openheart

Pregnancy complications and long-term risk of cardiovascular events in women with structural heart disease

Elin Täufer Cederlöf ,[1] Lars Lindhagen,[2] Maria Lundgren,[3] Bertil Lindahl ,[1,2] Christina Christersson[1]

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/openhrt-2024-002833).

To cite: Cederlöf ET, Lindhagen L, Lundgren M, *et al*. Pregnancy complications and long-term risk of cardiovascular events in women with structural heart disease. *Open Heart* 2024;**11**:e002833. doi:10.1136/openhrt-2024-002833

Received 16 August 2024
Accepted 4 September 2024

Check for updates

© Author(s) (or their employer(s)) 2024. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

[1]Department of Medical Sciences, Cardiology, Uppsala University, Uppsala, Sweden
[2]Uppsala Clinical Research Center, Uppsala University, Uppsala, Sweden
[3]Department of Women's and Children's Health, Uppsala University, Uppsala, Sweden

Correspondence to
Dr Elin Täufer Cederlöf; elin.cederlof@medsci.uu.se

ABSTRACT

Background To determine the frequency of pregnancy complications and their association with the risk of cardiovascular outcomes in women with structural heart disease (SHD).

Methods This nationwide registry-based cohort study included women in Sweden with SHD (pulmonary arterial hypertension, congenital heart disease or acquired valvular heart disease) with singleton births registered in the national Medical Birth Register (MBR) between 1973 and 2014. Exposures were pregnancy complications; pre-eclampsia/gestational hypertension (PE/gHT), preterm birth and small for gestational age (SGA) collected from MBR. The outcomes were cardiovascular mortality and hospitalisations defined from the Cause of Death Register and the National Patient Register. Cox regression models were performed with time-dependent covariates, to determine the possible association of pregnancy complications for cardiovascular outcomes.

Results Among the total of 2 134 239 women included in the MBR, 2554 women with 5568 singleton births were affected by SHD. Women without SHD (N=2 131 685) were used as a reference group. PE/gHT affected 5.8% of pregnancies, preterm birth 9.7% and SGA 2.8%. Preterm birth (adjusted HR, aHR 1.91 (95% CI 1.38 to 2.64)) was associated with an increased risk of maternal all-cause mortality. PE/gHT (aHR 1.64 (95% CI 1.18 to 2.29)) and preterm birth (aHR 1.56 (95% CI 1.19 to 2.04)) were associated with an increased risk of hospitalisations for atherosclerotic CVD.

Conclusions Pregnancy complications were frequent in women with SHD. With a median follow-up time of 22 years, preterm birth was associated with a higher risk of cardiovascular mortality, and PE/gHT and preterm birth were associated with cardiovascular morbidity. In women with SHD, pregnancy complications may provide additional information for the risk assessment of future cardiovascular outcomes.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Pregnancy complications are associated with an increased risk of atherosclerotic cardiovascular disease in the general population, but their importance for the long-term risk in women with structural heart disease is unknown.

WHAT THIS STUDY ADDS

⇒ The study highlights that pregnancy complications are common in women with structural heart disease and several are associated with an increased long-term risk of atherosclerotic cardiovascular disease.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Pregnancy complications, including also fetal complications, can provide additional information in the risk evaluation of women with structural heart disease and may be used to identify women in need of improved primary prevention strategies.

INTRODUCTION

Improved early surgical and medical treatment of congenital and acquired heart disease increases the possibility of pregnancy in women of childbearing age with structural heart disease (SHD).[1] SHD is associated with a risk of both maternal and fetal complications during pregnancy[2–4] and clinical recommendations highlight the importance of structured follow-up to prevent adverse outcomes of pregnancy.[5]

SHD is a heterogeneous group of diseases with varying risks that are dependent on the severity of the underlying condition.[5] Maternal mortality is high in pregnant women with pulmonary arterial hypertension (PAH)[6] and is associated with an increased risk of preterm birth (PTB), fetal or neonatal death and low birth weight.[6 7] Congenital heart disease (CHD) includes simple and complex lesions of varying severity, and the risk of pregnancy complications varies for different conditions and severity of CHD.[8] Acquired valvular heart disease (aVHD) is often due to rheumatic heart disease in childbearing age but can also be degenerative[5] and is associated with an increased risk of pre-eclampsia (PE), PTB, intrauterine growth restriction and fetal death.[9 10] Knowledge of pregnancy complications in women with SHD has

Open Heart: first published as 10.1136/openhrt-2024-002833 on 13 September 2024. Downloaded from https://openheart.bmj.com on 4 February 2025 by guest. Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

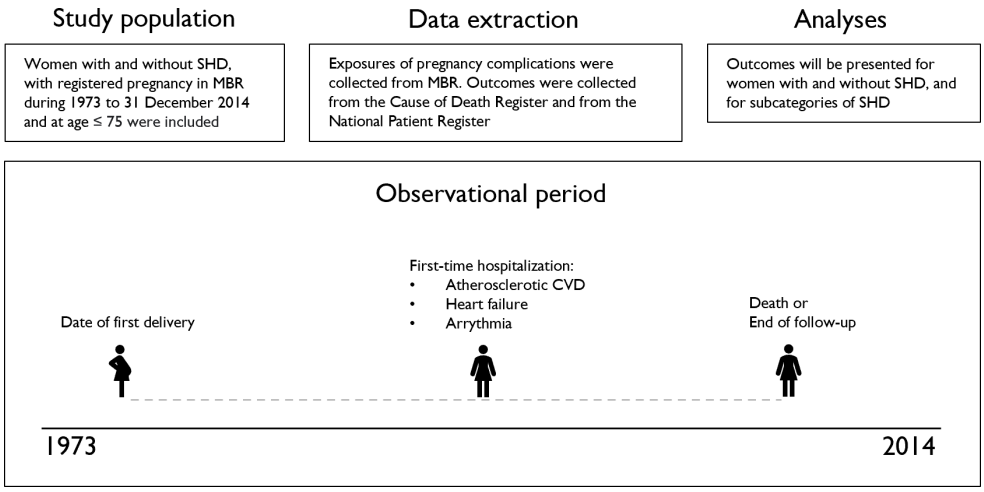

Figure 1 Study design. CVD, cardiovascular disease; MBR, Medical Birth Register; SHD, structural heart disease.

improved over the last decades, but recent guidelines address the need for larger cohort studies to evaluate the frequency of pregnancy complications and cardiovascular events in this population.[5]

Pregnancy complications, including PE, gestational hypertension (gHT), PTB and small for gestational age (SGA), are associated with an increased risk of early asymptomatic coronary artery disease as well as ischaemic heart disease, stroke and peripheral artery disease in the general population.[11 12] Whether pregnancy complications have prognostic value for the long-term risk of atherosclerotic cardiovascular disease (CVD) and deterioration of heart function for women with SHD is unknown.[5]

The objectives were to determine the frequency of pregnancy complications in women with SHD (defined as PAH, CHD and aVHD) and to evaluate the association of these complications for the long-term risk of atherosclerotic CVD and deterioration of heart function in this population.

METHODS

Study population

In this register-based cohort study among 2 134 239 women with singleton births registered in Sweden's Medical Birth Register (MBR) between 1973 and 2014, 2554 women had SHD (PAH, CHD or aVHD, figures 1–2). The study population has been described in detail elsewhere.[12] The study cohort was followed from the date of a woman's first delivery until death or the end of follow-up (31 December 2014). In order to focus on women at risk for an earlier onset of CVD, only women aged 75 years or younger at the end of 2014 or, women who died before the end of 2014, who were younger than 76 at the time of death, were included. Multiple gestation pregnancies and pregnancies with missing delivery dates were excluded. Data in MBR from the included women without SHD (N=2 131 685) were used as a reference group.

Data sources

Baseline characteristics and pregnancy complications exposures were collected from MBR and linked to outcomes of mortality (Cause of Death Registry, CDR) and hospitalisations (National Patient Registry, NPR). Information about comorbidities was collected from both the MBR and NPR. Diagnoses were registered according to International Classification of Diseases (ICD) codes (ICD-8, ICD-9 and ICD-10, online supplemental table S1).[12]

Women with PAH, CHD and aVHD were identified by the ICD codes (online supplemental table S1) for diagnoses registered in both MBR and NPR, from 1 year before and 5 years after delivery for all registered deliveries. This was based on the assumption that a diagnosis of SHD within this time interval was likely present during pregnancy. If there were several registrations of the same SHD diagnosis in more than one pregnancy, the first registered diagnosis was used. If there were several different diagnoses of SHD, women were divided into groups according to this hierarchical order: PAH, CHD and aVHD.

Baseline characteristics

Baseline characteristics considered in each pregnancy were maternal age, body mass index (BMI), smoking and civil status. Parity was calculated from the total number of deliveries registered in MBR. Comorbidities (diabetes mellitus, hypertension, chronic kidney disease and venous thromboembolism) from two time points were considered: both those in association with each pregnancy (diagnoses registered in MBR and NPR dating from 1 year before delivery date to 6 months postpartum), and at hospitalisation(s) (main and secondary diagnoses registered in NPR).

Pregnancy complications

Three pregnancy complications were studied: PE or gHT, PTB and SGA. PE/gHT was defined based on corresponding ICD codes collected from MBR and NPR

Open Heart: first published as 10.1136/openhrt-2024-002833 on 13 September 2024. Downloaded from https://openheart.bmj.com on 4 February 2025 by guest. Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

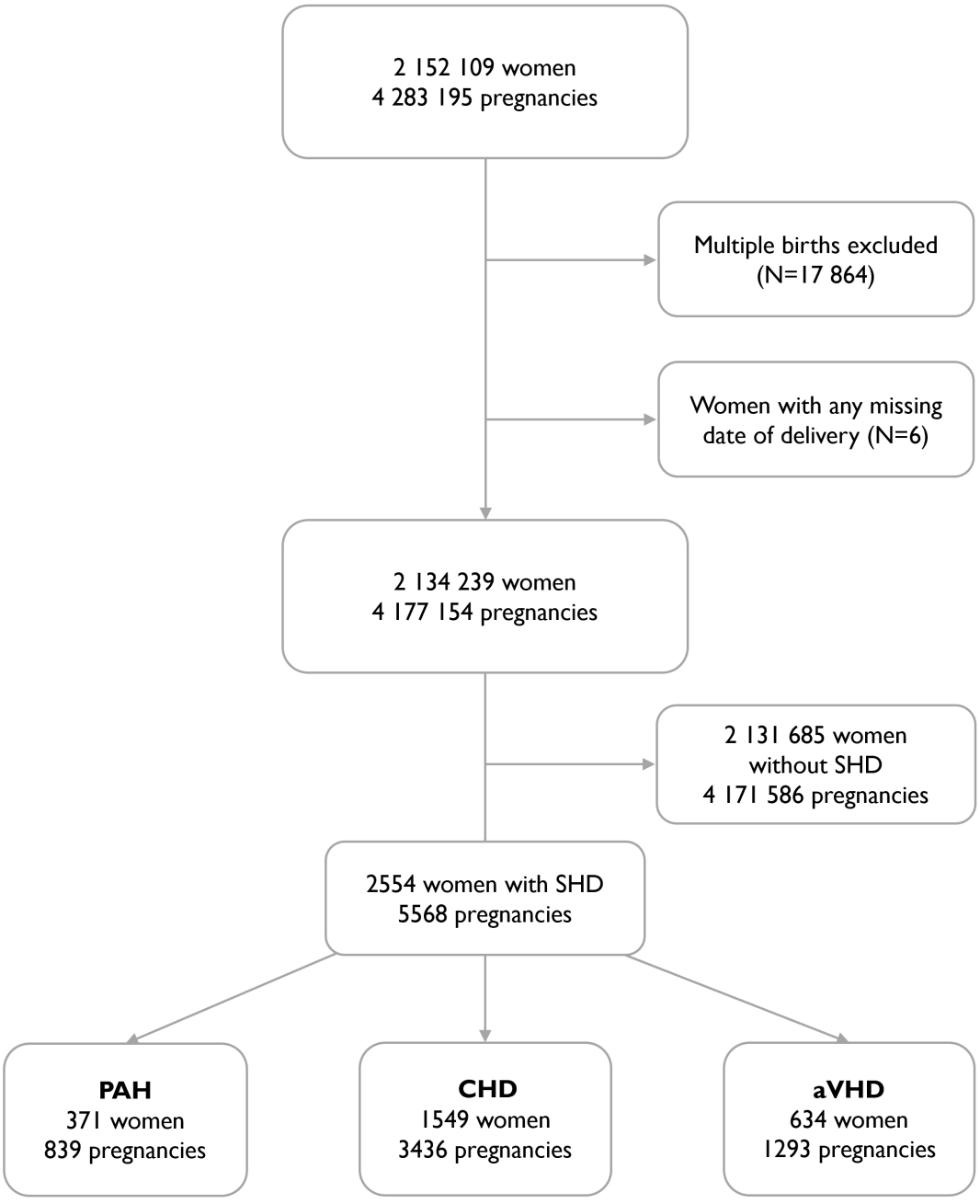

Figure 2 Flow chart of the study population with births in Sweden 1973–2014. aVHD, acquired valvular heart disease; CHD, congenital heart disease; PAH, pulmonary arterial hypertension.

(registered from 1 year prior to delivery to 6 months postpartum) (online supplemental table S1). PTB was defined as a gestational age of less than 37 weeks, both iatrogenic and spontaneous. SGA was defined as a birth weight for gestational age and sex less than 2 SDs for weight below the Swedish reference curve. Pregnancy complications were studied separately for all registered pregnancies.

Cardiovascular outcomes

Mortality

Mortality was classified according to the underlying cause of death and included all-cause mortality and cardiovascular mortality due to ischaemic heart disease or ischaemic stroke.

Hospitalisation for CVDs

Hospitalisation for CVD was defined as a first-time hospital admission based on a main diagnosis of atherosclerotic CVD (ischaemic heart disease/ischaemic stroke/transient ischaemic attack/peripheral artery disease), heart failure or arrhythmia (both supraventricular and ventricular). Hospitalisations for the same main diagnosis with less than 24 hours between discharge and the next admission were treated as one hospital admission and the

Open Heart: first published as 10.1136/openhrt-2024-002833 on 13 September 2024. Downloaded from https://openheart.bmj.com on 4 February 2025 by guest. Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

main diagnosis of the first hospitalisation was defined as the outcome. Heart failure in association with pregnancy was defined as hospitalisation or a diagnosis registered in MBR (between 1 year before delivery and 6 months post partum) for each registered pregnancy. The women were followed until the first registered hospitalisation for atherosclerotic CVD, heart failure or arrhythmia, separately. The ICD codes for outcomes of mortality and hospitalisations are described in online supplemental table S1. Women with outcome events before the date of the first delivery were excluded, separately for each outcome (24 with atherosclerotic CVD, 63 with heart failure and 170 with arrythmia).

Confounders

Potential confounders were identified by direct acyclic graphs described in online supplemental figure S1. Maternal age, BMI, smoking, civil status, parity and comorbidities in pregnancy or in hospitalisations (ie, diabetes mellitus, hypertension, chronic kidney disease or venous thrombosis registered in MBR, or any of these registered as a main or secondary diagnosis in NPR) were considered as potential confounders. BMI and maternal smoking were registered from 1982 onward. BMI was categorised as below 18.5 (underweight), 18–24.9 (normal weight), 25–29.9 (overweight) or above 30 kg/

Table 1 Baseline characteristics

	Women with SHD (N=2554)	PAH (N=371)	CHD (N=1549)	aVHD (N=634)	Women without SHD (N=2 131 685)
Maternal age at first pregnancy (N=2554)					
<18	38 (1.5)	9 (2.4)	19 (1.2)	10 (1.6)*	25 164 (1.2)
18–25	969 (37.9)	151 (40.7)	640 (41.3)	178 (28.1)	688 661 (32.3)
25–30	854 (33.4)	134 (36.1)	520 (33.6)	200 (31.5)	772 377 (36.2)
30–35	474 (18.6)	49 (13.2)	270 (17.4)	155 (24.4)	468 335 (22.0)
35–40	178 (7.0)	24 (6.5)	81 (5.2)	73 (11.5)	149 749 (7.0)
>40	41 (1.6)	4 (1.1)	19 (1.2)	18 (2.8)	27 396 (1.3)
Body mass index in first pregnancy, available from 1982 (N=976)					
Underweight (<18.5)	134 (13.7)	19 (14.3)	75 (12.6)	40 (16.1) ns	84 980 (10.3)
Normal weight (18.5–24.9)	561 (57.5)	86 (64.7)	330 (55.6)	145 (58.5)	481 773 (58.4)
Overweight (25–29.9)	207 (21.2)	23 (17.3)	136 (22.9)	48 (19.4)	180 520 (21.9)
Obesity (>30)	72 (7.4)	5 (3.8)	52 (8.8)	15 (6.0)	77 172 (9.4)
Smoking in first pregnancy, available from 1982 (N=1760)					
Non-smoker	1447 (82.2)	203 (77.5)	863 (81.8)	381 (86.0)*	1 199 690 (84.5)
Smoker	313 (17.8)	59 (22.5)	192 (18.2)	62 (14.0)	219 978 (15.5)
Civil status at first pregnancy (N=2335)					
Cohabitation/married	1897 (81.2)	265 (78.2)	1149 (81.0)	483 (83.7) ns	1 642 698 (83.0)
Single parent/previously married/unmarried/other	438 (18.8)	74 (21.8)	270 (19.0)	94 (16.3)	336 721 (17.0)
Parity (N=2554)					
1	719 (28.2)	110 (29.6)	374 (24.1)	235 (37.1)*	714 076 (33.5)
2	1071 (41.9)	127 (34.2)	700 (45.2)	244 (38.5)	949 872 (44.6)
3	497 (19.5)	85 (22.9)	317 (20.5)	95 (15.0)	355 941 (16.7)
4	182 (7.1)	35 (9.4)	110 (7.1)	37 (5.8)	83 060 (3.9)
5 or more	85 (3.3)	14 (3.8)	48 (3.1)	23 (3.6)	28 736 (1.3)
Mode of delivery, per pregnancy					
Number of pregnancies	5568	839	3436	1293	4 171 586
Vaginal	3795 (68.2)	593 (70.7)	2350 (68.4)	852 (65.9)	3 246 154 (77.8)
C-section	1179 (21.2)	173 (20.6)	722 (21.0)	284 (22.0)	526 083 (12.6)
Missing	594 (10.7)	73 (8.7)	364 (10.6)	157 (12.1)	399 349 (9.6)

Data are presented as frequency N (%). Comparisons between distributions in groups of heart disease by χ^2 test.
*p<0.05.
aVHD, acquired valvular heart disease; CHD, congenital heart disease; ns, not significant; PAH, pulmonary arterial hypertension; SHD, structural heart disease.

Open Heart: first published as 10.1136/openhrt-2024-002833 on 13 September 2024. Downloaded from https://openheart.bmj.com on 4 February 2025 by guest. Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

m^2 (obese) in the description of the baseline characteristics. Smoking was categorised as non-smoker or smoker. Civil status was categorised as cohabitation/married or single parent/previously married/unmarried/other. To adjust for societal and medical changes over time, we adjusted for decades.

Statistics

Categorical variables were described as frequencies and percentages, and continuous variables were categorised or presented as means with SD. Simon-Makuch's modified Kaplan-Meier curves describe the cardiovascular outcomes in women with and without pregnancy complications. All reported p values were two sided. All Simon-Makuch curves were started at age 20 to avoid instabilities. Associations between pregnancy complications and adverse cardiovascular outcomes were studied by Cox regression models and reported as HR with 95% CI with age as the time scale. We studied all registered pregnancies with exposures of pregnancy complications fixed to each pregnancy and with time-dependent confounding. Robust SEs were used to handle multiple pregnancies. Adjustments were performed for the identified potential confounders: BMI at pregnancy, smoking (smoker/non-smoker), civil status (cohabitation/married and single parent/previously married/unmarried/other), parity, decade and comorbidities (described above). Comorbidities were assumed to persist for all the remaining time after the first registration. Multiple imputation was performed for missing variables (BMI, civil status and smoking), using confounders and outcomes as predictors. Descriptive statistics and data processing were performed with SPSS Statistics V.28, Python (used for data management) and R (V.4.2.1). The Cox regression models and Simon-Makuch curves were performed in R.

RESULTS

Baseline characteristics

Baseline characteristics of the 2554 women with SHD included in the study are described in table 1 and refer to the first pregnancy registered. Women with aVHD were older and the proportion of non-smokers was lower in women with PAH. Baseline characteristics of the women without SHD are also described in table 1. The total number of deliveries per year between 1973 and 2014 for women with SHD and without is visualised in online supplemental figure S2.

Pregnancy complications

All of the pregnancy complications studied were more common in women with SHD compared with women without. PE/gHT was present in 5.8% and 4.2% (p<0.00001), PTB in 9.7% and 5.2% (p<0.00001), and SGA in 2.8% and 1.9% (p<0.00001) of women with SHD and without, respectively. The frequency of pregnancy complications for the different groups of SHD is described in figure 3.

Comorbidities

The proportions of comorbidities were low overall, but higher than in women without SHD (table 1 and online supplemental table S2).

Outcomes

Mortality

The median follow-up time was 22 years. In total, 8.4% (n=214) of the women with SHD died during follow-up. All-cause mortality in women with PAH was 18.9% (n=70), 5.6% (n=86) in women with CHD and 9.1% (n=58) in women with aVHD. Simon-Makuch curves for all-cause mortality are visualised in figure 4. In women with SHD, the cardiovascular mortality was 0.7% (n=17), visualised in online supplemental figure S3. The adjusted HRs (aHR) for all-cause mortality and cardiovascular mortality for each of the pregnancy complications studied are presented in figure 5.

First-time hospitalisations for atherosclerosis, heart failure and arrhythmia

During follow-up, there were 321 first-time hospitalisations for atherosclerotic CVD. PE/gHT and PTB were associated with a higher risk of first-time hospitalisation for atherosclerotic CVD: the aHR for PE/gHT was 1.64 (95% CI 1.18 to 2.29) and the aHR for PTB was 1.56 (95% CI 1.19 to 2.04). The aHR for SGA was 1.47 (95% CI 0.95 to 2.28), compared with women without SGA (figure 6 and online supplemental figure S4a).

Heart failure was registered in association with pregnancy in 1.4% (N=80) of the pregnancies in women with SHD (1.1% (N=9) in women with PAH, 0.8% (N=29) in women with CHD, 3.2% (N=42) in women with aVHD). During follow-up, there were 238 first-time hospitalisations for heart failure and 501 for arrhythmia.

PE/gHT was not significantly associated with an increased risk of first-time hospitalisation for heart failure, with an aHR of 1.33 (95% CI 0.89 to 1.99). In contrast, both PTB (aHR 1.97 (95% CI 1.47 to 2.65)) and SGA (aHR 1.96 (95% CI 1.25 to 3.07)) were associated with a higher risk of first-time hospitalisation for heart failure compared with women without these pregnancy complications (figure 6 and online supplemental figure S4b). SGA was the only pregnancy complication in women with SHD associated with a higher risk of first-time hospitalisation for arrhythmia, with an aHR of 1.48 (95% CI 1.03 to 2.13) (figure 6 and online supplemental figure S4c).

DISCUSSION

In this nationwide cohort of 2554 women with SHD and 5568 singleton pregnancies with a median follow-up time of 22 years, we can confirm that pregnancy complications are more common in women with SHD than in women without. Furthermore, PE/gHT and PTB in women with SHD were associated with an increased risk of future atherosclerotic disease. These findings support that pregnancy complications, both maternal and fetal, should

Open Heart: first published as 10.1136/openhrt-2024-002833 on 13 September 2024. Downloaded from https://openheart.bmj.com on 4 February 2025 by guest. Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

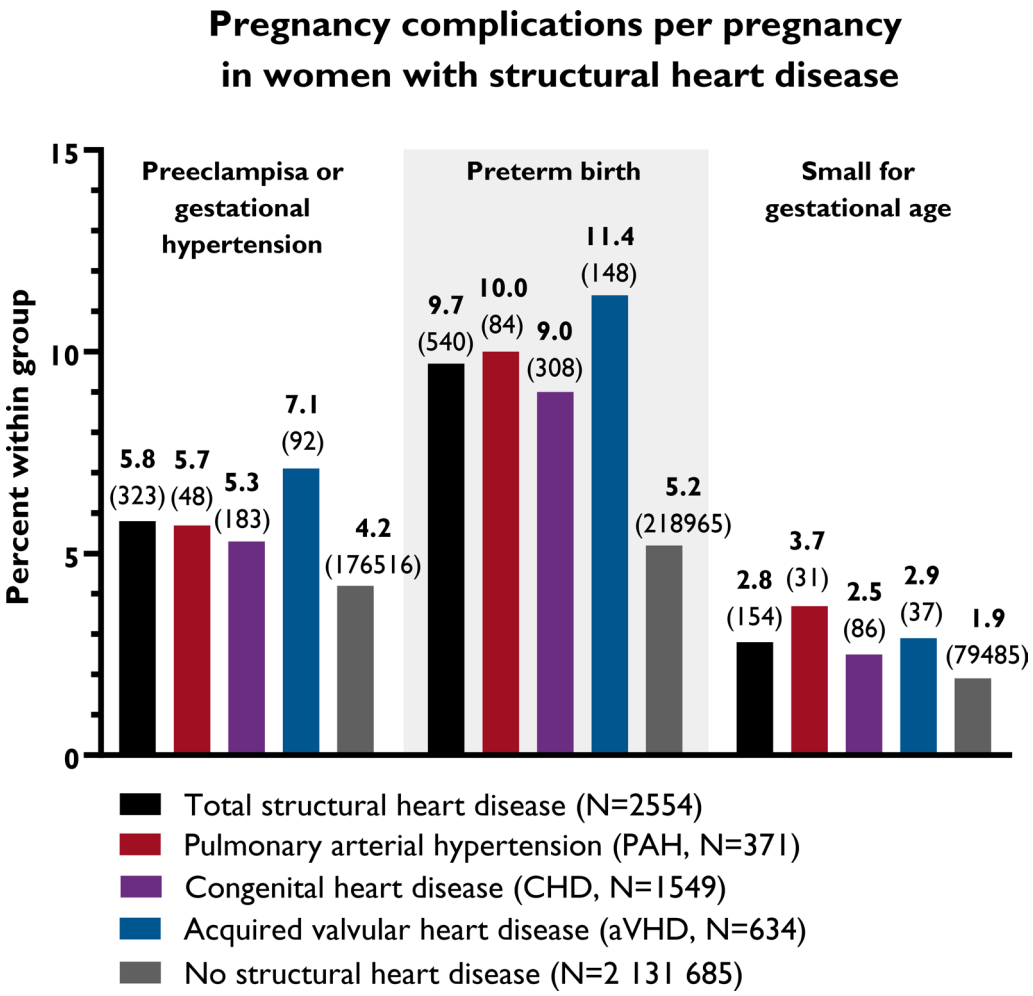

Figure 3 Frequency of pregnancy complications per pregnancy in women with structural heart disease. Described as % (N) over each bar.

be monitored during pregnancy and considered in the cardiovascular risk evaluation of women with SHD.

The mechanisms behind the increased risk of pregnancy complications in women with SHD are not fully elucidated, but pre-existing suboptimal cardiac performance has been described to be associated with poor placentation, a mechanism involved in pregnancy complications.[13] We found a high prevalence of PE/gHT in women with SHD. We found the numbers of PE/gHT to be higher in women with CHD and aVHD compared with what has been published elsewhere.[14] Hypertensive disorders of pregnancy have been reported to be more common in CHD,[15] although a systematic review and meta-analysis did not find an increased incidence of PE above the expected baseline risk in women with CHD, except for women with aortic stenosis.[16] In a recent Registry of Pregnancy and Cardiac Disease (ROPAC) study, the prevalence of PE was as high as 11.1% in women with PAH, and an association was found between PE and maternal mortality in pregnancy in these women.[14] ROPAC is based on data reported from selected centres, in contrast to our study, which is based on nationwide data that includes all pregnancies and women with simple and complex heart disease, and this might explain the lower proportion in women with PAH in our study. More studies are needed to elucidate the risk in specific diagnoses of SHD. The incidences of PTB and SGA in our study were lower than previously shown in the literature[17] but in accordance with other Swedish findings for women with CHD[18] and another study that included PTB in women with CHD.[2] PE/gHT and PTB were most common in women with aVHD in our study, as well as in a recent cohort study based on a more selected group of subjects.[19] This finding might be explained by the higher age in this group of patients, but possibly also by aortic valve disease, which has been reported to be associated with PE.[20]

Several of the pregnancy complications studied were associated with an increased long-term risk of cardiovascular mortality and first-time hospitalisations for atherosclerotic CVD. Placental anomalies have been described to be common in women with SHD, especially uteroplacental insufficiency that leads to growth restriction in the infant, although inflammatory mechanisms also seem involved.[21] Endothelial dysfunction is an early mechanism of atherosclerosis involved in both CVD[22] and the pregnancy complications studied.[23] Increased carotid intima–media thickness as an early sign of atherosclerosis has been found in young women with CHD,[24] and

Open Heart: first published as 10.1136/openhrt-2024-002833 on 13 September 2024. Downloaded from https://openheart.bmj.com on 4 February 2025 by guest. Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

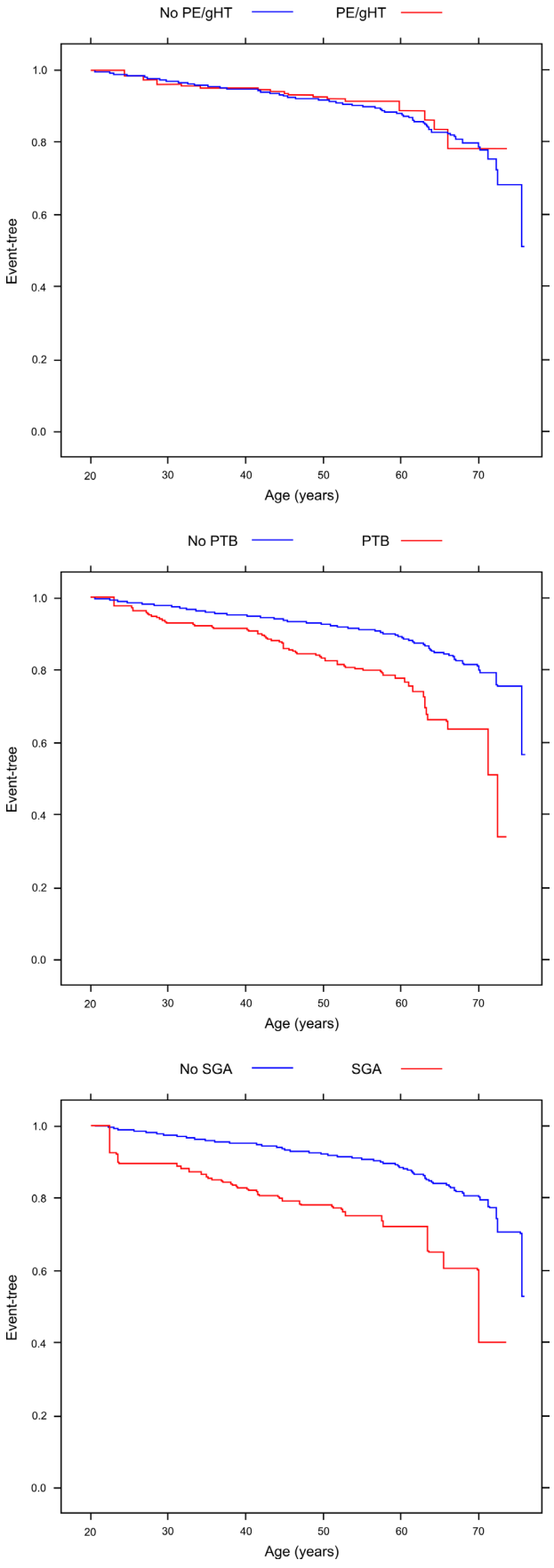

Figure 4 Simon-Makuch curves for all-cause mortality. PE/gHT, pre-eclampsia or gestational hypertension; PTB, preterm birth; SGA, small for gestational age.

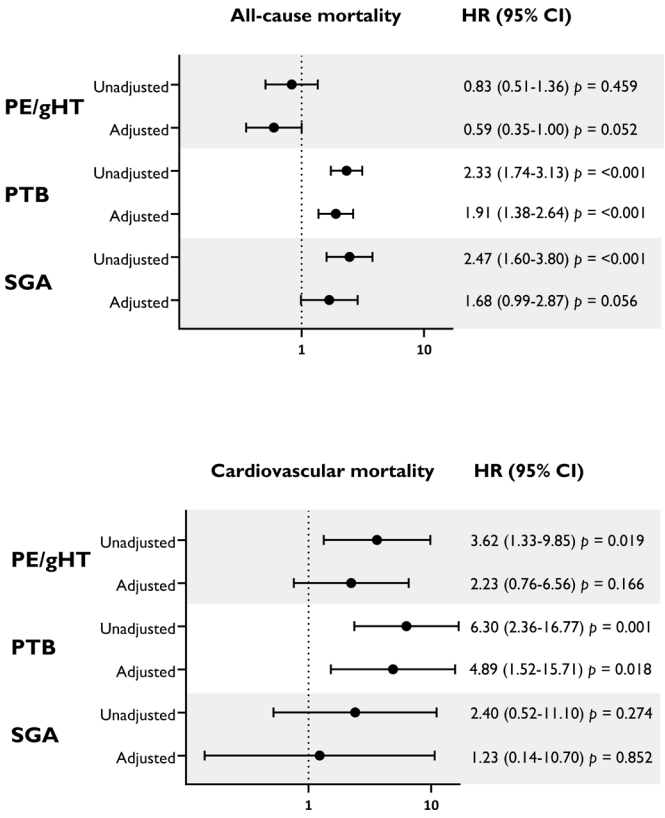

Figure 5 Forest plots for all-cause mortality and cardiovascular mortality. Adjusted for BMI, smoking, civil status, parity, decade and comorbidities (diabetes mellitus, hypertension, chronic kidney disease and venous thrombosis). BMI, body mass index; PE/gHT, pre-eclampsia or gestational hypertension; PTB, preterm birth; SGA, small for gestational age.

increased intima–media thickness has been associated with pregnancy complications.[25 26]

A recent study on a Danish registry-based cohort of women with CHD also found an association between PE/gHT and increased risk of long-term cardiovascular morbidity.[27] In our study, PTB and SGA were more clearly associated with mortality and hospitalisations than PE/gHT. A possible explanation for this might be a change in how women with SHD are treated during as opposed to after a pregnancy, complicated by increased blood pressure, which can be symptomatic in these women. During the time span of the study, blood pressure has been structurally monitored in the Swedish antenatal care. Whether pregnancy in women with SHD contributes to a higher long-term risk of CVD including heart failure and arrhythmias is not fully explored and since there is great variation in disease severity among these women, findings depend on the cohort included.[28] Hypertensive disorders of pregnancy have been described to be associated with an increased risk of heart failure,[29] but this could not be corroborated in our study. In the present study, the fetal complications seem important in the prediction of long-term risk of heart failure as well as arrhythmias and, within the group of women with SHD, pregnancy complications might help to identify those with the highest risk

Open Heart: first published as 10.1136/openhrt-2024-002833 on 13 September 2024. Downloaded from https://openheart.bmj.com on 4 February 2025 by guest. Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

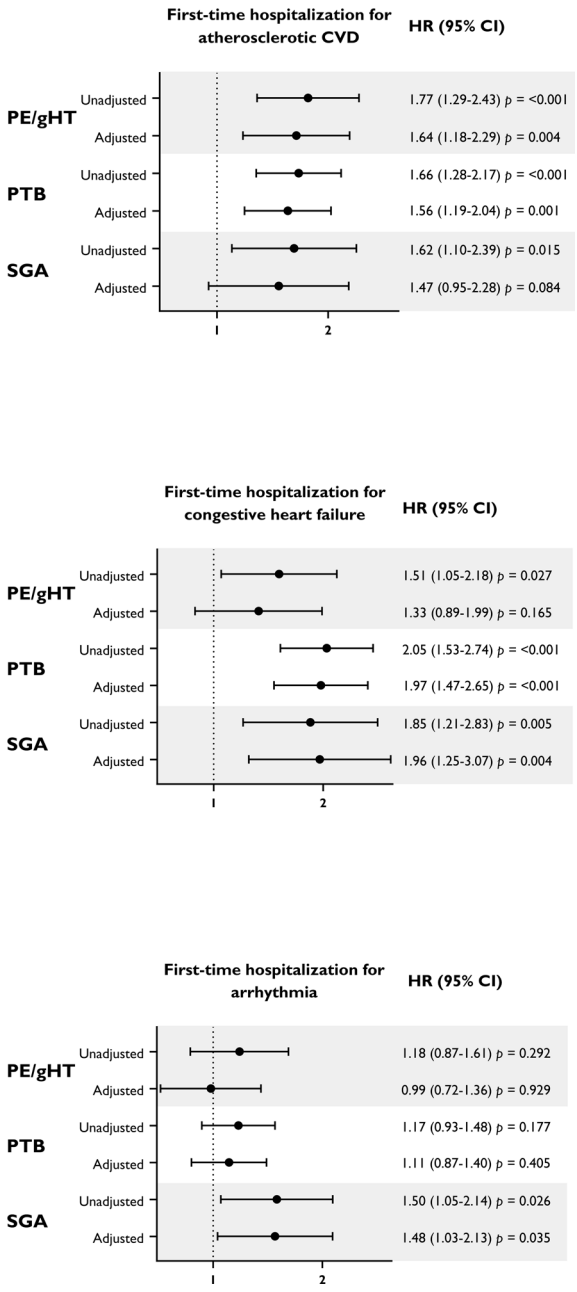

Figure 6 Forest plots for first-time hospitalisations for atherosclerotic CVD, heart failure and arrhythmia. Adjusted for BMI, smoking, civil status, parity, decade and comorbidities (diabetes mellitus, hypertension, chronic kidney disease and venous thrombosis). BMI, body mass index; CVD, cardiovascular disease; PE/gHT, pre-eclampsia or gestational hypertension; PTB, preterm birth; SGA, small for gestational age.

for complications such as heart failure and arrhythmias but these findings need to be studied further.[27]

Primary prevention of CVD is important in women with SHD, and pregnancy complications may be useful in identifying women at increased risk. Further studies are needed to evaluate whether the long-term risk of cardiovascular events can be reduced by enhanced cardiovascular prevention in SHD after pregnancy complications. Fetal complications could help to identify women with SHD at increased risk for heart failure and arrhythmias.

Strengths and limitations

Almost all childbearing women in Sweden are included in the MBR, which enabled us to identify a large number of women with SHD, with a long follow-up. Information about all registered pregnancies has been taken into account as well as time-dependent confounding factors. To reduce missing diagnoses, we included information on exposures and comorbidities from both the MBR and NPR. As with all registry studies, registration quality may vary and there is a potential for missing data. Overall, however, the quality of the MBR, NPR and CDR registries is high. With the use of historical ICD codes, there is also a potential for misclassification and diagnostic overlap. Since the study is based on registries there is no information on the severity of the SHD, results of previous surgery procedures, or functional status during pregnancy. Because the study spans over five decades and definitions of PE and gHT have changed over the study period, they were, therefore, analysed as a combined variable. Another limitation is that data on comorbidities at outpatient visits were not accessible. We had limited diagnostic and risk-factor profile details on the women with SHD. We were, however, able to adjust for major confounding, including BMI, smoking and comorbidities. BMI and smoking were only included in the MBR from 1982 onward, so we performed multiple imputations for these variables, with its limitations. For women with SHD, information about smoking was missing for 31.0%, civil status for 8.5%, weight for 42.3% and height for 33.4%, at first pregnancy. Data on the amount of smoking were missing, and more detailed sociodemographic variables, such as education and income. However, in this patient group, individual characteristics have been suggested to explain the differences in outcomes between centres and countries to a greater extent than socioeconomic factors.[30] Information on race and ethnicity was limited and the diversity of the study population could, therefore, not be described.

CONCLUSION

Pregnancy complications were frequent in women with SHD. PTB was associated with an increased future risk of cardiovascular mortality. Together with PE/gHT, PTB was also associated with a future risk of atherosclerotic CVD. Pregnancy complications, including also fetal complications, can provide additional information in the risk evaluation of women with SHD and may be used to identify women in need of improved primary prevention strategies.

Acknowledgements This work was included in the thesis of the first author ETC.

Contributors CC, BL, ML and ETC conceived of the presented idea. ETC performed data management and statistical analyses with support from LL. All authors discussed the methods and results of the study and contributed to the final manuscript. ETC is the guarantor.

Open Heart: first published as 10.1136/openhrt-2024-002833 on 13 September 2024. Downloaded from https://openheart.bmj.com on 4 February 2025 by guest. Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

Funding This work was supported by grants from the Erik, Karin and Gösta Selander Foundation.

Disclaimer The founders had no role in the design of the study, or in the analysis, interpretation of data, or the writing of the manuscript.

Competing interests ETC, LL, ML and BL report no disclosures. CC reports speaker fees or advisory board participation fees from AstraZeneca, Bristol Myers Squibb, Bayer, Novartis, Orion Pharma and Pfizer.

Patient consent for publication Not applicable.

Ethics approval The study was approved by the Uppsala Regional Ethics Committee, which belongs to the Swedish Ethical Review Authority (Ref. no. 2015/524). The National Board of Health and Welfare approved to dispense pseudo-anonymised data. Caregivers are obliged to report to the register without informed consent according to Swedish law. The study was conducted in accordance with the Declaration of Helsinki and institutional guidelines.

Provenance and peer review Not commissioned; internally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. Restrictions apply to the availability of the data, as these were used under licence for this study.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iDs
Elin Täufer Cederlöf http://orcid.org/0000-0001-7523-0511
Bertil Lindahl http://orcid.org/0000-0002-5795-0061

REFERENCES

1 Lima FV, Yang J, Xu J, *et al*. National Trends and In-Hospital Outcomes in Pregnant Women With Heart Disease in the United States. *Am J Cardiol* 2017;119:1694–700.
2 Linder AH, Wen T, Guglielminotti JR, *et al*. Delivery outcomes associated with maternal congenital heart disease, 2000–2018. *The Journal of Maternal-Fetal & Neonatal Medicine* 2024;35:9991–10000.
3 Ng AP, Verma A, Sanaiha Y, *et al*. Maternal and Fetal Outcomes in Pregnant Patients With Mechanical and Bioprosthetic Heart Valves. *J Am Heart Assoc* 2023;12:e028653.
4 Roos-Hesselink J, Baris L, Johnson M, *et al*. Pregnancy outcomes in women with cardiovascular disease: evolving trends over 10 years in the ESC Registry Of Pregnancy And Cardiac disease (ROPAC). *Eur Heart J* 2019;40:3848–55.
5 Regitz-Zagrosek V, Roos-Hesselink JW, Bauersachs J, *et al*. 2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy. *Eur Heart J* 2018;39:3165–241.
6 Sliwa K, van Hagen IM, Budts W, *et al*. Pulmonary hypertension and pregnancy outcomes: data from the Registry Of Pregnancy and Cardiac Disease (ROPAC) of the European Society of Cardiology. *Eur J Heart Fail* 2016;18:1119–28.
7 Zhang Q, Zhu F, Shi G, *et al*. Maternal Outcomes Among Pregnant Women With Congenital Heart Disease-Associated Pulmonary Hypertension. *Circulation* 2023;147:549–61.
8 Ramage K, Grabowska K, Silversides C, *et al*. Association of Adult Congenital Heart Disease With Pregnancy, Maternal, and Neonatal Outcomes. *JAMA Netw Open* 2019;2:e193667.
9 Minhas AS, Rahman F, Gavin N, *et al*. Cardiovascular and Obstetric Delivery Complications in Pregnant Women With Valvular Heart Disease. *Am J Cardiol* 2021;158:90–7.
10 van Hagen IM, Thorne SA, Taha N, *et al*. Pregnancy Outcomes in Women With Rheumatic Mitral Valve Disease: Results From the Registry of Pregnancy and Cardiac Disease. *Circulation* 2018;137:806–16.
11 Sederholm Lawesson S, Swahn E, Pihlsgård M, *et al*. Association Between History of Adverse Pregnancy Outcomes and Coronary Artery Disease Assessed by Coronary Computed Tomography Angiography. *JAMA* 2023;329:393–404.
12 Täufer Cederlöf E, Lundgren M, Lindahl B, *et al*. Pregnancy Complications and Risk of Cardiovascular Disease Later in Life: A Nationwide Cohort Study. *J Am Heart Assoc* 2022;11:e023079.
13 Kampman MAM, Bilardo CM, Mulder BJM, *et al*. Maternal cardiac function, uteroplacental Doppler flow parameters and pregnancy outcome: a systematic review. *Ultrasound Obstet Gynecol* 2015;46:21–8.
14 Ramlakhan KP, Malhamé I, Marelli A, *et al*. Hypertensive disorders of pregnant women with heart disease: the ESC EORP ROPAC Registry. *Eur Heart J* 2022;43:3749–61.
15 Goldstein SA, Savu A, Islam S, *et al*. Risk Factors and Outcomes Associated With Hypertensive Disorders of Pregnancy in Maternal Congenital Heart Disease. *JACC Adv* 2022;1:100036.
16 Martinez-Portilla RJ, Poon LC, Benitez-Quintanilla L, *et al*. Incidence of pre-eclampsia and other perinatal complications among pregnant women with congenital heart disease: systematic review and meta-analysis. *Ultrasound Obstet Gynecol* 2021;58:519–28.
17 Drenthen W, Pieper PG, Roos-Hesselink JW, *et al*. Outcome of pregnancy in women with congenital heart disease: a literature review. *J Am Coll Cardiol* 2007;49:2303–11.
18 Furenäs E, Eriksson P, Wennerholm U-B. Effect of maternal age and cardiac disease severity on outcome of pregnancy in women with congenital heart disease. *Int J Cardiol* 2017;243:197–203.
19 Quiñones JN, Walheim L, Mann K, *et al*. Impact of type of maternal cardiovascular disease on pregnancy outcomes among women managed in a multidisciplinary cardio-obstetrics program. *Am J Obstet Gynecol MFM* 2021;3:100377.
20 van Hagen IM, Roos-Hesselink JW, Donvito V, *et al*. Incidence and predictors of obstetric and fetal complications in women with structural heart disease. *Heart* 2017;103:1610–8.
21 Wu FM, Quade BJ, Carreon CK, *et al*. Placental Findings in Pregnancies Complicated by Maternal Cardiovascular Disease. *JACC Adv* 2022;1:100008.
22 Sun HJ, Wu ZY, Nie XW, *et al*. Role of Endothelial Dysfunction in Cardiovascular Diseases: The Link Between Inflammation and Hydrogen Sulfide. *Front Pharmacol* 2019;10:1568.
23 Kornacki J, Gutaj P, Kalantarova A, *et al*. Endothelial Dysfunction in Pregnancy Complications. *Biomedicines* 2021;9:1756.
24 Reiner B, Oberhoffer R, Häcker A-L, *et al*. Carotid Intima-Media Thickness in Children and Adolescents With Congenital Heart Disease. *Can J Cardiol* 2018;34:1618–23.
25 Catov JM, Snyder GG, Bullen BL, *et al*. Women with Preterm Birth Have Evidence of Subclinical Atherosclerosis a Decade After Delivery. *J Womens Health (Larchmt)* 2019;28:621–7.
26 Milic NM, Milin-Lazovic J, Weissgerber TL, *et al*. Preclinical atherosclerosis at the time of pre-eclamptic pregnancy and up to 10 years postpartum: systematic review and meta-analysis. *Ultrasound Obstet Gynecol* 2017;49:110–5.
27 Kloster S, Tolstrup JS, Nielsen DG, *et al*. Long-Term Cardiovascular Health After Pregnancy in Danish Women With Congenital Heart Disease. A Register-Based Cohort Study Between 1993 and 2016. *J Am Heart Assoc* 2022;11:e023588.
28 Son SL, Hosek LL, Stein MC, *et al*. Association between pregnancy and long-term cardiac outcomes in individuals with congenital heart disease. *Am J Obstet Gynecol* 2022;226:124.
29 Hansen AL, Søndergaard MM, Hlatky MA, *et al*. Adverse Pregnancy Outcomes and Incident Heart Failure in the Women's Health Initiative. *JAMA Netw Open* 2021;4:e2138071.
30 van Hagen IM, Baart S, Fong Soe Khioe R, *et al*. Influence of socioeconomic factors on pregnancy outcome in women with structural heart disease. *Heart* 2018;104:745–52.

Open Heart: first published as 10.1136/openhrt-2024-002833 on 13 September 2024. Downloaded from https://openheart.bmj.com on 4 February 2025 by guest. Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.