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RESEARCH ARTICLE

Epidemiology

Microvascular dysfunction in women with a history of hypertensive disorders of pregnancy: A population-based retrospective cohort study

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Abstract

Objective: To evaluate microvascular function in women with previous hypertensive disorders of pregnancy (HDP).

Design: Retrospective population-based cohort study.

Setting: Linköping, Sweden.

Population: Women aged 50–65 years, participating in the Swedish CArdioPulmonary bioImage Study (SCAPIS) at one site (Linköping) 2016–18, who underwent microcirculatory assessment ($N = 1222$).

Methods: Forearm skin comprehensive microcirculatory assessment was performed with a PeriFlux PF6000 EPOS (Enhanced Perfusion and Oxygen Saturation) system measuring oxygen saturation and total speed resolved perfusion. Obstetric records were reviewed to identify women with previous HDP. Data on cardiovascular risk factors, comorbidities, medication, lifestyle, anthropometric data, and biochemical analyses were obtained from SCAPIS. The microcirculatory data were compared between women with and without previous HDP.

Main outcome measures: Skin microcirculatory oxygen saturation and total speed resolved perfusion at baseline and post-ischaemic peak.

Results: Women with previous pre-eclampsia displayed impaired post-ischaemic peak oxygen saturation compared with women with normotensive pregnancies (88%, interquartile range [IQR] 84–89% vs 91%, IQR 87–94%, $p = 0.001$) 6–30 years after pregnancy. The difference remained after multivariable adjustment (β −2.69, 95% CI −4.93 to −0.45).

Conclusions: The findings reveal microvascular dysfunction at long-term follow up in women with previous pre-eclampsia and strengthen the possible role of endothelial dysfunction as a link to the increased risk of cardiovascular disease in women with HDP.

KEYWORDS
cardiovascular disease, endothelial dysfunction, hypertension pregnancy-induced, microcirculation, pre-eclampsia, pregnancy

1 | INTRODUCTION

Hypertensive disorders of pregnancy (HDP) affect up to 10% of pregnant women and include gestational hypertension (GH) and pre-eclampsia, the latter defined by onset of hypertension after gestational week 19^{+6} combined with proteinuria, organ dysfunction or signs of uteroplacental dysfunction.[1,2] Women with pre-eclampsia have an

increased risk of later cardiovascular disease (CVD), with a two-fold increased risk of cardiovascular death, coronary artery disease (CAD) and stroke, and a four-fold increased risk of heart failure.[3–5] It is not fully elucidated if HDP, especially pre-eclampsia, is an independent risk factor for CVD or if the association is mediated by conventional risk factors.[6,7] Endothelial dysfunction seems to play a crucial role in pre-eclampsia pathophysiology[8,9] and changes in vascular function are evident before, during, and for a period of time afterwards.[10] Although the long-term effects are not extensively evaluated and results are conflicting, one study showed endothelial dysfunction up to 15 years after pregnancy.[10,11] Furthermore, impaired vascular function and endothelial dysfunction are evident early in the development of atherosclerosis and are associated with CVD, hypertension and diabetes mellitus.[12,13] There are several non-invasive methods for assessing endothelial function, some of them exploring microvascular beds.[14] A new method, PeriFlux PF6000 EPOS (Enhanced Perfusion and Oxygen Saturation; Perimed AB), for comprehensive skin microcirculatory assessment, can measure microcirculatory perfusion and oxygen saturation in absolute units and therefore provides the possibility to perform true between-subject comparisons.[15] Measurements of forearm skin microcirculation with EPOS during a post-occlusive reactive hyperaemia protocol showed that impaired post-ischaemic skin peak oxygen saturation was associated with virtually all traditional cardiovascular risk factors.[16] The perfusion and oxygen saturation measured with EPOS correlates significantly to Peripheral Arterial Tonometry examination, which is a commonly used and commercially available modality for examination of endothelial function in the microcirculation.[17]

In summary, it is unclear for how long the endothelial dysfunction associated with HDP, mainly pre-eclampsia, remains after pregnancy. The study objective was therefore to evaluate microvascular function several decades after childbirth in women with a history of HDP. We hypothesised that women with previous HDP show signs of disturbed microvascular function, reflecting a decreased endothelium-dependent vasodilatation, to a greater extent than women with previous normotensive pregnancies, and that the follow-up time between HDP and the microcirculatory assessment may affect the outcome.

2 | METHODS

2.1 | Study design

This was a retrospective cohort study where individuals were included from an add-on study (SCAPIS micro) to the Swedish CArdioPulmonary bioImage Study (SCAPIS) – a prospective multicentre study including 30 154 individuals aged 50–65 years, randomly selected from the general Swedish population. The participants, recruited at the Linköping local site, underwent cardiovascular examinations, biochemical analyses and anthropometric measurements and answered a detailed questionnaire on medical history, medication, heredity and lifestyle behaviours.[18] Forearm skin microcirculatory examination with EPOS was performed in SCAPIS micro.[16] The method of recruitment for the SCAPIS population has been described elsewhere.[18]

2.2 | Study population

A flow chart of the derivation of the study population is presented in Figure S1. The inclusion criteria were: (1) participation in SCAPIS Linköping with available data from EPOS measurements, (2) available self-reported data on previous childbirth, (3) sufficient data in obstetric records to be able to confirm or dismiss previous HDP and (4) eligible background data in the SCAPIS questionnaire on cardiovascular risk factors. Women who completely lacked questionnaire data were excluded. Among 2526 women included in SCAPIS Linköping, 56 lacked all data from the SCAPIS questionnaire on cardiovascular risk factors and were excluded. EPOS measurements were performed in 1857 women, of whom 1466 were according to the study protocol, and the remaining 391 were excluded. Obstetric records were available and reviewed for 1503 of the women with EPOS measurements, whereof 1414 had complete data on all stated childbirths as well as on HDP or essential hypertension in all pregnancies, and the remaining 89 women were excluded. In addition, women with essential hypertension during pregnancy were excluded ($n = 16$). When merging these data sets, 1222 women had complete data on the exposure (HDP status) and outcome (EPOS data) variables, as well as any data on possible confounders (cardiovascular risk factors and menopause status from the SCAPIS questionnaire) and constituted the study population. The 149 women who participated in SCAPIS Linköping with available EPOS measurements, but who were nulliparous, were not included in the study population, but their baseline characteristics as well as EPOS measurements are presented.

2.3 | Data collection

All available archived obstetric records, including laboratory findings as well as electronic medical records (Obstetrix®) were reviewed by two research assistants (AM, AK) and the PhD student/resident in Obstetrics (SBj) to determine if HDP was present in any pregnancy according to Swedish Society of Obstetrics and Gynaecology diagnostic criteria, which are in line with international guidelines.[1,19] In case of disagreement, the second author (CL) was consulted. The following variables were extracted: parity (number of children delivered from gestational week 22^{+0}), multiple birth, age at first childbirth, body mass index (BMI, kg/m^2) at the beginning of the first pregnancy, pre-eclampsia, GH, essential hypertension, gestational diabetes and pre-pregnancy diabetes, preterm birth (birth before gestational week 37^{+0}) and low birthweight (<2500 g). Cardiovascular risk factors were collected from SCAPIS,

including laboratory results and anthropometric measurements (BMI), waist circumference, systolic blood pressure (BP), total cholesterol, high- and low-density lipoprotein cholesterol (HDL and LDL), fasting glucose and HbA1c. CVD was defined as self-reported previous myocardial infarction and/or coronary revascularisation and/or stroke. Medically treated hypertension and dyslipidaemia were self-reported, as was menopausal status. Postmenopausal status was self-reported and defined as not having had menstruation in the last year, due to menopause. Diabetes was defined as self-reported or de novo diagnosis based on an elevated HbA1c (≥48 mmol/mol) or fasting plasma glucose (≥7.0 mmol/L) at the baseline SCAPIS examination. Smoking was self-reported and classified as never, previous, or current smoking.

2.4 | Microcirculatory assessments

Non-invasive microcirculatory measurements at the forearm skin surface were performed using the PeriFlux 6000 EPOS system (Perimed AB).[15] The system consists of an incorporated PF 6010 laser-Doppler unit, a PF 6060 spectroscopy unit, a fibre-optic probe, and a white light source. The optical system integrates laser Doppler flowmetry and diffuse reflectance spectroscopy into a multimodal joint model allowing calculation of microcirculatory oxygen saturation and speed-resolved perfusion. The calculation of physiological parameters in absolute units facilitates the comparison of data between individuals, not possible with traditional laser Doppler techniques.[15]

2.5 | EPOS study protocol

The participants were asked to abstain from coffee and large meals for 3 hours, alcohol for 12 hours, nicotine for 4 hours and morning medications before the microcirculatory assessments. Anticoagulants, contraceptives, or medications for Parkinson's disease, epilepsy, spasticity, diabetes, or chronic pain were exceptions. To evaluate endothelium-dependent vascular response the post-occlusive reactive hyperaemia protocol was used.[20] The protocol included 5-minute baseline measurement of skin microcirculation at the volar surface of the lower arm followed by a 5-minute arterial occlusion and a 10-minute reperfusion phase. Calculations of baseline oxygen saturation and total perfusion values were performed as well as corresponding values during maximal vasodilatory response (after cuff release). The detailed protocol is described elsewhere.[16] The following variables were obtained: total perfusion (% red blood cells [RBC] × mm/s) and oxygen saturation (%) at baseline and peak.

2.6 | Statistical analysis

The microvascular data are presented as medians with 25th and 75th centiles, and the Kruskal–Wallis test was used for group comparisons because the data were non-normally distributed according to the Kolmogorov–Smirnoff test. Categorical variables are presented as number and percentages and the Pearson's chi-square test, or when fewer than five individuals in one group, the Fisher's exact test, was used for group comparisons. In women without a history of CVD, multivariable linear regression models were assessed with oxygen saturation and total perfusion at baseline and peak as dependent variables, and HDP, pre-eclampsia or GH as the independent variables, together with age, medically treated hypertension, elevated BP (systolic BP ≥140 mmHg and/or diastolic BP ≥90 mmHg), diabetes mellitus, waist circumference, menopausal status and smoking at time of SCAPIS inclusion as co-variables. These cardiovascular risk factors were chosen as possible confounders as they have previously been shown to be associated with microcirculatory dysfunction.[16,21] To explore differences in relation to time between first pregnancy and the microcirculatory measurements the groups were stratified based on the median follow-up time, which was 30 years. The same linear regression using the total study population (i.e. not excluding women with CVD) was performed as a supplemental analysis (Table S1). In addition, a sensitivity analysis was performed comparing the EPOS microcirculatory variables between women excluded due to complete missing of SCAPIS questionnaire data and the study population (Table S2). A p value ≤0.05 was regarded as statistically significant. IBM SPSS, version 28 (SPSS) was used for the statistical analysis.

2.7 | Patient and public involvement

In the current study there was no patient or public involvement in the study planning.

2.8 | Ethical considerations

This study was approved by the Swedish Ethical Review Authority (Dnr 2020–05485), with earlier approval of the SCAPIS study (Dnr 2010–228-31M with amendment) and the add-on study SCAPIS micro (Dnr 2018/156–31). It was performed in accordance with the Declaration of Helsinki and the recommendations of the Swedish Research Council.

3 | RESULTS

3.1 | Obstetric characteristics

The final study population, with SCAPIS questionnaire data and complete data on EPOS measurements as well as HDP status, consisted of 1222 women. Obstetric characteristics are presented in Table 1. Among the study population, 104 (8.5%) had HDP in any of their pregnancies. Out of these, 55 (4.5%) and 49 (4.0%) had pre-eclampsia and GH, respectively. The groups were similar concerning parity, multiple gestation,

TABLE 1 Background and obstetric characteristics of the study population.

	Normotensive reference group *N* = 1118	HDP *N* = 104		PE *N* = 55		GH *N* = 49	
N = 1222	*n* (%)	*n* (%)	*p*	*n* (%)	*p*[a]	*n* (%)	*p*[b]
Parity							
1	132 (11.8)	13 (12.5)	0.834	10 (18.2)	0.199	3 (6.1)	0.357
≥2	986 (88.2)	91 (88.2)		45 (81.8)		46 (93.9)	
Multiple gestation							
No	1085 (97.0)	101 (97.1)	1.000	53 (96.4)	0.678	48 (98.0)	1.000
Yes	33 (3.0)	3 (2.9)		2 (3.6)		1 (2.0)	
Diabetes during pregnancy							
No	1102 (98.7)	99 (95.2)	**0.022**	54 (98.2)	0.539	45 (91.8)	**0.007**
Yes	15 (1.3)	5 (4.8)		1 (1.8)		4 (8.2)	
Preterm birth (before GW 37^{+0})							
No	1022 (91.5)	93 (89.4)	0.473	44 (80.0)	**0.008**	49 (100.0)	0.054
Yes	95 (8.5)	11 (10.6)		11 (20.0)		0 (0.0)	
Low birthweight (<2500 g)							
No	1051 (94.3)	91 (87.5)	**0.011**	42 (76.4)	**<0.001**	49 (100.0)	0.106
Yes	64 (5.7)	13 (12.5)		13 (23.6)		0 (0.0)	
BMI (kg/m^2) at first maternal clinic visit[c], median (25th–75th centiles)	21.3 (19.5–23.4)	22.2 (20.8–24.9)	**<0.001**	22.0 (20.2–24.2)	0.107	22.7 (21.3–26.0)	**<0.001**
Age at first birth[c], median (25th–75th centiles)	27.0 (24.0–30.0)	27.0 (23.0–30.0)	0.907	28.0 (24.0–31.0)	0.319	26.0 (23.0–28.5)	0.218

Note: Missing data: Normotensive group: Diabetes during pregnancy *n* = 1, Preterm birth *n* = 1, BMI *n* = 104. HDP group: BMI *n* = 6. Bold indicates statistical significance.

Abbreviations: BMI, body mass index kg/m^2; GH, gestational hypertension; GW, gestational week.; HDP, hypertensive disorders of pregnancy including pre-eclampsia and gestational hypertension; PE, pre-eclampsia.

[a]Comparison between pre-eclampsia and normotensive pregnancy.

[b]Comparison between GH and normotensive pregnancy.

[c]Kruskal–Wallis test.

and age at first pregnancy. Women with previous HDP as well as women with previous GH had higher BMI at the beginning of their first pregnancy compared with women without such history and 22.7 versus 21.3 kg/m^2, $p < 0.001$. Diabetes mellitus during pregnancy was more common in women with a history of HDP (4.8 versus 1.3%, $p = 0.022$) or GH (8.2 versus 1.3%, $p = 0.007$), but no significant difference could be detected in women with a history of pre-eclampsia, compared with women with normotensive pregnancies (Table 1). Compared with normotensive pregnancies, preterm birth was more common in the group with pre-eclampsia (20.0 versus 8.5%, $p = 0.008$) and low birthweight was more common in women with HDP (12.5 versus 5.7%, $p = 0.011$) or pre-eclampsia (23.6 versus 5.7%, $p < 0.001$).

3.2 | Clinical characteristics and biochemical analyses

Data on clinical characteristics and biochemical findings are presented in Table 2. The median time from first pregnancy to SCAPIS inclusion was 29.9 years and the median age was 56.8 years. Women with normotensive pregnancies and women with previous HDP did not differ significantly concerning the time between first pregnancy and inclusion in SCAPIS, age and smoking status. Women with previous HDP had higher BMI than women with normotensive pregnancies (27.2 versus 25.5 kg/m^2, $p < 0.001$), as had women with previous pre-eclampsia (27.2 kg/m^2, $p = 0.009$) or GH (27.1 kg/m^2, $p < 0.001$). The prevalence of diabetes was higher in women with previous HDP, or GH compared with women with normotensive pregnancies (11.7% and 14.6% versus 4.8%, $p = 0.006$ and $p = 0.009$, respectively). Hypertension was more common in the HDP group compared with women with normotensive pregnancies, whereas hyperlipidaemia did not significantly differ between groups. A history of CVD was more common in women with HDP and pre-eclampsia than in women with normotensive pregnancies (5.9% and 9.4% versus 1.5%, $p = 0.009$ and $p = 0.002$, respectively). Women with HDP, pre-eclampsia and GH had higher systolic BP compared with women with normotensive pregnancies. Total cholesterol, LDL and HDL did not differ significantly between the groups. Menopausal status did not significantly differ between groups, with 69.4% of women in the total study population being postmenopausal. Nulliparous women did not significantly differ from women

TABLE 2 Clinical characteristics of the study population at inclusion in SCAPIS.

N = 1222	Normotensive reference group *N* = 1118	Nulliparous *N* = 149	*p*[a]	HDP *N* = 104	*p*[b]	PE *N* = 55	*p*[c]	GH *N* = 49	*p*[d]
Years since first pregnancy *n* (%)[e]									
6–30	566 (50.6)	NA	NA	53 (51.0)	1.000	31 (56.4)	0.412	22 (44.9)	0.468
31–54	552 (49.4)			51 (49.0)		24 (43.6)		27 (55.1)	
Age at first SCAPIS visit[e], median (IQR)	56.8 (53.4–61.12)	57.4 (53.8–60.8)	0.354	57.3 (53.8–60.8)	0.816	57.6 (53.7–60.8)	0.732	57.3 (53.9–60.2)	0.987
Years since first pregnancy, median[e] (IQR)	29.9 (25.6–35.4)	NA	NA	30.5 (25.5–34.6)	0.543	29.3 (24.4–34.6)	0.556	30.3 (26.4–34.8)	0.464
Menopause[f]									
No	343 (31.3)			26 (25.2)	0.263	12 (22.2)	0.178	14 (28.6)	0.755
Yes	761 (68.9)			77 (74.8)		42 (77.8)		35 (71.4)	
BMI (kg/m^2)[e], median (IQR)	25.5 (22.9–28.9)	25.9 (23.0–29.6)	0.394	27.2 (24.8–30.3)	**<0.001**	27.2 (23.9–30.0)	**0.009**	27.1 (25.3–31.2)	**<0.001**
Waist circumference (cm)[e], median (IQR)	85.0 (78.0–94.0)	87.0 (77.5–98.0)	0.420	91.5 (81.2–100.8)	**<0.001**	90.0 (81.0–100.0)	**0.008**	92.0 (83.0–101.5)	**<0.001**
Systolic BP (mmHg)[e], median (IQR)	127.0 (117.0–140.25)	132.0 (115.5–146)	0.109	134.0 (126.0–150.0)	**<0.001**	134 (126.0–150.00)	**<0.001**	134.0 (125.0–150.0)	**<0.001**
Cholesterol (mmol/L)[e], median (IQR)	5.6 (4.9–6.3)	5.5 (4.9–6.2)	0.314	5.6 (4.9–6.2)	0.456	5.5 (4.9–6.2)	0.415	5.7 (5.0–6.2)	0.805
LDL (mmol/L)[e], median (IQR)	3.2 (2.7–3.9)	3.2 (2.5–3.8)	0.237	3.4 (2.8–3.9)	0.552	3.3 (2.7–3.9)	0.903	3.4 (2.9–3.9)	0.452
HDL (mmol/L)[e], median (IQR)	1.8 (1.5–2.2)	1.8 (1.5–2.2)	0.679	1.7 (1.5–2.0)	0.076	1.7 (1.4–2.0)	0.054	1.8 (1.6–2.0)	0.399
Smoking[f], *n* (%)									
Current	112 (10.2)	14 (9.5)	0.953	9 (9.1)	0.928	4 (7.8)	0.850	5 (10.4)	0.782
Former	371 (33.8)	49 (33.3)		33 (33.3)		19 (37.3)		14 (29.2)	
Never	615 (56.0)	84 (57.1)		57 (57.6)		28 (54.9)		29 (60.4)	
Diabetes[g], *n* (%)									
No	1062 (95.2)	140 (94.0)	0.494	91 (88.3)	**0.006**	50 (90.9)	0.188	41 (85.4)	**0.009**
Yes	53 (4.8)	9 (6.0)		12 (11.7)		5 (9.1)		7 (14.6)	
Medically treated hyperlipidaemia[f], *n* (%)									
No	1064 (95.8)	135 (90.6)	**0.006**	95 (92.2)	0.130	50 (90.9)	0.093	45 (93.8)	0.718
Yes	47 (4.2)	14 (9.4)		8 (7.8)		5 (9.1)		3 (6.3)	
Medically treated hypertension[f], *n* (%)									
No	949 (85.4)	126 (84.6)	0.782	74 (71.8)	**<0.001**	39 (70.9)	**0.006**	35 (72.9)	**0.024**
Yes	162 (14.6)	23 (15.4)		29 (28.2)		16 (29.1)		13 (27.1)	

(Continues)

TABLE 2 (Continued)

N = 1222	Normotensive reference group *N* = 1118	Nulliparous *N* = 149	p^a	HDP *N* = 104	p^b	PE *N* = 55	p^c	GH *N* = 49	p^d
Cardiovascular disease[f], *n* (%)									
No	1094 (98.5)	144 (96.6)	0.110	95 (94.1)	**0.009**	48 (90.6)	**0.002**	47 (97.9)	0.536
Yes	17 (1.5)	5 (3.4)		6 (5.9)		5 (9.4)		1 (2.1)	

Note: Missing data: Normotensive group: menopause *n* = 14, systolic BP *n* = 8, LDL *n* = 6, smoking *n* = 20, diabetes = 3, hyperlipidaemia *n* = 7, hypertension *n* = 7, cardiovascular disease *n* = 7. HDP group: menopause *n* = 1, LDL *n* = 2, smoking *n* = 5, diabetes *n* = 1, hyperlipidaemia *n* = 1, hypertension *n* = 1, cardiovascular disease *n* = 3. Bold indicates statistical significance.

Abbreviations: BMI, body mass index kg/m^2; BP, blood pressure; GH, gestational hypertension; HDL, high-density lipoprotein; HDP, hypertensive disorders of pregnancy including pre-eclampsia and gestational hypertension; IQR, interquartile range; LDL, low-density lipoprotein; PE, pre-eclampsia.

[a]Comparison between nulliparous and normotensive pregnancy.

[b]Comparison between HDP and normotensive pregnancy.

[c]Comparison between pre-eclampsia and normotensive pregnancy.

[d]Comparison between GH and normotensive pregnancy.

[e]Kruskal–Wallis test.

[f]Self-reported data.

[g]Self-reported data or de novo diagnosis based on an elevated HbA1c (≥48 mmol/mol) or fasting plasma glucose (≥7.0 mmol/L) at the baseline SCAPIS examination.

with previous normotensive pregnancies in other ways than that they more often had hyperlipidaemia (9.4% versus 4.2%, $p = 0.006$).

3.3 | Microcirculatory measurements

The results of the microcirculatory assessments are shown in Table 3. Women with previous pre-eclampsia showed lower oxygen saturation at baseline compared with normotensive women (47% versus 52%, $p = 0.017$). Besides that, we could not detect any significant differences in total perfusion or oxygen saturation at baseline or peak, when comparing women with normotensive pregnancies with women with HDP in the total study population. When stratifying the women into groups according to time between first pregnancy and the microcirculatory assessments, a reduced peak oxygen saturation was seen in women with HDP and its subgroup pre-eclampsia compared with women with normotensive pregnancies (88% and 88% versus 91%, $p = 0.007$ and $p = 0.001$, respectively) 6–30 years after first childbirth. Moreover, the total perfusion at peak was lower in the GH group compared with women with normotensive pregnancies more than 30 years since their first pregnancy (0.47% versus 0.56% RBC × mm/s, $p = 0.041$). Also, total perfusion at baseline was reduced in the HDP group compared with normotensive women (0.11% versus 0.12% RBC × mm/s, $p = 0.026$). Oxygen saturation at baseline was reduced in women with pre-eclampsia compared with normotensive women at 6–30 years follow up (47% versus 53%, $p = 0.013$). Nulliparous women did not significantly differ from women with previous pregnancies without HDP in any of the EPOS variables (Table 3). There were no significant differences between the study population and women excluded due to complete missing of SCAPIS questionnaire data in any of the EPOS variables (Table S2).

In the multivariable linear regression models, no significant difference in total perfusion was found more than 30 years after the first childbirth between normotensive and HDP pregnancies. However, among women with 30 years or less since their first pregnancy, HDP and pre-eclampsia were associated with a reduced oxygen saturation at peak ($\beta = -1.79$, 95% CI −3.49 to −0.08 and $\beta = -2.69$, 95% CI −4.93 to −0.45, respectively) and a history of GH was associated with slightly increased total perfusion at peak ($\beta = 0.15$, 95% CI = 0.03–0.27) (Table 4). The results were virtually the same in women without excluding women with previous CVD (Table S1).

4 | DISCUSSION

4.1 | Main findings

In this study, women with previous pre-eclampsia showed impaired microvascular function, measured with forearm skin microcirculatory assessment, 6–30 years after their first

TABLE 3 Oxygen saturation and total perfusion at baseline and peak.

	Normotensive reference group			HDP		PE		GH	
N = 1222	Median (min–max)	Nulliparous	*P*[a]	Median (min–max)	*P*[b]	Median (min–max)	*p*[c]	Median (min–max)	*p*[d]
Total population (*n*)	1118	149		104		55		49	
Oxygen saturation baseline (%)[e]	52.00 (43.00–63.00)	51.00 (42.00–60.00)	0.087	51.00 (42.00–60.00)	0.222	47.00 (37.00–58.00)	**0.017**	55.00 (45.00–61.00)	0.478
Oxygen saturation peak (%)[e]	90.00 (86.00–93.00)	89.00 (85.00–93.00)	0.635	89.00 (84.00–92.00)	0.070	88.00 (84.00–92.00)	0.094	90.00 (84.00–92.00)	0.356
Total perfusion, baseline (%RBC×mm/s)[e]	0.12 (0.09–0.16)	0.12 (0.09–0.16)	0.375	0.12 (0.09–0.14)	0.120	0.12 (0.09–0.14)	0.160	0.12 (0.09–0.15)	0.409
Total perfusion, peak (%RBC×mm/s)[e]	0.56 (0.43–0.75)	0.57 (0.43–0.74)	0.676	0.52 (0.41–0.74)	0.128	0.54 (0.41–0.73)	0.314	0.50 (0.42–0.74)	0.229
30 years or less since first pregnancy (*n*)	566			53		31		22	
Oxygen saturation baseline (%)[e]	53.00 (44.00–64.00)	NA		54.00 (39.00–61.00)	0.290	47.00 (35.00–57.00)	**0.013**	59.00 (47.00–67.00)	0.204
Oxygen saturation peak (%)[e]	91.00 (87.00–94.00)	NA		88.00 (85.00–92.00)	**0.007**	88.00 (84.00–89.00)	**0.001**	91.00 (87.00–94.00)	0.687
Total perfusion, baseline (%RBC×mm/s)[e]	0.12 (0.09–0.16)	NA		0.12 (0.09–0.15)	0.989	0.12 (0.09–0.15)	0.884	0.12 (0.09–0.15)	0.879
Total perfusion, peak (%RBC×mm/s)[e]	0.61 (0.41–0.74)	NA		0.56 (0.41–0.72)	0.821	0.56 (0.40–0.70)	0.525	0.56 (0.42–0.81)	0.689
31 years or more since first pregnancy (*n*)	552			51		24		27	
Oxygen saturation baseline (%)[e]	51.00 (42.00–62.00)	NA		50.00 (43.00–60.00)	0.535	48.00 (42.00–61.00)	0.415	51.00 (45.00–60.00)	0.918
Oxygen saturation peak (%)[e]	89.00 (85.00–92.00)	NA		89.00 (84.00–92.00)	0.923	90.00 (85.00–94.00)	0.378	89.00 (83.00–91.00)	0.488
Total perfusion, baseline (%RBCxmm/s)[e]	0.12 (0.10–0.16)	NA		0.11 (0.09–0.14)	**0.026**	0.11 (0.08–0.14)	0.061	0.11 (0.08–0.15)	0.175
Total perfusion, peak (%RBC×mm/s)[e]	0.56 (0.44–0.77)	NA		0.50 (0.42–0.75)	0.052	0.53 (0.42–0.84)	0.465	0.47 (0.42–0.72)	**0.041**

Note: Data presented as median (interquartile range). Missing data: EPOS variables were available for all participants as this was an inclusion criterion. Bold indicates statistical significance.

Abbreviations: GH, gestational hypertension; HDP, hypertensive disorders of pregnancy including pre-eclampsia and gestational hypertension; PE, pre-eclampsia.

[a]Comparison between no childbirths and normotensive pregnancy.

[b]Comparison between HDP and normotensive pregnancy.

[c]Comparison between pre-eclampsia and normotensive pregnancy.

[d]Comparison between GH and normotensive pregnancy.

[e]Kruskal–Wallis test. Note: Kolmogorov–Smirnov's test for normality was performed. None of the microcirculation variables could be deemed normally distributed.

TABLE 4 Linear regression analyses on oxygen saturation and perfusion after multivariable adjustment in women without previous cardiovascular disease.

	Oxygen saturation, baseline	Oxygen saturation, peak	Perfusion, total baseline	Perfusion, total peak
N **= 1148[a]**	***β*** **(95% CI)**	***β*** **(95% CI)**	***β*** **(95% CI)**	***β*** **(95% CI)**
Total population, *N* = 1148[a]				
HDP, *n* = 1148	−0.23 (−3.29 to 2.84)	−0.81 (−2.02 to 0.41)	0.00 (−0.02 to 0.02)	0.00 (−0.06 to 0.06)
PE, *n* = 1103	−3.18 (−7.48 to 1.12)	−0.93 (−2.62 to 0.76)	−0.01 (−0.04 to 0.02)	−0.02 (−0.10 to 0.07)
GH, *n* = 1105	2.50 (−1.70 to 6.70)	−0.72 (−2.39 to 0.94)	0.00 (−0.02 to 0.03)	0.01 (−0.07 to 0.10)
≤30 years since first pregnancy, *n* = 587				
HDP, *n* = 587	0.48 (−3.73 to 4.69)	**−1.79 (−3.49 to −0.08)**	0.01 (−0.02 to 0.04)	0.06 (−0.02 to 0.14)
PE, *n* = 566	−3.85 (−9.44 to 1.73)	**−2.69 (−4.93 to −0.45)**	0.00 (−0.04 to 0.04)	−0.02 (−0.12 to 0.08)
GH, *n* = 562	5.49 (−0.57 to 11.55)	−0.73 (−3.19 to 1.74)	0.02 (−0.02 to 0.07)	**0.15 (0.03 to 0.27)**
≥31 years since first pregnancy, *n* = 561				
HDP, *n* = 561	−1.10 (−5.61 to 3.41)	0.32 (−1.43 to 2.06)	−0.02 (−0.04 to 0.01)	−0.05 (−0.14 to 0.10)
PE, *n* = 537	−2.40 (−9.20 to 4.40)	1.45 (−1.13 to 4.03)	−0.02 (−0.06 to 0.02)	0.05 (−0.13 to 0.14)
GH, *n* = 543	0.34 (−6.23 to 5.54)	−0.60 (−2.85 to 1.66)	−0.01 (−0.04 to 0.02)	−0.10 (−0.22 to 0.02)

Note: Data presented as β-coefficients with 95% CI after adjustment for age at microcirculatory measurement, waist circumference, smoking status, menopause, diabetes mellitus at time of SCAPIS inclusion, hypertension (current diagnosis or systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg at time of SCAPIS inclusion). Missing data: essential hypertension *n* = 5, diabetes *n* = 4, smoking *n* = 25, menopause *n* = 15, CVD = 10. One person may have more than one variable with missing data thus disabling summary of the number of missing across variables. Bold indicates statistical significance.

Abbreviations: CI, confidence interval; GH, gestational hypertension; HDP, hypertensive disorders of pregnancy including pre-eclampsia and gestational hypertension; PE, pre-eclampsia.

[a]Women with previous cardiovascular events are excluded from the analyses (*n* = 23) as well as women with missing data on any of the included co-variates as well as cardiovascular disease (*n* = 51).

pregnancy. We also show that hypertension, CVD and diabetes are more common in women with previous HDP than in women with normotensive pregnancies. This is one of the largest long-term follow-up studies evaluating microcirculatory function after previous HDP.

4.2 | Interpretation

HDP and CVD share common pathophysiological features.[22] Persistent microvascular dysfunction is strongly associated with atherosclerosis development and is hypothesised to precipitate the accelerated cardiovascular aging noticed in women with previous HDP, especially pre-eclampsia.[5,23] It is previously shown that women with previous pre-eclampsia have endothelial dysfunction during the acute phase,[24] as well as 1–5 years after pregnancy in short-term follow-up studies using flow-mediated dilation (FMD).[25–28] Consistent findings were seen in microvascular function measured with peripheral arterial tonometry examination 2–3 years postpartum.[29] These early state findings may reflect a generalised endothelial dysfunction derived from the placental hypoxia during pregnancy and may explain the link between pre-eclampsia and CVD.[20]

Regarding long-term alterations in microvascular function, the evidence is less consistent.[10,24] In the present study, women had their first pregnancy in median 30 years before microvascular assessment, and an impaired vascular function measured as lower oxygen saturation was seen up to 30 years postpartum. The results are in line with a study based on the UK Biobank that found HDP associated with microvascular dysfunction expressed by reduced retinal vascular density 28.4 years after pregnancy independent of BP, arterial stiffness, and CVD risk factors.[30] Consistent with our study, pre-eclampsia mediated these findings. GH is linked to chronic hypertension development whereas pre-eclampsia, characterised by systemic endothelial dysfunction, vasoconstriction, and end-organ ischaemia deriving from defect placentation, appears to have an independent association with microvascular as well as macrovascular dysfunction.[5,31] However, the exact pathophysiology is not fully understood.[9,22]

Other studies suggest an endothelial recovery potential, as pathological FMD was found up to 3 years but not 10–11 years after pre-eclampsia.[24,32] This heterogeneity may be due to different vascular assessment methods, where FMD evaluates endothelial function in the larger brachial artery, whereas others, including EPOS and post-occlusive reactive hyperaemia, assess microvascular reactivity.[33,34] Further, examination in different parts of the vessel tree might reflect different stages of arterial disease, where dysfunction in larger vessels likely reflects already established atherosclerosis.[20] Our results showed impaired microvascular reactivity in terms of oxygen saturation but not in total perfusion. This is consistent with a 23-year follow-up study of women with pre-eclampsia that did not find a difference in post-occlusive reactive hyperaemia response in perfusion measured by laser Doppler flowmetry.[35] This may be due to the larger variability of the perfusion parameter compared with oxygen saturation, suggesting that the latter may be a more robust

parameter for clinical use. In addition, we did not find any effect of HDP or any of its components past 30 years after pregnancy. At greater age, other cardiovascular risk factors are more common and may mitigate the risk that HDP plays on the cardiovascular system. This is congruent with clinical studies, where the association of HDP, and especially pre-eclampsia, is more evident in premenopausal than postmenopausal women.[5] Nevertheless, in our study menopause was accounted for in the multivariable regression analysis and did not affect any of the associations.

Finally, nulliparous women had higher prevalence of hyperlipidaemia, but no significant difference in microvascular function compared with parous women without previous HDP. Studies on associations between nulliparity and CVD have found conflicting results. Parikh and colleagues found higher risk of CVD in nulliparous versus parous women,[36] whereas another population-based study found positive associations between parity and CVD, with the lowest risk in nulliparous women.[37] One possible explanation for this seeming discrepancy may be differences in multivariable modelling when controlling for traditional cardiovascular risk factors. Infertility, one reason behind nulliparity, is associated with CVD, as these conditions share common risk factors, such as diabetes, hypertension and obesity.[38]

In summary, our findings suggest that women with previous pre-eclampsia have a remaining microvascular dysfunction up to 30 years after pregnancy, independent of other CVD risk factors. We have previously reported that post-ischaemic peak oxygen saturation is negatively associated with several CVD risk factors, e.g. hypertension, dyslipidaemia, waist circumference and diabetes mellitus.[16] In line with this, we present evidence that previous pre-eclampsia is associated with impaired oxygen saturation, which strengthens the theory that persisting microvascular impairment is preceding CVD in these women.

4.3 | Strengths and limitations

Strengths of this study are the large number of population-based recruited participants with long-term follow up as well as the use of obstetric records for HDP diagnosis instead of self-reported data with the risk of re-call bias. Further, the prevalence of pre-eclampsia and GH reflects the prevalence in the normal population, suggesting a representative selection of women. There are some limitations of this study. Although this is one of the largest long-term follow-up studies in this research area, some comparisons are still based on few cases, and there is an inherent risk of type 2 error, meaning that findings of no significant differences between groups should be interpreted with caution. In addition, data from the obstetric records were old with some missing laboratory and ultrasonography data, implying that some cases of pre-eclampsia according to current classification might have been missed. Nevertheless, if some pre-eclampsia cases were overlooked, these women might have ended up in the normotensive group, implying that the differences could be even greater. The forearm skin microvascular assessment method EPOS is novel and has not previously been used in large populations. Previous studies have mostly used macrovascular function such as FMD as a marker for endothelial function, but measurement of the microcirculatory function can provide additional insights into the impact of pre-eclampsia on vascular function and CVD risk. Forearm skin microcirculation is easily accessible and is a promising marker for microcirculatory disturbances in other vascular beds, e.g. the coronary arteries. The EPOS method has several advantages, such as using a joint model for analysing oxygen saturation and speed resolved perfusion combined. This provides robust data in absolute units, facilitating comparisons between individuals.[15] Future research ought to evaluate the HDP population with EPOS in a longitudinal prospective study with a targeted selection of study participants. It is a limitation that some women did not undergo EPOS measurements with assessable results, as we cannot rule out that these women might differ in microcirculatory function compared with those who successfully underwent the procedure. Finally, we did not have information on menstrual phase or hormonal contraceptive use in premenopausal women nor information about hormonal replacement therapy among postmenopausal women.

5 | CONCLUSION

Our results show endothelial dysfunction up to 30 years after pre-eclampsia, suggesting that remaining microvascular disturbances might explain the increased CVD risk seen in these women. Future studies ought to evaluate whether comprehensive skin microcirculatory assessment could be used for risk stratification after HDP, especially pre-eclampsia, and, if signs of early microvascular changes occur before overt atherosclerosis, whether this finding could be used to identify women who would benefit from cardiovascular prevention.

AUTHOR CONTRIBUTIONS

SBe, CJÖ and TS contributed to the design, data acquisition and analysis of the SCAPIS-micro study. SBj, CL, MB, SBe and SSL contributed to the design, research questions, planning and data acquisition of the work. AM, AK and SBj were responsible for journal review. SBj was responsible for validation of the journal data, with contribution from CL. MB was responsible for the statistical analysis. SBj was responsible for writing the main part of the draft of the manuscript with contribution from MB, SBe, CL and SSL. SSL was responsible for the final editing of the paper. All authors are accountable for all aspects of the work and ensure the accuracy and integrity of any part of the work, have revised it critically for important intellectual content, and approved the final version of the paper.

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CONFLICT OF INTEREST STATEMENT

SSL has received lecture fees from Bayer and Pfizer. All other authors—none declared.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

This study was approved by the Swedish Ethical Review Authority (Dnr 2020–05485), with earlier approval of the SCAPIS study (Dnr 2010–228-31M with amendment) and the add-on study SCAPIS micro (Dnr 2018/156–31). It was performed in accordance with the Declaration of Helsinki and the recommendations of the Swedish Research Council.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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