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ORIGINAL RESEARCH

CONGENITAL HEART DISEASE

Sex-Related Differences and Influence of Pregnancy in Transposition of Great Arteries With Systemic Right Ventricle

Naïma-Ayane Mahdi, MD,[a] Léa Guerma, MD,[a] Charles Desrosiers-Gagnon, Bsc,[a] Annie Dore, MD,[a] François-Pierre Mongeon, MD SM,[a] Blandine Mondésert, MD,[a] Réda Ibrahim, MD,[a] Nancy Poirier, MD,[a] Marie-Claude Guertin, PhD,[b] Line Leduc, MD,[c] Elisabeth Codsi, MD,[c] Paul Khairy, MD PhD,[a,b] Marie-A Chaix, MD PhD[a]

ABSTRACT

BACKGROUND There is a paucity of data regarding sex-related differences on cardiac outcomes in the context of transposition of the great arteries (TGA) with a systemic right ventricle and biventricular physiology (sRV-biV). Moreover, the long-term impact of pregnancy on cardiac outcomes remains unknown.

OBJECTIVES The purpose of this study was to identify sex-related differences and the influence of pregnancy on cardiac outcomes in TGA sRV-biV population.

METHODS A retrospective cohort study was conducted on 213 adults with TGA sRV-biV, 82 (38.4%) women, age 42.6 ± 12.8 years, with a median follow-up of 16 years. Cardiac events, interventions, last follow-up sRV-biV dysfunction, and heart failure (HF) medications were compared between men vs women, and women with vs without pregnancies resulting in live births.

RESULTS Women had a lower incidence of nonsustained ventricular tachycardia (HR: 1.80; 95% CI: 1.04-3.09, $P = 0.035$) and nonsignificantly fewer HF-related hospitalizations than men (HR: 2.10; 95% CI: 0.95-4.67, $P = 0.069$) in univariable analysis. At the last follow-up, women had a lower prevalence of moderate to severe sRV-biV dysfunction than men ($P < 0.001$) and were less frequently prescribed HF therapy. Women had fewer implantable cardioverter-defibrillators for primary prevention than men ($P = 0.016$), with no difference for secondary prevention. Women who had pregnancies resulting in live births (N = 47), had a high prevalence of cardiac events in the 15 (IQR: 9-28) years following pregnancy with no significant differences with those without (N = 32) pregnancies.

CONCLUSIONS Women with a sRV-biV have fewer adverse cardiovascular events than men. Due to sRV-biV, pregnancy remains with high maternal risk but is not associated with worse long-term cardiac outcomes under rigorous multidisciplinary cardio-obstetrical care. (JACC Adv 2024;3:101015) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

From the [a]Adult Congenital Heart Center, Montreal Heart Institute, Department of Medicine, Université de Montréal, Montreal, Quebec, Canada; [b]Montreal Health Innovation Coordinating Center (MHICC), Montreal, Quebec, Canada; and the [c]Centre de médecine fœto-maternelle, CHU Sainte-Justine, Université de Montréal, Montréal, Québec, Canada.

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ABBREVIATIONS AND ACRONYMS

ccTGA = congenitally corrected transposition of the great arteries

DTGA/AS = complete transposition of the great arteries with an atrial switch operation

HF = heart failure

ICD = implantable cardioverter-defibrillator

LFU = last follow-up

PH = pulmonary hypertension

PMP = permanent pacemaker

sRV-biV = systemic right ventricle and biventricular physiology

TGA = transposition of great arteries

A systemic right ventricle associated with biventricular physiology (sRV-biV) occurs in the context of complete transposition of the great arteries with an atrial switch operation (DTGA/AS),[1,2] and congenitally corrected transposition of the great arteries (ccTGA).[3] Despite good survival in childhood, the sRV-biV is associated with severe morbidity and a shortened lifespan during adulthood.[4-6] After the 3rd decade of life, the sRV-biV often begins to fail.[7-12] Although the arterial switch has been the gold standard surgery since the late 1980s, individuals with DTGA/AS are now in their 4th and 5th decades of life thereby allowing assessment of long-term outcomes. sRV-biV dysfunction and remodeling have been associated with an increased prevalence of heart failure (HF), pulmonary hypertension (PH), atrial and ventricular arrhythmias, and mortality.[11-17]

Sex-related differences have been described in several types of acquired heart disease such as ischemic heart disease and different forms of HF. The CONgenital CORvitia (CONCOR) Dutch national congenital heart diseases registry reported sex-related differences associated with PH, aortic outcomes, infective endocarditis, and implantable defibrillators.[18] It remains unknown whether there are sex-related differences in cardiac outcomes in patients with TGA and sRV-biV. Moreover, while pregnancy has been associated with acute deterioration in sRV-biV function and short-term postpartum morbidity, it is uncertain whether pregnancy impacts long-term prognosis.[19] The modified World Health Organization risk classification recognizes the heightened risk of maternal morbidity in women with sRV-biV even when the ejection fraction is normal or mildly depressed, with pregnancy considered contraindicated in those with moderate to severe sRV-biV dysfunction.[20] We conducted a retrospective cohort study on adults with TGA and sRV-biV followed at the Montreal Heart Institute Adult Congenital Center to explore potential sex-related differences in cardiac outcomes and determine whether long-term outcomes are influenced by pregnancy.

METHODS

STUDY POPULATION. The study population consisted of all patients ≥18 years of age with D-TGA/AS and ccTGA followed at the Montreal Heart Institute Adult Congenital Center. Eligible patients were identified through the institutional tailored clinical and research informatics system for congenital heart disease, CONGENERATE, which contains comprehensive diagnostic and procedural codes for all patients followed at the Montreal Heart Institute Adult Congenital Center since 1989. Patients with univentricular physiology and double outlet right ventricle were excluded. The study was approved by our local Institutional Review Board.

DATA COLLECTION. Electronic and paper medical records were reviewed for all potentially eligible patients, including pertinent surgical, echocardiographic, and hemodynamic charts and databases, supplemented by secondary source material from referring hospitals with a last update in October 2022. Variables of interest included standard demographic parameters (eg, age, sex), type of TGA (DTGA or ccTGA), associated congenital heart lesions (eg, pulmonary stenosis, ventricular septal defect), and comorbidities (eg, current and past tobacco use, diabetes, systemic hypertension, dyslipidemia). Obstetrical histories including the number and dates of all pregnancies were collected for each woman. Data were extracted at the time of referral to the Montreal Heart Institute and the last follow-up (LFU). Echocardiogram reports at LFU were reviewed for sRV-biV systolic function and degree of tricuspid regurgitation. The Montreal Heart Institute echocardiography laboratory protocol defines the sRV-biV dysfunction as absent, mild, moderate, or severe according to visual assessment in combination with recommended indices of right ventricular function, namely, tricuspid annular plane systolic excursion, tricuspid annular peak systolic velocity on tissue Doppler imaging, right ventricular fractional area change, and right ventricular free wall and septal systolic strain.[21] The degree of tricuspid regurgitation is qualitatively assessed as absent, mild, moderate, or severe by color Doppler imaging in accordance with published guidelines.[22]

OUTCOMES. Adverse cardiac events included brady-tachyarrhythmias (atrial and ventricular), HF-related hospitalizations, PH defined as a mean pulmonary arterial pressure >20 mm Hg at rest, as measured by cardiac catheterization and all deaths.[23] Electrophysiological interventions and surgeries included permanent pacemaker (PMP) implantation, implantable cardioverter-defibrillator (ICD), tricuspid valve interventions, and heart transplants. The indication for ICD therapy (primary or secondary) was specified for each patient.[24] At LFU, medications (eg, beta-blockers, loop diuretics, angiotensin-converting

enzyme inhibitors/angiotensin II receptor blockers, mineralocorticoid receptor antagonists), moderate to severe sRV-biV dysfunction, and severe tricuspid regurgitation were collected. Ages were recorded at the time of an adverse cardiac event, PMP or ICD implantation, and surgery. Time to event analyses (ie, supraventricular arrhythmia, nonsustained ventricular tachycardia (NSVT), ICD implantation, HF-related hospitalizations, a composite of death, heart transplantation, or ventricular assist device) were calculated from date of birth to date of first occurrence of the event. For the composite outcome, the first occurrence of any component of the composite was considered. Subjects with no event were censored at the time of their LFU.

STATISTICAL ANALYSIS. Continuous variables are expressed as mean ± SD or median (IQR) (25th, 75th percentile), depending on the symmetry of the distribution. Discrete variables are expressed as frequencies and percentages. Continuous and discrete variables are compared between men vs women and women with pregnancies resulting in live births vs women without one. Comparisons between continuous variables were performed using Mann-Whitney *U* tests. Discrete variables were compared using chi-squared or Fisher exact tests. The incidence rates of outcomes were estimated in patient-years and compared using Poisson regression. Event-free survival was plotted using the Kaplan-Meier product limit method, with censoring at the time of the LFU or cardiac transplantation. The association between sex and cardiac event-free survival rates was assessed by the log-rank test, univariable and multivariable Cox regression analysis. In the multivariable model, we incorporated 2 baseline characteristics: the type of transposition of the great arteries and associated congenital heart defects, as they have the potential to impact long-term cardiac events. Two-tailed *P* values <0.05 were considered statistically significant. Statistical analyses were performed using SPSS version 26.0.

RESULTS

PATIENT POPULATION. The study population was comprised of 213 adults, age 42.6 ± 12.8 years at LFU, with a sRV-biV followed for a median of 16 (IQR: 8-20) years. A total of 141 (66.2%) patients had DTGA/AS and 72 (33.8%) ccTGA. Women comprised 38.5% (N = 82) of the study cohort. Among the 82 women, 47 (57.3%) had at least 1 pregnancy resulting in a live birth. Baseline characteristics are summarized in Table 1.

TABLE 1 Baseline Characteristics

	Women (n = 82)	Men (n = 131)	Total (n = 213)	*P* Value
DTGA	53 (64.6)	88 (66.2)	141 (66.2)	0.703
Age at atrial switch surgery, y	1.9 ± 2.7	1.8 ± 2.1	1.9 ± 2.4	0.736
ccTGA	29 (35.4)	43 (32.8)	72 (33.8)	0.703
Age at diagnosis, y	12.0 ± 17.3	12.6 ± 19.4	12.3 ± 18.4	0.717
Associated congenital heart lesions	43 (52.4)	62 (47.3)	105 (49.3)	0.468
Cardiovascular risk factors				
Active or past tobacco use	8 (9.8)	10 (7.6)	18 (8.5)	0.588
Diabetes	4 (4.9)	9 (6.9)	13 (6.1)	0.555
Dyslipidemia	7 (8.5)	18 (13.7)	25 (11.7)	0.251
Systemic hypertension	16 (19.5)	23 (17.6)	39 (18.3)	0.720
Alcohol use	0	2 (1.5)	2 (0.9)	0.524
Pregnancy				
≥1 pregnancy resulting in live birth	47 (57.3)			
Pregnancies per woman	2 (1, 2)			
Age of first pregnancy, y	26.2 ± 6.3			
Follow-up from first pregnancy, y	15 (9, 28)			

Values are n (%), mean ± SD, or median (25th, 75th percentile).
ccTGA = congenitally corrected transposition of the great arteries; DTGA = complete transposition of the great arteries.

IMPACT OF SEX ON CARDIAC OUTCOMES AND THERAPIES. Table 2 and Figure 1 provide the prevalence of cardiac outcomes in women vs men with a sRV-biV (Central Illustration). Women had a lower prevalence of supraventricular arrhythmias (50.0% vs 65.6%, $P = 0.024$; HR: 1.45 [95% CI: 0.99-2.11, $P = 0.055$]) and NSVT (22.0% vs 38.2%, $P = 0.013$; HR: 1.80 [95% CI: 1.04-3.09, $P = 0.035$]) than men. Women had a lower prevalence of supraventricular arrhythmias than men in both DTGA/AS group 27/53 (50.9%) vs 59/88 (67.0%), respectively, and ccTGA group 14/29 (48.2%) vs 27/43 (62.8%), respectively. However, the age of onset for supraventricular and ventricular arrhythmias was similar between men and women.

No sex-related difference was identified in the prevalence of PMP, with devices implanted for sick sinus syndrome in 46 (21.6%) patients, complete atrioventricular block in 42 (19.7%), both sick sinus syndrome and atrioventricular block in 9 (4.2%), and tachycardia-bradycardia syndromes in 2 (0.9%). In contrast, women had fewer ICDs compared to men (6.1% vs 20.6%, $P = 0.004$; HR: 3.46 (95% CI: 1.33-9.01, $P = 0.011$), with a younger age at implantation (32.8 ± 7.9 years vs 43.2 ± 10.5 years, $P = 0.036$). The sex-related difference in the prevalence of ICDs was driven by fewer ICDs for primary prevention indications (4.9% vs 18.3%, $P = 0.012$), with no difference in secondary prevention ICDs (1.2% vs 2.3%,

TABLE 2 Sex-Related Distribution of Cardiac Outcomes and Therapies

	Women (n = 82)	Men (n = 131)	Total (N = 213)	*P* Value
Age at the last follow-up, y	41.4 ± 13.1	43.3 ± 12.5	42.6 ± 12.8	0.203
Duration of follow-up at the adult cardiac center, y	16 (7.0-20.3)	16 (9.0-20.0)	16 (8.0-20.0)	0.325
Electrophysiologic cardiac events				
Supraventricular arrhythmia	41 (50.0)	86 (65.6)	127 (59.6)	0.024
Age of onset, y	32.8 ± 16.9	32.5 ± 15.6	32.6 ± 15.9	0.669
Ventricular arrhythmia				
NSVT	18 (22.0)	50 (38.2)	68 (31.9)	0.013
Age of onset, y	42.4 ± 12.7	40.4 ± 13.0	40.9 ± 12.9	0.726
SVT	4 (4.9)	11 (8.4)	15 (7.0)	0.329
Age of onset, y	35.6 ± 8.2	36.1 ± 18.6	36.0 ± 16.2	0.794
Electrophysiological interventions				
Permanent pacemaker	34 (41.5)	65 (50)	99 (46.7)	0.225
Age at implantation	25.4 ± 16.8	23.5 ± 16.1	24.1 ± 16.3	0.653
Cardiac resynchronization therapy	3 (3.7)	9 (6.9)	12 (5.6)	0.322
ICD	5 (6.1)	27 (20.6)	32 (15.0)	0.004
Age at implantation, y	32.8 ± 7.9	43.2 ± 10.5	41.6 ± 10.7	0.036
Primary prevention	4 (4.9)	24 (18.3)	28 (13.1)	0.012
Secondary prevention	1 (1.2)	3 (2.3)	4 (1.9)	1.000
DTGA	4 (4.8)	18 (13.7)	22 (10.3)	0.066
ccTGA	1 (1.2)	9 (6.9)	10 (4.7)	0.095
Hemodynamic cardiac adverse events				
Heart failure hospitalization	8 (9.8)	26 (19.8)	34 (16.0)	0.050
Age at first hospitalization, y	38.2 ± 8.3	44.2 ± 11.6	42.8 ± 11.1	0.180
Pulmonary hypertension	17 (32.1)	36 (45.0)	53 (39.8)	0.136
Age at diagnosis, y	34.4 ± 10.7	40.6 ± 11.7	38.1 ± 11.7	0.028
Cardiac surgeries				
SAVV intervention	9 (11)	21 (16.0)	30 (14.1)	0.302
Age at intervention, y	26.8 ± 15.1	38.5 ± 18.8	35.0 ± 18.3	0.099
Heart transplant/ventricular assist device	1 (1.2)	4 (3.1)	5 (2.3)	0.651
Age at intervention, y	33.4	52.6 ±9.7	48.7 ± 12.1	0.157
At the last follow-up visit				
Moderate-severe sRV-biV dysfunction	21 (25.6)	75 (57.3)	96 (45.1)	<0.001
SAVV severe regurgitation	10 (12.3)	14 (16.3)	24 (11.4)	0.741
Medications				
Beta-blocker	34 (41.5)	81 (61.8)	115 (54.0)	0.004
Diuretics	14 (17.1)	37 (28.2)	51 (23.9)	0.063
ACEI/ARB/ARNI	29 (35.4)	68 (51.9)	97 (45.5)	0.018
MRAs	6 (7.3)	24 (18.3)	30 (14.1)	0.025
Death				
Death	6 (7.3)	15 (11.5)	21 (9.9)	0.325
Age at death, y	39.3 ± 20.2	52.5 ± 14.4	48.7 ± 16.9	0.062
Cardiac cause	5 (6.1)	12 (9.2)	18 (8.4)	0.422

Values are mean ± SD, median (IQR), or n (%).

ACEI = angiotensin-converting enzyme inhibitors; ARB = angiotensin II receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; ICD = Implantable cardioverter-defibrillator; MRAs = mineralocorticoid receptor antagonists; NSVT = nonsustained ventricular tachycardia; SAVV = systemic atrioventricular valve; sRV-biV = systemic right ventricle in biventricular physiology; SVT = sustained ventricular tachycardia; other abbreviations as in Table 1.

$P = 1.00$). Among the 96 patients with moderate to severe sRV-biV, there were no significant sex-related differences in the prevalence of an ICD (19.0% vs 29.3% in women vs men, $P = 0.299$).

Women had a lower prevalence of moderate to severe sRV-biV dysfunction at LFU (25.6% vs 57.3%, $P < 0.001$), with a trend toward fewer HF-related hospitalizations (9.8% vs 19.8%, $P = 0.050$). Women were less likely to receive beta-blockers ($P = 0.004$), angiotensin-converting enzyme inhibitors/angiotensin receptor blockers/angiotensin receptor-neprilysin inhibitors ($P = 0.018$), and mineralocorticoid receptor antagonists ($P = 0.025$) at LFU. PH was diagnosed in 53 (24.9%) patients, with

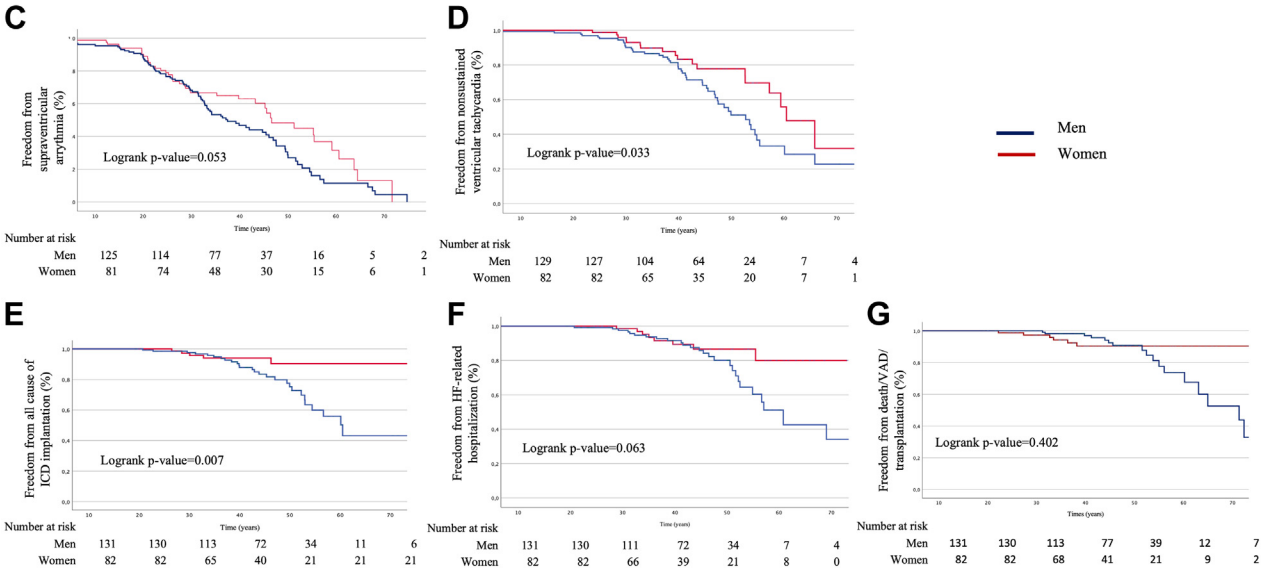
FIGURE 1 Incidence Rate (Events per 100 Patient-Years) and Kaplan-Meier Comparing the Sex-Related Distribution of Cardiac Outcomes

A

	Number of events per 100 patient-years		P-value
	Women	Men	
Supra-ventricular arrhythmias	1.40	1.93	0.090
Non sustained ventricular arrhythmias	0.54	0.93	0.051
All cause of ICD implantation	0.15	0.49	0.014
HF-related hospitalization	0.24	0.47	0.088
Death/ VAD/ transplantation	0.20	0.31	0.329

B

	Univariable Cox Regression		Multivariable Cox Regression	
	HR (95%CI)	P-Value	HR (95%CI)	P-value
Supra-ventricular arrhythmias	1.45 (0.99-2.11)	0.055	1.45 (0.99- 2.13)	0.054
Non sustained ventricular arrhythmias	1.80 (1.04-3.09)	0.035	1.78 (1.03 -3.07)	0.039
All cause of ICD implantation	3.46 (1.33-9.01)	0.011	3.21 (1.23-8.41)	0.018
HF-related hospitalization	2.10 (0.95-4.67)	0.069	2.19 (0.98-4.91)	0.058
Death/ VAD/ transplantation	1.45 (0.60-3.49)	0.404	1.37 (0.56 -3.32)	0.492



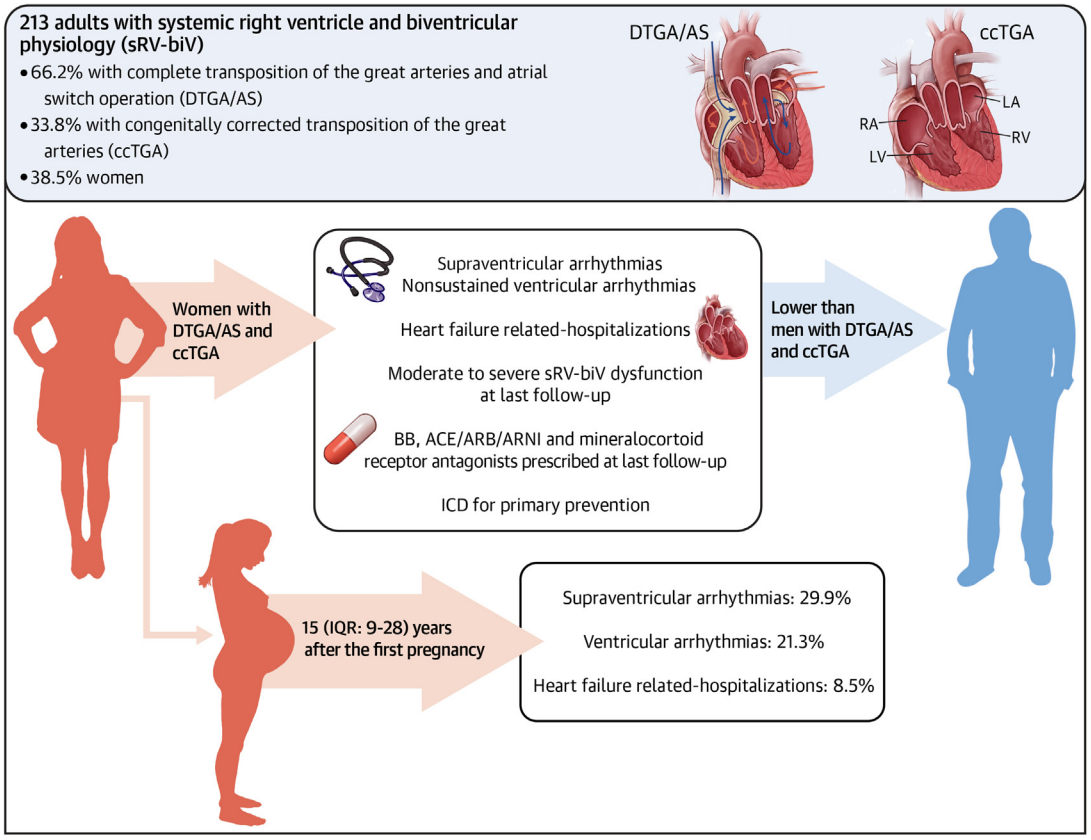
(A) Sex distribution of event rate (per 100 patient-years). (B) Univariable and multivariable cox regression analysis, with HRs and 95% CI, type of transposition of great arteries and associated congenital heart lesions were the baseline variables selected for the multivariable analysis. (C) Kaplan-Meier curve indicating the occurrence of supraventricular arrhythmias from the diagnosis until the last follow-up/transplant in women vs men. (D) Kaplan-Meier curve indicating the occurrence of non-sustained ventricular arrhythmias from the diagnosis until the last follow-up/transplant in women vs men. (E) Kaplan-Meier curve indicating all causes of ICD implantation from the diagnosis until the last follow-up/transplant in women vs men. (F) Kaplan-Meier curve indicating HF-related hospitalizations from the diagnosis until the last follow-up/transplant in women vs men. (G) Kaplan-Meier curve indicating the occurrence of the combined endpoint death/VAD/transplantation from the diagnosis in women vs men. HF = heart failure; ICD = implantable cardioverter-defibrillator; VAD = ventricular assist device.

no sex-related difference. Similarly, among the 88 (41.3%) patients who had a cardiac catheterization, the prevalence of PH was 60.2%, with no significant sex-related difference. Coronary angiography was performed in 73 (34.3%) patients, with significant coronary disease identified in 4 (5.5%), all of whom were male. Both patients with left ventricular assist devices were male, 1 of whom died after the intervention. One woman and 2 men had a heart transplant.

Univariable and multivariable cox regression analysis associated with sex are summarized in **Figure 1B**, nonsustained ventricular arrhythmias (HR: 1.78; 95% CI: 1.03-3.07, $P = 0.039$) and all-cause of ICD (HR: 3.21; 95% CI: 1.23-8.41, $P = 0.018$) were significantly higher in men than women after adjustment for the type of TGA and associated congenital heart lesions. Considering death as a competing risk in the analysis does not alter the conclusions.

CARDIOVASCULAR EVENTS IN WOMEN WITH 1 OR MORE PREGNANCIES RESULTING IN LIVE BIRTH. At LFU, women with at least 1 pregnancy resulting in a live birth had a mean age of 44.1 ± 12.3 years with a first pregnancy at 26.2 ± 6.3 years. The median number of pregnancies per woman was 2 (IQR: 1-2) (**Table 1**). The median follow-up since the first pregnancy was 15 (IQR: 9-28) years. In the 47 women with

CENTRAL ILLUSTRATION **Sex-Related Differences in Adults With Transposition of Great Arteries With a Systemic Right Ventricle and Biventricular Physiology**



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Sex-related differences in terms of supraventricular and ventricular arrhythmias, heart failure (HF), ventricular systemic dysfunction incidence, HF medications in adults with transposition of great arteries with a systemic right ventricle and biventricular physiology but also the influence of pregnancy on cardiac outcomes in women are depicted. ACE inhibitors = angiotensin-converting enzyme inhibitors; ARB = angiotensin II receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; BB = beta-blockers; ccTGA = congenitally corrected transposition of the great arteries; DTGA/AS = complete transposition of the great arteries with an atrial switch operation; ICD = implantable cardioverter-defibrillator; sRV-biV = systemic right ventricle in biventricular physiology.

pregnancies resulting in a live birth, 46.8% and 23.4% had supraventricular arrhythmias and sustained/nonsustained ventricular arrhythmias, respectively. Supraventricular arrhythmias occurred for the first time after pregnancy in 29.9% (14/22) after a median of 18.1 (IQR: 3.6-32.2) years later. Ventricular arrhythmias occurred for the first time after pregnancy in 21.3% (10/11) after a median of 15.5 (IQR: 8.0-25.4) years. Four (8.5%) patients were, respectively, hospitalized for HF at 2, 6, 14, and 24 years after the first pregnancy. A PMP was implanted in 6 patients (12.8%) between 1 and 38 years after the first pregnancy. One patient required a systemic atrioventricular valve replacement 20 years after the first pregnancy.

One patient with DTGA/AS presented with HF at the age of 32 years, 5 years after her first pregnancy, and was diagnosed with postcapillary PH. She was admitted for HF at the age of 33, following medical interruption of a subsequent pregnancy at 12 weeks. An ICD was implanted for primary prevention in the context of severe sRV-biV dysfunction and NSVT. In

the same year, she underwent a heart transplant at the age of 33 years.

Two women died during follow-up, 14 years and 47 years after their first pregnancy. One woman had TGA/AS, 4 uneventful term pregnancies, moderate to severe systemic sRV-biV, and moderate tricuspid regurgitation. She had no history of HF or arrhythmias but experienced atypical chest pain on exertion since the age of 29 years. Serial testing revealed no electrocardiographic or ischemic changes during exercise by myocardial perfusion scintigraphy. She died suddenly at 38 years of age while walking at work, with documented ventricular fibrillation. Her autopsy showed acute massive myocardial infarction of the hypertrophied sRV-biV with normal coronary arteries and chronic subendocardial ischemic lesions.[10] The second patient had ccTGA and died from terminal HF at the age of 79 years.

A total of 13 (27.7%) patients had at least 1 cardiac event defined as a supraventricular arrhythmia, NSVT, sustained ventricular tachycardia, pacemaker or ICD implantation, HF-related hospitalizations, diagnosis of PH, heart transplantation, or cardiac death in the 15 years following their first pregnancy.

CARDIOVASCULAR EVENTS IN WOMEN WITH PREGNANCIES VS NULLIPAROUS WOMEN. Three women among the 82 patients presented a prohibitive maternal mortality risk (ie, World Health Organization class IV) during their childbearing years.[25] Among them, 2 had DTGA/AS with moderate to severe sRV-biV dysfunction and primary prevention ICDs. The third patient had ccTGA with tricuspid valve replacement, hospitalizations for HF, PH, and a secondary prevention ICD. She died from HF at 36 years old. These 3 women complied with recommendations to avoid pregnancy.

After excluding the 3 women with pregnancy contraindications, 47 (59.5%) of the remaining 79 women had at least 1 pregnancy resulting in a live birth. The mean age of women who did not have a pregnancy was 37.8 ± 14.1 years at LFU, with a median follow-up since their baseline visit of 11 (IQR: 4.25-18) years. There were no differences between women with or without pregnancies at baseline for the type of TGA (DTGA vs ccTGA [$P = 0.870$]), associated congenital heart lesions ($P = 0.650$), and cardiovascular risk factors. Comparisons of cardiovascular events in women with and without pregnancies are summarized in **Table 3**. Despite a longer follow-up period for women with pregnancies resulting in live births and older ages at LFU, there were no significant differences observed in the incidence of cardiac events, surgeries, electrophysiological interventions, age at the time of cardiac events, or the proportion of women with moderate to severe sRV-biV dysfunction.

DISCUSSION

We report cardiac outcomes in a large retrospective cohort of 213 patients with a diagnosis of TGA and sRV-biV followed over a median of 16 (IQR: 8-20) years. A preponderance of males was observed (61.5%), consistent with the CONCOR (CONgenital CORvitia) Dutch national registry and a European cohort.[18,26] First, we compared the incidence of cardiac outcomes between men and women. To the authors' knowledge, our study is the first study documenting the impact of sex on cardiac outcomes in TGA and sRV-biV adults. Women had a lower prevalence of ventricular arrhythmias, fewer ICDs for primary prevention, and a lower prevalence of moderate to severe sRV-biV dysfunction at LFU compared to men. Then, by comparing cardiac outcomes in women who had 1 or more pregnancies resulting in live births and those who did not, our study showed no difference in the incidence and age at the time of cardiac events after long-term follow-up nor in the proportion of moderate to severe sRV-biV dysfunction at LFU.

SEX-RELATED DIFFERENCES IN CARDIAC OUTCOMES. Sex-related differences were identified with a nonsignificant lower prevalence of supraventricular and HF-related hospitalizations and a significant lower prevalence of nonsustained ventricular arrhythmia and moderate to severe sRV-biV dysfunction at LFU in women. Accordingly, women had fewer HF medications at LFU and a lower prevalence of primary prevention ICDs. Non significative increase of HF-related hospitalizations in men vs women could be explained by the usual ambulatory management in outpatient clinics or HF clinics. Differences between men and women appear to manifest more prominently after the fourth decade of life. Underlying reasons as to why women had superior cardiovascular outcomes remain speculative and merit further study. Potential underlying reasons include estrogen protective effects, later age of onset of traditional risk factors, and lesser extent of myocardial fibrosis. In HF with reduced ejection fraction of a systemic left ventricle, sex-related disparities have been described with men presenting earlier onset of symptoms than women.[27] Furthermore, the profile of HF associated with the left ventricle is also different between men and women, with men more likely to develop HF with reduced ejection fraction, macrovascular disease, and scar.[27] In contrast, women have a predominance of HF with preserved

TABLE 3 Cardiovascular Events in Women With vs Without Pregnancies Resulting in Live Births

	≥1 Pregnancy Resulting in Live Birth (n = 47)	No Pregnancy Resulting in Live Birth (n = 32)	*P* Value
Age at the last follow-up, y	44.1 ± 12.3	37.8 ± 14.1	0.025
Duration of follow-up at the adult cardiac center, y	16 (8.0-20.0)	11 (4.25-18.0)	0.029
Electrophysiologic cardiac events			
Supraventricular arrhythmia	22 (46.8)	17 (53.1)	0.581
Age of onset, y	35.5 ± 18.6	29.9 ± 15.4	0.322
Ventricular arrhythmia			
NSVT	10 (21.3)	6 (18.8)	0.366
Age of onset, y	46.0 ± 12.4	40.2 ± 13.1	0.143
SVT	1 (2.1)	1 (3.1)	1.000
Age of onset, y	38.0	46.2	0.317
Electrophysiological interventions			
Permanent pacemaker	16 (34.0)	15 (46.9)	0.252
Age at implantation, y	27.5 ± 19.4	23.6 ± 15.4	0.635
ICD	1 (2.1)	1 (3.1)	1.000
Age at implantation, y	32.8	46.3	0.317
Hemodynamic cardiac adverse events			
Heart failure hospitalization	4 (8.5)	3 (9.4)	1.000
Age at first hospitalization, y	40.8 ± 10.2	35.4 ± 7.5	0.480
Pulmonary hypertension	11 (33.3)	5 (27.8)	0.683
Age of onset, y	35.1 ± 11.1	34.5 ± 10.2	1.000
Cardiac surgeries			
SAVV valve intervention	4 (8.5)	4 (12.5)	0.708
Age at intervention, y	30.5 ± 11.4	27.2 ± 19.2	1.000
Heart transplant	1 (2.1)	0 (0.0)	1.000
At the last follow-up visit			
Moderate-severe sRV-biV dysfunction	8 (17.0)	11 (34.4)	0.076
SAVV severe regurgitation	6 (13.0)	4 (12.5)	1.000
Death			
Death	3 (6.4)	2 (6.3)	1.000
Age at death, y	49.9 ± 25.1	24.8 ± 3.6	0.083
Cardiac cause	2 (4.3)	2 (6.3)	1.000

Values are mean ± SD, median (IQR), or n (%).
Abbreviations as in Table 2.

ejection fraction, endothelial inflammation, and coronary microvascular dysfunction.[27] It is thought that estrogen has protective effects on the development of cardiovascular disease.[28] Compared to the left ventricle, the role of sex hormones on right ventricular function is less known. Ventetuolo et al noted that higher levels of estradiol were associated with superior right ventricular systolic function in postmenopausal women using hormone replacement therapy.[29]

The lower prevalence of primary prevention ICDs in women observed in our cohort is consistent with the literature in patients with heterogeneous forms of congenital heart disease that indicates that 65% to 75% of sudden deaths occur in men.[30] Primary prevention ICD indications remain debated in patients with SRV-biV. A weak Class IIb recommendation based on Level of Evidence: C evidence states that it is reasonable to consider an ICD if the sRV-biV ejection fraction is <35%, particularly in the presence of additional risk factors such as complex ventricular arrhythmias, unexplained syncope, NYHA functional class II or III symptoms, QRS duration 140 ms, or severe systemic atrioventricular valve regurgitation.[24] Secondary prevention indications are better established. Although statistical comparisons were limited by the small number of patients, we did not detect a sex-related difference for secondary prevention indications. In the CONCOR registry that included a mixed cohort of patients with congenital heart disease, women had a 55% lower risk of receiving an ICD compared to men, although there was no detected

difference in the frequency of ventricular arrhythmia.[31] Only 8 patients with TGA/AS had an ICD, and no patients with ccTGA.[18] Nevertheless, underdiagnosis of HF and sRV-biV dysfunction in women may explain some sex-related differences. Gender disparities in ICD implantation for acquired heart disease are well-documented, with men being 3.2 times more likely to receive ICD therapy in primary prevention.[32,33] Despite clear guidelines for ICD implantation in left systemic ventricle dysfunction, gender disparities persist in treatment decisions. In challenging risk stratification for ICD implantation in TGA with sRV-biV, gender bias may be also expected.

IMPACT OF PREGNANCY ON LONG-TERM OUTCOMES. Our study reports a higher incidence of cardiac events in women who have had pregnancies compared to previous literature, which likely reflects the longer follow-up duration.[34-36] A total of 29.9% of patients developed supraventricular arrhythmia, 21.3% ventricular arrhythmia, and 8.5% were hospitalized for HF in the 15 (IQR: 9-28) years following the first pregnancy. Studies that focused on the short-term postpartum period reported a 7% to 22% incidence of arrhythmia and a 7% to 21% incidence of HF.[36-40] Serial echocardiography showed a reduction in ejection fraction of the sRV-biV during and after the pregnancy.[39,41] In a series of 19 pregnant women with sRV-biV, 2 had cardiac arrests, 1 during pregnancy and the second 6 months postpartum.[42] More recently, the ROPAC (Registry Of Pregnancy And Cardiac disease) registry reported a lower frequency of outcomes with a 7% incidence of arrhythmia and a 9.8% incidence of HF 6 months after the pregnancy.[43] Cardiac events were more frequent in women with prepartum arrhythmias and a sRV-biV ejection fraction <40% before pregnancy.[19,43]

After excluding women with a prohibitive maternal mortality risk who complied with recommendations to avoid pregnancy, there were no differences regarding frequency and age of cardiac events between women with and without at least 1 pregnancy resulting in a live birth. In our study, women with pregnancies were older at LFU and had longer follow-ups, reducing the risk of underestimating cardiac event frequencies in the pregnancy group compared to those without pregnancies. All patients were followed during their pregnancy in the same center with the same rigorous protocol that included serial cardiac follow-up and specialized high-risk obstetrical follow-up. The high incidence of cardiac events in the nulliparous population highlights the high-risk nature of this population independent of pregnancy. The similar incidence of cardiac events despite high-risk pregnancies described in our study occurred in the context of a rigorous prepregnancy assessment, perpartum, and postpartum follow-up by the cardio-obstetrical team, thereby underscoring the importance of a multidisciplinary cardio-obstetrical team for pregnant women with sRV-biV.[44,45]

STUDY LIMITATIONS. The study is retrospective with inherent limitations related to data collection on diagnostic assessments and pregnancies, detection of cardiac outcomes, and therapeutic decisions. Due to the retrospective nature of the analysis, we did not have access to the original images from transthoracic echocardiography for standardized reassessment and rely on the LFU echocardiography reports. Only pregnancies resulting in live birth are reported. Miscarriages and abortions were not included due to the anticipated significant missing data in the context of retrospective analyses. Our study is limited by the small sample size of the congenital population of TGA, which arises from the condition's rarity. This small sample size increases the risk of both type I and type II errors.

CONCLUSIONS

Women with sRV-biV had a lower prevalence of nonsustained ventricular arrhythmias and moderate to severe sRV-biV dysfunction at LFU than men. Women had fewer ICDs for primary prevention than men, with no difference in the prevalence of secondary prevention ICDs.

Despite the high incidence of cardiac events, no long-term differences were identified between women with and without a pregnancy resulting in a live birth. Further mechanistic studies are required to elucidate sex-related differences, including the influence of hormonal factors on arrhythmias and sRV-biV function.

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ADDRESS FOR CORRESPONDENCE: Dr Marie-A Chaix, Montreal Heart Institute Adult Congenital Center, Montreal Heart Institute, 5000 Belanger Street E, Montreal, Quebec H1T 1C8, Canada. E-mail: marie-alexandre.chaix@icm-mhi.org.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Women with a sRV-biV had a lower prevalence of moderate to severe sRV-biV dysfunction than men with a trend toward fewer hospitalizations for HF. Women had a lower prevalence of ventricular arrhythmias and fewer implantable cardioverter-defibrillators for primary prevention than men.

TRANSLATIONAL OUTLOOK: Pregnancy in women with a sRV-biV remained with a high cardiac maternal risk but in the context of rigorous multidisciplinary cardio-obstetrical care, pregnancy was not associated with adverse long-term cardiovascular outcomes.

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