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ORIGINAL ARTICLE

Pregnancy after heart transplantation: a well-thought-out decision? The Quebec provincial experience – a multi-centre cohort study

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SUMMARY

Despite reports of successful pregnancies in heart transplant (HTx) recipients, many centers recommend their patients against maternity. We reviewed our provincial experience of pregnancy in HTx recipients by performing charts review of all known gestations following HTx in the province of Quebec (Canada), stratified between planned and unplanned pregnancies. Long-term survival was compared to HTx recipient women of childbearing age who did not become pregnant. Eighteen pregnancies, 56% unplanned, occurred in eight patients, 10.1 (2.6–27.0) years after HTx. Immunosuppression was CNI-based, with a mean dose increase of 48.3% (tacrolimus) and 26.5% (cyclosporine), without rejection. Cardiometabolic complications were high compared to the general Canadian population, including preeclampsia (15.4% vs. 5.5%), hypertension (38.5% vs. 4.6%), and diabetes (15.4% vs. 5.6%). Mean gestational age was 35.1 (23.4–39.6) weeks (72.2% live births; 53.8% prematurity). Mean birthweight was 2418 (660–3612) g. Serum creatinine increased during pregnancy, becoming significant after delivery ($P = 0.0239$), and returning to preconception level in all but three patients within a year. After 4.6 (1.2–17.2) years of follow-up, two rejection episodes occurred in one patient. Long-term mortality was similar to overall HTx women (Kaplan–Meier; $P = 0.8071$). Pregnancy in HTx carries high cardiometabolic complications and decreased kidney function, but is feasible with acceptable outcomes and no impact on mother's survival.

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Key words
calcineurin inhibitor, heart transplant, immunosuppression, pregnancy, renal function

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Introduction

"Medicine is a science of uncertainty and an art of probability"; this quote probably reflects Dr. Murray's mind in 1958 when one of his renal transplant patients, from an identical twin donor, shared her intention to become pregnant [1]. Although immunosuppression impact and adjustment were of no concern, the absence of previous report made it difficult to foresee the impact of the pregnancy on the abdominal graft. Fast-forward to 2003, multiple case reports pushed the American Society of Transplantation [2] and the

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International Society for Heart & Lung Transplantation (ISHLT) [3] to articulate recommendations on pregnancy in solid organ transplant recipients. They include need for preconception counseling, graft function stability, waiting time after transplantation, immunosuppression maintenance, and high-risk obstetrical management [3]. As the bulk of the knowledge came from the renal transplant community, some conclusions are barely transferable to recipients of other solid organs [2].

In heart transplantation (HTx), the management of these pregnancies raises even more challenges, with the first successful pregnancy described only in 1988 [4] and recent reports showing satisfactory outcomes [5–8]. Nevertheless, pregnancy is still considered contraindicated by many programs and even the hint of future gestation conveys some reluctance from the medical team. Indeed, published reports revealed increased risk of complications, including miscarriages, prematurity, low birthweights, and rejection [9]. On the other hand, the environment of HTx is evolving with an increasing proportion of female [10] and a shift toward younger recipients [11], as patients with complex congenital heart diseases are now surviving into adulthood and are being increasingly referred for HTx [12]. As a result, an increasing number of women are considering maternity after HTx, half being unplanned [13] despite recommendation for preconception counseling to potentially reduce the complications. Therefore, the HTx team has to provide accurate information to help their patients make an enlightened decision. Unfortunately, the available literature comes from incomplete registry or case reports, leading many unknowns, especially concerning optimal immunosuppressive regimen, renal function, and long-term outcomes for both the mother and her baby. To address these knowledge gaps, we reviewed our provincial experience with pregnancies in HTx recipients.

Methods

We conducted a retrospective analysis among all known pregnancies in female HTx recipients followed at one of the four HTx centers in the province of Quebec, Canada, between 1998 and 2016. All patients were included in the study, regardless of the outcome. Patients and newborn data were retrieved from medical charts and local database at each site, using a standardized form. Studied variables included demographics, transplant indication, pharmacological regimen, antenatal care, renal function, and maternal, graft, and neonatal outcomes. The renal function was assessed by serum creatinine and glomerular filtration rate (eGFR, using the Modification of Diet in Renal Disease (MDRD) Study equation). Endomyocardial biopsy (EMB) was analyzed according to the revised ISHLT 2004 criteria [14] and cardiac allograft vasculopathy (CAV) according to the ISHLT 2010 nomenclature [15]. We further divided our cohort between planned (PP) and unplanned pregnancies (UPP), the latter including all gestations that were not anticipated by the medical team in time to intervene, whether the mother planned it or not.

Statistical analysis

Continuous variables are presented by mean values and range. Categorical variables are presented with counts and proportions. For kidney function, paired *t*-tests were used to evaluate the evolution of creatinine over time, and standard *t*-tests were used to assess the effects of calcineurin inhibitor (CNI) (tacrolimus versus cyclosporine). For the impact of pregnancy on long-term survival, we compared HTx recipients from our cohort with HTx women of childbearing age (16–45 years) from the Montreal Heart Institute database who did not become pregnant after HTx, using Kaplan–Meier analysis. Comparison of outcomes between PP and UPP was performed using the Mann–Whitney test for non-normally distributed continuous variables or using chi-square/Fisher's exact tests for categorical variables, whenever appropriate. All statistical analyses were two-sided at a 5% level of significance, using STATISTICAL ANALYSIS Software, version 9.4 (SAS Institute Inc., Cary, NC, USA), and GRAPHPAD PRISM, version 6 (GraphPad Software Inc., La Jolla, CA, USA).

The protocol was approved by the internal research boards of all four centers and was held accordingly to the Declaration of Helsinki and Good Clinical Practice guidelines.

Results

Preconception demographics

Eighteen pregnancies occurred in eight recipients at 25.5 (17.6–33.3) years of age, on average 10.1 (2.6–27.0) years after HTx (Table 1). This cohort represents 2.95% of all the patients transplanted during the study period in the four institutions. Specifically, 826 cardiac transplantations were performed in the four centers during the study period, including 218 women of which 107 were of childbearing potential (defined as 16–45 years of age); only eight (7.47% of the those of

Table 1. Maternal demographics and baseline characteristics of the heart transplant (HTx) recipients before first pregnancy.

	HTx (n = 8) Mean (min–max) or n (%)
Transplant-related	
Mean age at HTx (year)	16.0 (6.2–26.6)
Mean age at pregnancy (year)	25.5 (17.6–33.3)
HTx–pregnancy interval (year)	10.1 (2.6–27.0)
HTx–1st pregnancy interval (year)	8.2 (2.6–24.6)
Underlying cardiac disease	
Congenital	4 (50)
Dilated CMP	3 (37.5)
Peripartum	1 (12.5)
Age of donor (year)	24 (7–56)
|Mean| donor–recipient age difference (year)	12 (0.8–39)
Gender of donor	
Male; female	6 (75); 2 (25)
Lifestyle habits	
Cigarette smoking	3 (37.5)
Drug use*	3 (37.5)
Clinical comorbidities	
Mean body mass index (kg/m²)	22.2 (17.3–28.6)
Hypertension	2 (25)
Dyslipidemia	6 (75)
Diabetes	1 (12.5)
Microalbuminuria; proteinuria	1 (12.5); 0 (0)
Cancer	0 (0)
Mean eGFR (cc/min/ 1.73 m²)	73.4 (64.2–90.0)
Graft-related	
NYHA class 1	8 (100)
Last TTE–1st pregnancy mean interval (months)	10.9 (1.0–47.3)
Mean LVEF	61.1 (55–65)
TR ≥2 (%)	25
Last CAG–1st pregnancy mean interval (year)	3.1 (0.4–13.8)
CAV grade 0	6 (75)
CAV grade 1	1 (12.5)
CAV grade >1	0 (0)
Unknown	1 (12.5)
Last EMB–1st pregnancy mean interval (year)	9.5 (2.0–18.6)
Biopsy result	
0R	5 (62.5)
1R	3 (37.5)
>1R	0 (0)
Within 1 year post-HTx	4; 5 (62.5)
>1 year post-HTx	3; 3 (37.5)
Last >1R rejection–1st pregnancy mean interval (year)	5.9 (0.61–17.6)

CMP, cardiomyopathy; eGFR, estimated glomerular filtration rate; TTE, transthoracic echocardiography; LVEF, left ventricular ejection fraction; TR, tricuspid regurgitation; CAG, coronary angiography; CAV, cardiac allograft vasculopathy; EMB, endomyocardial biopsy.

*Including cannabis and narcotics.

childbearing potential, 3.67% of all women) have become pregnant.

They were all asymptomatic and carried few comorbidities, except for dyslipidemia in seven (75%), and more than a third smoked tobacco and/or cannabis. The latter were transplanted at a pediatric age, and their pregnancies were unplanned. Lastly, one patient required fertility treatment for both of her pregnancies. Immunosuppression adjustment for women who wish to conceive varied by institution, but globally MMF was decreased and then stopped with no substitute, with sequential biopsies being performed after each decrement/stopping. Patients remained on CNI monotherapy (tacrolimus for the majority) after delivery. For those on cyclosporin and AZA from the earlier experience, no immunosuppression adjustment was made, as this combination was believed to be safe based on the renal transplant experience.

Rejection grade >1R episodes occurred mostly early after HTx (n = 5, four patients), but also later (n = 3, three patients) due to noncompliance (n = 2) and switch in immunosuppressive agent before planned conception (n = 1). The time interval between last >1R rejection and pregnancy was 5.9 (0.6–17.6) years. A transthoracic echocardiogram (TTE) performed 10.9 (1.0–47.3) months before conception revealed a normal graft function in all. One patient declined any cardiac evaluation, leaving seven having a coronary angiogram performed 3.1 (0.4–13.8) years before conception, which were normal except for one CAV-1.

Drug therapy and adjustment

In the PP group, discontinuation of potentially unsafe medications was performed as soon as the

desire for pregnancy was known (Tables 2 and 3). Two patients (three pregnancies) were on mycophenolate mofetil (MMF), which was interrupted 5.2 (1.3–7.6) months before conception, while rapamycin was stopped 1.7 months before conception in one. In the UPP group, one patient became pregnant on MMF and had an early miscarriage; statins were interrupted late in three pregnancies, without influence on outcome.

All patients received CNI, with tacrolimus ($n = 14$) or cyclosporine ($n = 4$), requiring an average dosage increase of 48.3% and 26.5%, respectively. In addition, four patients (nine pregnancies) were on maintenance prednisone (2–5 mg daily) and/or azathioprine, with

Table 2. Comparison between unplanned (UPP) and planned pregnancies (PP) during pregnancy follow-up.

	PP ($n = 8$) Mean (min–max) or *n* (%)	UPP ($n = 10$) Mean (min–max) or *n* (%)	All ($n = 18$) Mean (min–max) or *n* (%)
Medication			
Tacro	4	5	9
Tacro + Aza + Pred	4	1	5
CsA + Aza	0	2	2
CsA + Aza + Pred	0	2	2
Sirolimus*	0	0	0
MMF†	0	1	1
Statins	0	4	4
ACEi/ARBs	0	0	0
Lifestyle habits			
Tobacco	0	6 (60)	6 (33.3)
Drug use‡	0	7 (70)	7 (38.9)
Pregnancy complications			
Gestational hypertension	2 (28.6)	3 (50)	5 (38.5)
Gestational diabetes	1 (14.3)	1 (16.7)	2 (15.4)
Microalbuminuria; macroalbuminuria	3; 0 (42.9)	3; 1 (66.7)	6; 1 (53.8)
Preeclampsia	1 (14.3)	1 (16.7)	2 (15.4)
HELLP syndrome	0 (0)	0 (0)	0 (0)
Increased transaminases	1 (14.3)	0 (0)	1 (7.7)
Thrombocytopenia	0 (0)	0 (0)	0 (0)
Maternal infection	1 (14.3)	2 (33.3)	3 (23.1)
Cardiac and obstetric surveillance			
Mean no. of cardiology visits/pregnancy	6.1 (3–10)	6.2 (4–9)	6.2 (3–10)
Mean no. of obstetric visits/pregnancy	8.2 (5–11)	8.6 (5–11)	8.4 (5–11)
Total no. of hospitalizations/pregnancy	4 (0–2)	8 (0–6)	12 (0–6)
Cardiac cause	0	0	0
Obstetrical cause	50	37.5	41.7
Other cause	50	62.5	58.3
Mean no. of TTE/pregnancy	1.1 (0–2)	3.7 (0–7)	2.3 (0–7)
Mean LVEF	63.3 (50–70)	60.6 (53–70)	62.1 (50–70)
TR ≥2 (%)	50	0	30
No. of CAG; result	0	1; 0	1; 0
No. of EMB; result	0	1; 0R	1; 0R
Clinically diagnosed rejection	0 (0)	0 (0)	0 (0)

Tacro, tacrolimus; Aza, azathioprine; Pred, prednisone; CsA, cyclosporine A; MMF, mycophenolate mofetil; ACEi/ARBs, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; TTE, transthoracic echocardiography; LVEF, left ventricular ejection; TR, tricuspid regurgitation; CAG, coronary angiography; EMB, endomyocardial biopsy.

*Sirolimus was interrupted 1.7 months before conception for one patient.

†MMF was interrupted for 5.2 (1.3–7.6) months before conception for two patients.

‡Including cannabis and narcotics. To maintain consistency across presented data, the number of live births ($n = 13$) plus stillbirths ($n = 0$) was used as the denominator for both "Pregnancy complications" and "Cardiac surveillance." For "Lifestyle habits" and "Medication," the total number of pregnancies, 18, was used as the denominator. *P*-values resulting from the group comparison are ≥0.05.

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Table 3. Detailed immunosuppressive therapy during pregnancy in cardiac transplant recipients (N = 13 live births).

	Tacro Mean (min–max)	CsA Mean (min–max)
No. of cases	9	4
Last trough level before PPT (ng/ml)	7.9 (3.0–14.0)	142.5 (82–237)
Mean trough level during pregnancy (ng/ml)	5.6 (4.0–8.0)	136.4 (103–203)
Min. trough level during pregnancy (ng/ml)	3.9 (3.0–5.5)	96.0 (72–168)
Max. trough level during pregnancy (ng/ml)	7.5 (5.4–10.6)	189 (133–240)
No. of dose adjustments	2 (1–4)	3.5 (2–6)
Initial daily dose (mg/day)	5.8 (4–10)	260 (180–360)
Final daily dose (mg/day)	8.6 (4–18)	328.8 (300–380)

Tacro, tacrolimus; CsA, cyclosporine A; PPT, positive pregnancy test.

stable dosage during pregnancy for all but one. Both dose adjustments and immunosuppressive agent switch were well tolerated except for one patient, who had an acute rejection episode with arrhythmia after her MMF was switched to azathioprine and prednisone. She was successfully treated with high-dose prednisone, increase in azathioprine, and a pacemaker implantation. The same strategy of increased prednisone was successful in her subsequent pregnancies.

Follow-up during pregnancy

All patients were followed by a high-risk pregnancy obstetrician and the HTx clinic, with 8.4 (5–11) and 6.2 (3–10) visits, respectively (Table 2). Among all 18 pregnancies, 56% were unplanned, with announcement to the HTx teams at 10.8 (6–21) weeks. The pregnancy complications include hypertension (38.5%), preeclampsia (15.4%), and diabetes (15.4%). Four patients had 12 hospitalizations for various reasons such as diabetes, hyperemesis gravidarum, acute kidney injury, hypertension, proteinuria with suspicion of preeclampsia, pneumonia, gastroenteritis, fatigue, recurrent abdominal pain (with negative workups), and narcotic dependence. Cardiac grafts were closely followed, with an average of 2.3 (0–7) TTE per pregnancy, showing stable LV function in all but one patient, who exhibited hypertrophy and mildly decreased LVEF prompting biopsy and angiogram, which were normal. No episode of rejection occurred in the whole cohort.

Pregnancy and neonatal outcomes

Of the 18 pregnancies, 72.2% were live births (UPP = 60% vs. PP = 87.5%, P = NS) (Table 4). Elective and spontaneous abortions occurred in 27.8% (UPP = 40% vs. PP = 12.5%, P = NS), between 5 and 7 gestational weeks (GW). Three patients required labor induction for acute kidney injury, preeclampsia, and a combination of clinical problems (hypertension, diabetes, and acute kidney injury). Indications for C-sections (38.5%) were obstetrical (marginal placenta praevia, breech presentation, and umbilical cord prolapse with polyhydramnios). The postpartum period was uneventful except for three patients: two with gynecological bleeding and one with toxic megacolon complicating Clostridium difficile colitis, requiring colectomy and ileostomy.

Mean gestational age was 35.1 (23.4–39.6) weeks, with an average weight of 2418 (660–3612) g. Apgar score was satisfactory (1-min > 7) for all except one, who had severe intrauterine growth restriction and extreme prematurity (23.4 GW). One cardiac malformation was found in the offspring, a perimembranous ventricular septal defect, which eventually closed spontaneously. There were seven preterm births and three admissions to the neonatal intensive care unit (13–90 days): One had apnea, bradycardia, and feeding issues (34 GW); another (27.9 GW) had respiratory distress syndrome; and a third (23.4 GW, UPP) had a traumatic birth and was resuscitated but died of intraventricular hemorrhage. Mean hospital stay duration for all newborns was 13.8 (3–90) days. Breast-feeding was not proscribed, but occurred in only one patient.

One-year follow-up postpartum

All patients were asymptomatic and were closely followed with TTE (13/18 pregnancies, showing a normal graft function), coronary angiograms (8/18), and EMB (8/18); one poorly compliant UPP patient had grade 2R rejection successfully treated with prednisone and switch

Table 4. Pregnancy outcomes in heart transplant recipients, compared between unplanned (UPP) and planned pregnancies (PP).

	PP (n = 8) Mean (min–max), n or n (%)	UPP (n = 10) Mean (min–max), n or n (%)	All (n = 18) Mean (min–max), n or n (%)
Mother-related			
Outcomes (n, %)			
Stillbirth	0 (0)	0 (0)	0 (0)
Elective abortion	0 (0)	2 (20.0)	2 (11.1)
Miscarriage	1 (12.5)	2 (20.0)	3 (16.7)
Live birth	7 (87.5)	6 (60.0)	13 (72.2)
Delivery			
Spontaneous vaginal delivery	1 (14.3)	3 (50.0)	4 (30.7)
Induction	2 (28.6)	1 (16.7)	3 (23.1)
Forceps	0 (0)	1 (16.7)	1 (7.7)
Cesarean section	4 (57.1)	1 (16.7)	5 (38.5)
Postpartum depression	0 (0)	0 (0)	0 (0)
Mean hospital stay (day)	6.6 (4.0–13.0)	4.8 (3.0–6.0)	5.8 (3.0–13.0)
Recurrent hospitalization	1 (12.5)	0 (0)	1 (5.6)
Newborn-related			
Mean gestational age (week)	34.6 (27.9–38.4)	35.6 (23.4–39.6)	35.1 (23.4–39.6)
Preterm births <37 weeks	5 (71.4)	2 (33.3)	7 (53.8)
Term births 37–42 weeks)	2 (28.6)	4 (66.7)	6 (46.2)
Mean birthweight (g)	2282 (1190–3612)	2578 (660–3510)	2418 (660–3612)
Low birthweight <2500 g (n)	5	1	6
SGA	0	0	0
IUGR	1	0	1
Macrosomia	0	0	0
Apgar <7 at 1 min	1 (14.3)	2 (33.3)	3 (23.1)
Shoulder dystocia	1	0	1
Respiratory distress	1	0	1
Severe jaundice	0	0	0
Cardiac anomaly	0	1	1
Breast-feeding	0	1	1
Admission to NICU	2	1	3
Neonatal death	0	1	1
Mean hospital stay (days)	23.6 (4–90)	4.0 (3–7)	13.8 (3–90)
Recurrent hospitalization	1 (14.3)	0 (0)	1 (7.7)

SGA, small for gestational age; IUGR, intrauterine growth restriction; NICU, neonatal intensive care unit.

Other neonate-related complications include meconial aspiration, membrane hyaline disease, other malformation, transient hypokalemia, perinatal infection, hypoglycemia, and convulsions, but were all absent in our cohort.

from azathioprine to MMF (Table 5). Another UPP patient developed CAV grade 1 after her second pregnancy, which progressed to grade 2 after her third pregnancy. All other coronary angiograms remained identical to preconception (CAV grade 0–1).

Renal function

There was a trend for creatinine rise during pregnancy (from 87.1 ± 3.1 at baseline to 94.9 ± 6.2 μmol/l, P = 0.0919), reaching significance shortly after delivery (110.3 ± 7.9 μmol/l, P = 0.0239) and normalizing within a year (92.3 ± 5.6 μmol/l), regardless of the CNI used (Tables 6 and 7 and Fig. 1). At long-term follow-up, creatinine remained stable overall (102.6 ± 15.2 μmol/l, P = 0.31), but three patients developed stage III renal failure (eGFR of 54.8, 32.8 and 34.3 ml/min/1.73 m^2); however, a renal biopsy was not performed in these patients.

Late follow-up

On average, 15.9 (5.4–28.9) years after HTx and 4.6 (1.2–17.2) years after the last pregnancy, comorbidities were typical of any transplant cohort, namely hypertension (75%), dyslipidemia (all), and diabetes (25%),

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Table 5. Maternal characteristics within 1 year postpartum.

	All (n = 18) Mean (min–max), n or n (%)
NYHA class 1	18 (100)
Mean LVEF)	62.3 (52–70)
TR ≥2 (%)	15.4
>1R rejection	1 (5.6)
Rejection episodes incl. 1R	5 (27.8)
1R; 2R; 3R	80; 20; 0
CAV grade 0	6 (33.3)
CAV grade 1	1 (5.6)
CAV grade 2	1 (5.6)
CAV unknown	10 (55.6)

LVEF, left ventricular ejection; TR, tricuspid regurgitation; CAV, cardiac allograft vasculopathy; HTx, heart transplant; PTLD, post-transplant lymphoproliferative disorder; eGFR, estimated glomerular filtration rate.

Table 6. Maternal characteristics on long-term follow-up of heart transplant pregnant recipients.

	PP + UPP (n = 8) Mean (min–max), n or n (%)
Mean age at last follow-up (year)	31.9 (23.6–37.9)
Mean time since last pregnancy (year)	4.6 (1.2–17.2)
Mean time since HTx (year)	15.9 (5.4–28.9)
NYHA class 1	7 (87.5)
Hypertension	6 (75)
Dyslipidemia	8 (100)
Diabetes	2 (25)
Microalbuminuria; macroalbuminuria	3 (37.5); 1 (12.5)
Cancer; PTLD	1 (12.5); 0 (0)
Mean eGFR (cc/min/1.73 m²)	68.8 (32.8–127.3)
Mean LVEF (%)	54.4 (37–65)
TR ≥2	37.5
Patients with >1R rejection	1 (12.5)
Patients with rejection incl. 1R	3 (37.5)
1R; 2R; 3R	83.3; 16.7; 0
CAV grade 0	2 (25)
CAV grade 1	1 (12.5)
CAV grade 2	1 (12.5)
CAV grade 3	1 (12.5)
CAV unknown	3 (37.5)
Deaths	3 (37.5)
Mean age at death (year)	31.1 (23.6–37.1)
Time from last pregnancy (year)	3.9 (2.6–5.4)
Time from HTx (year)	15.0 (5.4–22.3)
Mean age of children (year)	5.8 (2.6–11.8)

LVEF, left ventricular ejection; TR, tricuspid regurgitation; CAV, cardiac allograft vasculopathy; HTx, heart transplant; PTLD, post-transplant lymphoproliferative disorder; eGFR, estimated glomerular filtration rate.

with half of the latter having proteinuria and a depressed renal function (Table 7). All patients were asymptomatic (NYHA I), except the one who suffered a rejection episode early after pregnancy, who faced a second one (2R) 3.2 years after delivery and subsequently developed CAV-3. Likewise, two other patients developed coronary artery vasculopathy (all UPP). The most recent TTE showed a mean LVEF of 54.4% (37–65), with the two depressed LVEF (45% and 37%) occurring in hospitalized patients, 9–13 days before their death.

Lastly, one patient developed a vulvar cancer, but there was no case of post-transplant lymphoproliferative disorder nor subsequent organ transplantation.

Effects on survival

Three patients (37.5%) died 15.2 (5.8–22.3) years after HTx and 3.9 (2.6–5.4) years after their last delivery; causes of death were severe graft rejection and arrhythmia for one patient (noncompliance) and substance abuse for a second; these two patients were among the substance abusers at baseline; the third patient had sudden death with acute cellular rejection and CAV-3 (by autopsy report), occurring 5 months after she had mentioned her willingness to become pregnant again (Table 5 and Fig. 2). As no contact occurred with the HTx team afterward, we cannot exclude the possibility that her death was related to recurrent gestation without immunosuppressive medication adjustment. The children were 5.8 (2.6–11.8) years old at the time of their mothers' death. Despite this outcome, the long-term survival of HTx recipient women who had at least one pregnancy was not statistically different when compared to female HTx recipients of childbearing age (P = 0.8071).

Discussion

Pregnancy after HTx is still considered a contraindication by many HTx teams; accordingly, only a very small percentage (3.67%) of our overall female transplanted population became pregnant. We showed that pregnancy itself does not compromise the graft function and/or the recipient's long-term survival, despite having an increased overall rate of metabolic complications and a reversible decrease in renal function. The majority of babies were mildly preterm, and only one benign cardiac defect was identified. Despite these findings, the management of these high-risk pregnancies raises multiple challenges.

Table 7. Evolution of mean serum creatinine levels in HTx recipients (n = 8), serum creatinine in μmol/l (mean ± SEM).

Group	Before conception	During pregnancy	During hospital stay	Within 1-year FU	LTFU
All	87.1 ± 3.1	94.9 ± 6.2	110.3 ± 7.9[†]	92.3 ± 5.6	102.6 ± 15.2
P-value*	–	0.0919	**0.0239**	0.1747	0.3108
Tacro	83.2 ± 3.0	88.9 ± 7.5	103.5 ± 10.2	87.7 ± 7.3	–
CsA	95.8 ± 6.3	108.5 ± 8.5	120.5 ± 12.0	102.8 ± 6.1	–
P-value **	0.0624	0.1500	0.3161	0.2273	–

Tacro, tacrolimus; CsA, cyclosporine A; FU, follow-up; LTFU, long-term follow-up; SEM, standard deviation error of the mean.
**P*-value was obtained by a two-tailed paired *t*-test, comparing mean serum creatinine to baseline value before conception.
***P*-value was obtained by a two-tailed standard *t*-test, between mean serum creatinine of patients taking FK506 and CsA.
All $P \geq 0.10$, except [†]=0.0239. Significant p value is in bold.

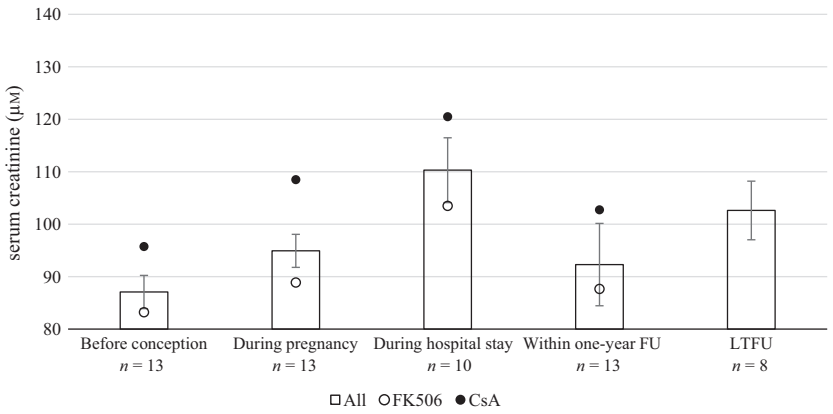

Figure 1 Evolution of mean serum creatinine levels at four periods [before conception, during pregnancy, during hospital stay after delivery, within one year postdelivery, and on long-term follow-up (LTFU)]. Mean serum creatinine of patients taking tacrolimus (FK506) or cyclosporine (CsA) as their main immunosuppressive regimen during pregnancy is also indicated (see Table 7 for numerical values).

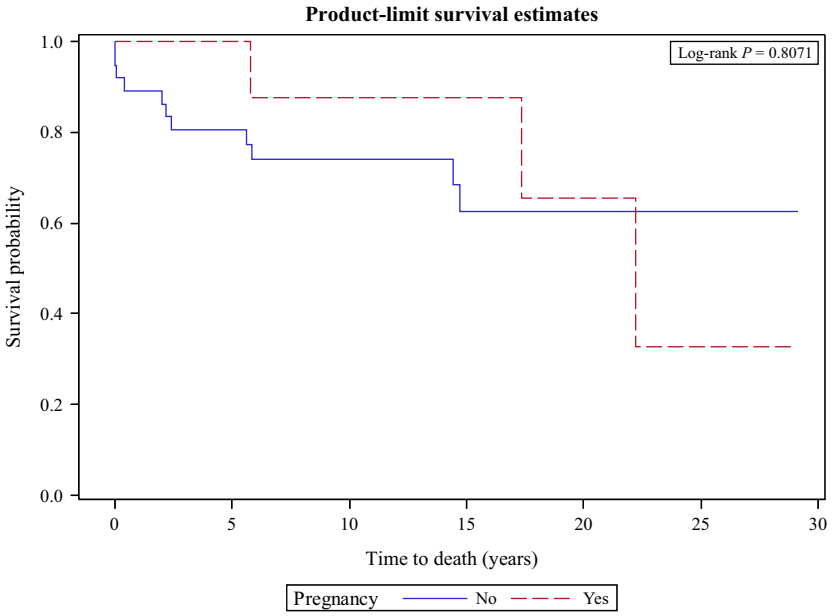

Figure 2 Kaplan–Meier estimates of survival in heart transplant (HTx) recipients of childbearing age from the Montreal Heart Institute database (blue line; n = 38; 11 deaths) and HTx recipients with pregnancies (red dotted line; n = 8; three deaths), for whom age at death was 31.1 ± 6.9 years and last delivery-to-death interval was 3.9 ± 1.4 years.

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We observed higher rates of gestational hypertension (38.5% vs. 4.6%), preeclampsia (15.4 vs. 5.5%), and diabetes (15.4 vs. 5.6%) compared to the Canadian general population [16,17], but similar rates have been reported by the National Transplant Pregnancy Registry (NTPR) registry [9], an improvement over the earlier NTPR published data [18]. This progress may be due at least in part to earlier recognition of hypertension [19] caused by CNI nephrotoxicity [20]. Likewise, whether the higher incidence of diabetes can be awarded to the diabetogenic effect of tacrolimus [21] remains controversial, with some reporting rates similar to ours (14%) [22], while others showing much lower incidence (0–2%), despite comparable immunosuppressive regimen [9,23]. Indeed, other risk factors for gestational diabetes were present in our cohort, such as DiGeorge syndrome in one and First Nations origin for another patient [24,25]. Whether these complications will be associated with increased cardiometabolic disorders later in the children's life [26] is currently unknown.

Reports of more than 20% graft rejection during pregnancy [27] with half requiring treatment [20] have pressed some centers to perform routine HLA testing for fathers to be prior to conception, to provide counseling about the increased risk of rejection in case of mismatch [28]. We have not encountered any rejection episode during pregnancy, questioning the value of this approach. While routine coronary angiogram and/or EMB are not recommended during pregnancy, they appear to be safe, with appropriate lead shielding for the mother and her fetus [18,29–31] like in the case of one of our patient. Still, TTE should remain the routine method of choice during pregnancy [2].

Hemodynamic changes occurring throughout pregnancy [32] modify the pharmacodynamics of various medications. Consequently, immunosuppressive drug levels should be closely monitored targeting the same levels, despite the known relative immunotolerance of pregnancy [33]. Indeed, the average dose of CNI needed to be markedly increased in our patients. We observed a steady rise in creatinine levels, while the opposite would have been expected due to both hemodilution and pregnancy-induced increase in GFR [34]. A similar pattern has been previously described by Mohamed-Ahmed *et al.* [22] during the third trimester, potentially caused by the increase in CNI dose during pregnancy [20], with return to baseline renal function and tacrolimus dose after delivery.

We observed more preterm deliveries (53.8%) and low birthweight (46.2%) in comparison with the Canadian population (7.8% and 6%, respectively) [35,36], and NTPR (38% and 39%) [9]. This finding could be explained by our higher incidence of hypertension and preeclampsia, two known risk factors for these conditions [20], potentially associated with the use of tacrolimus [37]. While there have been successful pregnancies under sirolimus [38–40], this agent was stopped early in our cohort as recommended [9] and more data are needed to establish its security. We did however have a higher incidence (7.7%) of cardiac congenital malformation than the Canadian incidence of 0.5–1.5% [41], but did not encountered any case of autoimmune diseases in the offspring of our patients on cyclosporine [7]. Finally, cesarean sections were being performed at the same rate as NTPR (38.5% vs. 40%) for obstetrical reasons only [9].

The majority of our pregnancies were unplanned, as previously reported [9]. Although the complications and outcomes seemed numerically worse in the UPP group, none reached statistical difference, possibly due to small sample size and poor statistical power. Alternatively, Bhagra *et al.* [23] also showed similar outcomes in 22 pregnancies, of which 82% were unplanned, including 91% live births, and 9.1% miscarriages with a mean gestational age of 35 GW and without any drug-induced malformation. One possible explanation might be that the medical teams were able to achieve a successful catch-up, with intense follow-up once they were aware of the ongoing pregnancy. Indeed, HTx recipients from both groups (PP and UPP) had the same number of medical visits, potentially increasing the chances of good outcomes. Noteworthy, our UPP cohort seems to be associated with a bundle of difficult psychosocial behaviors, with poor compliance and more smoking and drug abuse, which may impact long-term survival.

Despite similar outcomes, we think that caregivers should openly discuss pregnancy with their patients, even before transplantation if possible. Counseling should provide facts, like the ones from our group, in order for the HTx recipient and her partner to make an informed decision. Paternalistic objection against pregnancy should be avoided, as it may discourage them from seeking antenatal care, leading potentially to even more unplanned pregnancies. Nevertheless, in patients with problematic therapeutic adherence, the use of a reliable contraceptive method, such as an intrauterine device, should be considered [27]. Furthermore, many of these patients may require intense psychosocial support, as their lifelong health problems may have made them more susceptible to adopt unhealthy behaviors [42].

Finally, our findings suggest that the occurrence of pregnancy itself has no negative impact on survival in HTx recipients. Nevertheless, life expectancy after

cardiac transplantation is known to be limited, so that the new mother might not be alive to see her child growing up. Therefore, preconception counseling should also include a thoughtful discussion about the likelihood of reduced longevity for the future mother.

Conclusion

Pregnancy in HTx recipients is feasible with acceptable outcomes, and no impact on survival. Nevertheless, it carries increased risk of cardiometabolic complications. Frequent monitoring of CNI levels and LV function is required to optimize maternal and fetal outcomes. It has to be a well-thought-out decision, balancing the profound parenthood aspiration against the expected complications during pregnancy and reduced longevity of the mother. Prospective data are needed to provide further information on the subject.

Authorship

OD, NAL: contributed to the gathering and interpretation of data, the critical writing and revising the intellectual content; approved the final version to be published. MC, RC, EC, SdD, NG, LL, BC, NP, MJR, MW: contributed to the inclusion of patients, the interpretation of data, revision of the intellectual content; approved the final version to be published. AM: contributed to the interpretation of data and revision of the intellectual content; approved the final version to be published. AD: contributed to the concept and design; contributed to the inclusion of patients, interpretation of data, critical writing and revision of the intellectual content; approved the final version to be published.

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Conflict of interest

The authors declare that they have no relationships to industry or conflict of interest to disclose. Dr Ducharme holds the University of Montreal's Fondation Marcelle and Jean Coutu and Cal and Janine Moisan chair for best practices in advanced heart failure at Montreal heart Institute. Dr White holds the Carolyn and Richard J. Renaud Research Chair in Heart Failure.

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