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Pregnancy outcomes in heart transplant recipients

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KEYWORDS:
heart transplant;
pregnancy;
immunosuppression;
transplant pregnancy registry;
reproductive counseling

BACKGROUND: The population of female heart transplant recipients of reproductive age is growing, and counseling regarding reproductive decisions is important. We describe maternal and fetal outcomes of pregnancy in the Transplant Pregnancy Registry International.

METHODS: Data regarding pregnancies between 1987 and 2016 were collected via questionnaires, phone interviews, and medical records review. Demographics, comorbidities, changes in immunosuppressive regimens, rejection episodes during pregnancy, data on maternal retransplants, and deaths were recorded.

RESULTS: A total of 91 patients reported 157 pregnancies. Mean maternal age at conception was 27 ± 5.6 years. The most common indications for transplant were congenital heart disease (22%) and viral myocarditis (18%). Average transplant to conception interval was 7 ± 6.1 years. Immunosuppression was calcineurin inhibitor–based in almost all patients, with 20% of recipients taking mycophenolic acid (MPA) while pregnant. Complications during pregnancy included pre-eclampsia (23%) and infections (14%). Rejection was reported during 9% of pregnancies and within 3 months postpartum in 7%. Livebirths occurred in 69%, with no neonatal deaths. Miscarriages occurred in 26% of pregnancies, 49% of which had MPA exposure. Mean follow-up post pregnancy was 8.9 ± 6.5 years. At last follow-up, 30 recipients had died, an average of 9.4 ± 6.2 years after pregnancy. The most common causes included allograft vasculopathy and rejection.

CONCLUSIONS: This is the largest reported series of pregnancies in heart transplant recipients and demonstrates that two thirds of pregnancies reported are successful. MPA exposure is associated with increased risk of teratogenicity and miscarriage. Pre-pregnancy counseling should include discussions of risk of MPA exposure, rejection, graft dysfunction, and maternal survival.

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Women aged 18 to 39 years comprise 6.4% of all heart transplants performed from 2006 to 2012 and reported to the International Society for Heart and Lung Transplantation,[1] and the numbers of pediatric heart transplant recipients reaching reproductive age are rising. Five-year survival after transplant has increased from 55% to 80% (1982–1989 vs 2009–2014, respectively), and the median survival after the first year post-transplant in children aged 1 to 5 years is 18.2 years.[2] Providers must counsel this growing post-transplant population regarding reproductive decisions.

Of specific concern are maternal and fetal outcomes of pregnancy, as well as the risks of graft rejection and dysfunction.[3,4] In registries,[4,5] case series,[6,7] and case reports,[8] investigators have described maternal comorbidities such as hypertension and downstream effects of immunosuppression including infectious[9] and teratogenic complications[5] and complications including miscarriages, preterm birth, and low birthweights.[8]

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However, many of these findings come from small case series and reports, with sample sizes ranging from 11 to 22 patients. Larger series reviewing outcomes of other solid organ transplant recipients[5,8] do not address concerns unique to the heart transplant patient, such as adaptation of the transplanted heart to the hemodynamic load of pregnancy[9] or the potential risks for recurrent graft dysfunction in a recipient with a history of peripartum cardiomyopathy.[3,9]

The Transplant Pregnancy Registry International (TPR) is a voluntary international registry of solid organ transplant recipients who become pregnant.[5] In this report, we present outcomes of heart transplant recipients included in the TPR.

Methods

Transplant recipients contact the TPR after learning about it through their providers, the Internet, or brochures. Pregnancies have been enrolled in the TPR prospectively (before the outcome is known) since May 2010. Once informed consent is obtained, recipients are interviewed initially about transplant and pregnancy outcomes, and follow-up interviews regarding the mother's health and child's development are conducted periodically. Trained TPR nurses and research coordinators conduct the initial and follow-up structured interviews. All interviews are in English. Medical records are requested of the delivery hospital and transplant center after the records release is signed and received from the recipient. The TPR has been approved by an institutional review board since its inception and is currently approved by Advarra Institutional Review Board.[10]

Participants' medications before, during, and after pregnancy are recorded. The transplant team is also interviewed and the medical records reviewed to confirm medications and rejection episodes. Long-term follow-up interviews are conducted to monitor recipient and offspring health every 2 years.

Baseline characteristics and outcomes of pregnancies were compared across transplantation eras spanning from 1982 to 1991, 1992 to 2001, 2002 to 2009, and 2010 to 2017.[11]

Results

The registry included 91 female heart transplant recipients with a total of 157 pregnancies from January 1987 to June 2016 (Table 1). In this analysis, all of the participants were from North America, as the TPR started including international participants in October 2016. Twenty pregnancies were enrolled prospectively. Average follow-up was 8.9 ± 6.5 years post-conception. Forty-three patients (47%) had more than 1 pregnancy after transplant. Four patients had undergone more than 1 heart transplant.

Average maternal age at conception was 27 ± 5.6 years. Overall, the most common indications for heart transplant were congenital heart disease and cardiomyopathy (22%), viral myocarditis (18%), and idiopathic cardiomyopathy (13%) (Figure 1). Although the sample sizes were quite small for comparison across transplant eras, there were no large differences in indications for transplantation. In the 1 year before pregnancy, 16 patients (19%) reported rejection episodes, of which 8 reported acute cellular rejection (ACR) ≥ 2R or antibody-mediated rejection. Maternal comorbidities at conception included insulin-dependent diabetes (5%) and drug-treated hypertension (42%) (Table 1).

The average transplant to conception interval was 7 ± 6.1 years, with 8 pregnancies occurring <1 year after transplant. Of 127 responses, 59 pregnancies (46%) were unplanned. Of 119 responses, oral contraception had been used before 14 pregnancies. Complications during pregnancies included pre-eclampsia in 27 out of 119 responses (23%) and infections in 22 (14%) (Table 2), including urinary tract infection, upper respiratory infection, pneumonia, vaginal yeast, herpes, Group B *Streptococcus* infections, and groin abscess. Of 106 responses, 45 pregnancies were delivered by C-section, with indications including pre-eclampsia ($n = 7$), placental abruption ($n = 2$), and breech presentation ($n = 6$).

A total of 14 patients (9.1%) reported rejection during pregnancy, of which 6 reported ACR ≥ 2R and 2 reported antibody-mediated rejection (Table 3). Steroids alone were used for treatment in 6 patients, and 1 patient received antithymocyte globulin and intravenous immunoglobulin and underwent plasmapheresis. Data regarding surveillance strategies were limited; fluoroscopy was mentioned in 4 pregnancies complicated by rejection, with routine biopsy[1] and serial echocardiography[5] mentioned in pregnancies without rejection. A total of 11 patients (7.2%) reported rejection within 3 months postpartum, with 2 reporting ACR ≥ 2. A total of 2 patients were relisted for heart transplant within 2 years of pregnancy, both for cardiac allograft vasculopathy.

A total of 69% of pregnancies were successful (Table 4a), and there were no neonatal deaths. Reasons for the 7 terminated pregnancies included a history of peripartum cardiomyopathy, transplant to conception interval of 2 months, rejection either during pregnancy or in the 1 year prior, and concern for the heart transplant. A total of 41% of live births were preterm as defined by gestational age <37 weeks ($n = 46$), and 37% of the live births had a birthweight <2,500 g ($n = 41$). There were no large differences in outcomes of pregnancies by era of transplant, although sample sizes were small. Congenital malformations were identified in 9 children (Table 4b). A total of 7 infants inherited maternal cardiac disease, which included cardiomyopathy; bicuspid aortic valve; hypertrophic cardiomyopathy; mitochondrial myopathy ($n = 2$); restrictive cardiomyopathy; and a child with dilated ascending aorta, ventricular septal defect, and patent ductus arteriosus. A total of 3 out of these offspring underwent heart transplantation as children.

Miscarriages occurred in 63% of pregnancies exposed to mycophenolic acid (MPA), compared with 17% of those not exposed (Table 5). A total of 99% of patients were exposed to calcineurin inhibitors (CNI) during pregnancy, 46% to azathioprine, 20% to MPA, and 9% to mammalian target of rapamycin inhibitors (Table 6). Across transplant eras, 9% to 15% of respondents reported being treated with tacrolimus alone, but no clear trend emerged for increased use of this immunosuppression plan in more recent transplant eras. Between 9% and 40% of respondents in all eras reported MPA exposure during pregnancy. In 33

Table 1 Baseline Characteristics of Patients

Characteristic	Overall	1982–1991	1992–2001	2002–2009	2010–2017
Study numbers	N = 91 patients N = 157 pregnancies N = 162 outcomes (includes twins/triplets)	N = 29 patients N = 54 pregnancies N = 54 outcomes	N = 34 patients N = 58 pregnancies N = 59 outcomes	N = 22 patients N = 35 pregnancies N = 39 outcomes	N = 6 patients N = 10 pregnancies N = 10 outcomes
Mean age at transplant, years (range)	20 ± 8.4 (1 month–37 years)	20 ± 8.7 (1 month–37 years)	18 ± 8.6 (1 month–32 years)	22 ± 6.0 (11–31 years)	31 ± 4.5 (24–36 years)
Number of patients with					
>1 heart transplant (%)	4 (4)	—	—	3	1
ACR ≥2R or AMR 1 year before pregnancy (%)	8 (9)	5	2	1	—
>1 pregnancy after transplant (%)	42 (46)	17 (59)	12 (35)	10 (45)	3 (50)
Mean age at first conception, years (range)	27 ± 5.6 (16–40)	28 ± 5.1	26 ± 6.1	27 ± 4.2	33 ± 5.6
Transplant to first conception interval, years (range)	7 ± 6.1 (2 months–24)	8 ± 7.3	9 ± 6.3	5 ± 2.8	3 ± 1.5
Number of unplanned pregnancies (%)[a]	59 (46)	11/31 (35)	25/53 (47)	19/33 (58)	4/10 (40)
Number with treated hypertension before pregnancy (%)[b]	65 (42)	27/53 (51)	17/57 (30)	16/32 (50)	5/9 (56)
Number with insulin-dependent diabetes before pregnancy (%)[c]	7 (5)	1/52 (2)	2/57 (4)	3/35 (9)	1/10 (10)

Abbreviations: ACR, acute cellular rejection; AMR, antibody-mediated rejection.
[a]Out of 127 responses.
[b]Out of 151 responses.
[c]Out of 154 responses.

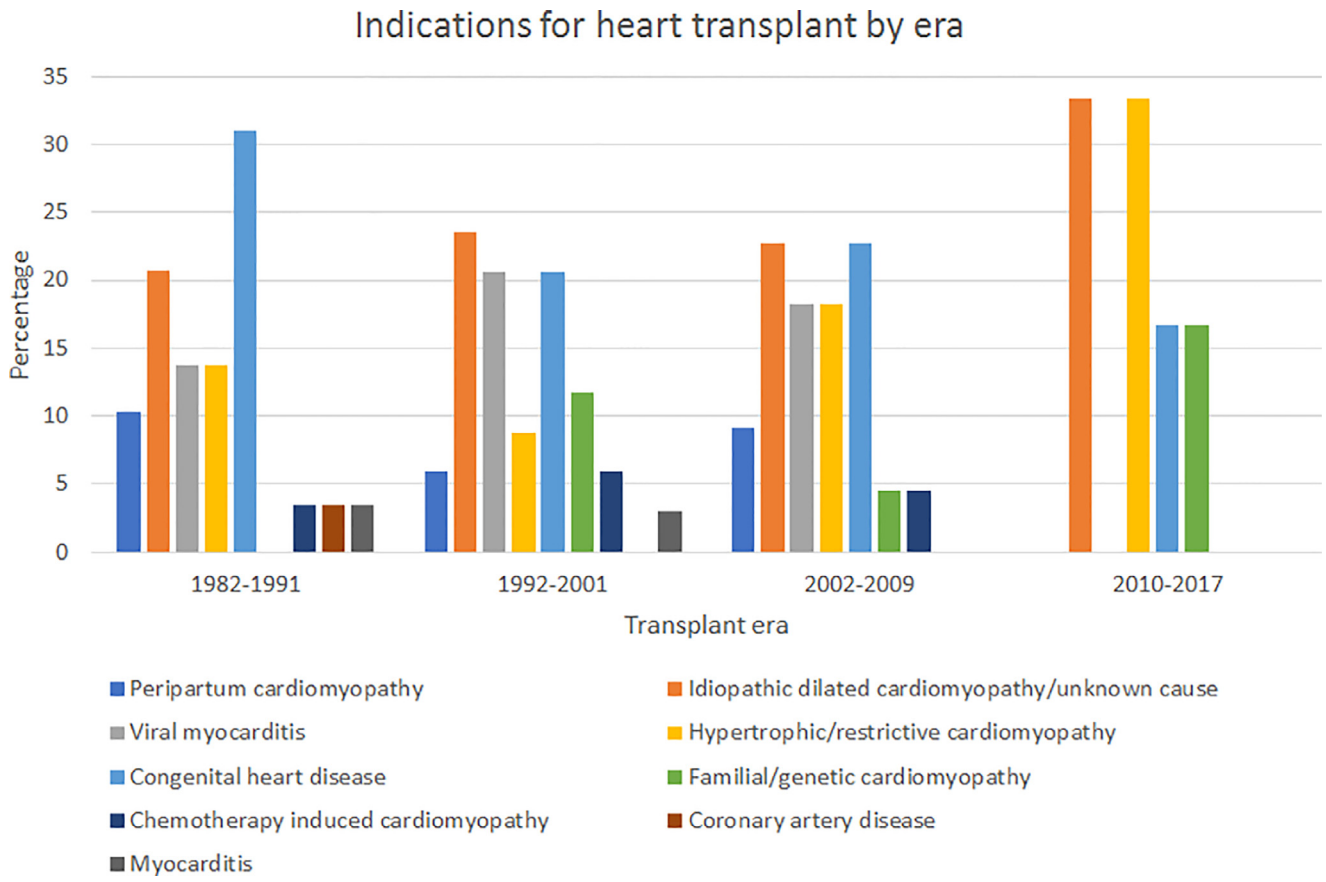

Figure 1 Causes of cardiomyopathy leading to heart transplantation in 91 recipients. CAD, coronary artery disease; HCM, hypertrophic cardiomyopathy; RCM, restrictive cardiomyopathy.

pregnancies, MPA was stopped an average of 28 weeks before conception. Among the 32 pregnancies exposed to MPA at conception, 6 stopped MPA during pregnancy and 3 were switched to azathioprine (Supplementary Table S1, available online at www.jhltonline.org).

Breastfeeding was reported following 31 pregnancies, with 90% exposed to CNI and 10% to MPA. Postpartum contraception was reported in 119 pregnancies, and included tubal ligation ($n = 45$), oral contraception ($n = 19$), hysterectomy ($n = 10$), partner vasectomy ($n = 4$), and intrauterine device ($n = 3$).

One patient was lost to follow-up and 30 patients (33%) died at an average of 9.4 ± 6.2 years after pregnancy (Table 7). The most common causes of death were cardiac allograft vasculopathy or myocardial infarction, cardiac arrest, and rejection. In 1 patient each, other reported causes were multisystem organ failure, graft failure,

Table 2 Maternal Complications During Pregnancy

Complication	N = 157 pregnancies (%)
Number with hypertension treated during pregnancy[a]	72 (46)
Number with insulin-dependent diabetes during pregnancy[b]	11 (7)
Number with pre-eclampsia[c]	27 (23)
Number with infection (URI, UTI, vaginal)[d]	22 (14)

Abbreviations: URI, upper respiratory infection; UTI, urinary tract infection.
[a]Out of 156 responses.
[b]Out of 157 responses.
[c]Out of 119 responses.
[d]Out of 150 responses.

Table 3 Graft Rejection During and After Pregnancy

Graft rejection	Outcome
Number with rejection during pregnancy (%)[a]	14 (9.1)
ACR ≥ 2R	6
Antibody-mediated rejection	2
Median time to rejection from time of conception (weeks, range)	7.2 (0.4–29)
Median time to rejection from transplant (years, range)	2.4 (1–11)
Number with rejection within 3 months postpartum (%)[b]	11 (7.2)
ACR ≥ 2R	2
Number relisted within 2 years of pregnancy (all CAV)	2

Abbreviations: ACR, acute cellular rejection; CAV, cardiac allograft vasculopathy.
[a]Out of 154 responses.
[b]Out of 153 responses.

Table 4a Outcomes of Pregnancies

Outcomes	Overall N = 162 outcomes (Including multifetal)[a]	1982–1991 N = 54 outcomes	1992–2001 N = 59 outcomes	2002–2009 N = 39 outcomes	2010–2017 N = 10 outcomes
Number of miscarriages (%)	41 (25)	9 (17)	20 (34)	9 (23)	3 (30)
Number of ectopic pregnancies (%)	2 (1)	0	2 (3)	0	0
Number of stillbirths (%)	1 (1)	0	1 (2)	0	0
Number of terminations (%)	7 (4)	4 (7)	1 (2)	2 (5)	0
Number of live births (%)	111 (69)	41 (76)	35 (59)	28 (72)	7 (70)
Number of neonatal deaths	0	0	0	0	0
Mean gestational age (weeks)	36 ± 3.4	37 ± 2.8	37 ± 2.6	35 ± 4.1	35 ± 5.6
≥37 weeks	66 (59%)	27 (66)	22 (63)	13 (46)	4 (57)
Preterm, <37 weeks	45 (41%)	14 (34)	13 (37)	15 (54)	3 (43)
<34 weeks	15 (14%)	5 (12)	2 (6)	6 (21)	2 (29)
Mean birthweight, g	2,600 ± 688	2,619 ± 570	2,723 ± 549	2,412 ± 852	2,626 ± 1,135
≥2,500 g	70 (63%)	25 (61)	24 (69)	16 (57)	5 (71)
Low birthweight, <2,500 g	41 (37%)	16 (39)	11 (31)	12 (43)	2 (29)
<1,500 g	9 (8%)	2 (5)	1 (3)	5 (18)	1 (14)

[a]A total of 4 multifetal pregnancies: 3 twin pregnancies, 1 triplet.

pulmonary embolism and infarct, sepsis, and non-adherence. A total of 2 patients died <1 year from conception, one from multisystem organ failure, with a pregnancy outcome of spontaneous abortion, and another from cardiac arrest and sepsis after a livebirth. At a mean of 8.9 years of follow-up, 57 (63%) recipients reported adequate function.

Discussion

TPR comprises the largest multicenter registry of pregnancy outcomes after heart transplant and provides a perspective into a young recipient population that is expected to grow significantly.[1,2] Heart transplant recipients in TPR were aged 20 ± 8.4 years at transplant and 27 ± 5.6 years at conception. Importantly, compared with prior case series and registry reports,[6–9] TPR data uniquely emphasize the need for early and emphatic pre-conception counseling for transplant recipients; 71% of heart transplant recipients had no pregnancy before transplant, and 46% report that the pregnancy was unplanned. Particularly given the teratogenicity of MPA exposure, pregnancy planning in transplant recipients is essential. Furthermore, early pre-conception counseling and/or genetic counseling must be particularly stressed in patients who have a history of peripartum cardiomyopathy (8%) and familial cardiomyopathy (7%).

Table 4b Congenital Malformations and Immunosuppressant Exposures

Congenital malformation	Immunosuppressant exposure
Duodenal atresia, tetralogy of Fallot	CNI, MPA
Laryngomalacia	CNI, MPA
Facial deformities	CNI, MPA, mTOR inhibitor
Vermian hypoplasia of the cerebellum (mild Dandy–Walker variant)	CNI, mTOR inhibitor
Hypospadias, undescended testicle	CNI, mTOR inhibitor
Cystic hygroma	CNI, mTOR inhibitor
Pectus excavatum	CNI, azathioprine
Lip and tongue tie	CNI
Long QT (late diagnosis)	CNI

Abbreviations: CNI, calcineurin inhibitor; MPA, mycophenolic acid; mTOR, mammalian target of rapamycin.

Maternal comorbidities in the heart transplant population underscore the importance of a multidisciplinary approach to counseling and management. A history of peripartum cardiomyopathy may warrant closer attention to the increased hemodynamic load of pregnancy and to monitoring for graft dysfunction.[3] The higher prevalence of maternal hypertension and diabetes compared with the general population (43% and 5% vs 0.93% and 0.83%, respectively)[12] emphasizes the need for consistent care and adherence to guideline-directed therapies. Pre-eclampsia rates reported in the TPR heart transplant recipients (23%) are higher than in the general population (3.8%).[13] These findings are comparable to earlier surveys of transplant centers (16 pregnancies)[7] and case reports (22 pregnancies),[9] which demonstrated maternal hypertension and pre-eclampsia prevalence rates of 36% to 48% and 14% to 24%, respectively.

Postulated mechanisms for graft rejection during pregnancy include (1) shedding of fetal placental antigens stimulating the expansion of maternal alloreactive T cells; (2) development of antibodies against fetal–paternal antigens that cross-react with the allograft;[14] and (3) subtherapeutic drug levels from changes in gastrointestinal motility,[4] liver metabolism, and tacrolimus pharmacokinetics during pregnancy.[15] In the TPR, rejection surveillance strategies during pregnancy in heart transplant recipients varied by center and included echocardiography and endomyocardial biopsy. Severe rejection in the intrapartum ($n = 14$) and postpartum

Table 5 Immunosuppressant Regimen and Pregnancy Outcomes

Number of pregnancies		Livebirths	Miscarriages	Birth defects in livebirths
Pregnancies with MPA exposure	32 (20%)[a]	13 (41%)	20 (63%)	3 (23%)
Pregnancies without MPA exposure	125 (80%)[a]	97 (78%)	21 (17%)	6 (6%)

Abbreviation: MPA, mycophenolic acid.
[a]Includes multiple births.

($n = 11$) period was not uncommon (out of 157 pregnancies). Median time to intrapartum rejection from the time of conception was 7.2 weeks (range 0.4−29 weeks).

Most pregnancies reported to TPR in heart transplant recipients were successful. The miscarriage rate of 25% is comparable to that of the general population.[16] Compared with the general population, preterm birth and low birthweight infants are more prevalent in heart transplant recipients, 41% vs 9.6% and 37% vs 2.7%, respectively.[17,18] In comparison, 2 earlier analyses of pregnancies in cardiothoracic transplant recipients ($n = 14−17$) reported preterm birthrates of 33% and low birthweight rates between 54% and 80%.[6,8]

To our knowledge, the TPR is the largest series describing immunosuppression regimens in pregnant heart transplant recipients. A review of the UK Transplant Registry identified 17 cardiothoracic transplant recipients (18 pregnancies) who became pregnant but did not report immunosuppression regimens.[6] An analysis of the UK Obstetric Surveillance System examined outcomes in 14 cardiothoracic transplant recipients and found that 2 were taking MPA either before or during pregnancy.[8]

Overall, 20% of patients were exposed to MPA during pregnancy. Immunosuppressant regimens reported in each transplant era included combinations of CNI with azathioprine, MPA, or (rarely) mammalian target of rapamycin inhibitors. Regimens based on tacrolimus alone were infrequently used. Prior TPR analyses, case series, and reports of pregnancies exposed to MPA have highlighted a pattern of birth defects that includes external auditory canal atresia; facial clefts; and anomalies of the cardiac, skeletal, and tracheoesophageal system.[19] Despite such evidence, significant numbers of patients in each transplant era continue to be exposed to MPA at the time of pregnancy. Birth defects in MPA-exposed pregnancies in this analysis included duodenal atresia, laryngomalacia, and facial deformities. There is insufficient data to note whether the teratogenic risks of MPA are timing- or dose-related or are because of drug interactions. In addition, the effect of maternal comorbidities, pharmacogenetic factors, and potential over- or underreporting of poor outcomes cannot be excluded.[19]

These data highlight the importance of pre-conception counseling, particularly given the high proportion of unplanned pregnancies in this high-risk population. Counseling is required to minimize exposure to teratogens such as MPA, but also to discuss concerns regarding inheritance of maternal heart disease[20] or genetic disorders and long-term maternal survival.[3]

We examined recipient outcomes in the overall cohort and also compared outcomes by era of transplant, based on the most recent International Society for Heart and Lung Transplantation Registry report.[11] In the TPR, 33% of recipients died during long-term follow-up, with leading causes being cardiac allograft vasculopathy, cardiac arrest, and rejection. A recent United Network for Organ Sharing analysis[21] reported similar causes of death after transplant. In comparing recipients with and without a history of peripartum cardiomyopathy, the United Network for Organ Sharing authors noted that 50% of recipients were alive at 8.2 and 10.1 years after transplant, respectively.

The main limitations of this study stem from its retrospective and voluntary nature; there may be reporting bias with respect to outcomes, and not all data elements could be collected for all recipients. In addition, the TPR contains limited to no data on graft function, rejection, and immunology—specifically, ejection fraction, hemodynamics, surveillance strategies for rejection, and data regarding donor

Table 6 Immunosuppressant Regimens during Pregnancy

Agent at conception and during	Overall N = 157 pregnancies (Including multifetal)	1982−1991 N = 54 pregnancies	1992−2001 N = 58 pregnancies	2002−2009 N = 35 pregnancies	2010−2017 N = 10 pregnancies
CNI (%)	156 (99)	54 (100)	58 (100)	34 (97)	10 (100)
CNI alone (%)	20 (13)	6 (11)	9 (16)	5 (15)	0
Tacrolimus alone (%)	16 (10)	6 (11)	5 (9)	5 (15)	0
CNI+ steroid (%)	23 (15)	10 (19)	5 (9)	5 (15)	3 (30)
Tacrolimus+ steroid (%)	14 (9)	3 (6)	4 (7)	4 (11)	3 (30)
MPA (%)	32 (20)	5 (9)	13 (22)	14 (40)	0
Azathioprine (%)	72 (46)	32 (59)	27 (47)	8 (23)	5 (50)
mTOR inhibitor (%)	14 (9)	1 (2)	4 (7)	7 (20)	2 (20)

Abbreviations: CNI, calcineurin inhibitor; MPA, mycophenolic acid.

Table 7 Long Terms Outcomes after Pregnancy

Outcome		1982–1991 N = 29 patients	1992–2001 N = 34 patients	2002–2009 N = 21 patients[a]	2010–2017 N = 6 patients
Average maternal follow-up time from first conception, years	8.9 ± 6.5	13.9 ± 6.8	8.1 ± 5.5	4.9 ± 2.8	3.6 ± 1.8
Number of patients reporting reduced graft function (%)	3 (3)	1 (3)	1 (3)	1 (5)	
Number of patients who died (%)	30 (33)	15 (52)	10 (29)	5 (23)	0
Mean time after first pregnancy to death, years (range)	9.4 ± 6.2 (0.5–26)	12.3 ± 6.3	7.2 ± 4.9	4.8 ± 3.2	—
Median time after first pregnancy to death (years)	8.9	11.4	6.6	5.0	—
Causes of death					
Unknown	7	5	1	1	—
Cardiac allograft vasculopathy or myocardial infarction	5	4	1	—	—
Cardiac arrest	5	1	2	2	—
Rejection	6	3	2	1	—
Acute rejection	4	2	1	1	—
Post-transplant lymphoproliferative disorder	2	1	1	—	—
Multisystem organ failure	1	—	1	—	—
Graft failure	1	1	—	—	—
PE/pulmonary infarct	1	—	1	—	—
Sepsis	1	—	1	—	—
Non-adherence	1	—	—	1	—

Abbreviation: PE, pulmonary embolism.
[a]One patient lost to follow-up.

human leukocyte antigens and fetal inherited paternal antigens. Although attempts are made by the TPR to verify the cause of recipient death with the transplant center, this is not verified in every case.

Despite these limitations, the TPR provides valuable information regarding pregnancy in heart transplant recipients, as their characteristics and outcomes are distinct from those of other solid organ recipients who become pregnant. For example, prevalence of comorbidities such as hypertension and diabetes and of complications such as preeclampsia is similar to renal transplant recipients.[4,5] More heart transplant recipients (20%) were exposed to MPA at conception compared with kidney (8%), liver (5.9%), and lung (13%) recipients.[5] Rejection episodes among heart transplant recipients in the intrapartum and postpartum periods are higher than those reported for kidney and liver recipients.[5]

In conclusion, most pregnancies in heart transplant recipients are successful. For transplant recipients of reproductive age who are considering pregnancy, transplant providers must focus on pre-conception counseling, closely manage maternal comorbidities, and provide counseling after pregnancy regarding complications such as graft rejection and maternal survival. Furthermore, providers may need to tailor surveillance strategies for rejection in the late pregnancy and early postpartum period, given the number of patients identified in TPR with early postpartum graft rejection. MPA exposure greatly increases the risk of poor pregnancy outcomes. Genetic counseling and fetal screening may be required in select cases.

Disclosure statement

The authors have no conflict of interest to declare.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.healun.2020.02.005.

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