ABSTRACT

Objectives Patients with congenital heart disease (CHD) are increasingly pursuing pregnancy, highlighting the need for data on late cardiovascular events (more than 6 months after delivery). We aimed to determine the incidence of late cardiovascular events in postpartum patients with CHD and evaluate the accuracy of the existing risk scores in predicting these events.

Study design We identified patients with CHD who delivered between 2008 and 2020 at a tertiary centre and had follow-up data for greater than 6 months post partum. Late cardiovascular events were defined as heart failure, arrhythmia, thromboembolic events, endocarditis, urgent cardiovascular interventions or death. Survival analysis and Cox proportional model were used to estimate the incidence of late cardiovascular events and determine the hazard ratio of factors associated with these events.

Results Of 117 patients, 19% had 36 late cardiovascular events over a median follow-up of 3.8 years. Annual incidence of any late cardiovascular event was 5.7%. Hazards of late cardiovascular events were significantly higher among those with higher Cardiac Disease in Pregnancy Study (CARPREG) II and Zwangerschap bij Aangeboren HARtAfwijking-Pregnancy in Women With Congenital Heart Disease (ZAHARA) risk scores and among patients with prepregnancy New York Heart Association class≥II. C-statistic to predict the late cardiovascular events was highest for ZAHARA (0.7823), followed by CARPREG II (0.6902) and prepregnancy New York Heart Association class≥II. (0.6677).

Conclusions Currently available risk tools designed for prognostication during the peripartum period can also be used to determine risks of late maternal cardiovascular events among those with CHD. These findings provide important new information for counselling and risk modification.

INTRODUCTION

Due to advances in cardiac care, an increasing number of patients with congenital heart disease (CHD) are now reaching childbearing age. The haemodynamic changes of pregnancy include increases in plasma volume, heart rate and cardiac output, which may not be well tolerated by these patients. Those with CHD can experience adverse cardiovascular outcomes during pregnancy, within 6 months post partum, and even after 6 months postpartum (late cardiovascular events). Although important for appropriate counselling and management, information regarding incidence and predictors of late cardiovascular events is limited.

One prior study demonstrated that prepregnancy maternal characteristics, such as ventricular/valvular function, cyanosis and adverse cardiovascular events during or before pregnancy are independent predictors of late cardiovascular events. However, these data were published prior to the availability of many of the contemporary pregnancy-related risk scores, such as the modified...
WHO classification (mWHO), Cardiac Disease in Pregnancy Study (CARPREG) score, CARPREG II score and Zwangerschap bij Aangeboren HartAfwijking-Pregnancy in Women With Congenital Heart Disease (ZAHARA) score. These scores were developed to determine risk of peripartum adverse events (in pregnancy and up to 6 months post partum), but their utility in predicting late maternal cardiovascular events has not been evaluated. Moreover, most research to date on peripartum cardiovascular events has evaluated a broad variety of native and acquired heart disease, risking overgeneralisation of the vast range of physiology. Understanding utility of these risk scores in the CHD population could allow use of familiar and validated tools to facilitate counselling and risk modification for these patients while considering late cardiovascular risks.

To this end, we used a database of pregnant patients with CHD managed by a multidisciplinary cardio-obstetric team at a tertiary centre to determine the (1) rates and predictors of late cardiovascular events and (2) accuracy of the contemporary risk scores in predicting these events.

**MATERIALS AND METHODS**

This study included all patients with CHD followed at the University of California, San Francisco (UCSF) multidisciplinary Pregnancy and Cardiac Treatment (PACT) programme. Founded in 2008, the PACT programme is run by a multidisciplinary group of specialists in maternal–fetal medicine, cardiology, obstetric anesthesiology and nursing managing preconception, antepartum, intrapartum and postpartum patients with CHD and other cardiac disease. Patients with CHD who delivered at UCSF between August 2008 and March 2020 were eligible for study inclusion. Those with isolated patent foramen ovale or isolated mitral valve prolapse were excluded, as previously described. For patients who had multiple pregnancies during the study period, only the first pregnancy was included. Pregnancies that did not continue beyond 20 weeks’ gestation were excluded. Patients who died during pregnancy or within first 6 months post partum were excluded.

All data were retrospectively collected from the electronic medical record, with review of obstetric and cardiovascular consultation notes, radiographic and echocardiographic reports and scanned records from referring physicians. Study data were collected and managed using the Research Electronic Data Capture tool, a secure, web-based software platform designed to support data capture for research studies.

The primary outcome was a composite outcome of any late cardiovascular event, defined as an adverse cardiovascular event occurring more than 6 months after delivery. Adverse cardiovascular events included: (1) heart failure or pulmonary oedema (defined by diuretic use, chest X-ray documentation of pulmonary oedema or physical examination documentation of rales heard more than one-third up lung fields); (2) sustained arrhythmia requiring treatment, documented by ECG, or regarded as symptomatic and significant by a cardiologist at the time of the event; (3) thromboembolic events, including myocardial infarction or cerebrovascular accident; (4) bacterial endocarditis; (5) the need for urgent invasive cardiac intervention or (6) any cardiovascular death. Any planned cardiac intervention, such as a planned closure of atrial septal defect diagnosed during pregnancy or planned valvular intervention, was excluded.

Predictor variables included maternal demographic characteristics, prepregnancy cardiac characteristics and pregnancy-related events. Demographic variables included age, race/ethnicity, insurance status, body mass index and multiparity. Prepregnancy cardiac characteristics were included based on the most recently available information up to 2 years before the last menstrual period. For patients who had no prepregnancy data available, information available during the first pregnancy-related visit was used to determine prepregnancy characteristics. Prepregnancy cardiac characteristics included type of CHD (severe or non-severe), New York Heart Association (NYHA) functional class, prior cardiovascular events (heart failure, arrhythmia or thromboembolic events), prior cardiovascular interventions, chronic hypertension, diabetes mellitus and use of any cardiac medication. Echocardiographic data collected included systemic ventricular function, systemic ventricular ejection fraction, Doppler quantification of obstructive and regurgitant lesions, and right ventricular systolic pressure estimates. mWHO group, CARPREG, CARPREG II and ZAHARA risk scores were calculated for each patient.

Pregnancy-related events included antepartum cardiovascular events, postpartum cardiovascular events and perinatal events. Antepartum events included any cardiovascular event (as defined above) that occurred between the patient’s last menstrual period and the day of delivery, and postpartum events included any cardiovascular event that occurred from the day after delivery through 6 months post partum.

Dichotomous variables were presented as number with percentage, and continuous variables as mean±SD or median with IQR as appropriate. Kaplan-Meier survival analysis was performed to estimate the incidence of late cardiovascular events. Patients who had the event were censored at the time of their first event; patients who did not have the event were censored at the time of their last follow-up. Unadjusted and adjusted Cox proportional hazard ratio (HR) with 95% confidence intervals (CI) were calculated to determine predictors of late cardiovascular events. Concordance statistic (C-statistic) with 95% CI was used to evaluate how well the various risk scores and other variables predict late cardiovascular events. Two-tailed p<0.05 was considered statistically significant. Statistical testing was performed with the use of Stata software V.14.2.
and there were no deaths. Annual incidence of any late infective endocarditis each occurred in three patients, and conduit replacement. Thromboembolic events and frequency arrhythmia ablation procedure and aortic valve replacement in the setting of endocarditis, radiofrequency arrhythmia ablation procedure and aortic valve and conduit replacement. Thromboembolic events and infective endocarditis each occurred in three patients, and there were no deaths. Annual incidence of any late cardiovascular event was 5.7%, heart failure was 5.3% and arrhythmia 5.5%. Using Kaplan-Meier survival analysis, we estimated that 25% of patients with CHD will experience a cardiovascular event by 4.4 years post partum.

Among the demographic, prepregnancy and pregnancy-related characteristics, the incidence of late cardiovascular events was higher for those with prepregnancy NYHA class II (56.3% vs 12.9%, p<0.001), any prepregnancy cardiovascular event (39.3% vs 12.4%, p=0.004), any cardiovascular event during pregnancy (50.0% vs 14.6%, p=0.005), and any cardiovascular event within 6 months post partum (75.0% vs 16.8%, p=0.021). Annual incidence of late cardiovascular events was significantly higher with higher pregnancy risk scores when

### RESULTS

A total of 502 consecutive pregnancies complicated by maternal cardiac disease were identified between 2008 and 2020. Of these with native and acquired cardiac disease, 176 pregnancies among 149 patients had a diagnosis of CHD. Finally, 117 out of the 149 patients with CHD had follow-up data for more than 6 months post partum and were included. About one-quarter of these patients did not have prepregnancy data; data available during their first pregnancy evaluation was used. There were 42 (36%) patients with severe CHD. The most common CHD lesions were aortic valve disease (16%), atrial septal defect (15%), tetralogy of Fallot (15%) and transposition of the great arteries (12%) (table 1). Baseline demographics, prepregnancy cardiac characteristics and pregnancy-related events are summarised in table 2.

### Rates and predictors of late cardiovascular events

Median follow-up time was 3.8 years (IQR 1.8–6.5). A total of 22 patients (19%) had 36 late cardiovascular events, most commonly arrhythmia (15, 42% of events) and heart failure (11, 31% of events). An urgent cardiac intervention was needed in four patients and included ascending aortic pseudoaneurysm repair, pulmonary valve replacement in the setting of endocarditis, radiofrequency arrhythmia ablation procedure and aortic valve and conduit replacement. Thromboembolic events and infective endocarditis each occurred in three patients, and there were no deaths. Annual incidence of any late cardiovascular event was 5.7%, heart failure was 5.3% and arrhythmia 5.5%.
using CARPREG (3.5% if score < 1 vs 9.8% if score ≥ 1, p = 0.044), CARPREG II (3.2% if score < 3 vs 10.7% if score ≥ 3, p = 0.009) and ZAHARA (1.0% if score < 0.51 vs 5.0% if score 0.51–1.49 vs 11.5% if score ≥ 1.50, p = 0.0007). However, incidence of late events was not significantly different between different mWHO groups (3.5% if mWHO ≤ II vs 6.9% if mWHO > II 1, p = 0.225) (figure 1).

Univariate and multivariate HR for the various risk scores and other key characteristics are shown in figure 2. After multivariate adjustment, the HR for late cardiovascular events remained significant for prepregnancy NYHA class ≥ II, CARPREG II score ≥ 3 and ZAHARA score ≥ 1.50. The C-statistic to predict the late cardiovascular events was highest for ZAHARA score, followed by CARPREG II score and prepregnancy NYHA class (table 3).

![Figure 1](image1.png) Late cardiovascular (CV) event rates by risk score Kaplan-Meier CV event rate by (A) mWHO class, (B) CARPREG score, (C) CARPREG II score and (D) ZAHARA score. CARPREG, Cardiac Disease in Pregnancy Study; mWHO, modified WHO; ZAHARA, Zwangerschap bij Aangeboren.

![Figure 2](image2.png) Unadjusted and adjusted HR for late cardiovascular (CV) events (>6 months after delivery) among postpartum patients with congenital heart disease (CHD) a Adjusted for maternal age, prepregnancy NYHA class, prepregnancy CV events, any CV event during pregnancy or any postpartum CV event within 6 months after delivery. b Adjusted for maternal age, prepregnancy NYHA class, any CV event during pregnancy and any postpartum CV event within 6 months after delivery. c Adjusted for maternal age, any CV event during pregnancy and any postpartum CV event within 6 months after delivery. CARPREG, Cardiac Disease in Pregnancy Study; NYHA, New York Heart Association; ZAHARA, Zwangerschap bij Aangeboren.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Hazard Ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-pregnancy NYHA ≥ II Unadjusted</td>
<td>4.0 (1.6-9.9)</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>4.8 (1.6-14.8)</td>
<td>0.008</td>
</tr>
<tr>
<td>Any Pre-pregnancy CV Event</td>
<td>2.6 (1.1-6.1)</td>
<td>0.031</td>
</tr>
<tr>
<td></td>
<td>2.6 (1.1-6.5)</td>
<td>0.055</td>
</tr>
<tr>
<td>Modified WHO group &gt; II Unadjusted</td>
<td>1.8 (0.7-4.7)</td>
<td>0.231</td>
</tr>
<tr>
<td></td>
<td>1.4 (1.0-2.0)</td>
<td>0.076</td>
</tr>
<tr>
<td>CARPREG score ≥ 1 Unadjusted</td>
<td>2.4 (1.0-5.6)</td>
<td>0.050</td>
</tr>
<tr>
<td></td>
<td>1.5 (0.9-2.3)</td>
<td>0.074</td>
</tr>
<tr>
<td>CARPREG II score ≥ 3 Unadjusted</td>
<td>3.0 (1.3-7.2)</td>
<td>0.023</td>
</tr>
<tr>
<td></td>
<td>2.7 (1.1-6.5)</td>
<td>0.013</td>
</tr>
<tr>
<td>ZAHARA score ≥ 1.50 Unadjusted</td>
<td>5.3 (2.0-14.6)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>5.6 (1.9-16.7)</td>
<td>0.306</td>
</tr>
<tr>
<td>Any CV Event During Pregnancy</td>
<td>1.8 (0.6-4.3)</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>0.6 (0.2-1.9)</td>
<td>0.355</td>
</tr>
<tr>
<td>Any Postpartum CV Event Unadjusted</td>
<td>4.1 (1.2-14.3)</td>
<td>0.026</td>
</tr>
<tr>
<td></td>
<td>1.8 (0.5-7.2)</td>
<td>0.276</td>
</tr>
</tbody>
</table>
and heart failure are known to be inter-
maternal CHD population and in the non-
most frequent peripartum cardiovascular events in the
This is unsurprising, given that these two events are the
failure as the most common late cardiovascular events.

patterns and management decisions might account for
clinical and functional considerations. Cardio-obstetric clini-
cians are already familiar with these existing risk scores
and can easily incorporate data from this study to provide
counselling regarding late cardiovascular events based on
risk scores. Additionally, we found that a prepregnancy
NYHA class is also a reliable predictor of late cardio-
vascular events; this is a simple tool that can easily be

Table 3 C-statistics for predictors of late cardiovascular
(CV) events

<table>
<thead>
<tr>
<th>Predictor</th>
<th>C-statistic</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZAHARA score</td>
<td>0.7823</td>
<td>0.6947 to 0.8710</td>
<td>Reference</td>
</tr>
<tr>
<td>CARPREG II score</td>
<td>0.6902</td>
<td>0.5773 to 0.8031</td>
<td>0.1300</td>
</tr>
<tr>
<td>Prepregnancy NYHA class</td>
<td>0.6677</td>
<td>0.5593 to 0.7761</td>
<td>0.0800</td>
</tr>
<tr>
<td>Modified WHO group</td>
<td>0.6163</td>
<td>0.5085 to 0.7241</td>
<td>0.0274</td>
</tr>
<tr>
<td>Any prepregnancy CV event</td>
<td>0.6605</td>
<td>0.5468 to 0.7743</td>
<td>0.0213</td>
</tr>
<tr>
<td>CARPREG score</td>
<td>0.6622</td>
<td>0.5478 to 0.7767</td>
<td>0.0203</td>
</tr>
<tr>
<td>Any CV event during preg</td>
<td>0.6222</td>
<td>0.5192 to 0.7253</td>
<td>0.0110</td>
</tr>
<tr>
<td>Any event &lt;6 months post</td>
<td>0.5629</td>
<td>0.4888 to 0.6370</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

CARPREG, Cardiac Disease in Pregnancy Study; NYHA, New York
Heart Association; ZAHARA, Zwangerschap bij Aangeboren.

COMMENT
Principal findings
In this single tertiary centre cohort of previously pregnant
patients with CHD, we found that approximately one in
four have a late cardiovascular event by 4.4 years of post-
partum follow-up. When adjusting for key confounding
variables, independent predictors of late cardiovascular
events were prepregnancy NYHA class ≥II, CARPREG
II score ≥3 and ZAHARA score ≥0.51. Of the existing
risk scores developed for predicting risk of peripartum
adverse events, the ZAHARA and CARPREG II scores
had highest C-statistic for predicting late cardiovascular
events. These data provide valuable information to guide
clinicians on preconception counselling, risk modifica-
tion and long-term surveillance for late cardiovascular
events among those with CHD.

Results in the context of what is known
The overall incidence of late cardiovascular events in
our study was 75% higher than that reported in a Cana-
dian cohort (21% vs 12%) despite similar complexity of
CHD population (~28% patients in both studies had
CARPREG risk score ≥1). Differences in baseline patient
characteristics (higher prevalence of prepregnancy
NYHA class ≥II, chronic hypertension, prepregnancy
cardiovascular event in our study), institutional referral
patterns and management decisions might account for
some of the disparity. Despite these differences, both our
findings and the prior report noted arrhythmia and heart
failure as the most common late cardiovascular events.
This is unsurprising, given that these two events are the
most frequent peripartum cardiovascular events in the
maternal CHD population and in the non-pregnant
CHD population. Furthermore, arrhythmias and heart failure are known to be inter-related, with one
complication typically serving as a marker or a risk factor
for the other.

Since the initial description of CARPREG score in
2001, multiple additional scoring systems (ie, ZAHARA,
mWHO11 22 and CARPREG II10) have been developed
and are being used to predict risk of peripartum cardio-
vascular events among those with maternal cardiac
disease. In this study, we expand on the utility of these
scoring systems to provide the data regarding their ability
to predict late cardiovascular events that occur more
than months post partum. We found that CARPREG II
and ZAHARA had the highest C-statistics for prediction
and that the mWHO class was not associated with risk of
late cardiovascular events. The mWHO class is unique in
including only the anatomic details of the cardiac diag-
nosis. In contrast, the other risk scores include clinical
history (eg, prepregnancy cardiac events) and physio-
logical status (eg, prepregnancy NYHA class) in their
prediction model. Since scores relying on cardiac history
and physiological status (CARPREG II and ZAHARA)
more accurately predicted late cardiovascular events
than mWHO in our study, we hypothesise that the clin-
ical history and NYHA class is likely more important than
the anatomical CHD diagnosis for prognostication of late
outcomes after pregnancy.

Clinical implications
Our findings provide important data for the growing
population of patients with CHD in their childbearing
decades. All patients with CHD of childbearing potential
should have routine counselling regarding cardio-
vascular risks during pregnancy, in the immediate post-
partum period, and in the long-term following a preg-
nancy. A detailed history about the patient’s functional
status and prior cardiac events should be the founda-
tion of such visits. Additionally, for those contemplating
pregnancy or who are newly pregnant, efforts should be
made to obtain in-depth cardiac evaluation (eg, compre-
hensive echocardiogram, ECG or cardiac rhythm moni-
tering) and a detailed medication history in order to
determine the patient’s specific pregnancy risk scores.
Since the American Heart Association and American
College of Cardiology generally recommend multidisci-
plinary care at a comprehensive CHD centre for these
patients, widespread knowledge of these risk scores by
general practitioners would help facilitate specialty refer-
als for patients with CHD who might be otherwise lost to
specialty care.

Rather than developing a new risk prediction tool, we
chose to evaluate the accuracy of existing pregnancy risk
scores that already incorporate some important anatom-
ical and functional considerations. Cardio-obstetric clini-
cians are already familiar with these existing risk scores
and can easily incorporate data from this study to provide
counselling regarding late cardiovascular events based on
risk scores. Additionally, we found that a prepregnancy
NYHA class is also a reliable predictor of late cardio-
vascular events; this is a simple tool that can easily be

ascertained via a thorough clinical history if a provider is not familiar with these cardiac risk scores.

Research implications

We found that NYHA class, CARPREG II score and ZAHARA score were predictive of late cardiac events in our single centre population of previously pregnant individuals with CHD. These findings should be confirmed in larger and multicentre longitudinal studies. Consideration should also be given to expanding our understanding in this area, including creation of a new risk prediction model specifically for late cardiac events following pregnancy. Additional research should focus on whether preconception counselling and targeted improvement of functional status can reduce the risk of late postpartum cardiac events. Given the finding that NYHA class was a strong predictor of late events, we hypothesise that improvement in pre pregnancy NYHA class might help to improve long-term cardiovascular outcomes; more research is needed to support this. Other areas for future work include evaluating how multiple pregnancies affect risk, and whether pregnancy itself is associated with cardiac decline in patients with CHD by using a comparison group of never-pregnant patients with CHD.

Strengths and limitations

This study is limited by its retrospective nature, which limits data collection to what is available in the medical record. This design also limited the sample size of patients with available long-term follow-up, since many patients at our tertiary care institution return to community care after pregnancy and long-term outcomes are unknown. Similarly, adverse outcomes may have been underestimated since we did not have information regarding adverse outcomes that occurred at other facilities. This study is also subject to referral bias, as patients seen in our single tertiary centre may represent a more complex population of patients with CHD, thus limiting the generalisability of our findings. However, as more centres move towards this recommended model of multidisciplinary care for patients with complex cardiac conditions, our findings will become applicable to these institutions and populations.

Despite these limitations, this study provides contemporary data on the accuracy of existing pregnancy risk scores to predict late cardiovascular events among patients with CHD. This study is strengthened by its long postpartum follow-up time and by the use of manual chart extraction, which allows for more granular detail and accurate assessment of cardiovascular events compared with studies that use admission, billing, or administrative data.

CONCLUSIONS

Late cardiovascular events more than 6 months after delivery are common in patients with CHD. The ZAHARA and CARPREG II scores are useful in predicting these events, emphasising their utility in predicting not only peripartum cardiovascular events but also late maternal cardiovascular risks. Pre pregnancy NYHA class is another simple, easy and reliable tool that can be used to predict late cardiovascular morbidity. These data provide important information for preconception counselling, risk modification and anticipation of adverse events late after pregnancy with CHD.

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Contributors

HS: conceptualisation, investigation, formal analysis, original draft-writing, responsible for the overall content. NC: conceptualisation, original draft-writing. SB: conceptualisation, formal analysis, review and editing. YJ: data curation, visualisation JH: investigation. ISH: visualisation, resources, methodology. NP: conceptualisation, methodology. JS: supervision, review and editing. AA: conceptualisation, supervision, original draft-writing, review and editing, and responsible for the overall content as guarantor.

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Competing interests

None declared.

Patient consent for publication

Not applicable.

Ethics approval

This study was approved by the UCSF Committee on Human Research (Institutional Review Board #10-04360).

Provenance and peer review

Not commissioned; internally peer reviewed.

Data availability statement

Data are available on reasonable request. Data are available on reasonable request. Deidentified patient data are available through primary the primary author. ORCID 0000-0001-5787-2772, although reuse would be permitted only through researchers at the primary institution.

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