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ORIGINAL ARTICLE
Adult congenital heart disease

High prevalence of pre-eclampsia in women with coarctation of the aorta

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Aims

The aim was to study pregnancy outcomes in women with coarctation of the aorta (CoA) and associations to hypertensive disorders of pregnancy. Maternal morbidity and mortality are higher in women with heart disease and pre-eclampsia. Chronic hypertension, frequently encountered in CoA, is a risk factor for pre-eclampsia.

Methods and results

Clinical data from the National Unit for Pregnancy and Heart Disease database was reviewed for pregnant women with CoA from 2008 to 2021. The primary outcome was hypertensive pregnancy disorders. The secondary outcomes were other cardiovascular, obstetric, and foetal complications. Seventy-six patients were included, with a total of 87 pregnancies. Seventeen (20%) patients were treated for chronic hypertension before pregnancy. Fifteen (20%) patients developed pre-eclampsia, and 5 (7%) had pregnancy-induced hypertension. Major adverse cardiac events developed in four (5%) patients, with no maternal or foetal mortality. Maternal age at first pregnancy [odds ratio (OR) 1.37], body mass index before first pregnancy (OR 1.77), and using acetylsalicylic acid from the first trimester (OR 0.22) were statistically significantly associated with pre-eclampsia. At follow-up (median) 8 years after pregnancy, 29 (38%) patients had anti-hypertensive treatment, an increase of 16% compared to pre-pregnancy. Five (7%) patients had progression of aorta ascendens dilatation to >40 mm, seven (9%) had an upper to lower systolic blood pressure gradient >20 mmHg, and six (8%) had received CoA re-intervention.

Conclusion

Pre-eclampsia occurred in 20% of women with CoA in their first pregnancy. All pre-eclamptic patients received adequate anti-hypertensive treatment. All CoA patients were provided multi-disciplinary management, including cardiologic follow-up, to optimize maternal–foetal outcomes.

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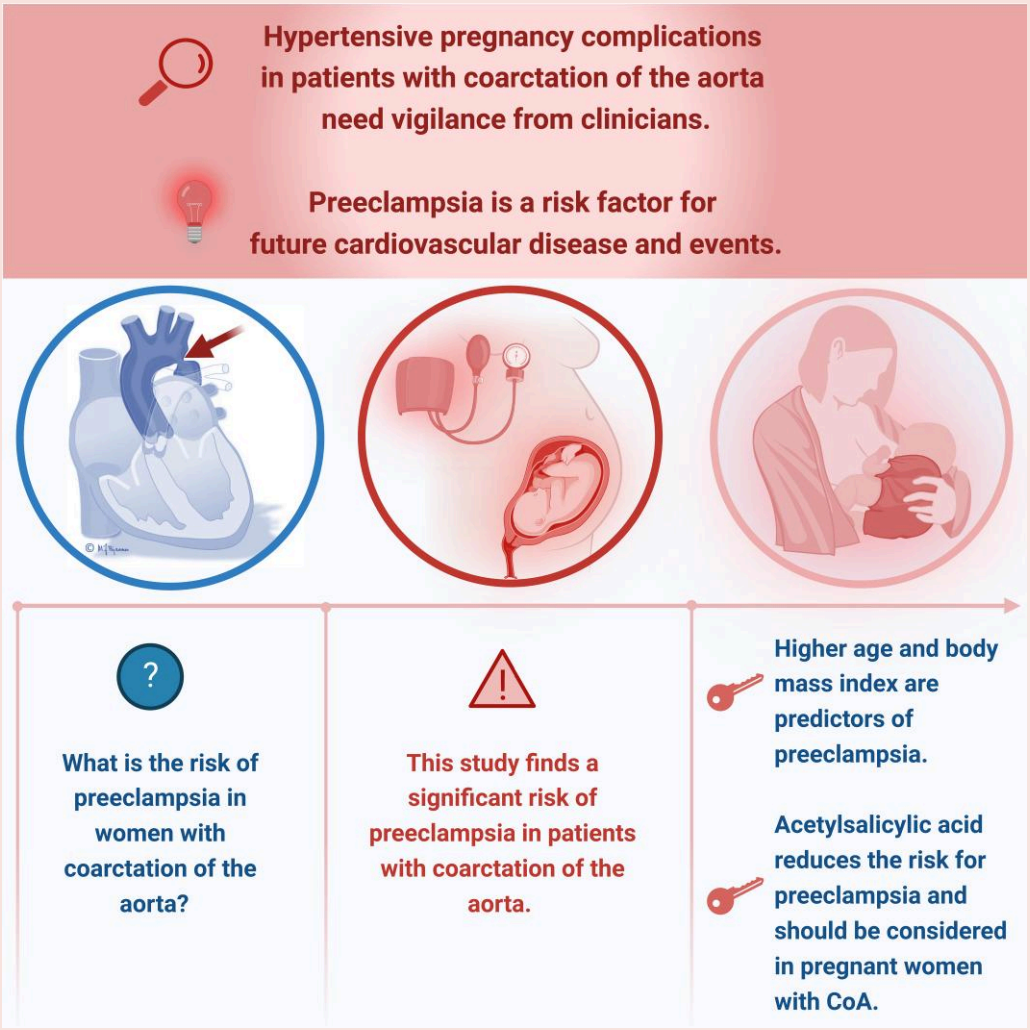
Graphical Abstract



Keywords Coarctation of the aorta • Congenital heart disease • Pre-eclampsia • Hypertension • Pregnancy complications

Introduction

Women with repaired coarctation of the aorta (CoA) are expected to reach fertile age due to improvements in early surgical repair, surgical techniques, management of arterial hypertension, and other complications.[1,2] Pregnant women with repaired CoA are considered to have an intermediate risk of maternal mortality and moderate-to-severe risk of morbidity, with a previously reported event rate of 10–19% during pregnancy. Women with repaired CoA correspond to modified World Health Organization (mWHO) Classes II and III, while women with unrepaired severe CoA are classified as mWHO Class IV.[3] The complication rates have varied due to reports on different endpoints and variable proportions of pregnant women with repaired vs. unrepaired CoA.[4–7] Despite improvements in survival for patients with CoA, cardiac complication rates are relatively high, with re-coarctation in 34%, aortic aneurysms in 18%, chronic hypertension in 32%, and a 10-fold increase in cerebrovascular events compared to healthy controls.[2] Coarctation of the aorta is associated with progressive arterial stiffening, and the timing of surgery does not affect this systemic vascular remodelling.[8]

Women with structural heart disease such as CoA may have a higher risk of developing pre-eclampsia, as these disorders have shared risk factors such as chronic hypertension. Maternal mortality is higher in patients with a combination of heart disease and pre-eclampsia than in pregnant women without cardiovascular disease. The recent European Society of Cardiology (ESC) Registry of Pregnancy and Cardiac disease (ROPAC) report found maternal mortality of up to 3.5% of heart disease patients with pre-eclampsia. All pre-eclampsia-related deaths occurred post-partum, most associated with heart failure.[9] Prevention of pre-eclampsia is gaining increased awareness, and the prescription of low-dose acetylsalicylic acid (ASA) to women with a high risk of pre-eclampsia in Norway may explain the decline in the prevalence in the general population in the last decade. Low-dose ASA is used to prevent cardiovascular diseases in high-risk

populations, but women of reproductive age are rarely prescribed ASA for this indication.[10]

Contemporary data from the pregnancy history and its outcome are needed for an updated cardiovascular risk assessment in women with CoA. Our primary aim was to report on pregnancy outcomes in women with CoA in Norway. The secondary objective was to explore any associations between CoA and pre-eclampsia.

Methods

Study design and population

We performed a single-centre, retrospective study in pregnant women with CoA. By review of the database at the National Unit for Pregnancy and Heart Disease at Oslo University Hospital—Rikshospitalet in Norway—every pregnancy in women with CoA from 2008 to 2021 was included. Inclusion criteria were repaired and unrepaired CoA and pregnancy. A team of cardiologists dedicated to grown-ups with congenital heart disease (CHD) performed pregnancy risk stratification in all women with CoA and consequently counselled those with the lowest mWHO risk to delivery at their local hospital. Women with a higher mWHO risk were advised to have follow-up and delivery at our tertiary centre.

Clinical registrations

Clinical data were obtained from a review of the database at the National Unit for Pregnancy and Heart Disease at Oslo University Hospital—Rikshospitalet. Characteristics of the CoA, the status of the aortic valve, associated congenital heart defects, medication, and occupational status were registered. The last follow-up consultation, including clinical assessment and echocardiography, was recorded and included in the statistical analysis for the follow-up data.

Maternal cardiovascular endpoints

The cardiovascular endpoints registered through pregnancy until follow-up were hospitalization for cardiovascular reasons, heart failure, arrhythmias, thromboembolic events, aortic dissection, acute coronary syndrome, and death. A major adverse cardiac event[11] was defined as a composite outcome of these endpoints. Native and recurrent CoA and associated cardiac defects were diagnosed by echocardiography, magnetic resonance imaging (MRI), computed tomography (CT), or cardiac catheterization.

Obstetric and neonatal endpoints

Obstetric data from the mother and the neonate were obtained through a review of obstetrical charts, including blood pressure (BP) every trimester, pre-delivery, and post-partum before discharge from the birth clinic. Obstetric endpoints were pregnancy-induced hypertension, pre-eclampsia, or *haemolysis, elevated liver enzymes, low platelets* (HELLP) syndrome, and post-partum haemorrhage. Mode of delivery was registered, as spontaneous or assisted vaginal delivery, defined as the vaginal birth performed with the help of forceps or a vacuum device. A caesarean section was registered as planned or emergency. Neonatal endpoints were perinatal mortality >24 weeks of gestation, infant death (<6 months), pre-term delivery (<37 weeks of gestational age), low Apgar score (<7) at 1 and 5 min, and low birth weight.

Data handling

Women with repaired and unrepaired CoA were included in the study. Retrospective systolic BP (SBP) and diastolic BP (DBP) trajectories collected from the obstetric record throughout pregnancy were analysed. Hypertensive disorders of pregnancy were defined as pregnancy-induced hypertension, pre-eclampsia, or HELLP syndrome, according to the 2018 International Society for the Study of Hypertension in Pregnancy (ISSHP) statement.[12] Pre-eclampsia was defined as hypertension after 20 weeks' gestation accompanied by proteinuria and/or evidence of maternal acute kidney injury, liver dysfunction, neurological features, haemolysis or thrombocytopenia, or foetal growth restriction. We performed a subgroup analysis on the women who fulfilled the definition of pre-eclampsia. Postpartum haemorrhage was defined as >1000 mL blood loss or signs of hypovolaemia within 24 h after birth, regardless of the mode of delivery.[13] Birth weight was classified as low when <2500 g.[14] The non-invasive SBP gradient between the upper and lower extremities (ULE) was calculated to identify patients with a peak-to-peak gradient ≥20 mmHg, requiring increased vigilance and additional examinations on the status of the CoA situation.[15] Dilatation of the ascending aorta was defined as an ascending aortic diameter >40 mm.

Statistical analysis

Baseline characteristics and outcomes were compared in women with and without pre-eclampsia. Data are presented as mean ± standard deviations (SD) for normally distributed continuous variables. The median and range are presented for continuous and not normally distributed variables. Linearity was assessed by partial regression plots. Normality was assessed by Q-Q plot. Comparisons of continuous variables between groups were made by unpaired Student's *t*-tests, while the Mann–Whitney *U* test was applied to compare continuous variables with skewed distribution between groups. A comparison of categorical variables was made using Pearson's χ^2 or Fisher's exact test, as appropriate. Mixed model analysis was applied to analyse repeated measurements on retrospective BP data. To investigate the strength of association with pre-eclampsia, the relevant variables with significant associations in univariate analyses and clinical variables known to affect pre-eclampsia were selected for multiple regression analysis. The likelihood ratio test was used to determine the statistical significance of the independent variables. A $P < 0.05$ was considered statistically significant for all statistical tests. Data analysis was performed using STATA Standard Edition Version 17 (StataCorp LLC, Texas, USA).

Patient and public involvement

This research was approved by the Data Protection Officer (PVO) at Oslo University Hospital to safeguard the research participant's privacy, interest, and rights. Individual patients' consent was waived.

Results

Seventy-six women with CoA and 87 pregnancies were included in the study. Twelve of the women conducted delivery at their respective local hospitals. Baseline characteristics before pregnancy are presented in *Table 1*, comparing the CoA patients with and without pre-eclampsia. Surgical characteristics of the primary repair of the CoA is presented in the table as Supplementary material.

Seventy-two (95%) women had an initial repair of CoA before their first completed pregnancy. Four (5%) patients underwent uncomplicated pregnancy with unrepaired CoA. Re-operation was performed within the first 2 years of life in 17 (22%) patients. All patients were diagnosed by computed tomography or MRI scan, and all women had repeated echocardiography during clinical follow-up before and after pregnancy. Four (5%) patients underwent pregnancy with an unrepaired CoA without major cardiac events (MACE). Risk factors for pre-eclampsia, such as parity, age, body mass index (BMI), and chronic hypertension, were comparable in the CoA patients who developed pre-eclampsia vs. those women without pre-eclampsia. The two groups were comparable regarding cardiac function expressed by ejection fraction (EF) and valvular function. In the total study population, patients

Table 1 Baseline characteristics in women with CoA before pregnancy

	Total CoA patients $n = 76$	CoA patients without PE $n = 61$	CoA patients with PE $n = 15$	*P*-value
Demographics				
Maternal age at first pregnancy, years	30.3 ± 6	29.9 ± 6	30.6 ± 7	0.578
BMI before first pregnancy, kg/m^2	27.1 ± 4.7	26.2 ± 5.1	27.9 ± 3.1	0.182
Primipara, *n* (%)	65 (86)	53 (70)	12 (16)	0.105
Cardiovascular risk factors				
Smoking, *n* (%)	15 (20)	13 (17)	2 (3)	0.376
Diabetes mellitus, *n* (%)	5 (7)	4 (5)	1 (1)	0.579
Hypertension, *n* (%)	17 (20)	12 (16)	5 (7)	0.511
Supraventricular tachycardia, *n* (%)	2 (3)	2 (3)	0 (0)	0.051
Signs of heart failure, *n* (%)	1 (3)	1 (3)	0 (0)	0.380
LVEF < 50%, *n* (%)	2 (2)	1 (1)	1 (1)	0.711
Bicuspid aortic valve, *n* (%)	41 (54)	32 (42)	9 (12)	0.428
Aortic ascendens diameter ≥ 40 mm, *n* %)	7 (9)	5 (7)	2 (3)	0.434
Aortic stenosis	15 (20)	9 (14)	3 (5)	0.642
Mild, *n* (%)	12 (16)	9 (12)	3 (4)	
Moderate, *n* (%)	3 (4)	2 (3)	1 (1)	
Severe, *n* (%)	0 (0)	0 (0)	0 (0)	
Aortic regurgitation	26 (29)	24 (22)	3 (3)	0.686
Mild, *n* (%)	21 (23)	19 (23)	2 (3)	
Moderate, *n* (%)	3 (4)	3 (4)	1 (1)	
Severe, *n* (%)	2 (3)	2 (3)	0 (0)	
Mitral stenosis, *n* (%)	7 (8)	6 (7)	1 (1)	0.642
Mitral regurgitation	12 (13)	10 (11)	2 (2)	0.714
Mild, *n* (%)	7 (8)	6 (7)	1 (1)	
Moderate, *n* (%)	4 (4)	3 (3)	1 (1)	
Severe, *n* (%)	1 (1)	1 (1)	0 (0)	
Cardiac medication	20 (26)	16 (21)	4 (5)	0.601
Beta-blocker, *n* (%)	12 (16)	9 (12)	3 (4)	0.117
ACE inhibitor, *n* (%)	4 (5)	4 (5)	0 (0)	0.149
Calcium channel blockers, *n* (%)	2 (2)	1 (1)	1 (1)	0.781
Diuretics, *n* (%)	2 (2)	2 (2)	0 (0)	0.248

Values are given as mean ± SD or median [range]. Percentages calculated from the total CoA population. *P*-values (at a 95% confidence level) compare CoA patients with PE vs. those without PE.
ACE, angiotensin-converting enzyme; BMI, body mass index; CoA, coarctation of the aorta; LVEF, left ventricular ejection fraction; PE, pre-eclampsia.

with bicuspid aortic valve (BAV) ($n = 38$, 49%) had significantly more aortic regurgitation (25% vs. 12% $P < 0.001$), aortic valve stenosis (16% vs. 4%, $P = 0.004$), and larger diameter of ascending aorta on echocardiography before pregnancy (33 ± 4 mm vs. 28 ± 6 mm; $P = 0.002$) compared to women without BAV. Twenty-five (33%) women had intervention due to re-coarctation before pregnancy, either by open surgery ($n = 17$) or percutaneous balloon angioplasty ($n = 8$).

Maternal cardiovascular outcome during pregnancy

The occurrence of hypertensive disorders of pregnancy in 87 pregnancies in women with CoA is shown in *Figure 1*. Sixteen pregnancies (18%) in 15 women (20%) were complicated by pre-eclampsia. Five women (7%) with hypertension before pregnancy had superimposed pre-eclampsia. All the pre-eclamptic patients had proteinuria upon pre-eclampsia diagnosis. There were no cases of eclampsia or HELLP. One patient had pre-eclampsia with early onset, i.e. before the 34th week of gestation, and delivered by emergency caesarean section. One patient had a reoccurrence of pre-eclampsia in her second pregnancy without any other peri-partum or foetal complications. Five (7%) women were diagnosed with pregnancy-induced hypertension.

All three (4%) women who experienced MACE had pre-pregnancy hypertension. In patients with BAV, 16 (21%) had hypertension before pregnancy ($P = 0.01$).

A low-dose ASA was initiated in 22 (25%) pregnancies during the first trimester, and logistic regression analysis for pre-eclampsia showed an odds ratio (OR) 0.22 [95% confidence interval (CI) 0.10–0.41; $P = 0.021$]. Chronic hypertension and co-existing heart disease were identified as risk factors for pre-eclampsia and an indication for initiation of ASA in these patients.

There were no maternal deaths. There were no aortic dissections, acute coronary syndromes, cerebrovascular events, or interventions due to CoA in pregnancy. During pregnancy, only three (4%) patients

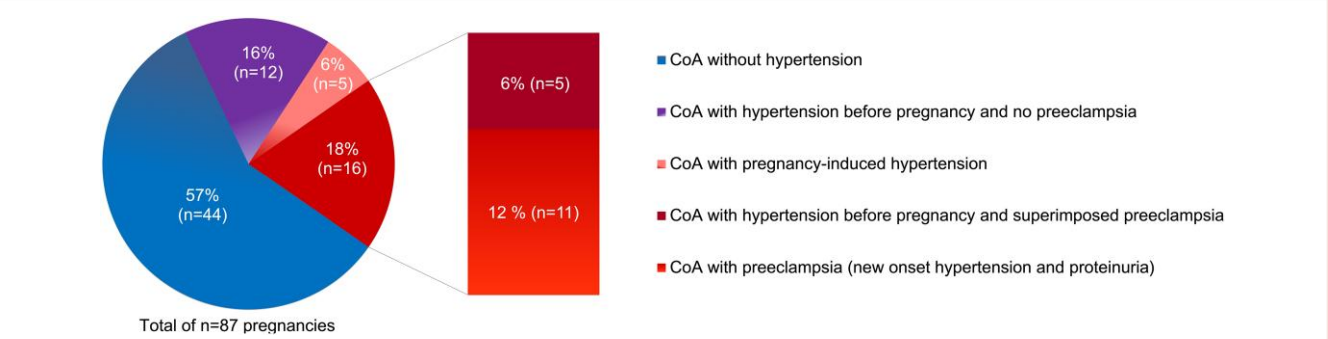


Figure 1 Hypertensive disorders during pregnancy in women with coarctation of the aorta. CoA, coarctation of the aorta.

had hospital admissions due to MACE. These three patients had repaired CoA, combined with a severe CHD: Patient 1 due to progression of mitral regurgitation and pulmonary hypertension (in the third trimester), Patient 2 due to dyspnoea and worsening of systolic and diastolic function (in the third trimester), and Patient 3 due to progressive symptoms of supraventricular tachycardia (in the second trimester). Patients 1 and 2 had combined congenital heart defects (mitral insufficiency and pulmonary hypertension; ventricular septal defect and aortic stenosis) and had EF < 50% on hospital admission. There were no cases of new onset of heart failure during pregnancy.

Obstetric and neonatal outcomes

Obstetric and neonatal data are shown in *Table 2*. During the study period, two women had a second pregnancy. These two pregnancies were not included in the analysis, because outcome data were not available at the time of registration.

The differences in BP between the measurements from the first trimester through pregnancy and post-partum were highly significant in the pre-eclamptic group. The stepwise and pairwise comparison of SBP throughout pregnancy is reported in *Table 3*. Repeated measures of retrospectively collected SBP and DBP during the first, second, and third trimesters, pre-delivery, and post-delivery before discharge from the maternal ward are shown in *Figure 2*. Blood pressure measurements before discharge showed higher SBP (131 ± 9 vs. 123 ± 11; $P = 0.119$) and DBP (75 ± 8 vs. 69 ± 12; $P = 0.051$) in the pre-eclamptic women compared to those without pre-eclampsia. All women with pre-eclampsia (without pre-pregnancy hypertension) ($n = 10$, 13%) were treated with calcium blocker and beta-blocker before delivery.

Caesarean section was performed in 25% of the deliveries, of which 3% were emergency caesarean sections. Preterm delivery was more common in women with pre-eclampsia. In women with pre-eclampsia, the Apgar score at 1 min was significantly lower compared to patients without pre-eclampsia ($P = 0.047$); the Apgar score at 5 min was comparable between the groups ($P = 0.651$). Four neonates had congenital heart defects: three atrial septal defects and one persistent ductus arteriosus. There were no perinatal or infant deaths.

Predictors of pre-eclampsia

Multi-variable logistic regression analysis for predictors of pre-eclampsia is displayed in *Figure 3*. Maternal age at first pregnancy (OR 1.37; 95% CI 1.09–1.71; $P = 0.006$), BMI before first pregnancy (OR 1.77; 95% CI 1.28–2.44; $P = 0.009$), and using ASA from the first trimester (OR 0.22; 95% CI 0.10–0.41) were statistically significantly associated with pre-eclampsia. The logistic regression model was statistically significant with a likelihood ratio of $\chi^2 = 73.75$ ($P = 0.000$). Assessing the goodness of fit of the model, the likelihood ratio pseudo-$R^2 = 0.749$.

Maternal cardiovascular function after pregnancy

Data from follow-up of patients with CoA after pregnancy are shown in *Table 4*.

After a median follow-up of 8 years since the first completed pregnancy, five (7%) women had undergone surgery or balloon angioplasty for re-coarctation, one (1%) woman for ascending aortic aneurysm, one (1%) for descending aortic aneurysm, and one (1%) for aortic valvular stenosis. Two patients had primary repair of their CoA after the first pregnancy, one had balloon angioplasty, and one had surgical repair with aortic valve replacement. Five (6%) women showed an increase in the diameter of the ascending aorta above 40 mm, one requiring surgery due to the dilatation. The two patients with combined congenital heart defects (mitral stenosis and pulmonary hypertension; ventricular septal defect and aortic stenosis) had reduced systolic and diastolic ventricular function, which did not worsen after pregnancy.

At follow-up, 29 (38%) women were on anti-hypertensive medication, compared to 22% before pregnancy. The mean SBP (119 mmHg ± 7 vs. 115 mmHg ± 11; $P = 0.119$) and DBP (71 mmHg ± 10 vs. 67 mmHg ± 8; $P = 0.639$) were comparable in CoA patients treated for hypertension vs. patients without anti-hypertensive medication. However, for patients with pre-eclampsia, the mean SBP was 9% higher ($P = 0.013$), and the mean DBP was 16% higher ($P = 0.001$) compared to patients without pre-eclampsia. Seven (9%) women had an ULE SBP gradient >20 mmHg. These women are followed-up with repeated echocardiography and MRI to evaluate the need for re-intervention of re-coarctation. At follow-up, the cardiac index was 10% lower in women with previous pre-eclampsia ($P = 0.052$).

Discussion

This report from the National Unit for Pregnancy and Heart Disease in Norway finds a prevalence of 20% of pre-eclampsia in women with CoA. This prevalence is much higher than in the healthy pregnant population[16] and substantially higher than in the last report on pregnancy outcomes in women with CoA from the ROPAC study. Age and BMI were significant predictors of pre-eclampsia. Aspirin decreased the OR and seemed to have a protective effect on the development of pre-eclampsia. We found low rates of MACE, in line with recent reports.[17]

Pre-eclampsia

The prevalence of 20% pre-eclampsia observed in our cohort is significantly higher than the 2.6% reported in the recent ROPAC study.[17] It is also higher than the prevalence observed in a recent, large population-based cohort study from Staff *et al.* using data from the Medical Birth

Table 2 Maternal and neonatal data from pregnancies in women with CoA

	Total number of pregnancies $n = 87$	Pregnancies without PE $n = 71$	Pregnancies with PE $n = 16$	*P*-value
Cardiovascular outcomes during pregnancy				
Maternal mortality, *n* (%)	0 (0)	0 (0)	0 (0)	n.a.
Hospital admission for cardiac reasons, *n* (%)	4 (5)	3 (4)	1 (1)	0.303
Atrial fibrillation or flutter, *n* (%)	1 (1)	1 (1)	0 (0)	0.779
Thromboembolic events, *n* (%)	1 (1)	0 (0)	1 (1)	0.579
Aortic dissection, *n* (%)	0 (0)	0 (0)	0 (0)	n.a.
Acute coronary syndromes in pregnancy, *n* (%)	0 (0)	0 (0)	0 (0)	n.a.
Overall MACE, *n* (%)	4 (5)	3 (4)	1 (1)	0.281
Use of acetylsalicylate in first trimester, *n* (%)	22 (25)	14 (16)	8 (9)	0.029
Hypertensive disorders during pregnancy				
Pregnancy-induced hypertension, *n* (%)	5 (6)	5 (6)	n.a.	n.a.
Pre-eclampsia, *n* (%)	16 (21)	n.a.	n.a.	
Eclampsia or HELLP, *n* (%)	0 (0)	n.a.	0 (0)	n.a.
Obstetrical outcomes				
Delivery at tertiary centre, *n* (%)	75 (86)	59 (67)	16 (18)	0.325
Delivery at local hospital, *n* (%)	12 (14)	12 (14)	n.a.	n.a.
Gestational diabetes, *n* (%)	5 (6)	3 (3)	2 (1)	0.231
Induction, *n* (%)	21 (24)	12 (14)	9 (10)	0.067
Mode of delivery:				
Spontan vaginal	80 (92)	66 (76)	15 (17)	0.495
Assisted vaginal delivery, *n* (%)	7 (8)	6 (7)	1 (1)	0.593
Elective caesarean delivery, *n* (%)	17 (20)	12 (16)	5 (7)	0.103
Emergency caesarean delivery, *n* (%)	3 (3)	2 (2)	1 (1)	0.391
Postpartum bleeding (>500 mL), *n* (%)	13 (15)	8 (9)	5 (6)	0.046
Neonatal outcomes ($n = 94$, twin included)				
Neonatal mortality	0 (0)	0 (0)	0 (0)	n.a.
Gestational age at birth, weeks/days	39.4 ± 1.4	39.3 ± 1.8	38.1 ± 2.2	0.073
Premature delivery (<37th GA week), *n* (%)	7 (10)	4 (7)	3 (25)	0.168
Twin pregnancies, *n* (%)	3 (3)	2 (1)	1 (1)	0.414
Apgar score 1 min [range]	8 [8–9]	9 [8–9]	7 [6–9]	0.047
Apgar score 5 min [range]	9 [7–10]	9 [8–10]	8 [7–9]	0.650
Mean infant weight, grams	3422 ± 533	3373 ± 522	3421 ± 591	0.270
With beta-blocker	3313 ± 574	3378 ± 345	3251 ± 595	0.413
Without beta-blocker	3513 ± 443	3544 ± 394	3375 ± 512	0.574
	$P = 0.305$*	$P = 0.410$*	$P = 0.613$*	
Low birth weight (<2500 grams), *n* (%)	10 (4)	6 (4)	4(7)	0.062
Congenital heart defect in neonates, *n* (%)	3 (3)	2 (3)	1 (1)	0.551

Values are given as mean ± SD or median [interquartile range]. Percentages calculated from the total CoA population. *P*-value (at a 95% confidence level) comparing CoA patients with PE vs. those without PE.
CoA, coarctation of the aorta; GA, gestational age; HELLP, haemolysis, elevated liver enzymes, low platelets; MACE, major cardiac events; n.a., not available. PE, pre-eclampsia.
**P*-values were calculated using unpaired t-tests for birth weight between CoA groups with and without the use of a beta-blocker.

Registry of Norway.[16] In previous studies, hypertensive disorders have been reported as the most frequent pregnancy complication in women with repaired CoA, with rates between 14% and 20%.[4,6] In the largest retrospective study to date period, Krieger *et al.*[18] found pre-eclampsia rates of 7% in their large CoA cohort. In the prospective study by Siegmund *et al.*[7] of 49 women with CoA, the authors found no difference in hypertensive disorder between healthy controls and women with CoA.

Our cohort of CoA women with and without pre-eclampsia had comparable BPs before pregnancy and in the first trimester. The pre-eclamptic women showed a significant increase in SBP and DBP in the second and third trimesters compared to women without pre-eclampsia, as expected from the commonly described clinical presentation of pre-eclampsia.[19] They were closely followed with repeated BP measurements and adjustment of anti-hypertensive treatment with beta-blockers and calcium blockers. At follow-up, 8 years after the first pregnancy, the SBP and the DBP were higher in the pre-eclamptic group than in patients without previous pre-eclampsia. The use of anti-hypertensive treatment was higher at follow-up (32%) compared to during pregnancy (12%).

Table 3 Changes in blood pressure during pregnancy in women with CoA

	1st trimester	2nd trimester	3rd trimester	Pre-delivery	Post-partum	95% (CI) change in preceding measurement	*P*-value
SBP in CoA without PE, mmHg	115 ± 11	119 ± 10	130 ± 11	128 ± 17	123 ± 20		
SBP in CoA with PE, mmHg	119 ± 10	131 ± 9	143 ± 13	152 ± 12	131 ± 18		
	P = 0.198	*P* = 0.000	*P* = 0.002	*P* = 0.000	*P* = 0.239		
Change in SBP in CoA with PE[a]							
1st to 2nd trimester, mmHg		9				(6,14)	*P* = 0.002
2nd to 3rd trimester, mmHg			12			(6,14)	*P* = 0.000
3rd to pre-delivery, mmHg				9		(4,12)	*P* = 0.004
Pre-delivery to post-partum, mmHg					−21	(−29,−12)	*P* = 0.000
DBP in CoA without PE, mmHg	69 ± 11	66 ± 8	72 ± 8	75 ± 11	72 ± 9		
DBP in CoA with PE, mmHg	72 ± 10	73 ± 8	79 ± 6	90 ± 7	77 ± 8		
	P = 0.306	*P* = 0.003	*P* = 0.048	*P* = 0.001	*P* = 0.051		
Change in DBP in CoA with PE[a]							
1st to 2nd trimester, mmHg		1				(−7,3)	*P* = 0.407
2nd to 3rd trimester, mmHg			6			(2,11)	*P* = 0.014
3rd to pre-delivery, mmHg				11		(6,14)	*P* = 0.004
Pre-delivery to post-partum, mmHg					−13	(−16,−7)	*P* = 0.000

The data are presented as mean ± SD.
CI, confidence interval; CoA, coarctation of the aorta; DBP, diastolic blood pressure; PE, pre-eclampsia; SBP, systolic blood pressure.
[a]Measures the change of blood pressure from the preceding measurement.

Contrary to our findings in the CoA cohort, the prevalence of pre-eclampsia in the Norwegian population has decreased from 4.3% to 2.7% over the last two decades. An increase in aspirin prescriptions among pregnant women and an overall increase in labour inductions are observed. This suggests that clinical interventions may partly explain the observed reduction in prevalence in the general population.[16] Lower average BP and improved health in the general population may also explain the decline in prevalence.[20]

Large population-based cohort studies have established the association between PE and cardiovascular disease[21] and the shared common risk factors (e.g. hypertension, obesity, and diabetes).[22] Studies indicate that cardiovascular dysfunction precedes pre-eclampsia, predominates in the clinical syndrome, and persists post-partum. Both endothelial dysfunction and cardiac changes have been documented from the clinical presentation of pre-eclampsia and beyond pregnancy. The most common cardiac changes include altered left ventricular (LV) geometry with hypertrophy, global diastolic dysfunction, and, in more severe cases, LV systolic dysfunction.[23,24] The endothelial dysfunction observed in early- and late-onset pre-eclampsia[25] exists beyond pre-eclamptic pregnancies.[26,27] Coarctation of the aorta is also associated with endothelial dysfunction, expressed in reduced vascular reactivity, and associated with hypertension and increased LV mass.[28]

A recent meta-analysis could demonstrate a weak association between maternal CHD and pre-eclampsia, except for aortic stenosis and pulmonary atresia.[29] Their meta-regression analysis for CoA of pre-eclampsia on a total of 13 studies, including eclampsia and HELLP syndrome (haemolysis, elevated liver enzymes, low platelets) in women with CHD, could not find a significant correlation ($P = 0.094$), though with heterogeneity in variability across studies considered to be moderate ($I^2 = 69\%$).[30] The rate of PE, eclampsia, and HELLP syndrome taken together was 4.3% (in a total of 33 included studies). None of the included studies presented data separately for early- and late-onset PE, so whether CHD specifically predisposes women to early- or late-onset PE could not be evaluated. Women with CHD included in the meta-analyses may have received ASA, but these data were unavailable.

One-fourth of the pregnancies in our study received low-dose ASA from the first trimester throughout pregnancy. The prophylactic effects of ASA have shown a modest ability to reduce the risk of developing pre-eclampsia and its sequelae.[31] The Aspirin for Evidence-Based Preeclampsia Prevention (ASPRE) trial showed that ASA initiated in the first trimester to a high-risk population identified by first-trimester screening test could reduce the incidence of early-onset pre-eclampsia by 62%.[32] In the ROPAC report on pregnancy outcomes in women with CoA, ASA was only used in 5.9% of pregnancies. It was not associated with a lower incidence of hypertensive disorders (OR 1.1).[17] Prescription of ASA for high-risk pregnancies has recently been incorporated in American,[33] British,[34] and Norwegian guidelines.[35]

With the high prevalence of pre-eclampsia in our study cohort, the risk of pre-eclampsia and hence the indication for ASA could be underestimated in certain CoA patients. Pre-existing cardiovascular disease, including CHD (and associated lesions like a BAV), may confer a higher risk of pre-eclampsia than previously assumed. Future prospective studies should explore this relationship.

Maternal mortality

There were no maternal deaths in our cohort. The worldwide prospective ROPAC data from the ESC EURObservational Research Program on pregnancies in women with CoA ($n = 303$ pregnancies)

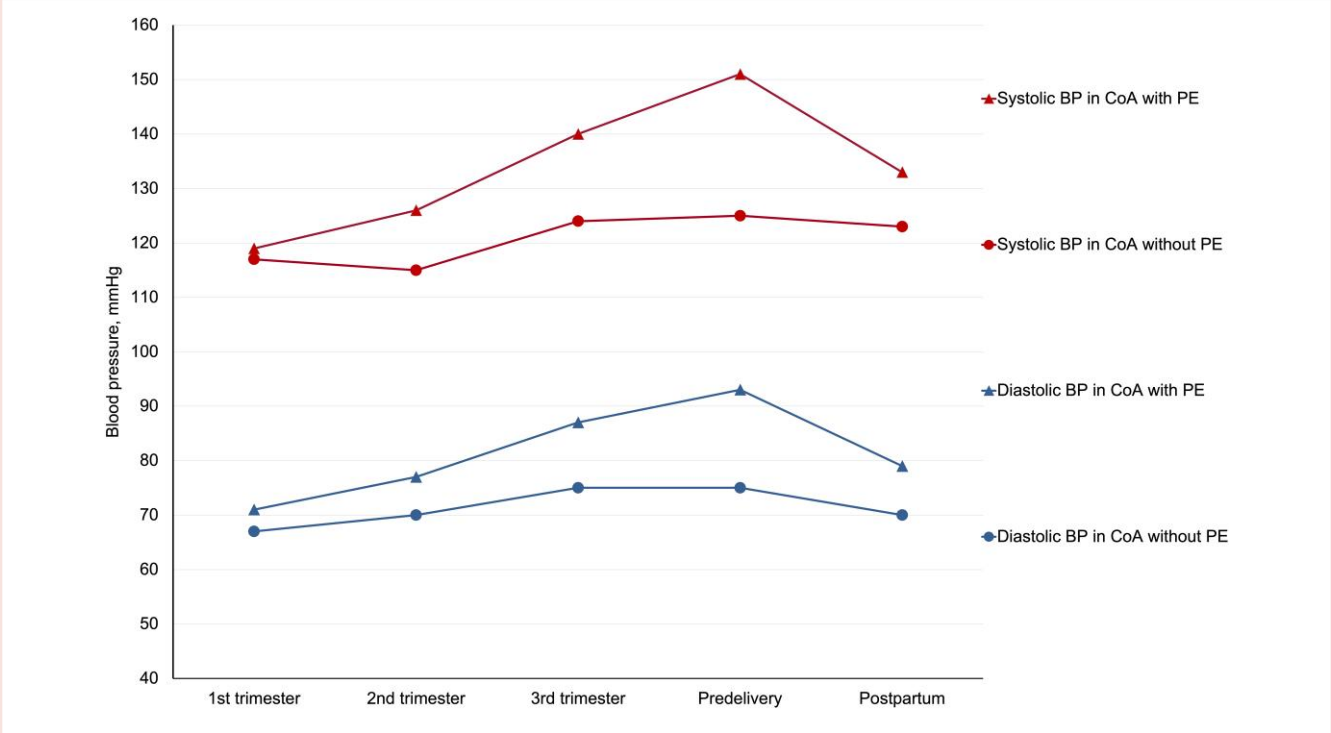


Figure 2 Blood pressure trajectory during pregnancy in women with coarctation of the aorta. BP, blood pressure; CoA, coarctation of the aorta; PE, pre-eclampsia.

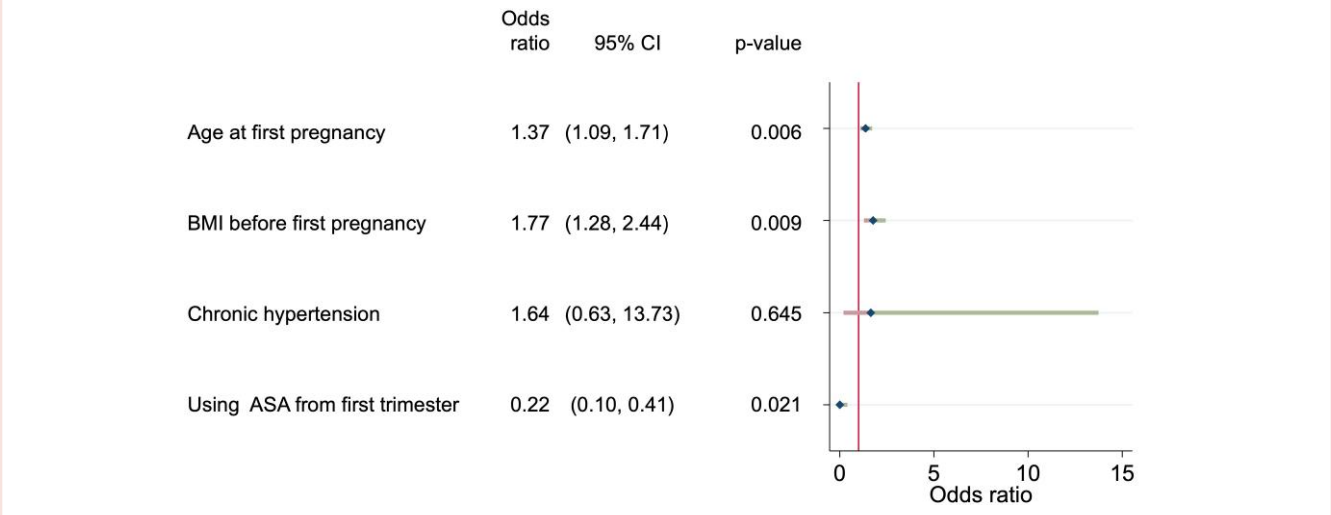


Figure 3 Predictors for pre-eclampsia in women with coarctation of the aorta. ASA, acetylsalicylic acid; BMI, body mass index; CI, confidence interval.

from 2007 to 2018 reported no maternal mortality.[17] This is in line with our results.

The most extensive retrospective data collection on American women with CoA ($n = 697$ deliveries) from 1998 to 2007 by Krieger *et al.*[18] included maternal deaths in their composite adverse cardiovascular outcome, preventing direct comparison on mortality to our results.

Major adverse cardiac events

We had a MACE rate of 5% during the first pregnancy in the CoA cohort, which is lower than the predicted 10–19% event rate for patients in the mWHO risk Classes II and III.[3] All patients developing MACE had an additional cardiac condition to the CoA (mitral stenosis and pulmonary hypertension; ventricular septal defect and aortic stenosis). Despite

Table 4 Clinical characteristics of women with CoA on follow-up after pregnancy

	Total CoA $n = 76$	CoA without PE $n = 61$	CoA with PE $n = 15$	*P*-value
Demographics				
Mean age at follow-up, years	38.4 ± 7	37.8 ± 6	39.5 ± 5	0.274
Median time from pregnancy to follow-up, years	8.1 ± 6.1	7.7 ± 6.6	9.8 ± 5.3	0.330
BMI at follow-up, kg/m2	26.5 ± 4.7	25.8 ± 3.2	27.2 ± 3.5	0.042
Number of pregnancies at follow-up, *n* (IQR)	1 [1–3]	1 [1–2]	1 [1]	0.298
Hypertension diagnosis, *n* (%)	29 (38)	16 (21)	13(17)	0.143
Cardiac medication, *n* (%)	31 (41)	18 (24)	13(17)	0.008
Beta-blocker, *n* (%)	15 (20)	11 (14)	4 (5)	0.017
AT-II or ACE inhibitor, *n* (%)	8 (11)	4 (5)	4 (5)	0.043
Calcium channel blockers, *n* (%)	6 (8)	1 (1)	5 (7)	0.001
Diuretics, *n* (%)	2 (3)	2 (3)	0 (0)	0.247
Composite MACE after first delivery, *n*%	5 (7)	4 (5)	1 (1)	
CoA intervention after first pregnancy				
Primary intervention CoA, *n* (%)	2 (3)	2 (3)	0 (0)	0.703
Re-intervention CoA, *n* (%)	5 (7)	4 (5)	1 (1)	0.231
Hemodynamic measurements				
SBP right arm, mmHg	121 ± 19	117 ± 21	126 ± 8	0.033
DBP right arm, mmHg	69 ± 9	66 ± 8	74 ± 5	0.011
MAP right arm, mmHg	85 ± 11	81 ± 11	89 ± 7	0.031
SBP right leg, mmHg	109 ± 16	105 ± 17	112 ± 11	0.006
ULE–SBP gradient right, mmHg	13.2 ± 15.7	12.6 ± 16.1	14.0 ± 15.4	0.361
Heart rate, b.p.m.	71 ± 14	70 ± 11	73 ± 16	0.467
Echocardiographic measurements				
Aorta ascendens diameter, mm	31 ± 11	30 ± 11	32 ± 13	0.703
Aorta ascendens diameter > 40 mm, *n* (%)	12 (16)	9 (12)	3 (4)	0.885
Aortic valve peak velocity	1.5 ± 0.5	1.4 ± 0.5	1.6 ± 0.7	0.245
CoA peak velocity, m/s	2.4 ± 0.3	2.4 ± 0.4	2.3 ± 0.3	0.643
LVIDd, cm	5.1 ± 0.6	5.1 ± 0.5	5.0 ± 0.1	0.371
IVSd, cm	1.0 ± 0.4	0.9 ± 0.3	1.0 ± 0.3	0.486
LVPWd, cm	0.9 ± 0.2	0.8 ± 0.3	0.9 ± 0.2	0.713
Number of women with EF < 50%, *n* (%)	4 (5)	3 (4)	1 (1)	0.452
Cardiac index, L/min/m^2	2.9 ± 0.2	3.1 ± 0.2	2.8 ± 0.1	0.052

Values are given as mean ± SD or median [interquartile range].
ACE, angiotensin-converting-enzyme; AT, angiotensin; CoA, coarctation of the aorta; DBP, diastolic BP; EF, ejection fraction; FU, follow-up; IVSd, intraventricular septum diastole; LVIDd, left ventricular internal diameter in diastole; LVPWd, left ventricular posterior wall diameter; MACE, major cardiac events; MAP, mean arterial pressure; SBP, systolic BP; ULE-SBP gradient, upper-to-lower-extremity systolic blood pressure gradient.

ongoing medical treatment, these patients had clinical worsening leading up to the cardiac event and hospitalization. Feared complications like aortic dissections, coronary artery dissections, cerebrovascular events, or endocarditis did not occur during pregnancy or post-partum in this cohort. Major cardiac event rates in the reports from the ROPAC cohort (4.3%) and Krieger *et al.* (5%) were also low (4.3%). The ROPAC report found predictors of MACE to be pre-pregnancy signs of heart failure, LVEF < 40%, NYHA Class > 1, and the use of cardiac medication before pregnancy.

Concerning risk, most of the patients in our cohort will be stratified into mWHO Risk Class II, corresponding to a small increased risk of maternal mortality or moderate increase in morbidity.

Obstetrical and neonatal outcome

Two-thirds of the patients in our cohort had a vaginal delivery, and 22% of the women had a caesarean section. This is substantially lower than the observed caesarean section rate of 50% in the ROPAC report on women with structural cardiac disease. Planned caesarean sections in uneventful pregnancies for patients with structural heart disease offer no maternal advantage, while they may increase adverse foetal outcomes.[36,37]

Evidence from randomized controlled trials that can inform practice regarding planned caesarean section vs. vaginal delivery for women with pre-eclampsia is lacking.[38]

There was a non-significant lower birth weight in infants of mothers treated with beta-blockers. This contrasts a recent study by Sørbye *et al.*[39], reporting a five-fold increased risk of delivering a small-for-gestational-age infant in women with heart disease treated with a high dose of beta-blocker, and a two-fold increased risk among those treated with a low dose, showing an apparent 'dose–response' relation. We found a low rate (3%) of CHD in the offspring, although the recurrence rate is reported to be up to 6.5% for non-syndromic maternal CoA.[40] Our data are in line with the recent ROPAC report.[17]

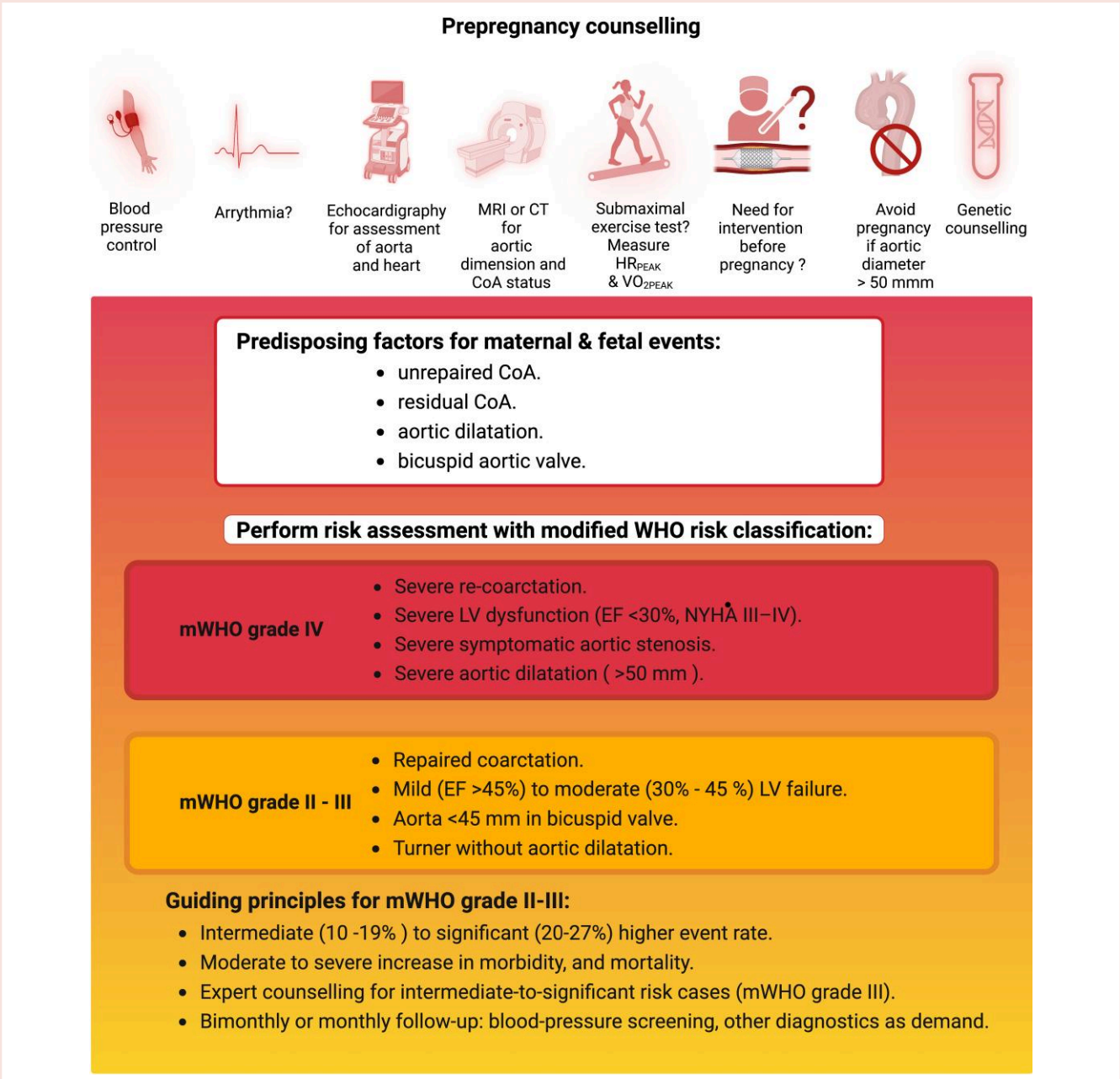


Figure 4 Pre-pregnancy counselling and pregnancy risk assessment in women with CoA. CoA, coarctation of the aorta; CT, computed tomography; EF, ejection fraction; HR_{PEAK}, heart rate at peak exercise; LV, left ventricular; MRI, magnetic resonance imaging; mWHO, modified World Health Organization; NYHA, New York Health Association; VO_{2PEAK}, volume of oxygen uptake during peak exercise. Created with BioRender.com.

Strengths and limitations of the study

The strength of this registry study was the complete inclusion of the CoA cohort for the pre-pregnancy and follow-up data. The study had no patients lost to follow-up. From the patient register, we had access to validated information on exposure and outcome variables on all the CoA patients after pregnancy.

In Norway, adults with CHD (ACHD), including patients with CoA, have regular follow-up by ACHD cardiologists at the outpatient clinic. This provides a complete overview of the ACHD population. The pregnant women with ACHD are referred to the National Unit for Pregnancy and Heart Disease for evaluation and follow-up.

Contrary to multi-centre registries, this may perhaps explain the difference in prevalence of pre-eclampsia from our study to previous reports. However, contemporary prospective studies should be performed to confirm our results. A dedicated team of cardiologists, obstetricians, anaesthesiologists, midwives, and nurses standardized the patient follow-up and treatment during the study period. Pre-pregnancy counselling and risk stratification, essential

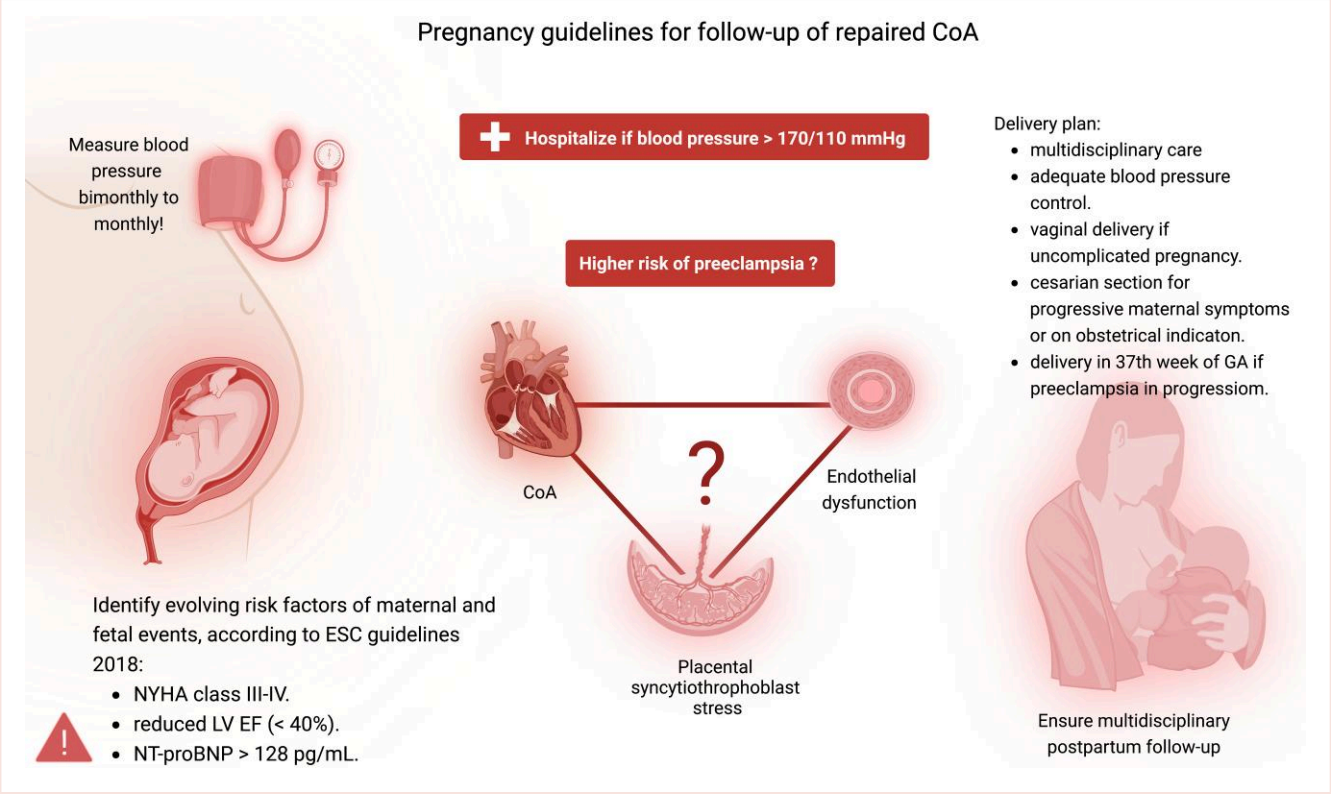


Figure 5 Pregnancy follow-up for patients with repaired coarctation of the aorta. CoA, coarctation of the aorta; ESC, European Society of Cardiology; GA, gestational age; HR_{PEAK}, heart rate at peak exercise; LV EF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Health Association; $\dot{V}O_{2PEAK}$, volume of oxygen uptake during peak exercise; WHO, World Health Association. Created with BioRender.com.

for fertile women with CoA to conduct a safe pregnancy, were performed according to current guidelines, illustrated in *Figures 4* and *5*.

This study has limitations due to the nature of the retrospective design and the observational data from a single centre. Inherent to our study design is selection bias to the results. Also, the number of events in our data is low. This should be considered in interpreting the study results. To draw any causal inference between pre-eclampsia and cardiovascular disease and CoA is challenging. Reports from considerable observational data across the past two decades can only show strong associations between pre-eclampsia and cardiovascular outcomes.

Conclusion

In our study, we found a high prevalence of pre-eclampsia in women with CoA. Pre-eclampsia is a cardiovascular risk factor, and ASA should be considered for women with CoA as prevention for pre-eclampsia. Our results show that pregnancy in women with repaired CoA is safe, but vigilance to the presentation of pre-eclampsia is critical to avoid severe peri-partum complications. Over one-fourth of the CoA patients received anti-hypertensive treatment after pregnancy. Long-term follow-up, with targeted anti-hypertensive treatment and lifestyle modifications, is mandatory to prevent cardiovascular disease.

Lead author biography

Lasse Gronningsaeter, MD, is a senior consultant in anaesthesiology and intensive care medicine at Oslo University Hospital, Norway. He is a PhD candidate and currently conducts research in the fields of pre-eclampsia and cardiovascular disease.

Data availability

All data relevant to the study are included in the article or uploaded as supplementary information. Data are owned by the National Unit for Pregnancy and Heart Disease at Oslo University Hospital.

Supplementary material

Supplementary material is available at *European Heart Journal Open* online.

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Data analysis and statistical analysis: L.G.
Manuscript draft: L.G., E.L., I.K.S., M.E.E.
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