Original Article

# Pregnancy & cardiovascular disease: the PREG-CVD-HH registry

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**Background:** Cardiovascular disease (CVD) remains the leading cause of death in pregnant and peripartal women in western countries. Physiological changes during pregnancy can lead to cardiovascular complications in the mother; women with pre-existing heart disease may not tolerate these changes well, increasing their susceptibility to adverse cardiovascular outcomes during pregnancy. The aim of this study is to characterize pregnancy-induced changes in cardiac function, biomarker concentrations and cardiovascular outcomes in women with CVD during pregnancy at a tertiary care hospital in Germany.

**Methods:** The PREG-CVD-HH study is a prospective single-center observational study of pregnant women with prevalent CVD treated at the University Medical Center Hamburg, Germany and currently includes 63 women with congenital or acquired heart disease and ten women from the general population included as controls. Participants underwent baseline assessment and dedicated comprehensive echocardiography. Biomarkers N-terminal pro B-type natriuretic peptide (NT-proBNP), MR-proadrenomedullin (MRproADM) and high-sensitivity cardiac troponin I (hs-cTnI) were measured serially throughout pregnancy and until 6 and 12 months postpartum. A maternal cardiac event was defined as death due to cardiovascular cause, arrhythmia, heart failure or hospitalization for other cardiac intervention.

**Results:** Mean maternal age was 34 years. A majority had a congenital heart disease (N=41), 10 patients developed pregnancy-associated CVD (e.g., preeclampsia, peripartum cardiomyopathy) and 12 women had known acquired heart disease (e.g., valvular disease, arrhythmia, cardiomyopathy). New-onset heart failure was observed in 14.1% of patients (N=9). Five patients developed arrhythmia and three patients developed preeclampsia. About 21.2% of patients were hospitalized due to cardiovascular events. Death from any or cardiovascular cause did not occur over the study period. Left and right ventricular global longitudinal strain (LV GLS, RV GLS) showed a transient worsening in the third trimester and peripartum period. NT-proBNP ranges broadened during the pregnancy and tended to progressively decrease postpartum in women

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with CVD. Hs-cTnI levels tended to trend upwards during pregnancy in patients with CVD, however, the hs-cTnI levels remained consistently low throughout pregnancy.

**Conclusions:** In our cohort, pregnancy was associated with a transient increase in cardiac biomarkers and worsening of cardiac function during the third trimester and peripartum. These temporal changes reversed at 6–12 months postpartum, potentially due to decreased cardiac load, fluid shifts and hormonal changes. Overall, data on reference ranges in echocardiographic and biomarker measurements in the pregnant cardiac population are limited and require further investigation. Albeit one third of our cohort was deemed at high and highest maternal risk during pregnancy, there was no maternal death. We recommend that women with CVD receive preconceptional counselling and ongoing management by a specialized "Pregnancy Heart Team" to optimize care and, potentially, maternal outcomes.

**Keywords:** Pregnancy; biomarker; echocardiography

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## Introduction

Cardiovascular disease (CVD) remains the leading cause of mortality in pregnant and peripartal women in western countries (1,2). Due to advances in integrated care for younger patients with congenital or acquired heart disease, more patients are reaching reproductive age (3-6). However, this presents a significant challenge during pregnancy due to physiologic changes that can result in maternal and fetal morbidity and mortality in the presence of maternal heart disease (4,5,7). As pregnancies are often deemed intermediate or high-risk, the intricate balance between maternal and fetal well-being warrants particular scrutiny by all involved medical specialties and professions (8).

The hemodynamic challenges of pregnancy, including increased blood volume and cardiac output, reduced peripheral vascular resistance and a hypercoagulative state, may increase the specific risk of arrhythmia, acute decompensated heart failure, stroke, and maternal death—potentially dose-dependent on the severity of maternal disease (4). The consensus-based modified World Health Organization (mWHO) classification offers a risk stratification method for assessing maternal risk during pregnancy with implications for peripartal care, delivery and follow-up (9). Current guidelines for managing women with CVD during pregnancy primarily focus on clinical diagnosis and conventional assessments, with limited data on clinical utility of cardiac biomarkers and advanced echocardiographic parameters (8,10-12). Hence, biomarker trends and thresholds, e.g., for troponin I as well as reference ranges for strain imaging have not yet been included into guideline recommendations (8,13).

This study aims to describe the pregnancy course in terms of cardiovascular events and outcomes and to study echocardiographic and biomarker reference ranges in a contemporary cohort of women with congenital and acquired CVD from the Metropolitan region of Hamburg. We present this article in accordance with the STROBE reporting checklist (available at https://cdt.amegroups.com/article/view/10.21037/cdt-24-248/rc).

### Highlight box

**Key findings**

- Pregnancy was associated with a transient increase in cardiac biomarkers and worsening of cardiac function during the third trimester and peripartum. These temporal changes reversed at 6–12 months postpartum.

**What is known and what is new?**

- Cardiovascular disease (CVD) remains the leading cause of mortality in pregnant and peripartal women in western countries.
- Reference ranges in echocardiographic and biomarker measurements in the pregnant cardiac population are limited and require further investigation according to the pre-existing condition.

**What is the implication, and what should change now?**

- Based on these observations, the authors recommend that women with CVD receive preconceptional counselling and ongoing management by a specialized "Pregnancy Heart Team" to optimize care and, potentially, outcomes.

## Methods

### *Study design*

The PREG-CVD-HH study is a prospective single center study conducted at the Hamburg University Medical Center in Hamburg, Germany, starting January 2019. At the time of the analysis, the registry included 73 women. Women with congenital or acquired heart disease visiting the cardiology and/or obstetrics outpatient clinics for preconception or pregnancy counseling ('Pregnancy Heart Clinic') during the study period were eligible for inclusion and invited to participate. As controls, we included ten overall healthy pregnant women with no known CVD from the general population that received counselling during pregnancy at the obstetric outpatient clinic.

Throughout pregnancy, the women received individualized clinical management by a multidisciplinary team of cardiologists, obstetricians and anesthesiologists according to international guideline recommendations.

Maternal cardiovascular pregnancy outcomes were defined as cardiac death, sustained arrhythmia requiring treatment, heart failure and hospitalization due to cardiac complications. All women underwent cardiac assessment at baseline and were afterwards followed-up serially throughout pregnancy and until 6 and 12 months postpartum. Baseline clinical, electrocardiographic and echocardiographic variables were collected.

Baseline data from before pregnancy were collected, including patient history, New York Heart Association (NYHA) functional class, prior cardiac events, surgery or interventions, co-morbidities, the use of medication and smoking status. Maternal risk was assessed according to the mWHO Classification of Maternal Cardiovascular Risk.

### *Echocardiographic measurements*

Transthoracic echocardiography was performed by qualified physicians according to the guidelines of the American Society of Echocardiography and, according to clinical necessity, adapted to the structural abnormality. Diastolic and systolic diameters were computed from the left ventricular end systolic and end diastolic diameters using the Teichholz formula and left ventricular ejection fraction (LVEF) were calculated using the Simpson's biplane method of summation of discs. Diastolic function was assessed by pulsed wave Doppler of the mitral inflow (E/A ratio) and tissue Doppler of the septal and lateral mitral annulus (E/E' ratio). The software tool Auto-Strain (IMAGE-COM, TOMTEC-ARENA, Tomtec Imaging System GmbH, Unterschleissheim, Germany) was used to generate LV, LA and RV strain measurements. This tool automatically tracked the myocardium throughout the cardiac cycle and the reference point for image analysis set at the onset of the QRS complex (R-R gating). TAPSE was measured by placing the M-mode cursor through the lateral tricuspid annulus in the four-chamber apical view and the peak excursion was recorded in mm.

### *Biomarker measurements*

Blood samples were centrally analyzed at University Heart and Vascular Center Hamburg by an accredited laboratory and measured as part of the clinical routine. Laboratory measurements included biomarkers such as N-terminal pro-B-type natriuretic peptide (NT-proBNP; immunoassay by Alere NT-proBNP for ARCHITECT, Abbott Diagnostics, USA), high-sensitivity cardiac troponin I (hs-cTnI) (ARCHITECT2000, Abbott Diagnostics, USA; detection limit <2 pg/mL) and MR-Proadrenomedullin. MR-proADM was measured on the BRAHMS KRYPTOR automated system with an immunoluminometric assay (BRAHMS/Thermo Fisher Scientific, Hennigsdorf, Berlin, Germany).

### *Statistical analysis*

Continuous variables are presented as median ($25^{th}$, $75^{th}$ percentile) and categorical variables are presented as frequencies and percentages. Comparisons between time points are evaluated considering paired Mann-Whitney *U* test for continuous and McNemar test for categorical variables.

Distribution per time point for specific parameters is assessed via boxplots. Median and $25^{th}$–$75^{th}$ percentile [interquartile range (IQR)] are shown in boxes (*Tables 1-3*, Table S1); Observations out of this range are depicted as line (1.5× IQR) and outliers as points. Cumulative incidence curves are shown based on Kaplan-Meier estimator. Log rank test is given to examine any group difference. To account for differentiation between cardiac pathologies, we conducted sensitivity analyses excluding patients with preeclampsia, cardiomyopathy and arrhythmia (Tables S2-S10).

All statistical models were implemented in R statistical software version 4.0.3 (The R Foundation for Statistical Computing, Vienna, Austria). A two-tailed P<0.05 was

 

**Table 1** Baseline characteristics of the study cohort.

| Variables | Total cohort (N=73) | Women with cardiovascular disease (N=63) | Control group (N=10) | P value |
|---|---|---|---|---|
| Maternal age (years) | 34.0 (29.7, 37.0) | 34.0 (29.2, 37.8) | 31.0 (29.6, 33.3) | 0.12 |
| Body mass index (kg/m$^2$) | 23.7 (21.2, 29.0) | 24.0 (21.3, 29.0) | 22.8 (20.7, 29.4) | 0.19 |
| Medical history | | | | |
| Nulliparous | 33 (45.2) | 26 (41.3) | 7 (70.0) | 0.26 |
| Previous pregnancies | 1.0 (0, 2.0) | 1.0 (0, 2.0) | 0 (0, 1.0) | 0.07 |
| Systolic blood pressure (mmHg) | 120.0 (111.0, 131,5) | 120.0 (110.7, 130.0) | 135.0 (120.0, 150.0) | 0.56 |
| Diastolic blood pressure (mmHg) | 70.0 (64.2, 76.0) | 70.0 (63.0, 76.0) | 79.0 (70.0, 88.0) | 0.64 |
| Preexisting hypertension | 8 (11.1) | 8 (12.9) | 0 (0) | 0.01 |
| Hypercholesterolemia | 3 (4.2) | 3 (4.8) | 0 (0) | 0.67 |
| Diabetes type I/II | 2 (2.8) | 2 (3.23) | 0 (0) | 0.03 |
| Current smoker | 16 (22.2) | 13 (21.0) | 3 (30.0) | 0.68 |
| Modified WHO group | | | | |
| I | 32 (43.8) | 22 (34.9) | 10 (100.0) | <0.001 |
| II | 20 (27.4) | 20 (31.7) | 0 (0) | 0.053 |
| III | 16 (21.9) | 16 (25.4) | 0 (0) | 0.10 |
| IV | 5 (6.8) | 5 (7.9) | 0 (0) | >0.99 |
| History of cardiogenic shock | 4 (5.5) | 4 (6.4) | 0 (0) | >0.99 |
| History of myocardial infarction | 1 (1.4) | 1 (1.6) | 0 (0) | >0.99 |
| History of stroke | 3 (4.1) | 3 (4.8) | 0 (0) | >0.99 |
| Family history of CVD | 25 (34.7) | 20 (32.3) | 5 (50.0) | 0.3 |
| Cardiac medication at inclusion | | | | |
| Antihypertensive medication | 11 (15.3) | 11 (17.4) | 0 (0) | 0.34 |
| Antiarrythmics | 2 (2.8) | 2 (3.2) | 0 (0) | >0.99 |
| ASS | 7 (9.7) | 7 (11.3) | 0 (0) | 0.58 |
| Diuretics | 6 (8.3) | 6 (9.7) | 0 (0) | 0.59 |
| Obstetric and fetal outcomes | | | | |
| Gestational age at delivery (weeks) | 39.0 (37.0, 40.0) | 39.0 (36.0, 40.0) | 39.5 (39.0, 40.1) | 0.09 |
| Offspring birth weight (g) | 3,210.0 (2,753.3, 3,608.3) | 3,150.0 (2,646.7, 3,548.3) | 3,420.0 (3,151.3, 3,703.8) | 0.35 |
| Mode of delivery | | | | |
| Vaginal | 25 (40.3) | 19 (35.2) | 6 (75.0) | 0.17 |
| Caesarian section | 37 (59.7) | 35 (64.8) | 2 (25.0) | 0.17 |

Missing values are excluded from the calculations. Baseline characteristics of the participants were described with median values for continuous variables (25$^{th}$, 75$^{th}$ percentile) and n (%) for categorical variables. WHO, World Health Organization; CVD, cardiovascular disease; ASS, aspirin.

**Table 2** Echocardiographic parameters across time points

| Echocardiographic parameters | Preconception (N=61) | Trimester 1/2 (N=61) | Trimester 3/peripartum (N=61) | 6/12 months postpartum (N=61) | P value | | |
|---|---|---|---|---|---|---|---|
| | | | | | Preconception *vs.* trimester 1/2 | Preconception *vs.* trimester 3/peripartum | Preconception *vs.* 6/12 months postpartum |
| LVEF | | | | | | | |
| >52% | 32 (80.0) | 31 (79.49) | 42 (73.68) | 40 (76.92) | <0.001 | 0.02 | 0.004 |
| 41–52% | 6 (15.0) | 7 (17.95) | 11 (19.30) | 8 (15.38) | <0.001 | <0.001 | <0.001 |
| 30–40% | 0 (0) | 1 (2.56) | 1 (1.75) | 3 (5.77) | <0.001 | <0.001 | <0.001 |
| <30% | 2 (5.0) | 0 (0) | 3 (5.26) | 1 (1.92) | <0.001 | <0.001 | <0.001 |
| MV_E (cm/s) | 98.00 (80.75, 114.00) | 103.50 (86.50, 120.33) | 96.50 (77.92, 110.00) | 87.00 (70.67, 104.33) | 0.16 | 0.23 | 0.13 |
| MV_A (cm/s) | 57.50 (44.92, 66.17) | 67.00 (52.33, 78.00) | 67.00 (54.00, 79.33) | 62.00 (45.67, 80.00) | 0.02 | 0.09 | 0.70 |
| MV_E' (cm/s) | 13.25 (11.00, 15.54) | 13.00 (11.00, 15.92) | 11.50 (8.71, 13.00) | 11.00 (9.50, 14.17) | 0.16 | 0.20 | 0.20 |
| E/e' | 7.00 (5.85, 8.53) | 8.00 (6.06, 10.73) | 8.15 (6.37, 11.06) | 7.00 (5.62, 9.89) | 0.19 | 0.87 | 0.89 |
| E/A | 1.72 (1.34, 1.89) | 1.43 (1.24, 1.75) | 1.43 (1.14, 1.75) | 1.38 (1.01, 1.82) | 0.045 | 0.005 | 0.22 |
| IVSd (mm) | 8.50 (8.00, 9.68) | 9.10 (8.04, 11.22) | 10.00 (8.63, 11.48) | 9.00 (8.22, 10.08) | 0.19 | 0.01 | 0.44 |
| LVDd (mm) | 45.00 (40.78, 49.00) | 45.95 (42.65, 52.35) | 46.30 (41.83, 51.00) | 46.50 (42.02, 51.82) | 0.14 | 0.93 | 0.17 |
| PWDd (mm) | 8.90 (8.23, 9.45) | 9.55 (8.30, 11.12) | 9.20 (8.52, 11.08) | 8.70 (7.52, 10.00) | 0.53 | 0.27 | 0.46 |
| IVSs (mm) | 13.10 (11.99, 15.12) | 14.20 (12.93, 15.35) | 14.40 (13.03, 16.10) | 14.00 (12.37, 15.33) | 0.19 | 0.20 | 0.47 |
| LVDs (mm) | 28.85 (26.48, 34.03) | 31.00 (26.03, 35.37) | 30.30 (27.27, 34.80) | 30.90 (27.23, 33.97) | 0.18 | 0.35 | 0.60 |
| PWDs (mm) | 13.35 (12.10, 14.81) | 14.90 (12.92, 15.53) | 14.70 (13.70, 16.30) | 14.25 (12.54, 15.58) | 0.14 | 0.02 | 0.27 |
| TAPSE (mm) | 22.00 (19.67, 24.00) | 24.00 (19.00, 25.08) | 21.70 (18.17, 24.00) | 21.00 (18.92, 26.00) | 0.33 | 0.19 | 0.07 |
| ≥ moderate valve disease | 34 (85.00) | 33 (84.62) | 51 (89.47) | 42 (80.77) | <0.001 | <0.001 | 0.001 |
| Strain 2d LV (%) | –21.40 (–23.97, –18.91) | –21.50 (–23.57, –18.67) | –19.80 –21.98, –16.82) | –21.35 (–22.77, –17.68) | 0.54 | 0.20 | 0.24 |
| Strain 2d LA (%) | 31.60 (15.98, 40.16) | 31.40 (24.47, 37.73) | 32.45 (25.78, 38.01) | 37.65 (29.02, 43.26) | 0.26 | 0.16 | 0.008 |
| Strain 2d RV (%) | –24.00 (–28.42, –18.52) | –21.60 (–25.73, –19.93) | –22.70 (–25.20, –17.83) | –22.85 (–27.56, –20.14) | 0.39 | 0.16 | 0.29 |

Echocardiographic parameters were described with median values for continuous variables ($25^{th}$, $75^{th}$ percentile) and n (%) for categorical variables. LVEF, left ventricular ejection fraction; MV_E, peak velocity of early diastolic transmitral flow, MV_A, peak velocity of late transmitral flow; MV_E', peak velocity of early diastolic mitral annular motion as determined by pulsed wave Doppler; E/e', ratio of E to é; E/A, ratio of E to A; IVSd, intrerventricular septum thickness at end-diastole; LVDd, left ventriculat diameter at end-diastole; PWDd, left ventricular posterior wall thickness at end-diastole; IVSs, interventricular septum thickness at end-systole; LVDs, left ventricular diameter at end-systole; PWDs, left ventricular posterior wall thickness at end-systole; TAPSE, tricuspid annular plane systolic excursion; LV, left ventricle; LA, left atrium; RV, right ventricle.

**Table 3** Biomarkers across time points

| Biomarkers | Preconception (N=61) | Trimester 1/2 (N=61) | Trimester 3/peripartum (N=61) | 6/12 months follow up (N=61) | P value | | |
|---|---|---|---|---|---|---|---|
| | | | | | Preconception *vs.* trimester 1/2 | Preconception *vs.* trimester 3/ peripartum | Preconception *vs.* 6/12 months follow up |
| NT-proBNP (ng/L) | 142.00 (86.75, 317.58) | 122.00 (70.67, 212.17) | 85.00 (46.92, 205.17) | 119.50 (76.75, 235.33) | 0.009 | <0.001 | 0.49 |
| Hs-cTnI (pg/mL) | 2.90 (2.07, 3.00) | 1.90 (1.90, 4.52) | 1.90 (1.90, 6.58) | 1.90 (1.90, 3.00) | 0.75 | >0.99 | 0.71 |
| Creatinine (mg/dL) | 0.68 (0.63, 0.81) | 0.55 (0.50, 0.60) | 0.57 (0.50, 0.64) | 0.69 (0.63, 0.79) | <0.001 | <0.001 | 0.65 |
| GFR (mL/min) | 114.00 (92.67, 120.00) | 118.50 (108.42, 125.58) | 112.00 (98.67, 122.33) | 106.00 (94.17, 113.83) | 0.003 | 0.66 | 0.051 |
| Total cholesterol (mg/dL) | 140.00 (124.83, 165.83) | 203.00 (174.67, 231.00) | 236.50 (209.25, 268.58) | 170.00 (149.00, 197.67) | 0.009 | <0.001 | 0.29 |
| Proadrenomedullin (nmol/L) | 0.42 (0.42, 0.42) | 0.96 (0.78, 1.08) | 1.25 (1.00, 1.40) | 0.46 (0.40, 0.54) | – | – | – |

Biomarkers were described with median values for continuous variables (25$^{th}$, 75$^{th}$ percentile). NT-proBNP, N-terminal pro B-type natriuretic peptide; Hs-cTnI, high-sensitivity troponin I; GFR, glomerular filtration rate.

considered statistically significant and confidence intervals (CIs) set at 95%.

### *Ethical statement*

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the University Heart & Vascular Center, University Medical Center Hamburg-Eppendorf (UKE) (No. PV7124) and informed consent was obtained from all individual participants.

## Results

A total of 73 pregnant women were included in this study with a median gestational age of 34.0 (29.7, 37.0) years. Among them, 10 were part of a healthy control group and 63 had CVD. Baseline characteristics of the study population are shown in *Table 1*. The most common lesion was congenital heart disease (CHD) in 41 women (65.1%), acquired heart disease (valve disease, cardiomyopathy or arrhythmia) was present in 12 women (19.0%). Ten patients developed pregnancy-associated heart disease (preeclampsia, arrhythmia, peripartum cardiomyopathy). Thirty women (58.8%) had at least one cardiovascular risk factor (hypertension, diabetes, hypercholesterolemia, alcohol abuse or smoking). Cardiac medication use was common with 42.5% of women at the first antenatal visit.

Left ventricular global longitudinal strain (LV GLS) and right ventricular global longitudinal strain (RV GLS) show a transient worsening in the third trimester and peripartum (*Figure 1*). Baseline and follow-up echocardiographic findings are shown in *Table 2*. Worsening valvular regurgitation was more common than worsening valvular stenosis.

The median NT-proBNP level (95% CI) was 142.0 (86.8–317.6), 122.0 (70.7–212.2), 85.0 (46.9–205.2), and 119.5 (76.8–235.3) ng/L for the preconception, first/second trimester, third trimester/peripartum and postpartum (*Table 3*). NT-proBNP ranges broadened during pregnancy and tended to narrow postpartum in the group with CVD (range, 18.0–2,467.0; 11.0–12,144.0 and 34.9–3,091.0 ng/L for the first/second trimester, third trimester/peripartum and postpartum) However, this trend was not observed in the healthy group (range, 34.9–143.0; 34.9–70.0 and 34.9–132.0 ng/L) (*Figure 2*, Tables S11,S12).

Hs-cTnI levels showed an upward trend as pregnancy progressed in patients with CVD (range, 1.90–44.0; 1.90–

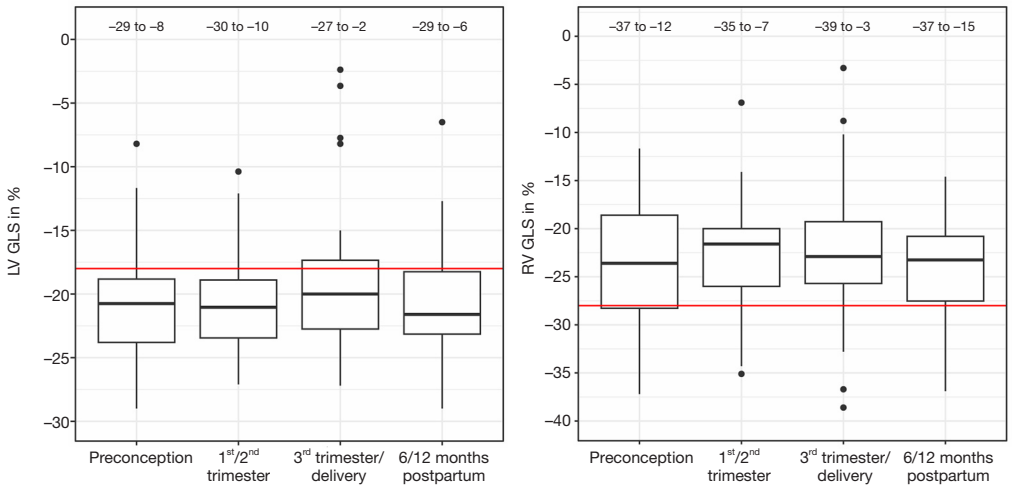


**Figure 1** LV GLS and RV GLS at preconception, first/second trimesters, third trimesters/peripartum and 6/12 months postpartum. The red lines highlight the LV GLS cut-off of –18% and RV GLS cut-off of –28% in the general population according to the ESC guideline. LV GLS, left ventricular global longitudinal strain; RV GLS, right ventricular global longitudinal strain; ESC, European Society of Cardiology.

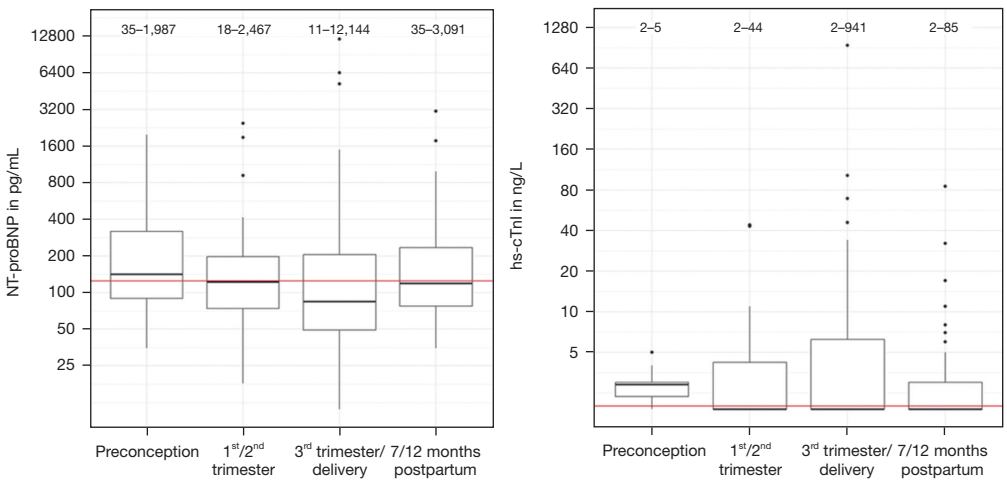


**Figure 2** NT-proBNP in pg/mL levels and hs-cTnI in ng/L at preconception, first/second trimesters, third trimester/peripartum and 6/12 months postpartum. The red lines highlight the cut-off of NT-proBNP of 125 pg/mL and of hs-cTnI of <2 ng/L in the general population according to the ESC guidelines. Y-axis is shown in log scale. NT-proBNP, N-terminal pro B-type natriuretic peptide; Hs-cTnI, high-sensitivity troponin I; ESC, European Society of Cardiology.

941.0; 1.90–85.0 pg/mL for the first/second trimester, third trimester/peripartum and postpartum) compared to the healthy group (range, 1.90–7.0; 1.90–8.0 and 1.90–16.0 pg/mL). The majority of women, had low and stable levels throughout pregnancy, with 63%, 58%, and 63% having levels below 2 pg/mL for first/second trimester, third trimester/peripartum, and postpartum (*Figure 2*). Among the women with CVD, 17 out of 63 (42.5%) had a peak hs-cTnI level >2 ng/L (range, 3–941 pg/mL) (*Table 3*).

Hospitalization due cardiovascular events was required in 21.2% patients (N=14), mainly because of heart failure (N=9, 14.1%). Five patients developed arrhythmias, three patients developed preeclampsia during pregnancy. There was no death during the study period (*Figure 3*).

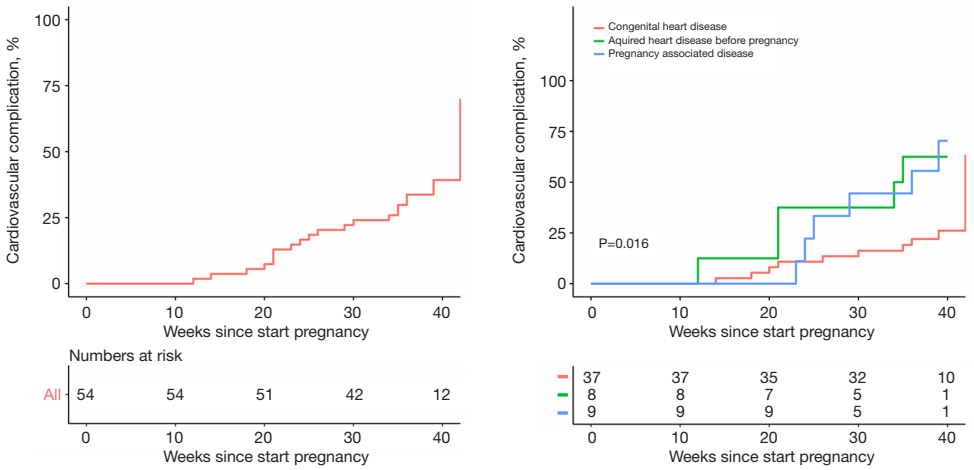


**Figure 3** Cardiovascular complications during pregnancy. Cardiovascular complications were defined as hospitalisation due to cardiovascular events, heart failure (any) and/or arrhythmia.

## Discussion

These preliminary observations from a prospective study of pregnant women with CVD receiving state-of-the-art care at a single tertiary care center in Germany could potentially be applicable to the future screening and management of an expanding, heterogenous population.

### *Outcomes*

One third of our cohort was either classified at mWHO class III indicting significantly increased risk of maternal mortality and/or severe morbidity or mWHO class IV with a contraindication to pregnancy. There was no maternal death in our cohort during pregnancy or peripartum. Overall, event rates in our cohort were low to moderate and one third of our patients had vaginal deliveries. These results are of note, as current guidelines and expert statements recommend discussing or advising termination of pregnancy in patients classified as mWHO class IV due to excessive maternal risk (8,14).

Patients with CHD showed overall less event rates compared with acquired heart disease and pregnancy-associated CVD (Table S1); these results may be partially explained by the broad spectrum of CHD with a severity range from lone atrial septal defects to more complex lesions with Fontan circulation (6). Due to advances in care for adults with lesions in the spectrum of CHD, these patients potentially receive dedicated management pre-pregnancy by tertiary centers with expertise in the field which may lead to a less-severe maternal outcomes compared with CVD of other, potentially underestimated etiology; this, however, in the absence of hard data, being speculative (3,6,14,15). In women with acquired heart disease before or during pregnancy, the majority of cardiovascular complications occurred between the 2$^{nd}$ and 3$^{rd}$ trimester, concomitant with rising plasma volume levels, peak cardiac output and rising peripheral vascular resistance, implying an aggravation of disease by physiologic changes during progressing pregnancy (16).

### *Biomarker levels*

During the course of pregnancies, we observed a broadened range of NT-proBNP during third trimester and peripartum period followed by a return to baseline levels at the time of follow-up 6–12 months postpartum. These changes potentially reflect continuously increased cardiac output and rising peripheral vascular resistance during the progression into the second-half of pregnancy, notwithstanding the fact that increased NT-proBNP levels at 20 weeks of gestation are an independent risk predictor of cardiovascular events (16,17). In our cohort, the hs-cTnI demonstrate a progressive increase as pregnancy advanced in individuals with CVD, although in the majority of individuals hs-cTnI levels remained low and unchanged throughout pregnancy. Similar trends have been described for women without CVD (18). Previous studies suggest an association between elevated levels of cardiac troponins during pregnancy and higher risk of maternal cardiovascular

 

complications (10,11). Recently, troponin I was discovered to have a role in predicting pre-eclampsia (19). Troponin I is a promising biomarker to identify individuals with higher risk for maternal complications during pregnancy, however, due limited sample size, further subgroup analyses were not feasible in our cohort. The role of troponin I in cardiovascular risk assessment during pregnancy will be the basis of further studies.

Proadrenomedullin is a promising biomarker for septic shock and multi-organ failure in critically-ill patients and has prognostic value for mortality and morbidity in patients with heart failure (20-22). Data on proadrenomedullin levels during pregnancy is limited, even more so for women with CVD. To date, there are no set reference ranges for apparently healthy or complicated pregnancies (23). In our cohort, proadrenomedullin levels increased up to a three-fold during the course of pregnancy peaking during the third trimester and peripartum period with reversal back to pre-pregnancy baseline during 6–12 months follow up, similar to NT-proBNP, as very limited previous data in non-pregnant patients would suggest (21).

### *Echocardiographic measurements*

In our cohort, LVEF worsened during pregnancy with postpartum reversal (12,24). Previous data from healthy pregnant women showed LVEF to be either unchanged or declining to low normal values during pregnancy with reversal during puerperium and postpartum (25-27). Global longitudinal strain of the left and right ventricle was decreasing throughout pregnancy; but these temporal changes were reversed at 6–12 months follow-up postpartum and statistically not significant. Prior studies on strain analyses during healthy pregnancy is somewhat conflicting; while the majority of authors describe global longitudinal strain to be preserved or decreasing to low-normal levels during the course of pregnancy, some authors describe an increase in longitudinal and circumferential strain and myocardial contractility (25-29). Commonly, the increase in cardiac output during pregnancy is explained by an increase in heart rate and stroke volume, the latter by increased end-diastolic volume and reversible remodeling of the LV (increased wall diameter and LV mass) while LV-contractility is reduced (25). Correspondingly, we have seen decreases in LVEF and GLS in women with CVD, however, there was no significant LV-remodeling. Overall, data is scarce and more prospective studies in the field, especially in women with a history of heart disease, are needed to understand (patho)physiology of ventricular systolic function during pregnancy. Evaluating left ventricular diastolic function during pregnancy is a challenging as trans-mitral inflow is critically influenced by loading conditions (24,30). We observed a decreasing E/A ratio during pregnancy throughout pregnancy, contrary to a previously described increase in E/A ratio during early pregnancy in uncomplicated pregnancies, indicating elevated left ventricular filling pressures or reduced preload in our cohort (24).

Reference ranges in echocardiographic measurements in pregnant patients with CVD are limited and require further investigation. Tailoring these reference ranges to individual pre-existing conditions may aid in distinguishing between adaptions to changes in (stroke)-volume during pregnancy and worsening of the underlying condition.

### *Overview and outlook*

In our cohort study of women with CVD, we observed that pregnancy was safe across all risk groups. We identified the 2$^{nd}$ to 3$^{rd}$ trimester as a vulnerable period due to increasing vascular resistance and higher plasma volume levels as a period of higher risk for complications in women with acquired heart disease. Serial biomarkers and dedicated echocardiographic assessment including strain imaging, e.g., at preconception counselling, at each term and at the discretion of the 'Pregnancy Heart Team' may contribute to in-depth assessment of maternal cardiovascular health and identify patients at risk for adverse cardiovascular events. Cut-offs for biomarkers and echocardiographic changes are speculative at this point as sufficient prospective data for individual patterns of disease is scarce, however, our analyses indicate that individual dynamic changes in biomarkers and echocardiographic parameters as compared to pre-pregnancy counselling may be useful in identifying individual risk constellations. Based on our observations, we conclude that comprehensive counselling and medical management before and throughout pregnancy in adults with CHD may contribute to lowering risk in these patients compared with other entities. A dedicated 'Pregnancy Heart Program' may help bring together all specialties ('Pregnancy Heart Team') to deliver the necessary care to pregnant women with CVD using a comprehensive clinical infrastructure. Such a program may particularly serve women who developed acquired heart disease or cardiovascular complications during pregnancy (e.g., peripartum cardiomyopathy, preeclampsia) and

 

close a 'care gap', as they may not already have access to care by specialist teams, most notably compared to adults with CHD.

### *Limitations*

The participants of the study represent a sample cohort of pregnant women with CVD managed at a tertiary care center in Hamburg, Northern Germany. The outcomes of other, non-tertiary centres may be different and caution is required in transferring our results to management in centers with different levels of care. Among participants, the aetiology of CVD as well as maternal risk group according to mWHO was heterogenous which may lead to a lack of generalizability of the data presented here. Two thirds of the patients that were included into our study were classified at mildly to moderately increased maternal risk (mWHO class I–II), which may skew the results towards more favourable outcomes since patients with uncommon and complex lesions may potentially be underrepresented. The overall sample size is small, limiting the power of the study and subgroup analyses. Similar to previous studies, we did not include pregnancies that did not progress beyond 20 weeks gestation. Moreover, we did not study obstetric complications during pregnancy or peripartum in this cohort.

## Conclusions

In a contemporary cohort of women with CVD managed at a tertiary care center, pregnancy was safe in terms of maternal mortality throughout all estimated levels of maternal risk. In our cohort, we found a transient increase in cardiac biomarkers and worsening of cardiac function during the third trimester and peripartum, reversing at 6–12 months postpartum, presumably due to decreased cardiac load, fluid shifts and hormonal changes. Dedicated management of patients with CVD during pregnancy, including serial echocardiography and biomarker assessment, may potentially contribute to better maternal pregnancy outcomes. Peripartal counselling and management provided by a "Pregnancy Heart Program" may identify patients particularly at risk for maternal morbidity and mortality and facilitate access to comprehensive care, e.g., serial cardiovascular assessments. Further prospective, multicentric data with sufficient follow-up is needed for optimal overall management strategies and echocardiographic as well as biomarker cut-offs.

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