicated in the first trimester, with either unfractionated heparin (UH) or low molecular weight heparin (LMWH) used instead;
- b) in the second and third trimesters, VKA or LMWH could be considered with monitoring of INR and anti-Xa levels (goal Factor Xa level 0.7-1.2 u/mL);
- c) before planned delivery, VKA should be discontinued in favor of UH, which in turn should be discontinued immediately before delivery to minimize hemorrhage. The ideal timing of resumption of anticoagulation after delivery is not known.

Though an uncommon complication, particularly with the latest generation continuous flow LVADs,<sup>181</sup> pump thrombosis may occur and requires specific anticoagulation strategies. If first line treatment with UH is ineffective, thrombolytic therapy may be considered<sup>183</sup> as these agents do not cross the placenta due to their high molecular weight,<sup>119</sup> though thrombolysis carries a low rate of success and high risk of bleeding.<sup>183,184</sup> Case series of prosthetic valve thrombosis during pregnancy demonstrate successful lysis with low rates of bleeding and fetal complications,<sup>185</sup> though it is not clear that experience with prosthetic valve thrombosis would translate to LVAD pump thrombosis as the latter patients do not have preserved left ventricular function. Pump exchange may ultimately be required and has been successfully reported in non-pregnant individuals,<sup>186</sup> however, there is no reported experience in pregnant patients.

### Overview of LVAD management during pregnancy

A multidisciplinary approach involving both the LVAD team and maternal-fetal specialists is paramount to provide safe care for the LVAD patient and fetus. Proposed collaborative assessment is summarized in [Figure 6](#). Particular attention needs to be paid to (1) management of maternal comorbidities and surveillance for complications—including hypertension, preeclampsia, and infections, (2) adequate support for the fetus to minimize the risk of low cardiac output leading to uteroplacental insufficiency, and (3) management of hemodynamics and anticoagulation through pregnancy and delivery.

### Maternal and fetal outcomes

The non-pulsatile non-laminar blood flow profile of continuous flow LVADs can cause endothelial cell dysfunction and inflammation,<sup>187</sup> but downstream effects on placental and fetal growth have not been described. Regardless of potential derangements to vascular remodeling in pregnancy, the few published cases of pregnancy in LVAD patients report acceptable short-term outcomes for 6 out of 7 pregnancies, with planned deliveries at week 32 - 34 and birthweights between 2000 and 2410 gm.<sup>168–171</sup>

## Consensus statements on pregnancy while on LVAD support

- Due to the risks of hemodynamic compromise and challenges of anticoagulation management, LVAD support is considered a contraindication to pregnancy and patients should be counseled on the importance of reliable contraception and a discussion of termination should be considered.
- If pregnancy occurs and the decision is made to proceed with pregnancy, a multidisciplinary team of specialists in LVAD management and maternal-fetal medicine is required to (1) manage maternal comorbidities and assess for complications—including hypertension, preeclampsia, and infections, (2) optimize support to the fetus to minimize the risk of low cardiac output leading to uteroplacental insufficiency, and (3) manage hemodynamics and anticoagulation through pregnancy and delivery.

## Pharmacologic considerations

Given the need to maintain adequate immunosuppression during pregnancy to prevent graft rejection and loss, several important pharmacologic considerations should be evaluated in the management of pregnancy after thoracic organ transplantation. The physiological changes observed during pregnancy can have a significant impact on the pharmacokinetics of immunosuppressants and other agents critical to a transplant recipient's medication regimen. The risks of fetal toxicities resulting from in utero medication exposure must be weighed against the pregnant transplant recipient's requirements. Many of these medications also transfer into human milk, and the potential for drug exposure to the infant via breastfeeding should be considered. The following section will address these issues, focusing on immunosuppression drug classes, summarized in Table 7.

Due to the inability to study the safety of medication use during pregnancy and lactation through robust, randomized controlled trials, data to guide clinical decision-making are limited to case reports and series. There is also no international standard for risk assessment in pregnancy and lactation in drug labeling. The Transplant Pregnancy Registry International is a critical source of information regarding maternal and fetal outcomes of pregnant transplant recipients. As a voluntary registry, clinicians are strongly encouraged to enroll pregnant patients to contribute to this body of knowledge.

Physiological changes effecting pharmacokinetics during pregnancy can have unpredictable effects on drug levels. Reduced gastrointestinal motility, nausea and vomiting, increased plasma volume and fat stores, changes in plasma binding protein concentrations, and drug metabolism can all impact immunosuppression levels.<sup>188–191</sup> While some studies have described no change in immunosuppression levels during pregnancy, others report the need for dosage escalation.<sup>14,100,106</sup> Due to this unpredictability, therapeutic

drug monitoring every 2–4 weeks with dose adjustment as required to achieve target levels is advised during pregnancy.<sup>14,100</sup> Frequent evaluation of immunosuppression levels after delivery is also essential as drug distribution and hepatic metabolism normalize in the postpartum period.

It is also important to consider that transplant recipients may have concerns relating to the impact of immunosuppressive medication on the fetus at the time of conception and through pregnancy, raising potential medication adherence issues. Detailed discussions with the transplant recipient and their partner regarding the rationale for prescribed medications and the potential implications of cessation of treatment without discussion with the transplant team are a key component of the counseling process.

## Calcineurin inhibitors

### Pharmacokinetics

Calcineurin inhibitors (CNI) remain the pillar of maintenance immunosuppression regimens for LT and HT recipients, and the majority of pregnancies report CNI exposure, primarily to tacrolimus.<sup>192</sup> The pharmacokinetics of both tacrolimus and cyclosporine are subject to significant changes during pregnancy, with the most notable alterations seen in drug distribution and metabolism. As highly-protein bound drugs, the known decreases in albumin, alpha 1-acid glycoprotein, and erythrocyte production during pregnancy are associated with increases in the unbound concentrations of CNIs.<sup>190,191</sup> In clinical practice, only whole-blood levels are routinely monitored, so the impact of altered drug distribution may not be fully appreciated.

### CNI metabolism in pregnancy

CNIs are primarily metabolized via the cytochrome P-450 (CYP) pathway, specifically by CYP3A4 enzymes.<sup>193,194</sup> The enzymatic activity of CYP3A4 increases nearly 40% throughout pregnancy across all trimesters.<sup>195</sup> This increased activity necessitates careful titration of CNI doses to maintain therapeutic concentrations. Case reports in pregnant LT and HT recipients demonstrate the need for total daily dose increases of cyclosporine and tacrolimus of approximately 20% to 40% of pre-pregnancy dosing.<sup>14,32,33</sup>

### CNI safety in pregnancy

Tacrolimus and cyclosporine both cross the placenta, posing a risk of in utero immunosuppression exposure to the fetus.<sup>196,197</sup> Despite this, the reported risk of congenital malformations in children born to transplant recipients with CNI use is similar to the general population.<sup>198</sup> Elevations in serum creatinine and potassium at time of birth have been noted in infants exposed to tacrolimus in utero.<sup>199–201</sup> In addition, immunological markers in cord blood, including T- and B-lymphocytes, and NK cells, may be below normal values at birth compared with those of children

**Table 7** Immunosuppressive Agents in Pregnancy

Drug class	Safety for use in pregnancy	Risk of teratogenicity	Special instruction	Safety for use while breastfeeding
Corticosteroids	Relatively safe at contemporary clinical dosing	Cleft palate may occur with high doses used in the first trimester (over, 10-15 mg prednisolone daily).	Continue treatment with corticosteroids when indicated	Yes
Calcineurin inhibitors • Cyclosporine • Tacrolimus	Relatively safe at contemporary clinical dosing	No teratogenic potential in human registries	Frequent monitoring of levels (every 2-4 weeks)	Yes
mTOR inhibitors • Everolimus • Sirolimus	Insufficient data to affirm safety	Limited data in humans; potential risk from animal studies	Discontinue 6-12 weeks before planned conception; evaluate risk vs benefit on case-by-case basis in heart transplant recipients with CAV	Limited evidence
Mycophenolate products • Mycophenolate mofetil • Mycophenolate sodium	No	Teratogen: risk of spontaneous abortion and congenital malformations	Discontinue 6-12 weeks before planned conception or immediately if unplanned	Not recommended
Azathioprine	No evidence of teratogenic effect in human studies	May use in place of mycophenolate depending on patient's risk of rejection	Relatively safe at contemporary clinical dosing	No evidence of teratogenic effect in human studies
Belatacept	Insufficient data to affirm safety	Limited data to establish risk	Pregnancy while on belatacept is strongly discouraged	Not recommended

Abbreviations: CAV, cardiac allograft vasculopathy; mTOR, mammalian target of rapamycin.

born to non-transplant recipients, but these abnormalities resolve within the first year of life.<sup>202</sup> The long-term sequelae of fetal exposure to CNI are not well-studied, but the impact on growth development and renal function appears minimal.<sup>92,203–205</sup>

### **CNI safety with breastfeeding**

Tacrolimus and cyclosporine are considered generally safe for use during breastfeeding based on case reports. Both medications can be detected in low quantities in samples of human breast milk; however, the anticipated infant exposure is low given the poor bioavailability of these agents.<sup>196,201,206–210</sup>

### **Mammalian target of rapamycin inhibitors**

#### **Pharmacokinetics**

The pharmacokinetic properties of the mTOR inhibitors sirolimus and everolimus are similar to those of CNI though mTOR inhibitors have longer half-lives. Both agents are highly protein-bound and metabolized primarily by

CYP3A4 enzymes.<sup>211,212</sup> Though less well studied, it likely that these agents will undergo the same pharmacokinetic changes during pregnancy as CNI and require dose increases to retain therapeutic concentrations.<sup>213</sup> Due to their molecular weights and prolonged half-lives, both agents are expected to cross the placenta by diffusion. Case reports of everolimus use in transplantation and sirolimus use for treatment of fetal cardiac rhabdomyomas confirm measurable mTOR inhibitor concentrations in cord blood.<sup>213–216</sup>

#### **mTOR inhibitor safety in pregnancy**

Data on the outcomes of pregnancy exposure in transplant recipients are limited to case reports and small case series that are confounded by concomitant medications and underlying patient condition. An early case series of sirolimus use in 4 kidney transplant pregnancies reported 3 live births and 1 neonate with a cleft lip and palate and ear deformity. In the case of the birth defects, the pregnancy also included mycophenolate exposure up until 24 weeks of gestation when sirolimus was added, so a causal relationship between the birth defects and sirolimus is not clear.<sup>217</sup>



To date, there are 51 pregnancies in 40 transplant recipients reported to the TPRI without concomitant mycophenolate exposure, primarily with sirolimus use.<sup>192</sup> Though low numbers, the greatest percentage of pregnancies with sirolimus exposure are reported in heart transplantation (9% of pregnancies vs 1%-6% in other organs). There is a pressing need to study the safety of these agents in pregnancy given the known benefits of mTOR inhibitors in prevention and progression of CAV.<sup>24</sup> Based on limited data, in utero sirolimus exposure without mycophenolate use does not appear to cause a specific pattern of birth defects and pregnancy outcomes seem similar to CNi outcomes.<sup>192</sup>

Nonetheless, given the limited data on the safety of the mTOR inhibitors, they are generally avoided in pregnancy and should be discontinued 6-12 weeks before conception.<sup>218</sup> Additionally, there may be impaired wound healing after cesarean section in patients on mTOR inhibitors.<sup>219-221</sup> However, in HT patients with known CAV, the continued use of mTOR inhibitors in pregnancy may be considered on a case-by-case basis, as stable graft function may provide a greater benefit to the recipient and fetus.

### ***mTOR inhibitors and breastfeeding***

There are similarly a paucity of data describing use of mTOR inhibitors during breastfeeding. Both agents are detectable in milk in animal studies at higher than plasma concentrations, and their pharmacokinetic properties make it likely that these agents do transfer and accumulate in human milk.<sup>211,212</sup> A case series evaluating the safety of tacrolimus in breastfeeding included 1 kidney-pancreas transplant recipient on tacrolimus, sirolimus, and prednisolone, but did not include details of milk concentrations or infant levels of sirolimus.<sup>207</sup>

In a report of everolimus use in a pregnant HT recipient, the level of everolimus was below the limit of detection in a colostrum sample at 48 hours postpartum.<sup>213</sup> A subsequent report of everolimus in a pregnant kidney transplant recipient showed detectable levels in colostrum with an estimated maximum infant dose of 0.38% of the transplant recipient's dose.<sup>216</sup> In both cases, the transplant recipient chose not to breastfeed. Given the lack of outcomes data and uncertainty in estimating drug exposure through milk, it is difficult to provide clear recommendations regarding breastfeeding while on mTOR inhibitors, and in fact the 2022 Guideline for the Care of the Heart Transplant Recipient recommends that breast-feeding should be avoided if the transplant recipient is taking sirolimus or everolimus due to lack of clinical information.<sup>24</sup>

## **Mycophenolate products**

### ***Mycophenolate teratogenicity in pregnancy***

The mycophenolate products, mycophenolate mofetil and mycophenolic acid, are widely recognized as teratogens

with an increased incidence of miscarriage and craniofacial birth defects from both animal studies and post-marketing reports in kidney transplant, LT, and HT recipients.<sup>222-225</sup> In the most recent TPRI annual report, 22% to 29% of miscarriages in LT recipients and 22% to 27% in HT recipients were associated with first trimester MMF exposure.<sup>34,110,226</sup> These risks do not appear to be dose-dependent and are associated with mycophenolate exposure early in pregnancy.<sup>227,228</sup> Of note, use of mycophenolate products by male transplant recipients has not been shown to impact fetal outcomes.<sup>11</sup>

In 2007, the Food and Drug Administration established a mandatory Risk Evaluation and Mitigation Strategy (REMS) with a goal of mitigating the risk of embryo and fetal toxicity associated with use of mycophenolate during pregnancy.<sup>229</sup> The goal of REMS is to educate both clinicians and patients of reproductive potential of these risks, to stress the importance of pregnancy prevention when taking mycophenolate, and to promote reporting of any pregnancies to the Mycophenolate Pregnancy Registry. Despite these efforts, mycophenolate exposure during pregnancy is significant, occurring in 11% and 20% of pregnancies in LT and HT recipients, respectively.<sup>192</sup> This number may be an underrepresentation of true exposures when considering pregnancies not reported to the registry.

Mycophenolate products should be discontinued immediately upon confirmation of pregnancy in LT and HT recipients, and discontinued at least 6 weeks before conception in planned pregnancies.<sup>24,222,223,229-232</sup> The 2022 ISHLT Guideline for the Care of the Heart Transplant Recipient<sup>24</sup> recommends discontinuation 90 days before conception though the basis for this time interval is not clear. The 6-week recommendation is based on guidance from both the United States Food and Drug Administration Risk Evaluation and Mitigation Program and the European Medical Agencies<sup>232</sup> as well as the medication package insert.<sup>222,223</sup>

The decision if and how to replace the mycophenolate product with an alternative agent should be tailored to the specific patient with consideration for risk of rejection, infection, and tolerability of potential adverse effects. For example, a transplant recipient who tolerates tacrolimus at therapeutic trough levels who remains on maintenance prednisone may tolerate tacrolimus alone while pregnant. On the other hand, a transplant recipient who has been weaned off prednisone and requires lower tacrolimus target trough levels due to side effects may warrant azathioprine at 50 - 100 mg.

The TPRI has limited information on surrogate pregnancies with eggs retrieved from 3 transplant recipients on mycophenolate. These retrievals resulted in 4 pregnancies with healthy live births without birth defects. The fetal risks of mycophenolate exposure are greatest after conception and in the first trimester during the period of organogenesis. Based on this limited data, as long as mycophenolate is discontinued before conception, pregnancy outcomes do not appear to be negatively affected by prior use of mycophenolate.<sup>233</sup>

## ***Mycophenolate and breastfeeding***

Mycophenolate transfers into human breast milk; however, there are minimal published data to guide recommendations regarding the safety of mycophenolate use in breastfeeding.<sup>234</sup> In a large case series of 157 pregnancies in 91 HT recipients, only 10% of the 31 participants who breastfed reported mycophenolate exposure.<sup>12</sup> The authors did not report infant adverse effects, but this information should be interpreted cautiously given small numbers and lack of details on extent of exposure.

## **Azathioprine**

### ***Pharmacokinetics***

Unlike the CNI and mTOR inhibitors, azathioprine is not metabolized via the CYP450 enzyme system. Its metabolism to active metabolites 6-thioguanine nucleotide (6-TGN) and 6-methylmercaptopurine (6-MMP) is altered during pregnancy, with 6-TGN significantly decreasing in the second trimester while 6-MMP levels increase to a lesser degree. These changes have not been associated with myelotoxicity or hepatotoxicity and after delivery, both 6-TGN and 6-MMP levels return to preconception baseline levels.<sup>235–237</sup> This change in azathioprine metabolism may be due to changes in the enzymatic pathways that metabolize the parent drug to its metabolites, namely thiopurine S-methyl transferase (TPMT).<sup>236</sup> In solid organ transplant, azathioprine dosing is not routinely guided by measurement of metabolite levels, and there is insufficient evidence to guide dose adjustments to azathioprine in pregnant transplant recipients.

### ***Azathioprine safety in pregnancy***

The safety of azathioprine and its metabolite 6-mercaptopurine (6-MP) have been widely studied during pregnancy due to their use in non-transplant indications.<sup>235,236,238–242</sup> Azathioprine use has also been reported in up to 70% of pregnancies after LT or HT.<sup>192</sup> Azathioprine crosses the placenta, and trace amounts of its pharmacologically active metabolites have been found in fetal blood at concentrations approximately 1% to 2% of maternal levels.<sup>242,243</sup> Fetal 6-TGN concentrations positively correlate with maternal 6-TGN levels,<sup>236</sup> though the risks of azathioprine in utero exposure may be limited as the fetal liver lacks the enzymes necessary for the metabolism to active drug.<sup>244</sup>

Azathioprine and 6-MP do not appear to be associated with an increased risk of structural malformations or congenital defects when used in pregnancy after transplantation or non-transplant indications.<sup>192,238,245</sup> Transient abnormalities in liver function tests in infants with in utero azathioprine have been described, but do not correlate with azathioprine metabolite levels at birth.<sup>235,236</sup> Hematologic disturbances have also been reported at varying frequencies, including anemia, neutropenia, thrombocytopenia, and

lymphopenia.<sup>237,238,246,247</sup> However, these disturbances resolve by 3 months of age.<sup>235,248</sup> Studies of long-term follow-up of children with in utero azathioprine exposure are small and heterogeneous, but do not show an increased risk of infection.<sup>235,240,249</sup>

## ***Azathioprine and breastfeeding***

Azathioprine and its metabolites can transfer into human breast milk, but non-transplant guidelines suggest it is compatible with breastfeeding.<sup>239,250,251</sup> Case reports describe azathioprine metabolite levels in varying concentrations in milk samples ranging from undetectable to levels that would correspond to an estimated infant dose of less than 1% of the maternal dose.<sup>252–254</sup> In small studies assessing metabolite levels in infant blood, 6-TGN and 6-MMP concentrations were not detected despite evidence of azathioprine metabolites in milk samples.<sup>253,255</sup> There is no evidence of infant adverse effects with azathioprine exposure via breastfeeding in small studies.<sup>240,249,253,254</sup>

## **Corticosteroids**

### ***Pharmacokinetics***

Prednisone and the biologically active prednisolone are the most commonly used corticosteroids in transplantation. Prednisolone is lipophilic and crosses the placenta, however fetal exposure is limited through extensive placental metabolism back to inactive prednisone.<sup>256</sup>

### ***Corticosteroid safety in pregnancy***

Data regarding use of corticosteroids in pregnancy comes from both transplant and non-transplant patient populations with various degrees and durations of exposure. From animal studies and retrospective studies in humans, there is a concern regarding an increased risk of fetal malformations specifically pertaining to orofacial clefts.<sup>257–259</sup> However, one of the only prospective cohort studies of prednisone use in pregnancy noted an increased rate of premature delivery and low birth weight, but no significant difference in major birth defects between groups with and without exposure.<sup>260</sup> While an accompanying meta-analysis did find a 3-fold increased risk of oral clefts with first trimester corticosteroid exposure, this meta-analysis included studies with any corticosteroids at any dose for any duration of use.<sup>260</sup> Overall prednisone and prednisolone use during pregnancy appears relatively safe at contemporary dosing in transplantation,<sup>192,261</sup> recognizing that the risk of premature delivery associated with corticosteroid use may be dose-related.<sup>262</sup> While there is no therapeutic drug monitoring for corticosteroids, dose adjustments are generally not performed due to pregnancy and there is little evidence of a clinically relevant impact of pregnancy on blood concentration.<sup>263</sup>

## Corticosteroids and breastfeeding

Prednisone transfers into human milk at doses commonly used in transplantation.<sup>263–266</sup> Despite its known use in breastfeeding, there are no published reports evaluating infant levels through milk exposure. A pharmacokinetic study of prednisolone concentrations estimated the average infant prednisolone dose of 0.025% after a 50 mg intravenous maternal dose, and the estimated exposure at typical doses in transplantation should be negligible.<sup>266</sup> Corticosteroids appear overall compatible with breastfeeding,<sup>192,267</sup> and many reports of transplant recipients who breastfed while on corticosteroids describe no adverse infant outcomes.<sup>207,208,254</sup>

## Other immunosuppression

### Belatacept

Belatacept is a selective T-cell costimulation blocker. It binds to CD80 and CD86 on antigen-presenting cells, thereby blocking CD28 mediated costimulation of T lymphocytes. While only approved for use in kidney transplantation, it has been used off-label in select LT and HT recipients.<sup>268–270</sup> It is not metabolized by the CYP or P-glycoprotein systems so pharmacokinetics are unlikely to be altered by pregnancy, but evidence of its use during pregnancy is limited.<sup>271</sup> In animal studies, belatacept has been shown to cross the placenta without reproductive toxicity at doses equivalent to up to 3 times the maximum recommended human dose.<sup>271</sup> It is not known whether belatacept crosses the human placenta.

To date, there are 7 known pregnancies in 4 kidney transplant recipients and 1 pregnancy in a liver transplant recipient with belatacept exposure.<sup>192,272</sup> Three of the pregnancies in kidney transplants included mycophenolate exposure and resulted in 2 miscarriages and 1 live birth.<sup>192</sup> Belatacept does pass into breast milk in animal studies but has not been studied in human milk. Its molecular size makes it unlikely to readily transfer into milk, but its prolonged half-life suggests the potential for accumulation of its metabolites.<sup>271</sup> Given the limited belatacept data in non-pregnant cardiothoracic transplant recipients, pregnancy and breastfeeding while on belatacept after LT or HT is strongly discouraged.

### Therapies for rejection

Treatment of rejection in pregnant transplant recipients is a challenging clinical scenario where the benefits of treatment for the graft must be weighed against the risk of toxicity to the fetus. Based on evidence when used as maintenance immunosuppression, corticosteroids are likely the safest option from a fetal risk perspective. There is a single case report of rabbit anti-thymocyte globulin use for

mixed cellular and antibody-mediated rejection in a pregnant kidney transplant recipient at 13 weeks of gestation that resulted in a live healthy birth.<sup>273</sup>

Intravenous immune globulin (IV Ig) products cross the placenta in varying degrees based on trimester, dose, and duration of treatment; passage increases after 32 weeks of gestation.<sup>274</sup> Clinical experience with IV Ig in non-transplant patients suggests that no harmful effects on the course of pregnancy or the fetus are to be expected.<sup>275–277</sup> Immunoglobulins are excreted into the milk and are a normal component of human breast milk.<sup>278</sup> It is likely compatible with breastfeeding and may even offer a benefit to the nursing infant through transfer of immunoglobulin G; few case reports describe a self-resolving rash in infants that may have been caused by IV Ig exposure via breast milk.<sup>278,279</sup>

### Antihypertensive therapy

Hypertension is very common in recipients of thoracic organ transplantation and also in pregnancy. Existing guidelines for the management of hypertension in pregnancy and in organ transplantation offer guidance on therapy.<sup>24,119,156–158</sup> Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers are contraindicated due to the risk of fetal malformations.<sup>280</sup> The dihydropyridine calcium channel blockers nifedipine and amlodipine are considered safe and do not interact with immunosuppression. Other alternative agents include methyldopa and hydralazine. Labetalol can be considered, although beta-blockers may theoretically be less well-tolerated in HT recipients due to denervation with reduced exercise tolerance. [Table 8](#) summarizes safe measures for management of hypertension in pregnant transplant recipients.

For breastfeeding, antihypertensive medications within a given class with the lowest transfer into breast milk should be selected.<sup>281</sup> Of beta-blockers, propranolol, metoprolol, and labetalol have the lowest transfer into milk, atenolol and acebutolol are more extensively excreted into breast milk, and there is little to no published experience with carvedilol or bisoprolol. Regarding calcium channel blockers, diltiazem, nifedipine, nicardipine, and verapamil are all associated with low excretion into breast milk. ACE inhibitors, while contraindicated during pregnancy, are transferred into milk at very low levels and may be used in lactating patients. Diuretics may theoretically reduce milk volume but are otherwise considered safe for the newborn during lactation. Methyldopa should be avoided in postpartum patients due to the reported association with depression,<sup>158</sup> but is otherwise safe, as is hydralazine.

### Antimicrobial agents

A comprehensive overview of the indications of commonly used antimicrobial agents is beyond the scope of this

**Table 8** Treatment of Hypertension During Pregnancy in Transplant Recipients

Measure	Rationale	Potential side-effects	Comments
Non-pharmacological			
Low-sodium diet	To prevent RAAS-mediated sodium and water retention	None	
Pharmacological			
Dihydropyridine calcium-channels blockers: • Amlodipine • Nifedipine	To promote peripheral vasodilation	Edema, headache, tachycardia	Safe during pregnancy and breastfeeding No significant interactions with CNI
Methyldopa	Available data about safety in offspring up to 7 years	Sedation, dizziness, depression	Safe during pregnancy; may be avoided during breastfeeding due to association with depression.
Beta-blockers: • labetalol	To lower systemic vascular resistance ( $\alpha$ -antagonism is more pronounced than $\beta$ -blocking activity) Often used for hypertensive crisis (intravenous)	Postural hypotension Bronchospasm (if history of asthma or COPD) Fetal bradycardia, growth restriction.	Beta-blockers may be less well-tolerated in heart transplant recipients due to denervation with reduced exercise tolerance; propranolol, metoprolol, and labetalol have the lowest transfer into breast milk.
Hydralazine	Peripheral vasodilatation	May increase CNI trough levels (by decreasing their metabolism)	TID dosing may limit adherence; safe during breastfeeding.
Diuretics: • loop diuretics • thiazide diuretics	To treat water retention; complementary treatment in severe drug-resistant hypertension and oliguria.	Hypovolemia, transient electrolytes and metabolic imbalance in mother and fetus.	Should be avoided in the first trimester (data about teratogenicity showed conflicting results); may reduce milk volume during breastfeeding.

Abbreviations: CCB, calcium channel blockers; CNI, calcineurin inhibitors; COPD, chronic obstructive pulmonary disease; HT, heart transplantation; RAAS, renin-angiotensin-aldosterone system.

document.<sup>24,282</sup> However, [Table 9](#) summarizes considerations for commonly used medications for prophylaxis and treatment of opportunistic infections with a focus on *Pneumocystis jirovecii*, *Toxoplasma gondii*, and antiviral agents.

### Consensus statements regarding pharmacologic considerations

- Mycophenolate products should be stopped at least 6 weeks before planned conception or immediately when an unplanned pregnancy is confirmed.
- Generally, mTOR inhibitors should be stopped 6-12 weeks before a planned pregnancy based on animal studies; an increase in fetal complications/birth defects has not been observed in human case reports so the risks vs benefits of mTOR use in individual patients should be evaluated.
- Calcineurin inhibitors should serve as the cornerstone of maintenance immunosuppression regimens. The use of corticosteroids and azathioprine at the lowest effective dose should be tailored to the patient's clinical risk profile.

- Therapeutic drug monitoring should be performed every 2-4 weeks with dose adjustment to achieve target levels as required.
- For hypertension, nifedipine and amlodipine are considered safe during pregnancy and do not interact with immunosuppression. Other options include methyldopa, labetalol, and hydralazine; beta-blockers may be less well tolerated in heart transplant recipients due to denervation with reduced exercise tolerance. Angiotensin receptor blockers and ACE inhibitors are contraindicated.

### Obstetric management

The management of pregnancies in individuals with LT or HT requires careful planning by a multidisciplinary team involving transplant physicians, high-risk obstetricians/maternal-fetal medicine physicians, anesthesiologists, neonatologists, specialist nurses, psychologists/social workers, and other healthcare professionals, based on the individual's health status. Obstetric management requires review and optimization of medications early in pregnancy, close

**Table 9** Antimicrobial Agents in Pregnancy

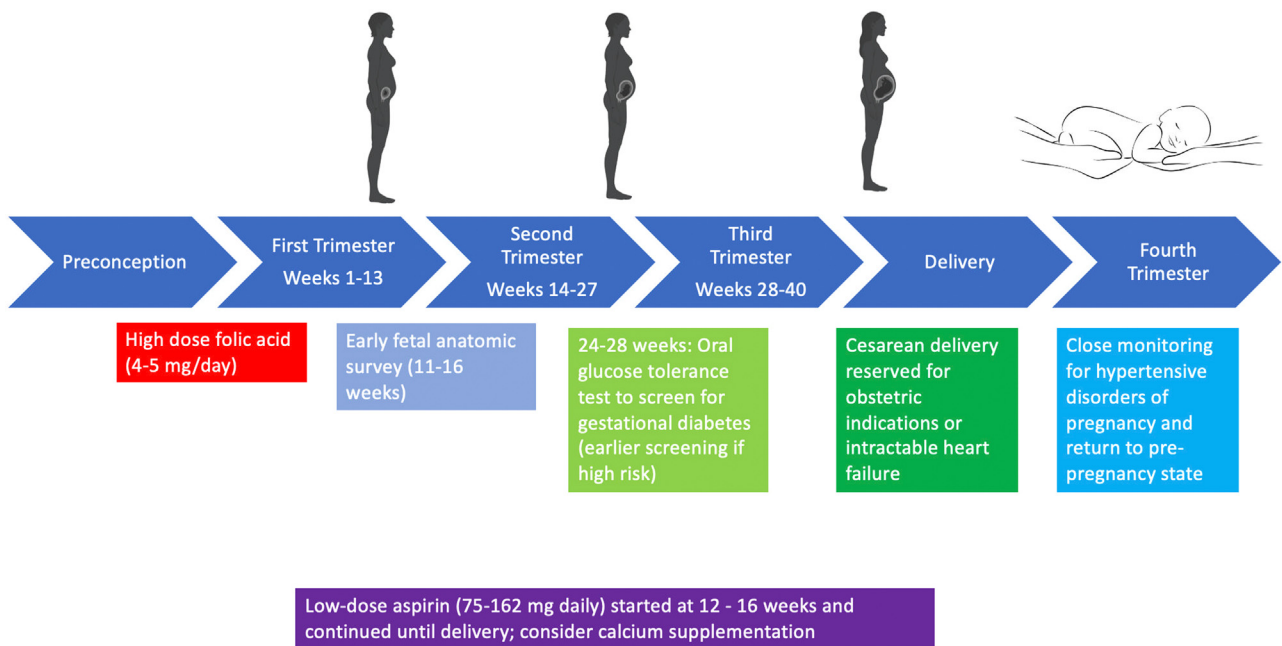
Medication	Potential for fetal exposure and risk	Clinical considerations for transplant recipient	Breastfeeding considerations
<i>Pneumocystis jirovecii</i> and <i>Toxoplasma gondii</i> prophylaxis and treatment			
Trimethoprim-sulfamethoxazole (TMP-SMX)	<ul style="list-style-type: none"> <li>Both components cross placenta<sup>283</sup></li> <li>Trimethoprim is a dihydrofolate reductase inhibitor; known risk of cardiovascular and neural tube defects and cleft palates with 1<sup>st</sup> trimester exposure<sup>284</sup></li> <li>Sulfonamides compete with bilirubin for plasma protein binding, theoretical risk of kernicterus with 3<sup>rd</sup> trimester exposure<sup>283</sup></li> </ul>	<ul style="list-style-type: none"> <li>Folic acid supplementation recommended to reduce risk of neural tube defects; caution with use in PJP treatment due to reports of treatment failure<sup>285</sup></li> </ul>	<ul style="list-style-type: none"> <li>Both components detectable in human milk<sup>286</sup></li> <li>Likely compatible with breastfeeding in healthy, full-term infants<sup>267,287</sup></li> <li>Avoid in preterm infant or those with hyperbilirubinemia due to potential risk of kernicterus; monitor for jaundice<sup>287</sup></li> <li>Avoid exposure in infants with glucose-6-phosphate-dehydrogenase (G6PD) deficiency<sup>287</sup></li> </ul>
Dapsone	<ul style="list-style-type: none"> <li>Crosses placenta<sup>288</sup></li> <li>Reports of safe use in non-transplant pregnancies for treatment of malaria, leprosy, and dermatitis herpetiformis<sup>288</sup></li> </ul>		<ul style="list-style-type: none"> <li>Detectable in milk and in breastfed infant blood levels<sup>289,290</sup></li> <li>Likely compatible with breastfeeding in healthy, full-term infants<sup>267,287</sup></li> <li>Monitor for jaundice and symptoms of hemolytic anemia<sup>287,290</sup></li> <li>Avoid exposure in infants with glucose-6-phosphate-dehydrogenase (G6PD) deficiency<sup>287</sup></li> </ul>
Atovaquone	<ul style="list-style-type: none"> <li>Unknown if crosses placenta</li> <li>Risk of birth defects appears low when used with proguanil for malaria prophylaxis<sup>291</sup></li> </ul>		<ul style="list-style-type: none"> <li>No data available regarding transfer into human milk; transfers into milk in animal studies<sup>292</sup></li> <li>No published data concerning outcomes of infants exposed via milk</li> </ul>
Aerosolized pentamidine	<ul style="list-style-type: none"> <li>Unknown if crosses placenta, may be limited given low systemic concentrations via aerosolized route</li> </ul>	<ul style="list-style-type: none"> <li>Risk of bronchospasms may limit utility in lung transplantation</li> </ul>	<ul style="list-style-type: none"> <li>No data available regarding transfer into human milk, transfer may be limited given low systemic concentrations via aerosolized route</li> <li>No published data concerning outcomes of infants exposed via milk</li> </ul>
Antiviral prophylaxis and treatment			
Valganciclovir and ganciclovir <sup>293</sup>	<ul style="list-style-type: none"> <li>Ganciclovir crosses placenta; as pro-drug of ganciclovir, valganciclovir expected to cross placenta<sup>294</sup></li> <li>Teratogenic in animal studies at 2 times the recommended human dose<sup>294</sup></li> <li>Limited number of published human pregnancies (&lt;5) with fetal exposure to ganciclovir and valganciclovir reported with no fetal malformations reported for prevention and/or treatment of maternal CMV infection<sup>295</sup></li> <li>Varying outcomes in 3 case reports of ganciclovir/valganciclovir exposure for treatment of fetal CMV infection: 1 premature stillbirth; 1 neonate with unilateral hearing loss; 1 neonate with no malformation at birth.<sup>295</sup></li> </ul>	<ul style="list-style-type: none"> <li>Approximately 35% of primary CMV infections during pregnancy result in transplacental passage of virus<sup>296</sup></li> <li>Utility of monitoring for CMV replication in transplant recipient throughout pregnancy not established, may be considered in effort to minimize drug exposure in those at high risk for CMV</li> </ul>	<ul style="list-style-type: none"> <li>No data available regarding transfer into human milk; transfers into milk in animal studies<sup>294</sup></li> <li>No published data concerning outcomes of infants exposed to either agent via milk</li> </ul>

(continued on next page)

**Table 9 (Continued)**

Medication	Potential for fetal exposure and risk	Clinical considerations for transplant recipient	Breastfeeding considerations
Acyclovir and valacyclovir	<ul style="list-style-type: none"> <li>Both agents readily cross placenta.<sup>293,297</sup></li> <li>Post-marketing registries and studies of both agents do not show an increase in number of birth defects compared to with the general population with no consistent pattern of defects.<sup>298,299</sup></li> </ul>	<ul style="list-style-type: none"> <li>Due to risk of perinatal transmission of primary HSV infection, treatment recommended to reduce duration and severity of symptoms and viral shedding.<sup>300</sup></li> <li>Suppressive viral therapy should be offered at or beyond 36 weeks of gestation for individuals with clinical history of genital herpes.<sup>300</sup></li> </ul>	<ul style="list-style-type: none"> <li>Detectable in human milk after both oral and intravenous administration.<sup>301,302</sup></li> <li>Likely compatible with breastfeeding.<sup>267,300</sup></li> </ul>

Abbreviations: PJP, pneumocystis jirovecii pneumonia.



**Figure 7** Obstetric management.

maternal and fetal surveillance for known pregnancy and graft-related complications, establishing antepartum and peripartum care plans, and the management of obstetric emergencies. Pertinent issues surrounding obstetric management in transplant recipients are summarized in [Figure 7](#).

**Early pregnancy considerations**

As outlined in Sections II, IV, and V, all individuals with LT or HT planning a pregnancy ideally would undergo preconception counseling to ensure optimal graft function for at least 1 year (2 years for LT) with stable immunosuppressive and other cardiac medications compatible with pregnancy.<sup>303-305</sup> If not initiated 3 months before conception, consideration should be given to high doses of folic acid (4-5mg per day), starting immediately after confirmation of pregnancy to reduce the risk of fetal neural tube defects.<sup>306</sup>

In the first trimester, a routine dating ultrasound (generally between 8-9 weeks of gestation) and nuchal translucency scan (generally between 11-14 weeks of gestation) are offered at most centers in high-resource settings. In addition, access to first-trimester ultrasound should be made available as clinically indicated (e.g., in the event of vaginal bleeding), given the higher miscarriage rates (13.6%)<sup>307</sup> among individuals with LT or HT. Should the pregnancy result in a miscarriage in the first trimester, both medical (mifepristone and misoprostol) and surgical (vacuum aspiration) options for pregnancy termination may be suitable if necessary, and decisions should be based on patient preferences and resource availability; more detailed description of options for pregnancy termination are described below.

Where available, an early (transabdominal or transvaginal) anatomy ultrasound, performed between 11 -16 weeks of gestation,<sup>308</sup> should be offered as 95% to 100%

visualization of major organs including the 4-chamber heart view, 3-vessel view, kidneys, stomach, bladder, abdominal wall, diaphragm, chest, umbilical cord, extremities, hands, feet, cerebellum, ventricles, orbits and umbilical cord is possible depending on week of gestation.<sup>309</sup> Given that birth defects associated with immunosuppressive and cardiac medications often involve these organs, and also since fetuses born to parents with cardiac disease are at increased risk for birth defects,<sup>310</sup> there is merit in performing early anatomy ultrasounds.

Diagnosis of a birth defect under 16 weeks of gestation allows for early counseling with maternal-fetal-medicine specialists regarding the nature of these defects and long-term implications, as well as options for termination of pregnancy.

In centers in which early anatomy scans are not offered, routine anatomy scans should be performed at 18-22 weeks of gestation. Referral to higher-volume centers for fetal echocardiograms should be considered when visualization is sub-optimal. Because individuals with LT or HT are at a considerably higher risk for serious maternal and fetal adverse events during pregnancy,<sup>110</sup> close maternal surveillance is warranted as outlined in Sections IV and V.

Given the high risk of placenta-mediated complications of pregnancy (hypertensive disorders of pregnancy including preeclampsia, preterm birth, and small-for-gestational age infants), low-dose aspirin (75-162 mg daily) should be initiated (in those transplant recipients not already on aspirin) between 12 and 16 weeks of gestation and continued until delivery.<sup>311-314</sup> Whether other preventive strategies, such as daily calcium supplementation (1.2-2.5 g/d), are effective in reducing the risk of preeclampsia is not clear, but calcium supplementation may be useful in high-risk patients, particularly in areas where dietary calcium intake is low.<sup>119,157,315</sup>

## Options for pregnancy termination

Of 385 pregnancies in a contemporary systematic review of LT and HT recipients, 6.8% ended in termination.<sup>110</sup> The option of pregnancy termination in a shared decision-making discussion of the risks to the mother and fetus is imperative, taking into account local, state and national laws and institutional policies.

Indications for pregnancy termination may include: (1) treatment for spontaneous miscarriage, (2) prohibitive pregnancy risk to the transplant recipient, or (3) identification of birth defects on screening of the fetus. Medical abortion usually entails mifepristone and misoprostol (safe with immunosuppression) and is used up to 11 weeks of gestation. The other option for a first trimester pregnancy termination is surgical aspiration which is generally performed up to 14 weeks.

If a second trimester pregnancy termination is necessary, options include dilation and evacuation (dilating the cervix followed by surgical extraction of products of conception) or medical induction with delivery of the fetus. At later

gestations (>16 weeks), many centers do not offer the option of surgical termination under general anesthesia. Should a decision be made to terminate pregnancy, this would require pharmacological or mechanical dilatation of the cervix and the initiation of uterine activity, which could take over 24 hours to complete.

Options for medication vs surgical termination depend upon duration of gestation as described above as well as upon patient preferences, clinician experience, availability of services, and legislative barriers. There are no guidelines nor studies examining the safety of different termination methods in transplant recipients. However, the psychological strain of pregnancy termination is well-established and pro-active psychosocial support is essential in the planning and recovery period. Patients should be monitored in the peri- and post-abortion periods for the impact of fluid shifts and risk of bleeding.

## Maternal and fetal surveillance in later pregnancy

Since LT and HT recipients are at increased risk for maternal and fetal adverse events during pregnancy, increased surveillance is warranted. In the second trimester, weekly antenatal visits may be reasonable, with a low threshold to increase surveillance depending on the clinical condition. Maternal obstetric surveillance in the second trimester should include serial monitoring of blood pressure and renal function assessment at least once per trimester, especially for those on immunosuppressive agents such as cyclosporine and tacrolimus that are associated with nephrotoxicity. Additionally, given higher rates of diabetes in LT<sup>110</sup> and HT<sup>2,12,33</sup> recipients, screening for diabetes should be offered early in pregnancy and again between 24-28 weeks of gestation.

Fetal surveillance should include serial ultrasound scans for fetal growth every 3-4 weeks as well as an assessment of amniotic fluid volume, biophysical profile testing when clinically appropriate, and umbilical artery and fetal Doppler studies in the event of fetal growth restriction.

Preterm birth rates in this population are extremely high, occurring in more than half of pregnancies in some series<sup>307</sup> and although many preterm births are iatrogenic, due to clinical deterioration of maternal and/or fetal health, spontaneous preterm birth may also occur. Transvaginal ultrasound measurement of cervical length at the time of the routine anatomy scan may help identify those at increased risk for preterm birth and allow interventions for reducing its incidence.<sup>315</sup> In instances where the cervical length is deemed to be low, referral to a preterm birth clinic for ongoing surveillance may be warranted.

## Management of pregnancy complications

The identification of any maternal and/or fetal complications should prompt appropriate referrals and treatment as indicated below.

## Hypertensive disorders of pregnancy

Hypertensive disorders, which include gestational hypertension, preeclampsia, HELLP syndrome and eclampsia,<sup>316</sup> are increased in individuals with LT and HT.<sup>307</sup> Due to the high prevalence of chronic hypertension and kidney dysfunction, such patients are considered at risk for preeclampsia and case series and registries demonstrate that preeclampsia may complicate 12% to 23% of pregnancies after LT or HT.<sup>12,17,33,110,141,226</sup> It is important to note that preeclampsia may be difficult to diagnose in the setting of baseline proteinuria, hepatic dysfunction, and hypertension. While the only effective treatment for preeclampsia is delivery, aspirin is recommended to decrease or prevent the onset of preeclampsia as noted above.

## Fetal and neonatal adverse events

In the event of threatened preterm birth, a single course of antenatal corticosteroids (2 doses of 12mg betamethasone 24 hours apart) is recommended for pregnant women between 24 0/7 weeks and 33 6/7 weeks of gestation who are at increased risk of preterm delivery within 7 days and those with ruptured membranes.<sup>317</sup> This should be administered even in those receiving oral or parenteral prednisolone for maintenance immunosuppression or graft rejection, as although the latter crosses the placenta, fetal uptake is extremely limited.<sup>318</sup> Fetal growth restriction should be managed in accordance with published guidelines,<sup>319</sup> and labor induction avoided at preterm gestations if possible.<sup>320</sup> Neonatal consultation should be sought where required.

## Peripartum management

In the absence of clinical deterioration of maternal or fetal condition, pregnancy should be continued until approximately 39 weeks of gestation.<sup>321</sup> When there is evidence of maternal or fetal clinical deterioration, labor induction should be considered in accordance with clinical guidelines,<sup>322</sup> and cesarean delivery reserved for obstetric indications or in the event of intractable cardiac complications including heart failure.<sup>323</sup> When possible, individuals should give birth in centers experienced with thoracic transplantation with a multidisciplinary team approach.

Appropriate analgesia should be recommended for labor, most commonly with epidural anesthesia. While no agent used for labor induction in contemporary obstetric practice is absolutely contraindicated in LT or HT recipients, caution should be exercised while using oxytocin for prolonged periods in patients with cardiac disease given the risk of vasodilation, tachycardia, and ischemia.<sup>324</sup> Intrapartum maternal and fetal monitoring should be dictated by the clinical condition, and an evidence-based approach should be followed to optimize the chances of a vaginal birth.<sup>325</sup> There is no contraindication to the use of oxytocin at standard recommended doses for the active management of the third stage of labor.<sup>323</sup> Use of preparations containing ergot alkaloids if postpartum hemorrhage is encountered should

be avoided in those with elevated blood pressure. Most other medications are acceptable to treat postpartum hemorrhage.

## Postpartum management

Given the increased risk of cardiovascular events in the immediate postpartum period, postpartum care in an intensive care unit setting is recommended and early discharge from hospital (<72 hours) should be discouraged. Postpartum thromboprophylaxis should follow local protocols. Postpartum monitoring of immunosuppression levels and for infection is critical. Counseling regarding the importance of health maintenance activities for the mother and adequate social support in the postpartum period should be provided.

The safety of immunosuppressive agents with breastfeeding is discussed in detail in Section VIII. In the general population, breastfeeding is associated with a myriad of immunologic, emotional, and nutritional benefits. In LT and HT recipients, the decision to breastfeed should be based on a risk-benefit analysis of the potential for immunosuppressive medications to be excreted in the breast milk. After 1 to 2 weeks of breast-feeding, it is reasonable to check the infant's serum for measurable drug levels of cyclosporine or tacrolimus.<sup>326</sup> If significant levels are detected, the mother may be counseled to discontinue breast-feeding. Limited data are available regarding the excretion of mTOR inhibitors in breast milk. Therefore, caution must be advised regarding breast-feeding in mothers taking mTOR inhibitors. The Drugs and Lactation Database (LactMed) and e-lactancia can be helpful resources for physicians and patients when determining which medications are safe for breast-feeding mothers after LT or HT.<sup>327–329</sup>

## Consensus statements on obstetric management

- High doses of folic acid (4-5mg per day) should be initiated 3 months before planned conception or immediately after confirmation of pregnancy.
- Early transvaginal or transabdominal anatomy ultrasound scan performed between 11 -16 weeks of gestation should be offered if available for early detection of potential congenital anomalies; earlier scans are useful when available.
- Given the high risk of placental complications of pregnancy (hypertensive disorders of pregnancy including preeclampsia, preterm birth, and small-for-gestational age infants), low-dose aspirin (75-162 mg daily) is recommended to start at 12 - 16 weeks of gestation and continued daily until delivery; calcium supplementation (1.2-2.5 g/d) may also be considered in areas where dietary calcium intake is low.
- Screening for diabetes should be performed early in pregnancy in those at risk for diabetes and repeated between 24-28 weeks of gestation.
- In the absence of clinical deterioration of maternal or fetal condition, pregnancy should be continued until 39



**Table 10** Summary of Consensus Statements by Section

Preconception counseling and shared decision-making	<ul style="list-style-type: none"> <li>• Preconception counseling of individuals of childbearing age should: 1) ideally occur as part of the pretransplant evaluation process; 2) be repeated at least annually after transplant during childbearing years; and 3) include a discussion of optimal contraception, timing of pregnancy, contraindications to pregnancy, and maternal and fetal risks, including those unique to transplant recipients such psychosocial aspects of family planning in the context of a disorder with limited life-expectancy.</li> <li>• Intrauterine devices (IUD) are the preferred long-term contraception option for many patients after transplantation given their low failure rate, ability to be in place for several years, lack of required daily adherence for effectiveness, lack of drug-drug interactions, and straightforward removal to reverse contraception. Experience with the use of assisted reproductive technology is limited in transplant recipients but may be considered on an individualized basis in collaboration with a reproductive endocrinologist, recognizing the risk of multiple gestations and ovarian hyperstimulation syndrome.</li> <li>• Pregnant transplant recipients are at high risk for anxiety and depression and psychosocial evaluation and support is an essential part of the preconception, antepartum, and postpartum process.</li> <li>• Issues surrounding pregnancy planning and contraception should be approached using a shared decision-making model.</li> </ul>
Risk assessment, management, and Outcomes of pregnancy after lung transplantation	<ul style="list-style-type: none"> <li>• Lung transplant recipients should wait 1-2 years post lung transplant before pursuing pregnancy. Before planned conception, recipients should have stable lung function (without chronic allograft lung dysfunction or donor-specific antibodies), no evidence of rejection in the preceding 12 months, stable doses of maintenance immunosuppression safe in pregnancy, and no acute infection.</li> <li>• Non-adherence with medical therapy, poorly controlled hypertension, diabetes, and renal dysfunction (eGFR &lt; 30 ml/min/1.73 m<sup>2</sup>) are considered contraindications to pregnancy.</li> <li>• Pregnant lung transplant recipients with cystic fibrosis require special attention to specific comorbidities including gastroesophageal reflux and nutritional supplementation.</li> <li>• Clinical evaluation and spirometry should occur at least monthly during pregnancy in lung transplant recipients; any changes in spirometric measures, and in particular FEV<sub>1</sub>, should be investigated as would be done in a non-pregnant lung transplant recipient, rather than being attributed to pregnancy itself.</li> <li>• The risk of chronic lung allograft dysfunction remains high in the postpartum period and as such regular monitoring should continue.</li> </ul>
Risk assessment, management, and outcomes of pregnancy after heart transplantation	<ul style="list-style-type: none"> <li>• Heart transplant recipients should wait at least 1 year post heart transplant before pursuing pregnancy. Before planned conception, recipients should have stable heart function (LVEF &gt; 45% without significant allograft vasculopathy or donor-specific antibodies), no rejection in the past 12 months, stable doses of maintenance immunosuppression safe in pregnancy, and no acute infection.</li> <li>• Non-adherence with medical therapy, poorly controlled hypertension, diabetes, and renal dysfunction (eGFR &lt; 30 ml/min/1.73 m<sup>2</sup>) are considered contraindications to pregnancy.</li> <li>• The pre-transplant diagnosis may have an impact of the risk for pregnancy: 1) those with PPCM have worse post-transplant outcomes compared to those without PPCM; 2) there is a risk of recurrence of congenital heart disease (CHD) in offspring of those with CHD; and 3) heritable cardiomyopathies may be passed to the fetus.</li> <li>• Clinical evaluation and echocardiography form the cornerstone of rejection surveillance; echocardiogram should be performed at least every trimester but ideally every 1-2 months until 24 weeks of gestation and then monthly until delivery. Noninvasive assessment of rejection with gene expression profiling may be useful but donor-derived cell-free DNA testing may result in false-positive findings during pregnancy as it will detect fetal DNA.</li> </ul>
Management of comorbid conditions during pregnancy	<ul style="list-style-type: none"> <li>• Pregnant lung transplant and heart transplant recipients should be screened for gestational diabetes at 24-28 weeks of gestation.</li> <li>• Treatment of diabetes during pregnancy in transplant recipients, in conjunction with consultation with endocrinology or maternal-fetal-medicine, requires non-pharmacological strategies (daily exercise, diet, self-monitoring of blood glucose) and pharmacological measures (insulin or metformin as cornerstone treatments; other oral agents such as sulfonylureas, GLP-1 receptor agonists, and SGLT-2 inhibitors are not recommended due to lack of safety data).</li> <li>• Hypertension is common in pregnant transplant recipients and should be managed to reduce the risk of preeclampsia and preterm delivery; nifedipine, amlodipine, labetalol, hydralazine, and methyldopa can be used safely during pregnancy.</li> </ul>

*(continued on next page)*

**Table 10** (Continued)

Pregnancy while on LVAD support	<ul style="list-style-type: none"> <li>• As CMV infection poses risks to the fetus, transplant recipients should be periodically tested for CMV viremia and CMV-seronegative patients advised to adopt specific behaviors to minimize the risk of primary infection.</li> <li>• Due to risks of hemodynamic compromise and challenges of anticoagulation management, LVAD support is considered a contraindication to pregnancy and patients should be counseled on the importance of reliable contraception and a discussion of termination should be considered.</li> <li>• If pregnancy occurs, a multidisciplinary team of specialists in LVAD management and maternal-fetal medicine is required to 1) manage maternal comorbidities and assess for complications—including hypertension, preeclampsia, and infections; 2) optimize support to the fetus to minimize the risk of low cardiac output leading to uteroplacental insufficiency; and 3) manage hemodynamics and anticoagulation through pregnancy and delivery.</li> </ul>
Pharmacologic considerations	<ul style="list-style-type: none"> <li>• Mycophenolate products should be stopped at least 6 weeks before planned conception or immediately when an unplanned pregnancy is confirmed.</li> <li>• Generally, mTOR inhibitors should be stopped 6-12 weeks before a planned pregnancy based on animal studies; an increase in fetal complications/birth defects has not been observed in human case reports so the risks vs benefits of mTOR use in individual patients should be evaluated.</li> <li>• Calcineurin inhibitors should serve as the cornerstone of maintenance immunosuppression regimens. The use of corticosteroids and azathioprine at the lowest effective dose should be tailored to the patient's clinical risk profile.</li> <li>• Therapeutic drug monitoring should be performed every 2-4 weeks with dose adjustment to achieve target levels as required.</li> <li>• For hypertension, nifedipine and amlodipine are considered safe during pregnancy and do not interact with immunosuppression. Other options include methyldopa, labetalol, and hydralazine; beta-blockers may be less well tolerated in heart transplant recipients due to denervation with reduced exercise tolerance. Angiotensin receptor blockers and ACE inhibitors are contraindicated.</li> </ul>
Obstetric management	<ul style="list-style-type: none"> <li>• High doses of folic acid (4-5mg per day) should be initiated 3 months before planned conception or immediately after confirmation of pregnancy.</li> <li>• An early transvaginal or transabdominal anatomy ultrasound scan performed between 11 -16 weeks of gestation should be offered if available for early detection of potential congenital anomalies; earlier scans are useful when available.</li> <li>• Given the high risk of placental complications of pregnancy (hypertensive disorders of pregnancy including preeclampsia, preterm birth, and small-for-gestational age infants), low-dose aspirin (75-162 mg daily) is recommended to start at 12 - 16 weeks of gestation and continued daily until delivery; calcium supplementation (1.2-2.5 g/d) may also be considered in areas where dietary calcium intake is low.</li> <li>• Screening for diabetes should be performed early in pregnancy in those at risk for diabetes and repeated between 24-28 weeks of gestation.</li> <li>• In the absence of clinical deterioration of maternal or fetal condition, pregnancy should be continued until 39 weeks of gestation and cesarean delivery reserved for obstetric indications or in the event of intractable heart failure.</li> </ul>

weeks of gestation and cesarean delivery reserved for obstetric indications or in the event of intractable heart failure.

### Gaps in knowledge and limitations

Most data regarding pregnancy in thoracic transplant recipients are based on small, single center experiences or voluntary registries. While the TPRI has gathered information in this field, participation is not mandatory. Unfortunately, national and international registries, such as those from UNOS and ISHLT, do not capture pregnancy data that could inform guidelines and recommendations.

In addition, many of the recommendations for appropriate care of these pregnant patients come from observational

cohort studies or anecdotal experience at tertiary and quaternary care centers. As pregnant individuals are frequently excluded from many clinical trials due to safety and ethical concerns, it is challenging to provide evidence-based guidelines for treatment of these populations.

There are likely significant between-center differences in management that may impact maternal and fetal outcomes. In 1 study of HT clinicians, 31% of survey respondents felt that pregnancy should be avoided in all HT recipients despite reports of safe pregnancy after transplant.<sup>95</sup> Notably, 60% of respondents had prior experience with pregnant HT recipients while only 43% indicated that their center had a formal policy regarding pregnancy following HT. At high-volume centers (>80 transplants annually), only 62% of respondents reported that their institutions had policies surrounding pregnancy.

More education also may be needed to improve outcomes. In this same study, 40% of respondents recommended hormonal contraception post-transplant although IUD is often preferred. Similarly, 2 respondents in the survey recommended MMF as part of the immunosuppressive regimen during transplant despite its known teratogenic effects.<sup>95</sup>

There is little known about how to communicate and factor in the risks of maternal life expectancy on the decision to become pregnancy and the psychosocial impact of pregnancy on transplant recipients. Future research is also needed regarding the long-term effects of ART, the health impacts of multiple gestation, the safety of breastfeeding after transplantation, and the longer-term impact of post-transplant pregnancy on the health of the parent and the child. Increasingly there are data regarding the risks of preeclampsia in patients without a history of thoracic transplantation and the implications for future cardiovascular health.<sup>329–331</sup> Data comparing matched women post-transplant who have had and not had a pregnancy would be useful to determine whether pregnancy impacts longer-term survival.

## Conclusion

With improved outcomes after lung transplantation and heart transplantation, there is a growing pool of individuals of childbearing age who may wish to consider pregnancy. Pregnancy after thoracic organ transplantation requires anticipatory planning and guidance, careful patient risk assessment with a discussion of individualized risk, close monitoring of graft function and immunosuppression, and vigilance for optimization of comorbid conditions. Consensus recommendations are summarized in [Table 10](#). With a multidisciplinary approach and team, pregnancy after lung or heart transplantation is feasible in selected patients. In the future, multicenter registries may provide much-needed experience to craft future guidelines and recommendations concerning pregnancy after thoracic organ transplantation.

## Disclosure statement

The authors have no conflicts of interest to disclose.

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