Functional and structural vascular biomarkers in women 1 year after a hypertensive disorder of pregnancy

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ABSTRACT

Objectives: Women with a previous hypertensive disorder of pregnancy (HDP: gestational hypertension and preeclampsia) have increased long-term cardiovascular disease risk. Recent *meta*-analyses show adverse levels of non-invasive functional and structural cardiovascular risk markers such as pulse wave velocity (PWV), heart-rate adjusted augmentation index (AIx75), carotid intima-media thickness (CIMT), and reactive hyperemia index (RHI) after HDPs, and suggest using these for cardiovascular risk stratification. However, it is not known if a previous HDP predict levels of these markers beyond classical cardiovascular risk factors.

Study design and main outcome measures. We assessed PWV, AIx75, CIMT, RHI, classical cardiovascular risk factors, and pregnancy characteristics in 221 women 1 year postpartum (controls: 95, previous HDP: 126). Uni- and multi- variate regression analysis were conducted to assess associations between previous HDP and PWV, AIx75, CIMT or RHI. We adjusted for classical cardiovascular risk factors and pregnancy characteristics. A p-level < 0.05 was considered statistically significant.

Results: PWV was associated with previous HDP on univariate analysis. This effect was confounded by blood pressure and not significant after adjustment. We found no significant associations between AIx75, RHI, CIMT, and a previous HDP, neither before nor after adjustments.

Conclusions: Associations between a previous HDP and PWV, AIx75, CIMT, or RHI 1 year postpartum can largely be explained by adverse levels of classical cardiovascular risk markers in women with a previous HDP. Women with previous HDP should receive primary prevention of cardiovascular disease, but PWV, AIx75, CIMT or RHI are unlikely to aid in cardiovascular risk stratification 1 year postpartum.

1. Introduction

A previous hypertensive disorder of pregnancy (HDP) like preeclampsia or gestational hypertension (GH) confers an increased risk of later maternal cardiovascular disease [1]. An HDP often precedes the debut of clinical cardiovascular disease by decades, and many types of cardiovascular disease can be prevented or postponed by timely intervention, justifying cardiovascular follow-up of women with a previous HDP [1,2].

Methods to identify the women with a previous HDP who will benefit the most by preventive interventions are not readily available. It is recommended to assess long-term cardiovascular disease risk using risk calculators [2,3], but we have previously shown that these fail to reflect the epidemiologically increased cardiovascular risk when applied 1 year postpartum [4].

Several studies have identified adverse levels of vascular markers such as pulse wave velocity (PWV), augmentation index, and carotid intima-media thickness (CIMT), and reactive hyperemia index (RHI) in women with a previous HDP [5–8]. Some have suggested that these could identify women at the highest risk and guide preventive measures

[5,6,9]. However, the ability of these markers to predict cardiovascular disease in women with previous HDPs has not been documented. It is also unclear if these markers predict cardiovascular disease beyond classical, and routinely available cardiovascular risk factors such as dyslipidemia, smoking, age, body mass index (BMI), and blood pressure [2,3,10].

The aim of this study was to evaluate levels of RHI, PWV, heart-rate adjusted augmentation index (AIx75), and CIMT in women with a recent pregnancy complicated by HDP, to compare levels of women with normotensive index pregnancies, and to investigate if potential associations were independent of classical cardiovascular risk factors.

2. Methods

All procedures were in accordance with institutional guidelines and with the Declaration of Helsinki. The Regional Committee for Medical and Health Research Ethics of South East Norway approved the study. All women provided written informed consent.

Women above 18 years who had delivered a singleton baby without congenital malformations at Oslo University Hospital, Ullevål, Norway, were invited to participate in the Health after pregnancy complications study 1 year postpartum. Women with diabetes, cardiovascular disease (except for HDP), renal or rheumatic disease, were excluded as these diseases may impact on CVD risk. We also excluded women who were still breastfeeding or pregnant at postpartum exam time.

Gestational age at the index delivery was based on routine ultrasound examination at gestational week 18–20, except for 18 pregnancies (2 by the first day of last menstruation prior to pregnancy and 16 by in vitro fertilization dating).

Gestational hypertension (GH) and preeclampsia in the index pregnancy were defined by the International Society for the Study of Hypertensive Disorders in Pregnancy guidelines [11]. GH is defined as new-onset hypertension after gestational week 20 while preeclampsia is defined by the addition of either new-onset proteinuria or other preeclampsia-associated organ dysfunction signs (including elevated liver transaminases and fetal growth restriction) [11]. Since previous studies comparing the same vascular cardiovascular markers between women with a previous HDP and parous controls have used the old preeclampsia-definition requiring mandatory new-onset proteinuria in addition to gestational hypertension, we also present a supplement applying this definition. Preterm and term preeclampsia were defined by delivery before or from 37th gestational weeks, respectively. The in-patient hospital blood pressure used to diagnose HDP was based on repeated measurement with a validated device (Dinamap Pro, 100VE, GE Medical Systems Information Technology, Inc. Milwaukee, WI, USA) [12].

Delivery of a small for gestational age (SGA) baby was defined as a baby below the 3rd birth weight percentile, adjusted for gestational age at delivery and fetal sex [13]. Controls were normotensive prior to and throughout any pregnancy and delivered a non-SGA baby from 37 gestational weeks onwards. None of the included women showed signs of hyperglycemia during pregnancy.

Fasting (≥ 6 h) morning serum samples were collected for all participants 1 year postpartum. Total cholesterol, low density lipoprotein cholesterol (LDL), high density lipoprotein cholesterol (HDL), and glucose were analyzed according to clinical routine by the Department of Clinical Biochemistry, Oslo University Hospital. Cholesterol, LDL and HDL were measured by an enzymatic colorimetric method (cobas 8000 c702, Roche Diagnostics).

At the 1 year postpartum exam, blood pressure was measured in the right upper arm with an identical blood pressure device as prior to delivery following guidelines from the European Society of Hypertension and European Society of Cardiology [14]. Height and weight were measured, and questionnaires regarding pregnancies before index pregnancy, cardiovascular health, cardiovascular risk factors, general health, and socioeconomic factors completed. Body mass

index (BMI) was defined as weight divided on squared height.

Examinations were performed in fasting (≥ 6 h) women in supine position in a temperature-regulated, quiet room with dimmed lights and with at least 10 min bedrest before PWV, AIx75, and RHI-assessments.

Four trained examinators assessed endothelial function using EndoPAT™-2000 (Itamar Medical Ltd., Caesarea, Israel). The RHI, a standardized post-occlusion to pre-occlusion-ratio, was calculated by the software. Lower RHI is associated with poorer endothelial function [15]. We assessed carotid-femoral PWV using Sphygmocor® CvMS, version 9 (AtCor Medical, Sydney, Australia) according to guidelines [16]. AIx75 was assessed with the same device. Carotid Intima-Media Thickness (CIMT) was measured using the multiarray echotracking system (Art.Lab®, Esaote, Maastricht, the Netherlands) equipped with a 10–5 MHz linear array. Measurements were performed according to guidelines from the European Stroke Conferences [17]. Details of the methods are presented in the supplemental file.

One examiner (KM) conducted all PWV, AIx75, and CIMT examinations. We have previously assessed reproducibility of PWV, AIx75 and CIMT by the intraclass correlation coefficient based on a mean-rating, absolute-agreement, 2-way mixed-effects model. All intraclass correlation coefficients were "excellent": PWV (0.930, 95%CI: 0.822–0.972, p < 0.001), AIx75 (0.985, 95%CI: 0.963–0.994, p < 0.001), and CIMT (ICC: 0.977, 95%CI: 0.937–0.991, p < 0.001).

Statistical analyses were performed with the Statistical Package for the Social Sciences (PASW Statistics 25). As most variables were not normally distributed, medians and ranges are presented. Differences between groups were tested with Mann-Whitney *U* test for continuous and Chi-square or Pearson's mid-corrected p-test for categorical variables. A p-value of < 0.050 was considered statistically significant for an association between the dependent and independent variable.

Univariate linear regression analysis was used to analyze associations between HDPs and the levels of PWV, AIx75, CIMT, and RHI. Multivariate linear regression analysis was used to adjust for possible confounders identified prior to the analyses based on previous literature. Continuous possible confounders were mean-centered. Age and BMI were introduced by forced entry in model 2. In model 3, we additionally introduced cardiovascular risk marker variables commonly used for cardiovascular disease risk stratification [18,19] if significant (p < 0.10) on univariate analysis. These were included in the final multivariate model if significant (p < 0.05). For model 4, we additionally introduced pregnancy characteristics variables associated to cardiovascular diseaserisk [20,21] in the same way as in model 3. Hence, we present 4 models: unadjusted, adjusted for age and BMI, also adjusted for classical cardiovascular risk markers, and finally also adjusted for pregnancy characteristics. Fig. 1 presents the variables used in the regression analyses.

Power appeared to be sufficient based on previous studies investigating the same markers in similar populations [7,9,22,23].

3. Results

Table 1 summarizes the clinical characteristics of the totally 221 women examined 1 year postpartum (2014–2018). The HDP group (n = 126) included 88 women with preeclampsia (54 with term and 34 with preterm preeclampsia) or GH (n = 38) in their index pregnancy. Median follow-up time was 13.8 months, and in median 19 days shorter in term preeclampsia women compared to controls. In all groups most women were of white ethnicity and educated beyond high school level.

Both term (n = 3) and preterm (n = 5) preeclampsia pregnancies were complicated by HELLP (hemolysis, elevated liver enzymes, and low platelets). The rates of SGA babies and primiparity were as expected higher for the previous preeclampsia groups.

At 1 year postpartum all groups with previous HDPs exhibited a worse cardiovascular disease risk profile with significantly higher diastolic and systolic blood pressures compared to controls (Table 1).
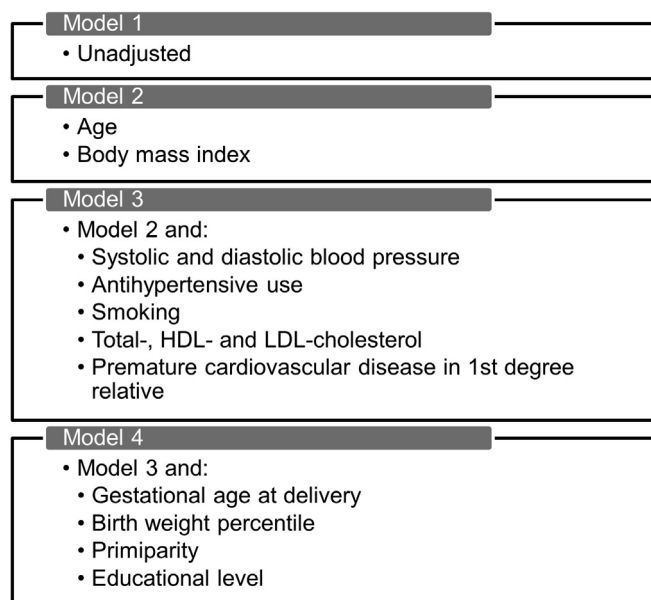
Fig. 1. Variables included in the regression analyses. HDL-cholesterol: High Density Lipoprotein Cholesterol. LDL-cholesterol: Low Density Lipoprotein Cholesterol.

Prehypertension and hypertension were significantly more common in all groups with a previous HDP, though not significantly for hypertension in term preeclampsia women. In women with previous GH, nearly half were either hypertensive or prehypertensive at follow-up. Two women (one with term preeclampsia and one with GH) were identified with untreated hypertension, necessitating follow-up.

BMI was higher within all previous HDP groups, although only significant for the total HDP group when compared to controls. Overweight and cardiovascular disease in a 1st degree relative were

more common in all groups with previous HDP, but not significantly so in the group with previous GH.

Due to technical failure of obtaining a technically satisfying result, or time constraint, PWV was analyzed in 86.0%, AIx75 in 87.3%, RHI in 95.4%, and CIMT in 90.5% of the women. All included women had at least one valid type of examination (Details are presented in Table 2) Table 2 also presents the unadjusted analysis when applying the old preeclampsia definition requiring proteinuria.

Mean values of PWV, AIx75, and CIMT for controls were consistent with published reference ranges for premenopausal women [24–26], while no reference values for RHI exist. Unadjusted results for the vascular markers for the different pregnancy groups are presented in Table 2.

PWV was significantly higher in the total group with HDP and in the subgroups with preterm preeclampsia and GH as compared to controls (Table 2). Although AIx75 and CIMT levels were higher in all groups with a previous HDP as compared to parous controls, none of these differences were significant (Table 2). For RHI, there were no significant differences in any group of pregnancy complication.

As shown in Table 3 and Fig. 2, we found no significant association between adverse levels of vascular markers for the total HDP group or for any of the HDP subgroups after adjustments in the multivariate regression analysis (Model 2–4).

For PWV, adjusting for diastolic blood pressure heavily mediated the association between PWV and a previous HDP. This was also the case for the HDP subgroups (Model 3). After this adjustment, neither the total HDP group nor any subgroup were significant independent predictors of PWV, and only BMI and age remained significant predictors of PWV at 1-year postpartum. No pregnancy factor was a significant predictor of PWV within the total HDP group or in any HDP subgroup (Model 4).

For AIx75, although the effect of an HDP on AIx75 levels increased in all groups after adjustment for age and BMI, still no association was significant (Model 2). Further adjustment for cardiovascular risk factors and pregnancy characteristics showed mediation from the

Table 1
Clinical data one-year postpartum.

	Controls (n = 95)		Hypertensive Disorder of Pregnancy (n = 126)		Term Preeclampsia (n = 54)		Preterm Preeclampsia (n = 34)		Gestational Hypertension (n = 38)	
Age (years)	34.9	23.5–43.7	34.2	21.7–45.1	34.3	21.7–43.3	34.9	24.5–43.2	34.0	23.0–45.1
BMI (kg/m²)	22.7	17.1–36.0	23.9*	18.3–37.6	24.1	19.9–37.6	24.6	18.3–32.5	23.7	18.9–33.7
Overweight (BMI > 25 kg/m²)	28.4%	27	46.0%*	58	44.4%*	24	50.0%*	17	44.7%	17
Systolic BP (mmHg)	106	90–122	114†	94–145	112†	94–140	114†	94–133	118†	99–145
Diastolic BP (mmHg)	62	53–82	71†	51–96	68†	56–84	71†	51–86	73†	53–96
Prehypertensive (BP 120–139/ 80–89 mmHg)	2.1%	2	27.0%†	34	20.4%†	11	20.6%	7*	42.1%†	16
New/treated hypertension	0.0%	0	4.8%*	6	3.8%	2	5.9%*	2	5.2%*	2
Antihypertensive use	1.1%	1	3.2%	4	1.9%	1	5.9%	2	2.6%	1
Smoking	9.6%	9	8.9%	11	3.8%	2	8.8%	3	16.2%	6
LDL-cholesterol (mg/dL)	103.5	59.1–202.7	105.4	44.4–184.9	104.8	59.5–185.0	110.4	44.4–184.6	102.1	48.3–156.5
HDL-cholesterol (mg/dL)	59.3	38.6–113.1	58.3	27.4–93.4	57.1	38.2–93.4	58.3	27.4–89.6	59.7	30.9–82.2
Cholesterol (mg/dL)	171.8	104.3–281.9	173.7	108.1–262.5	169.9	123.6–247.1	181.5	115.8–262.6	173.8	108.1–239.4
Premature CVD in 1st degree relative	16.8%	16	31.7%*	40	33.3%*	18	38.2%*	13	23.7%	9
Education > high school	91.7%	77	87.1%	101	91.7%	44	86.7%	26	81.6%	31
White/not stated ethnicity	94.7%	90	95.7%	112	96.3%	52	94.1%	32	97.4%	37
SGA in index pregnancy (< 3rd percentile)	0.0%	0	26.2%†	33	24.1%†	13	58.8%†	20	0.0%	0
Female offspring in index pregnancy	56.8%	54	46.8%	59	50.0%	27	41.2%	14	47.4%	18
Gestational age at delivery in index pregnancy (days)	275	261–296	268†	177–293	271*	259–291	233†	177–257	278	261–293
Primiparous	45.3%	43	71.4%†	90	79.6%†	43	67.6%*	23	63.2%	24
Follow-up time from index pregnancy (days)	420	342–543	407†	296–492	401*	296–492	419	346–484	417	327–487

BP: Blood Pressure. BMI: Body Mass Index. LDL: Low Density Lipoprotein. HDL: High Density Lipoprotein. CVD: Cardiovascular Disease. SGA: Small for Gestational age. Mann Whitney *U* test for continuous variables and Chi-square or Fisher's mid-p corrected test for categorical variables comparing pregnancy complication (e.g. GH) to controls: *:p-value < 0.050. †:p-value < 0.001.

Table 2

Reactive Hyperemia Index, Pulse Wave Velocity, Augmentation Index adjusted for a Heart Rate of 75 Beats per Minute, and Carotid Intima-Media Thickness in Women with index Pregnancy Hypertensive Disorder of Pregnancy and Parous Controls 1 Year postpartum. Values are given as Median (Range) and Number.

	PWV (m/s)		AIx75 (%)		CIMT (µm)		RHI	
Controls	5.78 (4.30–8.60)	80	11 (−15–28)	80	450 (353–676)	91	1.90 (1.05–3.08)	90
Hypertensive Disorder of Pregnancy	6.10† (4.50–8.35)	110	12 (−12–31)	113	464 (353–888)	119	1.89 (1.00–2.91)	121
Term Preeclampsia	6.10 (4.50–8.35)	47	10 (−5–31)	47	460 (367–676)	51	2.06 (1.03–2.91)	52
Term Preeeclampsia*	6.08 (4.50–8.35)	42	10 (−5–31)	43	461 (367–676)	46	2.07 (1.03–2.91)	47
Preterm Preeclampsia	6.35† (4.70–8.30)	30	13 (-6–27)	31	461 (376–888)	32	1.84 (1.00–2.73)	31
Preterm Preeclampsia*	6.40†(4.90–8.30)	27	13 (-6–27)	27	461 (376–888)	28	1.90 (1.00–2.73)	27
Gestational Hypertension	6.10 †(4.55–8.20)	33	13 (−12–27)	35	480 (353–634)	36	1.81 (1.05–2.55)	38
Gestational Hypertension*	6.10† (4.55–8.20)	41	12 (−12–27)	43	465 (353–634)	45	1.75 (1.05–2.55)	47

RHI: Reactive Hyperemia Index. PWV: Pulse Wave Velocity. AIx75: Augmentation Index adjusted for heart rate of 75 beats per minute. CIMT: Carotid Intima-Media Thickness. *: using definition of preeclampsia requiring proteinuria. †: $p < 0.050$ comparing controls with hypertensive disorder of pregnancy (e.g. late preeclampsia) using Mann-Whitney U test

Table 3

Regression analysis comparing levels of PWV, AIx75, CIMT, and RHI, in women with previous HDP to parous controls.

		Controls vs. Hypertensive Disorders of Pregnancy		Controls vs. Term Preeclampsia		Controls vs. Preterm Preeclampsia		Controls vs. Gestational Hypertension	
	Model	B	95%CI	B	95%CI	B	95%CI	B	95%CI
PWV (m/s)	1	0.35†	(0.12–0.59)	0.25	(−0.03–0.54)	0.50†	(0.16–0.84)	0.36*	(0.03–0.68)
n = 190	2	0.33†	(0.11–0.55)	0.26	(−0.01–0.53)	0.45†	(0.13–0.77)	0.35*	(0.03–0.67)
	3	0.02	(−0.19–0.24)	0.04	(−0.23–0.31)	0.13	(−0.10–0.36)	−0.01	(−0.04–0.02)
	4	0.02	(−0.19–0.24)	−0.01	(−0.28–0.27)	0.13	(−0.10–0.36)	−0.01	(−0.04–0.02)
AIx75 (%)	1	1.8	(−0.9–4.5)	1.2	(−2.2–4.7)	3.0	(−1.1–7.1)	1.5	(−2.5–5.6)
n = 193	2	2.2	(−0.3–4.7)	2.3	(−0.9–5.4)	3.3	(−0.6–7.2)	2.2	(−1.5–5.9)
	3	0.8	(−1.9–3.4)	0.4	(−2.9–3.6)	0.3	(−4.1–4.6)	−0.5	(−4.8–3.8)
	4	0.8	(−1.9–3.4)	0.4	(−2.9–3.6)	0.3	(−4.1–4.6)	−0.5	(−4.8–3.8)
CIMT (µm)	1	11	(−9–30)	7	(−17–30)	14	(−15–43)	13	(−11–38)
n = 210	2	9	(−10–28)	6	(−17–28)	12	(−17–40)	12	(−12–35)
	3	10	(−9–28)	6	(−17–28)	5	(–23–33)	12	(−12–35)
	4	10	(−9–28)	6	(−17–28)	5	(–23–33)	12	(−12–35)
RHI	1	−0.04	(−0.16–0.08)	0.05	(−0.11–0.21)	−0.10	(−0.28–0.08)	−0.12	(−0.29–0.05)
n = 211	2	−0.06	(−0.18–0.06)	0.04	(−0.12–0.20)	−0.11	(-0.30–0.07)	−0.13	(−0.30–0.04)
	3	−0.01	(−0.14–0.12)	0.02	(−0.14–0.18)	−0.11	(−0.30–0.07)	−0.11	(−0.28–0.06)
	4	0.07	(−0.07–0.21)	0.09	(−0.08–0.26)	−0.11	(−0.30–0.07)	−0.11	(−0.28–0.06)

HDP: Hypertensive Disorder of Pregnancy. GH: Gestational Hypertension. PWV: Pulse Wave Velocity (m/s). AIx75: Augmentation Index adjusted for Heart Rate (%). RHI: Reactive Hyperemia Index. CIMT: Common Carotid Artery Intima-media thickness (um). 95%CI: 95% confidence interval for B. *:$p < 0.05$ and †:$p < 0.01$ when comparing HDP, Term Preeclampsia, Preterm Preeclampsia or GH to controls on linear regression analysis. Model 1: unadjusted. Model 2: adjusted for body mass index (BMI), age. Model 3: adjusted for BMI, age and cardiovascular risk factors. Model 4: Model 3 adjusted for pregnancy characteristics.

cardiovascular risk factors; in particular diastolic blood pressure. Systolic blood pressure was in addition a significant predictor in the total HDP group. No pregnancy factor was a significant predictor of AIx75 within the total HDP group or in any HDP subgroup (Model 4).

For CIMT, antihypertensive use was a significant positive predictor of CIMT in the total HDP group, and in the preterm preeclampsia group, while LDL levels were only significant in the total HDP group. No pregnancy factor was a significant predictor of CIMT within any group.

For RHI, smoking was a significant predictor of low RHI in the term preeclampsia and GH groups, but only mediating the effect of term preeclampsia on RHI. Smoking was also mediating the effect of any previous HDP on RHI. In this comparison, diastolic blood pressure was also a significant predictor. When adjusting for pregnancy characteristics, delivery of an SGA baby mediated the effect of term preeclampsia on RHI. The same was the case for delivery of an SGA baby in the total HDP group. Here, primiparity was also a significant predictor.

As rates of delivery of an SGA baby and primiparity differed significantly between HDPs and controls, we also tested for interactions between HDPs and delivery of an SGA baby or primiparity, but no interaction was significant for any of the vascular markers.

Significant covariates in the multivariate regression analyses are presented in Supplemental Table 1. The regression analyses for AIx75 and CIMT contained outliers impacting the effect estimates. For AIx75 this was a control (AIx75: 11%), and for CIMT a woman with previous

preterm preeclampsia (CIMT: 888 µm). Regression analyses excluding these two women (Supplemental Table 2) show that the effect estimates are heavily impacted by these observations, though the non-significance of the associations to the outcomes was not altered.

Using the old preeclampsia definition requiring proteinuria produced similar results for relations between the vascular markers and previous HDPs (Table 2).

4. Discussion

This study shows that 1 year postpartum a previous HDP is associated with adverse pulse wave velocity (PWV) levels, but neither with levels of heart-rate adjusted augmentation index (AIx75), carotid intima-media thickness (CIMT), nor with reactive hyperemia index (RHI) levels. After adjustment for classical cardiovascular disease risk factors, no association between a previous HDP and PWV, AIx75, CIMT, or RHI was significant. In detail, PWV was higher 1 year after a pregnancy complicated by preterm preeclampsia or GH, but not term preeclampsia. No difference was significant after adjusting for classical cardiovascular risk factors.

Our study was designed for prospectively assessing cardiovascular outcomes after pregnancy complications. It is strengthened by the extensive cardiovascular and pregnancy data collected in a standardized way. This enabled us to adjust for common cardiovascular risk markers
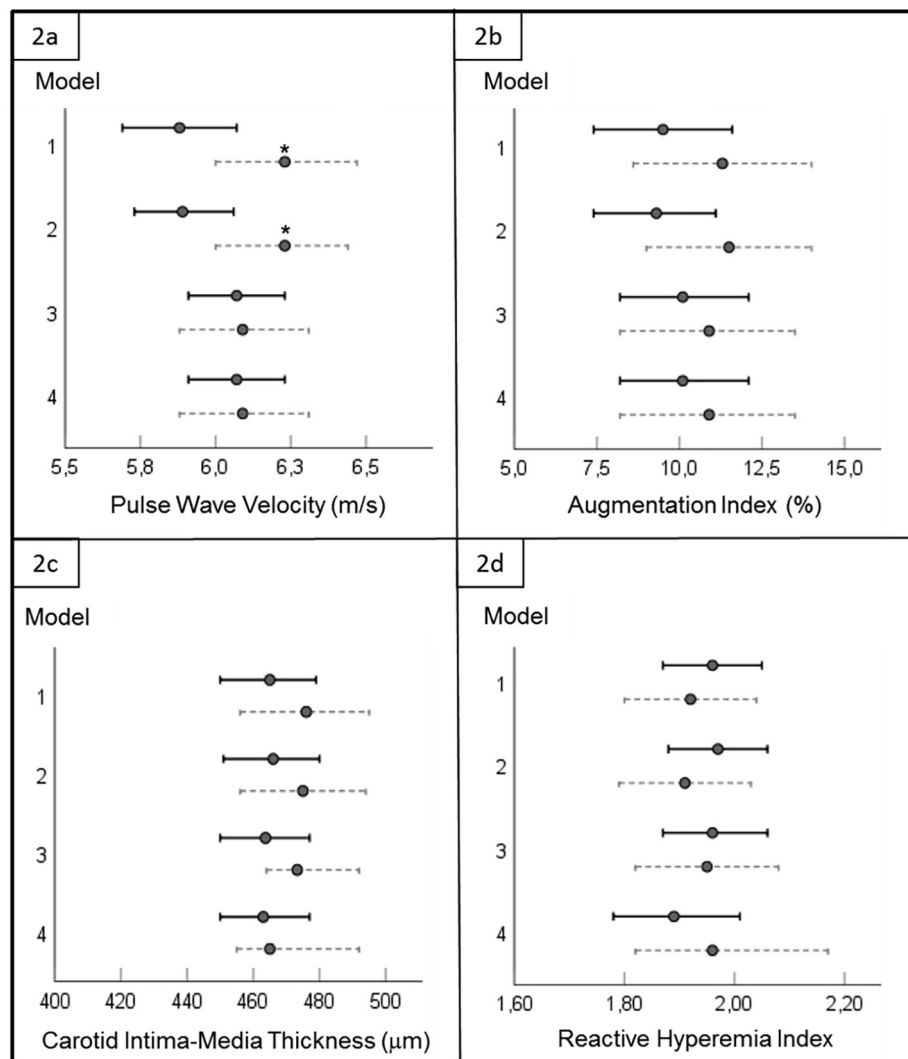
Fig. 2. Regression analysis of vascular biomarkers levels in women with previous hypertensive disorder of pregnancy (95% confidence interval: grey dotted lines) and controls (95% confidence intervals: black continuous lines). Means: filled circles. *p < 0.05. 1: unadjusted. Model 2: adjusted for age and body mass index at 1 year postpartum. Model 3: Model 2 + adjustment for classical cardiovascular risk factors. Model 4: model 3 + adjustment for pregnancy characteristics, and educational level.

recommended to use for assessing cardiovascular risk, and to exclude women with other conditions known to impact on this risk [2,3], e.g. chronic hypertension or diabetes mellitus. Furthermore, no women were breastfeeding, which otherwise could have impacted on blood pressures [27].

Controls in our study did have an index pregnancy without hypertension, hyperglycemia or delivery of a small for gestational age baby, features linked to a higher cardiovascular disease risk [1]. Thus, the controls constitute a very healthy group, increasing the power to detect possible differences between women with a previous HDP and controls.

Inter-observer bias was avoided for PWV, AIx75, and CIMT in our study, since all examinations were performed by the same examiner, and reproducibility was high. For RHI, EndoPAT-examinations are generally reproducible [28].

Our study population has a potential for a self-selection bias. The recruitment process for controls and cases was however identical, decreasing the risk of different bias. Furthermore, the mean PWV, AIx75, and CIMT in our control group are within reference ranges, suggesting that the controls are representative for the general population [24–26]. For RHI, we are not aware of any published reference ranges, and two studies investigating RHI postpartum have found higher RHI in the

controls than in our study [7,8]. Interpretation and use of RHI in young people is however difficult, as there is a paradoxical rise in RHI by age in the younger part of the population [29].

The external validity of the study is strengthened by this being the first study using updated definitions of preeclampsia and GH in group analyses of PWV, AIx75, CIMT, or RHI [11]. However, using the old preeclampsia definition (with mandatory proteinuria) only reclassified 9 women (Table 2), and did not significantly alter the level of any vascular marker for the HDP subgroups.

Several studies have looked at one or more of PWV, AIx75, RHI, and CIMT after an HDP. Few have however presented adjusted analyses. Thus, published *meta*-analyses, finding elevated PWV, Augmentation Index, and CIMT after HDP have not taken possible confounding factors into account [5,6]. The by far largest study investigating any of these markers postpartum, by Bergen et al [30], examined PWV 5–7 years postpartum in nearly 5000 women, of which 300 had a previous HDP. They found an increased PWV among women with previous GH, but not preeclampsia, as compared to controls [30]. In contrast to our study, the results in the preeclampsia group were not stratified by gestational age. Low gestational age in preeclampsia is associated with increased cardiovascular disease risk [1]. Our finding of an association between preterm preeclampsia and adverse PWV levels is also supported by

previous smaller studies [7,23]. Furthermore, although these three mentioned studies all found significant differences in blood pressure between groups, neither used blood pressure to adjust the PWV findings [7,23,30].

In the study by Ehrenthal et al, a previous HDP significantly predicted AIx75 1 year postpartum after adjusting for some classical cardiovascular risk factors, but not including blood pressure [31]. The unadjusted AIx75 values were higher for controls and women with a previous HDP than in our study, but detailed data about important cardiovascular risk factors were not presented. Furthermore, 24% of the total study population was of African-American origin, in contrast to our study where nearly all were of white ethnicity.

We did not confirm CIMT differences between parous controls and women with a previous HDP seen in some, but not all studies examining CIMT in women with a previous HDP in the same postpartum time frame [9,22,32–34]. Information on some important pregnancy characteristics and/or cardiovascular risk factors was unavailable in all these studies. This might have confounded the results [9,22,32,34]. Blaauw et al found increased CIMT 6 months postpartum in 22 women with early-onset preeclampsia compared to 22 women with uncomplicated pregnancies. After adjusting for multiple classical cardiovascular risk factors, this association was not significant. The study was however probably underpowered for multivariate regression analysis [35]. The same group found no differences in CIMT when investigating 33 of the same women 5 years postpartum [36], in line with previous studies investigating women with a previous HDP within a longer time frame [37–39].

Our study shows that adverse levels of vascular markers in premenopausal women with previous HDP are explained by levels of classical cardiovascular risk factors. It is also debatable whether any of the studied vascular markers independently predict cardiovascular disease in general [2,3,10]. Furthermore, none have been validated in a relatively young female population like ours. Our study indicates that differences in vascular markers between women with a previous HDP and controls found shortly after pregnancy (1 year) largely can be explained by differences in classical cardiovascular risk factors. These classical risk factors are easier to measure, and thus more applicable in the clinical setting. Our study does not however imply that follow-up for primary prevention of cardiovascular disease is unnecessary in women with a previous HDP. On the contrary, women with a previous HDP in our study did indeed exhibit a worse cardiovascular risk profile 1 year postpartum, thus constituting a high-risk group for cardiovascular disease development. This is supported by numerous epidemiological studies [1]. Together with physical inactivity, poor diet, and smoking, elevated BMI and blood pressure represent important modifiable cardiovascular risk factors. Thus, primary prevention of cardiovascular disease remains vital after an HDP. Such prevention should probably commence as early as 1 year postpartum, focusing on measurement and improvement of classical cardiovascular risk factors.

Funding

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.preghy.2020.04.008.

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