Cardiac magnetic resonance imaging characteristics and pregnancy outcomes in women with Mustard palliation for complete transposition of the great arteries

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1. Introduction

Right ventricular (RV) systolic dysfunction is a predictor of mortality in non-pregnant adults with a systemic RV [1–3]. Given

Abbreviations: ACHD, Adult congenital heart disease; BP, Blood pressure; CMR, Cardiovascular magnetic resonance imaging; EF, Ejection fraction; NYHA, New York Heart Association; RVEDV, Right ventricular end diastolic volume; RVF, Right ventricular ejection fraction; RV, Right ventricle; SSP, Steady state free precession; TGA, Transposition of the great arteries; TR, Tricuspid valve regurgitation.

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invariable hemodynamic adaptations to pregnancy, including prolonged augmentation of cardiac output, pregnant women with atrial redirection (Mustard or Senning operations) for underlying transposition of the great arteries (TGA) are at increased risk of heart failure and arrhythmias [4–7]. Accordingly, contemporary guidelines suggest in general terms that women with “more than moderate systemic RV dysfunction” should be advised against pregnancy [8]. In contradistinction to those with systemic left ventricular systolic dysfunction where adverse cardiovascular events in pregnancy are known to be more common with an ejection fraction (EF) less than 40% [9], a precise threshold RV EF for the systemic RV has not been defined, as all published studies to date have examined RV function only qualitatively using echocardiography alone [4–7].
Although cardiovascular magnetic resonance imaging (CMR) is considered to be the reference standard for quantification of RV volumes and function [10,11], there are as yet no data available regarding the CMR characteristics of women following atrial redirection surgery who undergo pregnancy. In this study, we sought to evaluate the relationship between CMR measurements of systemic RVEF and pregnancy outcomes in women who underwent atrial redirection surgery. We hypothesized that systemic RV dysfunction would be associated with increased risk of maternal and fetal/neonatal adverse events.

2. Methods

2.1. Study design

Women born with complete (D-loop) TGA palliated with atrial redirection surgery were retrospectively identified from institutional databases at two large Adult Congenital Heart Disease (ACHD) centers in Toronto (University Health Network/Mount Sinai Hospital) and Boston (Boston Children's Hospital/Brigham and Women's Hospital) from 1996 until 2011. The study cohort included consecutive women with atrial redirection surgery who had CMR imaging completed within 2 years of their delivery date [5]. Patients were excluded if CMR datasets were incomplete. The Research Ethics Boards of each respective institution approved this study.

2.2. Patient population

Baseline demographic data were recorded at the first clinic visit in the first trimester of pregnancy, including age, New York Heart Association (NYHA) functional class, baseline blood pressure (BP), parity status, associated cardiovascular lesions, medications, and history of previous cardiovascular events. A completed pregnancy was defined as >20 weeks gestation. Follow-up clinical data were obtained from available maternal and pediatric records. Maternal echocardiographic reports at baseline (prior to pregnancy or in first trimester), during pregnancy (second or third trimester) and post delivery (preferably >6 months post-partum) were reviewed for ventricular dimensions, ventricular systolic function, baffle stenosis/leak, outflow obstruction, and degree of tricuspid (systemic atrioventricular) valve regurgitation (TR). Severity of TR was graded as none, mild, moderate or severe according to published criteria [12].

2.3. Adverse outcomes

Adverse outcomes were classified as cardiovascular, obstetric and fetal/neonatal outcomes, as previously defined [9]. Cardiovascular events were defined as: 1) pulmonary edema (documented on chest radiograph or by crackles heard over more than one-third of posterior lung fields), 2) decline in NYHA functional class (≥2 classes) compared with baseline or need for urgent invasive cardiac procedures during pregnancy or within 6 months of delivery, 3) sustained tachyarrhythmia requiring medical therapy or intervention, 4) stroke, and 5) cardiac arrest and/or cardiac death. Obstetric events were defined as: 1) pregnancy-induced hypertension (blood pressure increase of systolic pressure ≥30 mm Hg and diastolic pressure ≥15 mm Hg over pre-pregnancy values), 2) pre-eclampsia (de novo hypertension with BP ≥140 mm Hg or diastolic BP ≥90 mm Hg and accompanied by new-onset proteinuria ≥ 0.3 g/24 h) or eclampsia [8], 3) pre-term labor, 4) post-partum hemorrhage (blood loss >500 mL after vaginal delivery or >1000 mL after cesarean section warranting transfusion or a drop in hemoglobin ≥20 g/L), and 5) non-cardiac obstetric maternal death. Fetal/neonatal events were defined as: 1) fetal death (categorized as stillbirth if ≥20 weeks gestation or spontaneous abortion if <20 weeks gestation) or neonatal death (within 28 days of birth), 2) premature delivery (<37 weeks of gestation), 3) small for gestational weight (<10th percentile), 4) respiratory distress syndrome, and 5) cerebral hemorrhage.

2.4. Cardiovascular magnetic resonance imaging (CMR)

All CMR studies were performed on commercially available 1.5 T whole-body scanners with phased array surface coils. All CMR datasets were acquired in expiratory breath-hold. Retrospectively ECG gated cine steady state free precession (SSFP) in axial and short-axis slice orientation was acquired with contiguous volume coverage (6–8 mm slice thickness with 2 mm interslice gap). Representative spatial resolution was 1.3 × 1.3 × 0.8 mm and temporal resolution was ±50 msec. Systemic RV and subpulmonic left ventricular volumes were contoured on SSFP cine imaging according to previously described methodology [13]. For the purposes of this study, all images were analyzed by a single experienced observer (JJ) using a dedicated workstation and commercial software (Argus, Siemens Healthcare, Erlangen, Germany) in a core laboratory at the University Heath Network, Toronto. Moderate RV systolic dysfunction was defined as RVEF <35% as previously established in non-pregnant adults with atrial redirection surgery for complete TGA [3,14–16].

2.5. Statistical analysis

Statistical analysis was performed using SSPS software version 20 (IBM SPSS Statistics 20, 2011). Continuous variables were described using means and standard deviation or medians and ranges, as appropriate. Categorical variables were described using frequencies and percentages. Multiple cardiovascular complications in a woman or multiple fetal/neonatal complications in a baby were counted as a single outcome event in the mother or child, respectively. The relationship between continuous variables was evaluated using the Spearman correlation co-efficient. The Mann–Whitney U test was used to compare CMR measurements in those with and without adverse events in pregnancy. Univariate logistic regression analysis was used to examine the effect of RVEF on the odds of an adverse outcome of pregnancy. Fisher exact test was used to assess the association between various RVEF thresholds and adverse cardiovascular events in pregnancy and likelihood ratios were used to obtain the optimal cut-off. McNemar Bowker test was used to compare echocardiographic parameters at baseline, during pregnancy and post-partum. A P value <0.05 was considered statistically significant.

3. Results

3.1. Clinical characteristics

A total of 17 women with 17 completed pregnancies met inclusion criteria (7 from Boston and 10 from Toronto). Women with atrial redirection surgery comprised approximately 9% of the overall cohort of pregnant women with congenital heart disease followed in Boston [17] and 4% of the pregnant women followed in Toronto [9]. Atrial redirection surgery consisted of the Mustard palliation for all of the women included in this study. None of the women had a Senning procedure for atrial redirection. All women were asymptomatic at baseline assessment (NYHA functional class 1). Clinical characteristics of the study population are summarized in Table 1. Echocardiographic data at baseline, antepartum, and post-partum are shown in Table 2. The majority of women did not have appreciable changes in RV global systolic function on echocardiography, as demonstrated by Fig. 1, although 3 women with mild RV systolic dysfunction at baseline had moderate RV systolic dysfunction following pregnancy.
3.2. Cardiovascular magnetic resonance imaging (CMR)

A total of 17 CMR studies were available for review and all CMR datasets were of adequate quality. The CMR data for the study population are summarized in Table 3. CMR studies were completed prior to pregnancy in 3 women (median 8 months, [range 1–10 months]), peripartum in 2 women (in 1 woman 24 h prior to delivery and in 1 woman 48 h following delivery), and postpartum in 12 women (median 15 months [range 7–23 months] following delivery).

3.3. Clinical events

Outcomes of pregnancy are summarized in Table 4. Adverse cardiovascular events related to pregnancy occurred in 3 women (18%) and consisted of sudden cardiac death in 1 woman and atrial tacharyrhythmia in 2 women. One woman had a resuscitated sudden death event 48 h following delivery. She was found to have pulmonary edema upon admission to hospital and was treated with diuretics and angiotensin converting enzyme inhibitor therapy. Notably, she was on beta-blocker therapy prior to pregnancy, however medications were discontinued antenatally. She did not have any additional obstetric or fetal/neonatal complications. A second woman developed a sustained atrial tacharyrhythmia and was treated with anti-arrhythmic therapy in the third trimester of pregnancy. She went on to develop clinical signs of heart failure (there were no other women in this cohort with congestive heart failure). In addition to her Mustard palliation she had undergone additional surgery to repair aortic coarctation at age 1 year. She was not on any medications prior to pregnancy. A deep venous thrombus was diagnosed during her pregnancy. There were no adverse events in her offspring.

A third woman had a syncopal event at 30 weeks gestation. The episode was attributed to an atrial tacharyrhythmia based on results from Holter monitoring. Beta-blocker therapy was commenced in pregnancy but was subsequently discontinued by the patient for unclear reasons. An electrophysiology study was recommended following pregnancy but was declined. She did not have any adverse obstetric or fetal/neonatal events.

No major adverse obstetric events were documented in this cohort. Obstetric complications not considered major adverse events included premature rupture of membranes in 1 woman and a placental abruption in 1 woman; each of these obstetric morbidities was associated with adverse events in the offspring. There were 17 live born infants in this cohort and complications were observed in 3 (18%). Three infants were born prematurely. One child was born at 36 weeks gestation to a mother diagnosed with placental abruption at 29 weeks gestation. A second baby was born at 34 weeks gestation and was admitted to a neonatal intensive care unit for further management. The third infant was born at 24 weeks gestation following premature rupture of membranes; this child died of sepsis in the neonatal intensive care unit.

All of the women with an adverse cardiovascular event documented in pregnancy had moderate RV dysfunction with a median RVEF of 33% (range 32–34%) (CMR studies in the women with cardiovascular events were performed within 24 h of delivery in 1 woman, at 22 months postpartum in a second and at 23 months post-partum in a third woman). In the remainder of the event-free population the median RVEF was 37% (range 30–51%). In a univariate logistic regression model, RVEF was not a significant predictor of adverse outcome (P = 0.214). The association between moderate RV dysfunction (RVEF <35%) and the presence of a cardiovascular event trended towards statistical significance (P = 0.051). Various threshold RVEF values between 30 and 50% were examined to determine the optimal RVEF cut-off associated with cardiovascular complications and the highest likelihood ratio was observed at RVEF of 35% (LR 6.3, P = 0.051). There was no statistically significant association between RVEF and maternal age at the time of delivery (P = 0.941). There was no association between RVEF and adverse outcomes in offspring. There were no statistically significant associations between other CMR variables (including right/left ventricular volumes and left ventricular EF) and adverse outcomes of pregnancy.

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### Table 1
Clinical characteristics of the study population (17 women with 17 completed pregnancies).

| Variable                  | Valuea                                    |
|---------------------------|-------------------------------------------|
| **Maternal data**         |                                           |
| Age                       | 2.2 (0.6–6)                               |
| At Mustard palliation (years) | 31 (25–37)           |
| At CMR study (years)      | 32 (27–37)                                |
| Cardiac anatomy           |                                           |
| Complete TGA with intact septum | 12 (70%)                              |
| Complete TGA with ventricular septal defect | 4 (24%)                             |
| Complete TGA with aortic coarctation | 1 (6%)                                |
| Gravidity                 |                                           |
| Gravida 1                 | 5 (31%)                                   |
| Gravida 2                 | 3 (19%)                                   |
| Gravida ≥ 3               | 8 (50%)                                   |
| Previous abortions        | 4 (23%)                                   |
| Spontaneous               | 1 (6%)                                    |
| Therapeutic               |                                           |
| Functional class at baseline |                                       |
| NYHA class I              | 17 (100%)                                 |
| Medications at baseline   |                                           |
| Digoxin                   | 1 (6%)                                    |
| Diuretics                 | 2 (12%)                                   |
| Beta blocker              | 0                                         |
| Angiotensin-converter enzyme inhibitors | 4 (24%)                               |
| Medications during pregnancy |                                   |
| Digoxin                   | 1 (6%)                                    |
| Diuretics                 | 2 (12%)                                   |
| Beta blocker              | 3 (18%)                                   |
| Angiotensin-converter enzyme inhibitors | 0                                         |
| Offspring data            |                                           |
| Gestational age at delivery (weeks) | 38 (24–39)                                 |
| Birth weight (g)          | 2770 (2195–3720)                          |
| Congenital heart disease in infant | 0                                         |

CMR, cardiovascular magnetic resonance; TGA, transposition of the great arteries; NYHA, New York heart association.

* Data given as median (range) or n (%).

### Table 2
Echocardiography data in women at baseline, during pregnancy, and post-partum.a

| Variable                          | Baseline (n = 16) | Pregnancy (n = 16) | Post-partum (n = 15) | McNemar Bowker P-value |
|-----------------------------------|-------------------|--------------------|----------------------|------------------------|
| Right ventricular function        |                   |                    |                      |                        |
| Normal                            | 4                  | 4                  | 4                    | 0.506                  |
| Mild dysfunction                  | 3                  | 3                  | 0                    |                        |
| Moderate dysfunction              | 7                  | 7                  | 10                   |                        |
| Severe dysfunction                | 2                  | 2                  | 1                    |                        |
| TV regurgitation                  |                   |                    |                      |                        |
| None                              | 1                  | 1                  | 1                    |                        |
| Mild                              | 10                 | 10                 | 10                   |                        |
| Moderate                          | 5                  | 5                  | 3                    |                        |
| Severe                            | 0                  | 0                  | 1                    |                        |
| Subpulmonary obstruction          |                   |                    |                      |                        |
| None                              | 13                 | 13                 | 14                   | 1                      |
| Mild                              | 2                  | 2                  | 0                    |                        |
| Moderate                          | 1                  | 1                  | 1                    |                        |
| Severe                            | 0                  | 0                  | 0                    |                        |
| Significant pulmonary venous channel obstruction |       |
| None                              | 16                 | 16                 | 15                   | 1                      |
| Significant systemic venous baffle obstruction | |
| None                              | 16                 | 16                 | 15                   | 1                      |
| Baffle leak                        | 1                  | 1                  | 0                    | 1                      |

* A baseline echocardiogram occurred prior to pregnancy or during the first trimester; the echocardiogram closest to delivery was selected to represent pregnancy; post-partum echocardiography was completed following delivery.
vascular event in pregnancy is a noteworthy dysfunction (RVEF (median RVEF 39%), the presence of at least moderate RV systolic had uncomplicated pregnancies despite RV systolic dysfunction in pregnancy. Although the majority of women studied in our cohort had uncomplicated pregnancies despite RV systolic dysfunction (median RVEF 39%), the presence of at least moderate RV systolic dysfunction (RVEF <35%) in all patients with a major adverse cardiovascular event in pregnancy is a noteworthy finding.

4. Discussion

Cardiovascular morbidity and mortality after atrial redirection surgery are known to escalate with advancing age [3]. Cardiovascular complications, commonly a result of heart failure and/or arrhythmia, can manifest during pregnancy and, in some women, these decline will persist despite completion of pregnancy [4–7]. Although contemporary guidelines caution against pregnancy in women with a systemic RV and moderate RV systolic dysfunction [8], a more precise definition has been lacking as assessment of systemic RV function by echocardiography has been mostly qualitative rather than quantitative. While echocardiographic assessment of systemic RV function can have important limitations [14], the CMR assessment of the RV has been shown to be accurate and reproducible [18–20] and is therefore accepted as the imaging reference standard for measurements within the right heart [10,11]. This is the first study to define the CMR characteristics of women after atrial redirection surgery undergoing pregnancy. Although the majority of women studied in our cohort had uncomplicated pregnancies despite RV systolic dysfunction (median RVEF 39%), the presence of at least moderate RV systolic dysfunction (RVEF <35%) in all patients with a major adverse cardiovascular event in pregnancy is a noteworthy finding.

Unlike other reports where decline in NYHA functional class was documented in approximately one third of pregnancies [4,5] and decompensated heart failure was observed in 4–7% of women studied [4,5,21], all of the women studied in our cohort were asymptomatic at baseline and progressive heart failure was not evident in any of the pregnancies. Of note, one woman had a resuscitated cardiac death event. In other respects, our findings are in keeping with the published literature. Arrhythmic events in pregnancy are the most common cardiovascular complication reported in women with atrial redirection surgery with a prevalence of 6–22% [5,6,21]. In our cohort, atrial tachyarrhythmias requiring escalating medical therapy were documented in 2 women (12%) and, although this frequency is in keeping with previous publications, we note that this may be an underrepresentation of the true arrhythmia burden given that women with pacemakers and/or defibrillators were excluded from this CMR-based study. Finally, prematurity was the most frequent fetal/neonatal complication in our population (18%), as reported by others [5,21].

While all women with cardiovascular complications in pregnancy had at least moderate RV systolic dysfunction, RVEF <35% and occurrence of a major adverse cardiovascular event related to pregnancy approached, but did not reach, statistical significance in our study population. This finding may reflect our small cohort size (type 2 error) and perhaps the association would in fact be significant in a larger sample. It is also worth noting that in the setting of hemodynamically significant tricuspid (systemic atrioventricular valve) regurgitation as is commonly seen following Mustard palliation, calculated RVEF may in fact be an overestimate of actual systemic ventricular function in the context of

**Table 3**

Cardiovascular magnetic resonance imaging data.

| CMR parameter (n = 17) | Median (range) |
|------------------------|----------------|
| RVEDV (mL)             | 199 (132–364)  |
| RVEDVi (mL/m²)         | 119 (85–214)   |
| RVESV (mL)             | 136 (71–245)   |
| RVESVi (mL/m²)         | 76 (144–44)    |
| RVSV (mL)              | 74 (57–138)    |
| RVEF (%)               | 37 (30–51)     |
| LVEDV (mL)             | 112 (87–304)   |
| LVEDVi (mL/m²)         | 62 (55–190)    |
| LVSV (mL)              | 67 (38–130)    |
| LVEF (%)               | 60 (45–73)     |

CMR, cardiovascular magnetic resonance; RVEDV, right ventricular end diastolic volume; RVEDVi, right ventricular end diastolic indexed volume; RVESV, right ventricular end systolic volume; RVESVi, right ventricular end systolic indexed volume; RVSV, right ventricular stroke volume; RVEF, right ventricular ejection fraction; LVEDV, left ventricular diastolic volume; LVEDVi, left ventricular end diastolic indexed volume; LVSV, left ventricular stroke volume; LVEF, left ventricular ejection fraction.

**Table 4**

Adverse events related to pregnancy.

| Variable                                  | Value |
|-------------------------------------------|-------|
| Cardiovascular events                     | 3 (18%) |
| Sustained atrial tachyarrhythmia resulting in heart failure | 1 (6%) |
| Resuscitated sudden cardiac death          | 1 (6%) |
| Syncope attributed to atrial tachyarrhythmia | 1 (6%) |
| Fetal/neonatal events\(^a\)                 | 3 (18%) |
| Premature delivery <37 weeks               | 2 (12%) |
| Death                                      | 1 (6%) |
| Obstetric events\(^b\)                     | 0     |

\(^a\) Events mutually exclusive.

\(^b\) Major adverse obstetric events were not observed in this cohort although obstetric complications observed included abruption in 1 woman and premature rupture of membranes in 1 woman.
atrioventricular valve competence. In our study, 5 women had moderate tricuspid regurgitation although no woman had severe tricuspid regurgitation. Furthermore, patients after Mustard surgery are often limited by chronotropic incompetence and inability to augment stroke volume given constraints imposed by the caval baffles and, therefore, an assessment of contractile reserve would perhaps be a higher fidelity measure in this population as compared with RVEF alone. Other parameters which may have potential value for stratification of cardiovascular risk in pregnancy (which were not uniformly available in our population) include peak aerobic capacity and heart rate response to exercise. Finally, although advancing age has been established as a risk factor for functional decline following atrial redirection surgery, in our cohort there was no relationship between age at the time of delivery and RV systolic function. Due to the small cohort size, we were unable to adjust for such parameters in addition.

Findings from this study may have implications for clinical practice in the following ways. Although CMR can provide important information regarding RV systolic function, particularly in the setting of a systemic RV, we found that CMR studies were infrequently completed prior to pregnancy and we therefore suggest that surveillance CMR be offered to women with palliated complete TGA of child-bearing age in advance of pregnancy, ideally at the time of preconceptional evaluation. Furthermore, beyond quantification of systemic EF, CMR can allow for evaluation of additional parameters which may have clinical benefit, including response to pharmacologic stress, quantification of TR, and interrogation of baffle integrity (although these data were not routinely obtained in our study cohort and were therefore not reported). We observed that, by and large, the women in our cohort had successful outcomes of pregnancy with morbidities that were managed medically with good effect; importantly there were no maternal deaths in our cohort. Although it might be tempting to suggest that current guidelines stating that women with atrial redirection surgery with more than moderate RV systolic dysfunction should avoid pregnancy [8] are perhaps too stringent, it should be noted that we did not have any patients with severe systemic RV dysfunction (all patients studied had an RVEF ≥ 30%) and those with pacemakers/defibrillators were excluded. Overall, we believe that the findings of this study suggest that patients with at least moderate RV systolic dysfunction should remain under close surveillance for detection and treatment of adverse cardiovascular events in pregnancy.

4.1. Study limitations

Several limitations of this study are worthy of mention. The retrospective control and the small sample size of the study cohort are noteworthy limitations of this study. The observed incidence of adverse events in pregnancy may be affected by exclusion of patients with manifest arrhythmias and indwelling pacemakers/defibrillators (these patients are typically deemed unsuitable for CMR) and therefore those excluded from the cohort may in fact represent the more severe end of the disease spectrum. In addition, patients were selected from tertiary care centers only, which may affect generalizability of the results. However, given the complexity of this patient population, it is unlikely that these patients would receive care in non-specialized centers. Pre and post CMR imaging would have been useful for the evaluation of the impact of pregnancy on systemic RV function, however there was only one CMR available for each patient. Although CMR studies just prior to the start of pregnancy would have been highly desirable, timing of conception is often unpredictable and the safety of CMR study in the first trimester of pregnancy is currently unknown. Therefore, it is often not possible to synchronize CMR prior pregnancy onset. We included CMR studies completed within 2 years of pregnancy as some authors have suggested that imaging is unlikely to change for the majority within this time frame [21]. Further reassurance is provided by general stability of RV systolic function on echocardiography in this cohort. Finally, long-term follow-up to assess the impact of pregnancy on the RV would be useful information but was not available in the majority of the women studied.

Ideally, future studies would allow for incorporation of multiple centers and would include longer follow-up to better understand the impact of pregnancy on longer-term outcomes in this cohort of women. Directions for future research would include prospective study of this population with inclusion of additional measurements with potential prognostic value in the adult patient with atrial redirection surgery, including incorporation of biomarkers (such as brain natriuretic peptide measurement before/during/after pregnancy), cardiopulmonary exercise studies prior to pregnancy (for measurement of heart rate response, peak aerobic capacity etc.), and stress testing for determination of contractile reserve in advance of conception.

5. Conclusion

While the majority of women in this cohort had successful outcomes during pregnancy, important cardiovascular complications were seen in a subset of pregnancies, all with systemic RV systolic function ~35%. The prognostic value of CMR measurements in women following atrial redirection surgery requires further study in a large cohort of women undergoing pregnancy, preferably followed prospectively.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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