Chapter 3

Cardiac adaption during pregnancy: comparison between women with congenital heart disease and healthy women.

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Submitted.
ABSTRACT

Background
Pregnancy in women with congenital heart disease (CHD) is associated with cardiovascular complications and with deterioration in cardiac function. Still data on longitudinal changes during pregnancy are scarce. Data on right ventricular function parameters are not yet reported. We aimed to describe serial changes in cardiac dimension and cardiac function during pregnancy in women with CHD and compare these to changes seen in healthy women. We focus on both left and right ventricular parameters.

Methods
We performed a prospective multicenter cohort study. Follow-up with clinical evaluation and standardized echocardiography at 20 and 32 weeks gestation and one year postpartum was performed. In women with CHD, pre-pregnancy echocardiograms were also evaluated.

Results
We studied 125 women with CHD and 49 healthy women. The absolute level of ventricular function parameters and diameters differs clearly between women with CHD and healthy women. No changes occurred in right and left ventricular function parameters and ventricular dimensions during pregnancy in the total population of women with CHD. However, women with right-sided CHD had a different profile of TAPSE over time compared to healthy women (p=0.043). Women with left-sided CHD had a different profile of LVEDD over time compared to healthy women (p=0.045).

Conclusion
Absolute levels of ventricular function parameters and diameters differ between women with CHD and healthy women. The different patterns over time seen for TAPSE and LVEDD in women with right-sided and left-sided CHD respectively, compared to healthy women indicate the importance of echocardiographic follow-up during pregnancy in women with CHD.

Key words: congenital heart disease, pregnancy, cardiac function, echocardiography.
INTRODUCTION

Pregnancy in women with congenital heart disease (CHD) is associated with increased incidences of cardiovascular, obstetric and neonatal complications. Cardiac complications, such as arrhythmia and heart failure, are thought to be due to the hemodynamic changes of pregnancy. Depending on the specific underlying congenital defect, pregnancy can be associated with persisting structural cardiac remodeling and deterioration in function, such as dilatation of the subpulmonary ventricle after pregnancy, deterioration of valvular dysfunction and worsening ventricular function. However, the observations in most of these studies were not based on longitudinal data. The majority of data on cardiovascular changes over time during pregnancy is based on studies in healthy women and only a few reports describe longitudinal cardiovascular changes in women with heart disease. Most of the available research focuses on left ventricular parameters. Data examining longitudinal changes in right ventricular function and dimension are scarce in healthy pregnant women and have never been reported in pregnant women with congenital heart disease.

Therefore, we aimed to describe serial measurements in cardiac dimensions and systolic and diastolic function of the right and left ventricle during pregnancy in women with congenital heart disease. In addition, we compared the serial measurements in women with congenital heart disease to the changes seen in healthy pregnant women.

METHODS

Study population

The ZAHARA II study (Zwangerschap bij Aangeboren HARtAfwijkingen; Pregnancy in CHD) is a national, prospective multicenter cohort study. All consecutive pregnant women with structural CHD, aged ≥ 18 years, pregnancy duration < 20 weeks and presenting in one of the eight participating centers were eligible for enrollment. Healthy pregnant women (nonsmokers, no medication use, aged ≥ 18 years) were recruited from low risk midwife practices in Groningen and Rotterdam, the Netherlands. The study design and primary results have been published previously.

Only women from the ZAHARA II study with singleton pregnancies and complete echocardiographic follow-up (preconception (only applicable for women with CHD), 20 and 32 weeks gestation, one year post-partum) were included for the current study and only the first pregnancy during the study period was taken into account. Women with a systemic right ventricle or Fontan physiology were excluded, since various echocardiographic measurements are not validated for these types of congenital heart disease.
The Research Ethics Committee of all participating centers approved the study protocol and all participating women gave written informed consent. The ZAHARA II study was supported by a grant from the Netherlands Heart foundation (2007B75).

Baseline characteristics and echocardiography
Baseline characteristics were collected using medical records during the first ante-partum visit and included maternal age, underlying congenital heart disease, previous interventions, prior cardiac events, cardiac medication use, New York Heart Association (NYHA) functional class, echocardiography data, co-morbid conditions and obstetric history.

Patients and healthy pregnant women visited the outpatient clinic at 20 and 32 weeks gestation and one year post-partum for clinical evaluation (including NYHA class assessment) and standardized echocardiography. All echocardiograms were evaluated offline by four experienced cardiologists at the University Medical Center Groningen, Groningen, the Netherlands. Transthoracic echocardiographic evaluation was performed according to current guidelines and recommendations, and adapted to the structural defect when necessary.

Left ventricular end-diastolic and end-systolic diameters (LVEDD, LVESD), as well as the left ventricular outflow tract (LVOT) diameter, were assessed on the parasternal long axis view (PLAX). Left ventricular outflow tract velocity time integral was derived from the apical view. Cardiac output was calculated by multiplying LVOT area with the LVOT velocity time integral and heart rate. Left ventricular ejection fraction was determined using Simpson's biplane method using the apical four chamber view and the apical two chamber view where possible, otherwise Simpson's monoplane or the eyeballing method were used.

Diastolic function was assessed by pulsed wave Doppler of the mitral inflow (E, A, E/A ratio) and color tissue Doppler of the septal and lateral mitral annulus (E/E').

Right ventricular function was measured using the Tricuspid Annular Plane Systolic Excursion (TAPSE) in the apical four chamber view and the peak systolic color tissue velocity Doppler of the right ventricular lateral wall assessed at the tricuspid annulus (S’ RV). Maximal right ventricular end-diastolic diameter was measured using the modified apical four chamber view. Left ventricular systolic dysfunction was defined as an ejection fraction < 45%. Right ventricular systolic dysfunction was defined as TAPSE < 16 mm.

Statistical analysis
Continuous variables are presented as mean with standard deviation (SD) or medians with interquartile ranges as appropriate. Absolute numbers and percentages are displayed for categorical data.

To investigate changes in the serial echocardiographic parameters over time in pregnant women with CHD and to compare the serial changes over time with healthy pregnant women, random slope, random intercept linear mixed-effects models were used, adjusted for age, race and parity. These hierarchical regression models include fixed and random
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(subject-specific) effects, allowing for within subject correlation between repeated measurements. As the evolution of parameters during pregnancy might not be linear, patterns were investigated graphically, and polynomial transformations were considered where appropriate. Best fit transformations were selected via combined assessment of Akaike's Information Criterium (AIC, lower is better) for fixed effects and likelihood ratio tests of nested models for random effects. Second degree polynomial transformations for changes over time were selected for the final models. Interaction terms for group membership (pregnant women with CHD vs. healthy pregnant women; pregnant women with right-sided CHD vs. healthy pregnant women; pregnant women with left-sided CHD vs. healthy pregnant women) were introduced as a fixed effect to check for differences in course over time. Women with Tetralogy of Fallot, atrial septal defects, partial atroventricular septal defects, pulmonary atresia with intact ventricular septum, Ebstein's anomaly, abnormal pulmonary venous return, sinus venosus defects and pulmonary valve stenosis were classified as having right-sided CHD. Women with ventricular septal defects, aortic valve abnormalities, aortic coarctation, Marfan syndrome and with a cleft mitral valve were considered to have left-sided CHD.

All statistical analyses were performed using STATA software package (version 11, college station, Texas, USA) and R: A language and environment for statistical computing (version 3.1.0, R Foundation for statistical computing, Vienna, Austria). A two-tailed p-value < 0.05 was considered significant.

RESULTS

During the study period, 213 women with congenital heart disease and 70 healthy women were included. Eighty-eight pregnancies in women with CHD were excluded because of a twin pregnancy (n=4), Fontan physiology or a systemic right ventricle (n=15), second pregnancy in the study period (n=9) or incomplete echocardiographic data (n=60), rendering 125 patients available for analysis. In one healthy woman a previously unknown atrial septal defect type II was found and 20 women did not have complete echocardiographic follow-up, resulting in 49 healthy pregnant women included in this analysis.

Baseline characteristics and underlying congenital defects are displayed in table 1. Mean age was comparable between women with CHD (29.4 ± 4.5 years) and healthy women (30.1 ± 4.1 years; p=0.31). The majority of patients and healthy controls was nulliparous (62.4% vs. 61.2%, p=0.89) and most of them were in NYHA functional class I (75.2% vs. 98.0%, p<0.001). Left ventricular systolic dysfunction was seen in 4 (3.2%) women with CHD and 15 (12.0%) had right ventricular systolic dysfunction.

Serial means over time of the ventricular function parameters and the ventricular dimensions of right and left ventricle are reported in table 2 and displayed in figure 1 and 2. No statisti-
**Table 1.** Maternal baseline characteristics (prior to pregnancy).

<table>
<thead>
<tr>
<th>Demographics and clinical data</th>
<th>Patients (N=125)</th>
<th>Healthy women (N=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maternal age at conception (years ± SD)</strong></td>
<td>29.4 ± 4.5</td>
<td>30.1 ± 4.1</td>
</tr>
<tr>
<td><strong>Parity status</strong></td>
<td></td>
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<tr>
<td>0</td>
<td>78 (62.4)</td>
<td>30 (61.2)</td>
</tr>
<tr>
<td>≥ 1</td>
<td>47 (37.6)</td>
<td>19 (38.8)</td>
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<tr>
<td><strong>NYHA class</strong></td>
<td></td>
<td></td>
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<tr>
<td>I</td>
<td>94 (75.2)</td>
<td>48 (98.0)</td>
</tr>
<tr>
<td>II</td>
<td>30 (24.0)</td>
<td>1 (2.0)</td>
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<tr>
<td>III</td>
<td>1 (0.8)</td>
<td></td>
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<tr>
<td><strong>Modified WHO class</strong>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>15 (12.0)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>81 (63.7)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>27 (21.6)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>2 (1.6)</td>
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<tr>
<td><strong>Mechanical valve prosthesis</strong></td>
<td>10 (8.0)</td>
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<tr>
<td><strong>Arrhythmia</strong></td>
<td>10 (8.0)</td>
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<tr>
<td><strong>Pacemaker</strong></td>
<td>2 (1.6)</td>
<td></td>
</tr>
<tr>
<td><strong>Congestive heart failure</strong></td>
<td>4 (3.2)</td>
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</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>10 (8.0)</td>
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<tr>
<td><strong>Type of congenital lesion</strong></td>
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<tr>
<td>Abnormal pulmonary venous return</td>
<td>1 (0.8)</td>
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<tr>
<td>Aortic valve stenosis / Bicuspid aortic valve</td>
<td>23 (18.4)</td>
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<tr>
<td>Atrial septum defect</td>
<td>14 (11.2)</td>
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<tr>
<td>Atrioventricular septal defect</td>
<td>7 (5.6)</td>
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<tr>
<td>Ebstein’s anomaly</td>
<td>1 (0.8)</td>
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<tr>
<td>Loeyz-Dietz syndrome</td>
<td>1 (0.8)</td>
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<tr>
<td>Marfan syndrome</td>
<td>7 (5.6)</td>
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<tr>
<td>Other*</td>
<td>1 (0.8)</td>
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<tr>
<td>Other complex cyanotic heart disease 1</td>
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<tr>
<td>Pulmonary valve stenosis</td>
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<tr>
<td>Surgically repaired Aortic coarctation</td>
<td>19 (15.2)</td>
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<tr>
<td>Tetralogy of Fallot after repair</td>
<td>28 (22.4)</td>
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<tr>
<td>Transposition of great arteries with arterial switch</td>
<td>2 (1.6)</td>
<td></td>
</tr>
<tr>
<td>Ventricular septal defect</td>
<td>9 (7.2)</td>
<td></td>
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<tr>
<td><strong>Echocardiographic parameters</strong></td>
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<tr>
<td>Left ventricular systolic dysfunction (LVEF &lt; 45%)</td>
<td>4 (3.2)</td>
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</tr>
<tr>
<td>Right ventricular systolic dysfunction (TAPSE &lt; 16 mm)</td>
<td>15 (12.0%)</td>
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</tbody>
</table>

*Patient with cleft mitral valve. † 1 patient with a corrected truncus arteriosus, type A; 1 patient with pulmo-
nary atresia, atrial septal defect and intact intraventricular septum.
Table 2. Longitudinal echocardiographic parameters in pregnant women with congenital heart disease and healthy women (mean ± SD).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pre-pregnancy</th>
<th>20 weeks</th>
<th>32 weeks</th>
<th>1-yr post-partum</th>
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<tbody>
<tr>
<td><strong>Right ventricular parameters</strong></td>
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<tr>
<td>Entire CHD population</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Tricuspid annular plane systolic excursion (TAPSE (mm))</td>
<td>21.2 ± 5.6</td>
<td>22.5 ± 6.1</td>
<td>21.5 ± 6.4</td>
<td>21.0 ± 5.5</td>
</tr>
<tr>
<td>Systolic tissue velocity of the lateral wall (S’ RV (cm/s))</td>
<td>8.4 ± 2.9</td>
<td>9.7 ± 2.9</td>
<td>9.5 ± 3.1</td>
<td>8.7 ± 2.9</td>
</tr>
<tr>
<td>Right ventricular end-diastolic diameter (RVEDD (mm))</td>
<td>38.2 ± 8.3</td>
<td>38.6 ± 7.4</td>
<td>39.1 ± 7.4</td>
<td>37.2 ± 8.0</td>
</tr>
<tr>
<td>Women with right-sided CHD</td>
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</tr>
<tr>
<td>Tricuspid annular plane systolic excursion (TAPSE (mm))</td>
<td>21.0 ± 6.1</td>
<td>20.5 ± 6.0</td>
<td>19.8 ± 6.1</td>
<td>20.1 ± 5.5</td>
</tr>
<tr>
<td>Systolic tissue velocity of the lateral wall (S’ RV (cm/s))</td>
<td>8.7 ± 3.2</td>
<td>9.3 ± 3.0</td>
<td>8.9 ± 3.3</td>
<td>7.6 ± 2.7</td>
</tr>
<tr>
<td>Right ventricular end-diastolic diameter (RVEDD (mm))</td>
<td>41.0 ± 8.4</td>
<td>41.0 ± 8.3</td>
<td>41.1 ± 8.8</td>
<td>40.3 ± 8.3</td>
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<tr>
<td>Women with left-sided CHD</td>
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<td></td>
</tr>
<tr>
<td>Tricuspid annular plane systolic excursion (TAPSE (mm))</td>
<td>21.9 ± 5.0</td>
<td>25.0 ± 5.1</td>
<td>23.5 ± 6.4</td>
<td>22.7 ± 5.1</td>
</tr>
<tr>
<td>Systolic tissue velocity of the lateral wall (S’ RV (cm/s))</td>
<td>7.8 ± 2.0</td>
<td>10.5 ± 2.5</td>
<td>10.4 ± 2.0</td>
<td>10.5 ± 2.0</td>
</tr>
<tr>
<td>Right ventricular end-diastolic diameter (RVEDD (mm))</td>
<td>35.2 ± 7.2</td>
<td>36.5 ± 5.7</td>
<td>37.2 ± 5.1</td>
<td>33.8 ± 6.2</td>
</tr>
<tr>
<td>Healthy women</td>
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</tr>
<tr>
<td>Tricuspid annular plane systolic excursion (TAPSE (mm))</td>
<td>--</td>
<td>26.6 ± 3.5</td>
<td>25.1 ± 4.0</td>
<td>23.9 ± 3.1</td>
</tr>
<tr>
<td>Systolic tissue velocity of the lateral wall (S’ RV (cm/s))</td>
<td>--</td>
<td>11.5 ± 1.3</td>
<td>11.5 ± 1.8</td>
<td>10.6 ± 2.3</td>
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<tr>
<td>Right ventricular end-diastolic diameter (RVEDD (mm))</td>
<td>--</td>
<td>35.8 ± 4.2</td>
<td>35.5 ± 4.2</td>
<td>35.8 ± 5.0</td>
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<tr>
<td><strong>Left ventricular parameters</strong></td>
<td></td>
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<tr>
<td>Entire CHD population</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Left ventricular ejection fraction (LVEF (%))</td>
<td>57.6 ± 8.0</td>
<td>57.6 ± 8.0</td>
<td>56.9 ± 8.0</td>
<td>55.8 ± 9.3</td>
</tr>
<tr>
<td>Mean systolic tissue velocity of the septal and lateral wall (S’ LV (cm/s))</td>
<td>6.2 ± 1.4</td>
<td>6.9 ± 1.8</td>
<td>7.0 ± 1.8</td>
<td>6.4 ± 1.7</td>
</tr>
<tr>
<td>Left ventricular end-systolic diameter (LVESD (mm))</td>
<td>29.8 ± 5.6</td>
<td>30.9 ± 5.4</td>
<td>30.7 ± 5.3</td>
<td>30.9 ± 5.5</td>
</tr>
<tr>
<td>Left ventricular end-diastolic diameter (LVEDD (mm))</td>
<td>46.3 ± 6.5</td>
<td>46.5 ± 6.9</td>
<td>48.0 ± 6.1</td>
<td>46.8 ± 5.7</td>
</tr>
<tr>
<td>Women with right-sided CHD</td>
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</tr>
<tr>
<td>Left ventricular ejection fraction (LVEF (%))</td>
<td>56.1 ± 7.9</td>
<td>58.1 ± 8.8</td>
<td>56.3 ± 8.1</td>
<td>53.9 ± 9.4</td>
</tr>
<tr>
<td>Mean systolic tissue velocity of the septal and lateral wall (S’ LV (cm/s))</td>
<td>6.3 ± 1.2</td>
<td>7.0 ± 1.9</td>
<td>7.1 ± 1.9</td>
<td>6.2 ± 1.7</td>
</tr>
<tr>
<td>Left ventricular end-systolic diameter (LVESD (mm))</td>
<td>29.1 ± 5.8</td>
<td>30.2 ± 5.2</td>
<td>29.6 ± 5.2</td>
<td>29.3 ± 5.0</td>
</tr>
</tbody>
</table>
### Table 2. Longitudinal echocardiographic parameters in pregnant women with congenital heart disease and healthy women (mean ± SD). (continued)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pre-pregnancy</th>
<th>20 weeks</th>
<th>32 weeks</th>
<th>1-yr post-partum</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Women with left-sided CHD</strong></td>
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<td></td>
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<tr>
<td>Left ventricular end-diastolic diameter (LVEDD (mm))</td>
<td>44.9 ± 5.9</td>
<td>45.7 ± 5.9</td>
<td>46.2 ± 5.8</td>
<td>45.0 ± 5.4</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (LVEF (%))</td>
<td>58.8 ± 8.1</td>
<td>57.5 ± 7.3</td>
<td>57.5 ± 7.9</td>
<td>57.9 ± 9.2</td>
</tr>
<tr>
<td>Mean systolic tissue velocity of the septal and lateral wall (S' LV (cm/s))</td>
<td>6.1 ± 1.6</td>
<td>6.8 ± 1.6</td>
<td>6.9 ± 1.7</td>
<td>6.7 ± 1.7</td>
</tr>
<tr>
<td>Left ventricular end-systolic diameter (LVEDD (mm))</td>
<td>30.7 ± 5.5</td>
<td>31.8 ± 5.7</td>
<td>31.8 ± 5.3</td>
<td>32.5 ± 5.7</td>
</tr>
<tr>
<td>Left ventricular end-diastolic diameter (LVEDD (mm))</td>
<td>47.9 ± 6.8</td>
<td>47.4 ± 7.9</td>
<td>49.9 ± 6.0</td>
<td>48.8 ± 5.6</td>
</tr>
<tr>
<td><strong>Healthy women</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left ventricular ejection fraction (LVEF (%))</td>
<td>--</td>
<td>62.3 ± 5.9</td>
<td>59.4 ± 6.1</td>
<td>60.0 ± 5.6</td>
</tr>
<tr>
<td>Mean systolic tissue velocity of the septal and lateral wall (S' LV (cm/s))</td>
<td>--</td>
<td>7.6 ± 1.5</td>
<td>7.7 ± 1.4</td>
<td>7.3 ± 1.1</td>
</tr>
<tr>
<td>Left ventricular end-systolic diameter (LVEDD (mm))</td>
<td>--</td>
<td>31.1 ± 4.0</td>
<td>31.6 ± 2.9</td>
<td>30.8 ± 4.0</td>
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<tr>
<td>Left ventricular end-diastolic diameter (LVEDD (mm))</td>
<td>--</td>
<td>48.1 ± 3.8</td>
<td>47.9 ± 3.5</td>
<td>47.2 ± 3.2</td>
</tr>
</tbody>
</table>

**Figure 1:** Serial changes (means with 95% confidence interval) in right ventricular function parameters for the entire population of women with CHD (A, Tricuspid Annular Plane Systolic Excursion (TAPSE (mm)(n=121)); B, Systolic tissue velocity of the right ventricle lateral wall (S’ RV (cm/s)(n=96)) and right ventricular end diastolic diameter (RVEDD (mm)(n=113)) (C).
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Cally significant changes occurred during pregnancy in either of the parameters assessed in the entire population of women with CHD.

Figure 3 compares the fitted longitudinal profiles over time of the right ventricular function parameters and right ventricular dimension. Women with CHD have lower values of right ventricular function parameters (TAPSE and systolic tissue velocity of the right ventricle) compared to healthy women. Right ventricular end-diastolic diameter was larger throughout pregnancy compared to healthy women. The changes observed in the entire cohort of women with CHD were comparable to the changes seen in healthy women; no statistically significant differences were found in the slope of any of the longitudinal profiles, indicating similar patterns of change over time for both populations.

In women with solely right-sided CHD, the fitted longitudinal profile of TAPSE over time was significantly different from that in healthy women (p=0.043), with TAPSE remaining unchanged in women with right-sided CHD (table 2).

The fitted longitudinal profiles over time of the left ventricular function parameters and left ventricular dimensions are shown in figure 4. Women with CHD have a worse left ventricular systolic function during pregnancy compared to healthy pregnant women, as displayed by lower LVEF and systolic tissue velocity. Left ventricular dimensions are comparable between
Figure 3: Fitted longitudinal profiles of right ventricular function parameters for women with CHD (—), and healthy women (-----). (A, Tricuspid Annular Plane Systolic Excursion (TAPSE (mm) (n=116 vs. 47)); B, Systolic tissue velocity of the right ventricle lateral wall (S’ RV (cm/s) (n=91 vs. 39)) and right ventricular end diastolic diameter (RVEDD (mm) (n=105 vs. 41)) (C) Error bars represent 95% confidence interval.

Figure 4: Fitted longitudinal profiles of left ventricular function parameters for women with CHD (——) and healthy women (-----). (A, Left ventricular ejection fraction (LVEF (%)) (n=116 vs. 49)); B, Mean systolic tissue velocity of the septal and left ventricular lateral wall (S’ LV (cm/s) (n=87 vs. 44)) and left ventricular end diastolic (C (n=118 vs 49)) and end systolic (D (n=118 vs 49)) diameter (mm) Error bars represent 95% confidence interval.
both groups. We found no statistically significant differences in the slope of the longitudinal profiles between women with CHD and healthy controls, indicating similar patterns of change over time for both populations. The fitted longitudinal profile of LVEDD in women with left-sided CHD over time was significantly different from that in healthy women ($p=0.045$) with LVEDD tending to increase over time in women with left-sided CHD (table 2).

**DISCUSSION**

This is the first study that compares the serial changes in ventricular function parameters and ventricular dimensions during pregnancy in women with CHD to healthy pregnant women. In addition, this is the first study that describes the serial changes in right ventricular parameters seen during and after pregnancy in women with CHD. For the serial changes in the heterogeneous population of women with CHD, we did not find any statistical significant effect of time and the serial changes in echocardiographic parameters during pregnancy in women with CHD were comparable to healthy pregnant women, indicating similar patterns in both populations. However, the absolute levels of ventricular function and dimensions did clearly differ between women with CHD compared to healthy women. For women with right-sided CHD fitted profiles of TAPSE over time differed from the pattern seen in healthy women. Women with left-sided CHD had a different profile of LVEDD over time compared to healthy pregnant women.

Comparison of our results to other studies is difficult since data on cardiac adaption during pregnancy in women with CHD or heart disease in general are very rare. Cornette et al. described a time effect during pregnancy towards a larger LVESD, lower fractional shortening and lower left ventricular ejection fraction. In addition, they found a parabolic effect for $E/E'$, stroke volume and cardiac output. In our study, visual patterns and model fit criteria suggest non-linear variation in parameters over time, however there was no statistically significant effect of time for any of these parameters. The heterogeneity of the population is most probably due to this observation, since differences might cancel out when women with right-sided and left-sided defects are considered together in one population. The fact that we did find differences in fitted profiles of TAPSE over time in women with right-sided CHD and of LVEDD over time in women with left-sided CDH compared to healthy controls also strengthens this argument. Our results on Doppler peak systolic velocity of the left ventricle were comparable to those described by Bamfo et al. in healthy pregnant women. Their results support our finding that the pattern of longitudinal changes does not differ essentially from healthy women.

Compared to healthy women, women with CHD in our cohort show lower fitted values for left ventricular ejection fraction (figure 4). Vasapollo et al. described significant lower LVEF in
healthy women with fetal growth restriction compared to healthy women with uncomplicated pregnancy outcome. The pattern we observe in our study is comparable, with lower LVEF during pregnancy in women with CHD compared to healthy women. Although we did not find any deterioration in systolic function during pregnancy, this finding suggests that there might be an impaired potential in women with CHD to provide the required cardiac adaptations necessary to meet the increased metabolic demands of pregnancy. This may contribute to the higher obstetric and offspring complication rate in women with CHD, since cardiac dysfunction is related to impaired uteroplacental circulation and offspring complications.

The observed difference in fitted values for LVEDD over time in women with left-sided CHD compared to healthy women may suggest that the volume load of pregnancy is not well tolerated in patients with these type of lesions; however, lesion-specific data are warranted. Data on right ventricular function and dimensions during pregnancy are extremely scarce and have never been described in a longitudinal manner for women with CHD. Vogt and colleagues were the first to report on systolic tissue velocities of the right ventricle (S') during pregnancy in healthy women and did not find a significant change in systolic velocity comparing the first with the third trimester. Ducas et al. described, in a study using magnetic resonance imaging (MRI), no change in TAPSE and systolic myocardial velocity of the right ventricle lateral wall in healthy pregnant women during the third trimester compared to post-partum values (which were used as baseline measurement). Our results on right ventricular systolic function in women with CHD are comparable to these findings, but the absolute values in our patients are considerably lower compared to the healthy women. TAPSE is related to impaired uteroplacental circulation and offspring complications. It might be that the absolute level of right ventricular systolic function is not sufficient to meet the increased demands of pregnancy, leading to adverse obstetric and offspring outcome. The observation that the evolution of TAPSE in women with right-sided CHD is significantly different from the pattern seen in healthy women, may also point into that direction. It might be that this subgroup has insufficient capacity to increase TAPSE, in order to accommodate cardiac output, which may contribute to the increased incidence rates of obstetric and offspring complications.

It is known for specific congenital lesions, i.e. systemic right ventricles and Tetralogy of Fallot, that pregnancy can be associated with persistent deterioration in cardiac function and women with cardiovascular complications during pregnancy are at risk for persistent dilatation of the right ventricle. Close follow up of high risk patients is still warranted, since small changes in cardiac function in the individual patient might be clinical relevant, although we did not find any statistical significant changes in our study cohort.
STRENGTHS & LIMITATIONS

This is the first study that assessed the serial changes in ventricular function and dimensions during pregnancy in women with congenital heart disease and compared these to changes in healthy pregnant women. The comparison with healthy pregnant women is unique and makes the results more valuable.

Due to the study design echocardiographic data before pregnancy from patients were collected retrospectively and in healthy women preconception echocardiography was not performed. This hampered the comparison of the serial changes in women with CHD and healthy controls, since preconception data were not included in this analysis. Several high-risk congenital lesions (Fontan physiology and systemic right ventricles) were excluded from analysis. These are the most vulnerable patient groups during pregnancy for cardiac complications and deterioration in cardiac function during and after pregnancy. Excluding these types of patients may underestimate the effects of pregnancy on maternal cardiac function.

In our study, the visual patterns and model fit criteria suggest non-linear variation in parameter values over time, however there was no statistically significant effect of time found for any of the parameters. This is most probably due to the heterogeneity of the study cohort. With subgroups analyses for right and left-sided CHD we attempted to compensate for that; however, insufficient power hampers analyses. Additional, lesion specific research is clearly warranted.

CONCLUSION

In this study, we showed that absolute levels of ventricular function parameters and ventricular dimensions differ between women with CHD and healthy controls. The patterns of change over time seen during pregnancy are comparable between women with CHD and healthy pregnant women. However, fitted profiles of TAPSE over time in women with solely right-sided CHD differed significantly from healthy women. In women with left-sided CHD, fitted profiles of LVEDD over time were significantly different compared to healthy controls. These findings indicate that serial follow-up of cardiac function and dimensions during pregnancy in women with CHD is an important part of the management of pregnancy in women with congenital heart disease.

ACKNOWLEDGEMENTS

The authors thank dr. J.P.M. Hamer for his contribution in evaluating the echocardiograms.
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