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Mieke Cathy Elisabeth Hooijschuur
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Promotor:
Prof. dr. M.E.A. Spaanderman

Co-promotores:
Dr. C. Ghossein-Doha
Dr. J.J. Brugts

Beoordelingscommissie:
Prof. dr. H.P. Brunner-La-Roca (Chair)
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Prof. dr. R.J.M.W. Rennenberg
Prof. dr. P.W. Teunissen

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Chapter 1

General introduction

Preeclampsia (PE) is a pregnancy-related vascular disorder complicating 2–8% of pregnancies.[1] Classically, PE is defined as new onset maternal hypertension after 20 weeks of gestation along with renal involvement (proteinuria), but current diagnostic criteria also include other disease-involved organs, amongst brain (eclampsia), vasculature (thrombocytopenic micro angiopathy amongst HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome), or uterus (fetal growth restriction).[2] As a consequence of vascular derangement, a wide spectrum of clinical organ dysfunction can develop including heart-, kidney-, liver-, brain- or thromboembolic problems.[1] Besides maternal comorbidities, PE also has fetal implications as it is associated with stillbirth, fetal growth restriction (resulting in small for gestational (SGA) infancy) and (iatrogenic) preterm birth.

Cardiovascular disease risk after preeclampsia

Generally, the acute clinical symptoms of PE disappear after delivery. However there is compelling evidence suggesting that PE, especially early-onset preeclampsia, is fundamentally a preexisting cardiovascular disorder hampering the cardiovascular system to adequately adapt to the changing cardiovascular demands of pregnancy.[3] Therefore, vascular derangements might not completely resolve after birth; women with a history of PE have a two- to seven-fold higher risk of developing overt cardiovascular disease (CVD) including ischemic heart disease, cerebrovascular accidents, arrhythmias, heart failure (HF), and diastolic dysfunction at relatively young age (i.e. within the 15 years following pregnancy) compared to women with normotensive pregnancies.[4,5] This increased risk likely originates from both underlying (pre-existing) cardiovascular and cardiometabolic risk factors and the circulatory consequences of the hypertensive gestation.

PE and CVD share common pathophysiological pathways and processes which may explain their close and insult-severity-dependent association.[6] These findings have led to the acknowledgement of PE as female-specific risk factor for CVD later in life.[7-9] However, there is no consensus regarding optimal management, including additional assessments and when to institute preventive measures regarding lowering CVD risk after PE.[10] As not all women who experience PE develop any form of early-onset CVD in later life, these observations suggests different levels of future risk.[11,12] Epidemiological studies suggests clinical disease severity, the need for preterm birth and other obstetric complications might help identify women at increased risk of CVD after PE, but also , in line with the origins of adult disease theorem, formerly preeclamptic women being born preterm or growth restricted, might additionally be at increased cardiovascular risk, early-onset high BP and cardiovascular dysfunction.[13-15]

The American Heart Association and European Society of Cardiology recognize PE as an early indicator of CVD risk and advise appropriate follow up after pregnancy for

monitoring and control of CVD risk factors.[9] However, structural periodic follow-up in all former PE women is yet to be implemented and is hampered by the absence of effective prediction models to distinguish high risk from low risk women. On the one hand, admitting all women after preeclampsia to a cardiovascular risk management program implicates an additional burden on health care capacities, on the other hand early and timely detection of cardiovascular risk factors and preventive measures might lower subsequent cardiovascular disease burden. To date, as there is currently no structural follow up, high risk women are undertreated and consequently not receiving the necessary cardiovascular risk management. Although obstetric parameters (e.g. time of onset of the disease in pregnancy, concurrent fetal complications) might indicate those at highest risk proper identification, lack of good performing risk assessment tools and the unexplored area of effectiveness of preventive medicine in this population does not facilitate the implementation of structured follow up programs after PE.[4]

The severity of PE can be divided in those that developed PE before 34 week of gestation (i.e. early-onset PE) and those that develop PE at- or after 34 weeks of gestation (i.e. late onset PE). Although not strict separate disease entities, poor placentation and circulatory maladjustment seems to play a key role in the pathogenesis of early-onset PE,[16] especially when pregnancy is also complicated with compromised fetal growth. The system biology in late onset PE, that is usually accompanied by normal grown offspring, seems to be more related to an incapacity to compensate for the increasing hemodynamic needs resulting in circulatory decompensation that becomes clinically relevant as pregnancy progresses. Possible underlying cardiovascular and cardiometabolic risk factors might contribute to this divergent expressions of the syndrome of preeclampsia.[4]

Hypertension

The development of chronic hypertension after pregnancies complicated by PE might explains most of the increased risk of developing CVD, especially coronary artery disease and heart failure in this cohort of women.[17, 18] This makes early recognition of consistently present high blood pressure in women who were normotensive in the first period after delivery, and as such usually discharged from care, a clinical priority. The increased risk of developing chronic hypertension is substantial and occurs much earlier after hypertensive complicated pregnancies.[19, 20] Epidemiological data from a Danish registry-based cohort study that included 1.5 million primiparous women show that the adjusted risk of hypertension was 4–10 times in women with PE compared with women with a normotensive pregnancy in the first five years after pregnancy.[20] Notably, the cumulative incidence of hypertension at ten years postpartum was 10% in women aged 20–29 years with a previous PE, which was even higher than in women aged 40–49 years with previous normotensive pregnancies.[20, 21] Furthermore, the earlier the onset and more severe PE, the higher the risk of developing postpartum hypertension.[20, 22] Phenotypical data indicate that individual circulatory characteristics strongly

predispose to the later development of chronic hypertension. Early recognition of those at risk for the development of chronic hypertension in apparently healthy and recovered formerly preeclamptic women might therefore be possible making use of individuals medical history and cardiovascular and cardiometabolic parameters.

Metabolic syndrome

Metabolic syndrome (MS) refers to a clustering of traditional CV risk factors (including impaired glucose tolerance, hypertension, obesity and dyslipidemia). Presence of MS raises the risk of CVD.[23] CVD risk factors defining MS also predispose to the development of PE.[24-26] Moreover, when MS is present after PE, this results in a fourfold increased risk of the presence of concurrent postpartum cardiac diastolic dysfunction. These findings suggest that these presence of these risk factors play a key role in the link between PE and the increased CVD risk after PE. However, in line with early detection of the development of chronic hypertension, it remains unclear if this increased risk to develop CVD applies to all former PE women; elucidating which former PE women are at risk of postpartum modifiable cardiometabolic- and cardiovascular risk factors, and how much each of these acknowledge risk factors contribute to the concurrent presence or later development of cardio-vascular dysfunction, could contribute to the development of structural follow up after pregnancy.

The mechanisms underlying the association between PE and subsequent development of CVD, are highly debated. On the one hand, PE might contribute independently to the development of postpartum CVD by remaining attenuated endothelial function, dysregulation of the renin-angiotensin-aldosterone system and/or an enduring high inflammatory state.[27] On the other hand, an preexisting impaired cardiovascular system might be unmasked by the increased cardiovascular demands required during pregnancy, which functions as a cardiovascular stress test.[28]

CVD is the leading cause of death among women.[29] Favorable CVD risk factor levels in early and middle age is associated with a lower lifetime risk for CVD and prolonged survival.[30, 31] When present, targeting CV risk factors by both lifestyle- and/or pharmacological interventions are likely to postpone or prevent the onset of CVD. The aim of this thesis was to expand knowledge about how pregnancy characteristics relate to postpartum maternal cardiovascular profile and -(asymptomatic) structural cardiovascular abnormalities. This information is essential in early detecting women at risk that could benefit from structural follow up after PE, aiming by timely intervening, finally reducing CVD burden after PE.

Aims and outline of this thesis

The relation between preeclampsia and remote cardiovascular disease is known for decades. Yet, to date, no structural follow up programs after preeclampsia have been implemented. Detection of former preeclamptic women with high cardiovascular risk factor profile is essential in the development of logical structural follow up after preeclampsia to personalized treatment of individually found cardiovascular risk factors before the development of overt cardiovascular disease. To this end, the aim of this thesis was to expand knowledge about how pregnancy characteristics relate to postpartum maternal cardiovascular functioning and -(asymptomatic) structural cardiovascular abnormalities. This information is essential in early detecting women at risk that could benefit from structural follow up after preeclampsia, aiming by timely intervening, finally reducing cardiovascular disease burden after preeclampsia.

In **CHAPTER 2**, we delineate the impact of preeclampsia on cardiovascular health and shed light on the phases between health and disease. We advocate early recognition of subclinical cardiovascular disease in order to apply preventive measures.

In **CHAPTER 3**, we sought to explore to what extent the presence of cardiometabolic and cardiovascular risk constitutions differ between pregnancies complicated by small for gestational age infancy, preeclampsia, or a combination of both.

In **CHAPTER 4**, we assessed whether a history of early onset preeclampsia along with a history of a small for gestational age infant is associated with high postpartum prevalence of cardiovascular risk factors defining metabolic syndrome compared to the other obstetric phenotypes. Moreover, in this chapter, we evaluated whether obstetric outcome in combination with screening parameters could predict metabolic syndrome.

In **CHAPTER 5**, we assessed whether there is an accelerated effect of aging on endothelial function depending on obstetric past. We investigated if the arterial aging regarding endothelial-dependent and -independent vascular function is more pronounced in women with a history of preeclampsia as compared to women with a history of solely normotensive gestation(s).

In **CHAPTER 6**, we developed a good-to-excellent performing predictive tool to identify incident hypertension following preeclampsia in women that were normotensive shortly after pregnancy.

In **CHAPTER 7**, we report on the additional value of a proactive screening program to identify, previously undiagnosed, cardiovascular disease and risk factors after preeclampsia.

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Chapter 2

Pre-eclampsia: A twilight zone between health and cardiovascular disease?

Chahinda Ghossein-Doha | Mieke C.E. Hooijschuur |
Marc E.A. Spaanderman

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The syndrome of pre-eclampsia (PE) complicates 2% to 8% of all pregnancies.[1] PE is thought to be an endothelial derangement superimposed upon pre-existing circulatory, metabolic, hemostatic, and immunological abnormalities and, in case of early-onset disease, often coincides with defective placentation.[1] In the short term, PE relates to serious fetal and maternal complications (2). Within 15 years after the troubled pregnancy, PE associates with a 2- to 7-fold increased cardiovascular disease (CVD) risk including ischemic heart disease, cerebrovascular accidents, arrhythmias, heart failure (HF), and diastolic dysfunction.[1, 3] Besides pre-existing cardiovascular (CV) and cardiometabolic risk factors, this increased risk may originate, at least partly, in the aberrant CV sequellae during PE. Before CVD emerges, formerly pre-eclamptic women show asymptomatic CV abnormalities. In the context of increased remote risk of serious CV events in these women later in life, PE may be viewed upon as the "twilight zone" between health and disease.

Normotensive pregnancy is a state of increased volume load and reduced pressure load, originating from adjustments to an early pregnancy drop in total peripheral vascular resistance (TPVR).[4] The early first-trimester decreased cardiac afterload and imminent decrease in blood pressure trigger compensatory mechanisms by activation of humoral (renin-angiotensin-aldosterone system) and central autonomic mechanisms to restore circulatory fullness and blood pressure–stabilizing rise in cardiac output (CO).[5] In the clinical phase of PE, TPVR increases along with increased blood pressure. Moreover, in a recent meta-analysis by de Haas et al.,[6] plasma volume (PV) expansion in complicated pregnancies was 13.3% lower than normotensive pregnancies (0.80 l [32.3%] vs. 1.13 l [45.6%], respectively). It is unclear whether or not the differences in circulatory volume originate from aberrations in PV expansion, loss in gained volume and with it edema formation, or differences in pre-pregnancy volume. In contrast to the clinical phase, preclinical responses have been more divergent based on clinical onset of the disease, and are characterized by subnormal first-trimester circulatory adjustments and suboptimal placentation.[7] Early-onset PE seems to be preceded by low cardiac index along with high TPVR, whereas women destined to develop late-onset PE showed at least a normal cardiac index and slightly increased TPVR at mid-gestation, whereas others report supranormal CO along with low TPVR.[8, 9] On the one hand, the latter authors did not normalize hemodynamic measures for body surface area or the significantly higher body mass index; on the other hand, this exaggerated hyperdynamic circulatory state may underlie the body mass index–associated increased risk of PE.[8, 9]

Left ventricular (LV) remodeling during normal pregnancy has been compared with morphological alterations seen in aerobic-trained athletes and is characterized by eccentric remodeling, the proportional increase of ventricular dimensions and LV wall thickness (relative wall thickness [RWT]).[10] Compared with nonpregnant conditions, during normal pregnancy, a large meta-analysis detailed that left ventricular mass (LVM) increased 28.3 g (24%) along with a slight increase in RWT of 0.03 (11%), whereas

in hypertensive pregnancies, LVM and RWT increase disproportionally (92 g, 95% and 0.14, 56%, respectively) (Figure 1).[10] Although the underlying causal mechanism of developing concentric remodeling during PE has not been evaluated, on the basis of physiological principles, increased pressure and attenuated volume load along with neurohormonal factors stimulate various signaling pathways that are essential for the induction of a hypertrophic response of the cardiomyocyte. LV remodeling in pre-eclampsia is asymmetrical, predominantly involving the basal anteroseptum.[11] Although most evident geometric changes appear from second trimester onwards, Melchiorre et al.[12] showed that in women destined to develop PE, LV mild diastolic dysfunction and segmental impaired myocardial relaxation was highly prevalent (30% and 70%, respectively), accompanied by increased afterload (higher mean arterial pressure and TPVR index) and LV concentric hypertrophy.

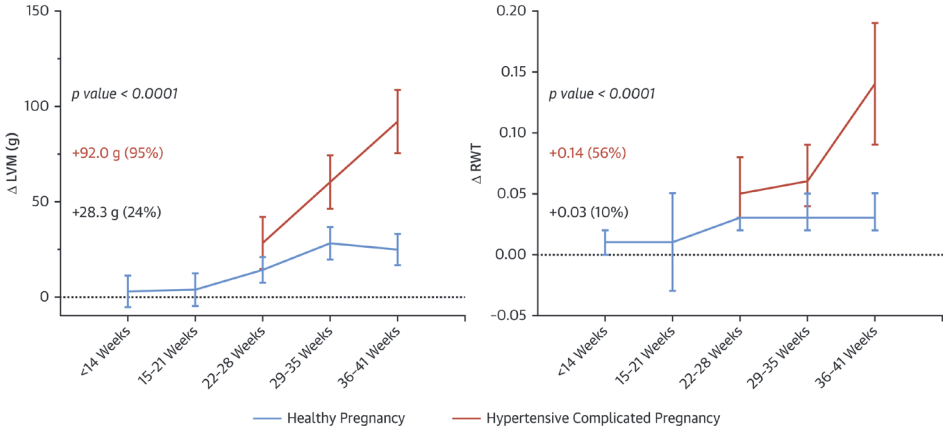

Figure 1. Change in Mean (95% CI) LVM and RWT Over the Course of a Normal and a Complicated Pregnancy.
Changes in left ventricular mass (LVM) in grams and relative wall thickness (RWT) are plotted against gestational age. LVM increased in normal pregnancy 28 g (24%) and in complicated pregnancies more than 3 times more with 92 g (95%), which was a significant difference (p<0.0001). RWT increases in a normal pregnancy 0.03 (10%) and in a complicated pregnancy 5 times more with 0.14 (56%) (p<0.0001). Adapted with permission from de Haas et al.[6] CI = confidence interval.

Despite the primary beneficial effect of a thicker wall to reduce wall stress, concentric LV remodeling is accompanied by excessive extracellular matrix, consisting of collagen and fibroblasts and deposition.[13] As such, concentric remodeling preludes loss in diastolic function as a consequence of reduced ventricular compliance (Figure 2). This is supported by the study of Vaught et al.[14] in this issue of the Journal showing lower values for diastolic function in women with severe PE compared with control patients. These findings are consistent with a number of other studies that reported high prevalence of LV global diastolic dysfunction in predominantly preterm PE.[12, 15, 16]

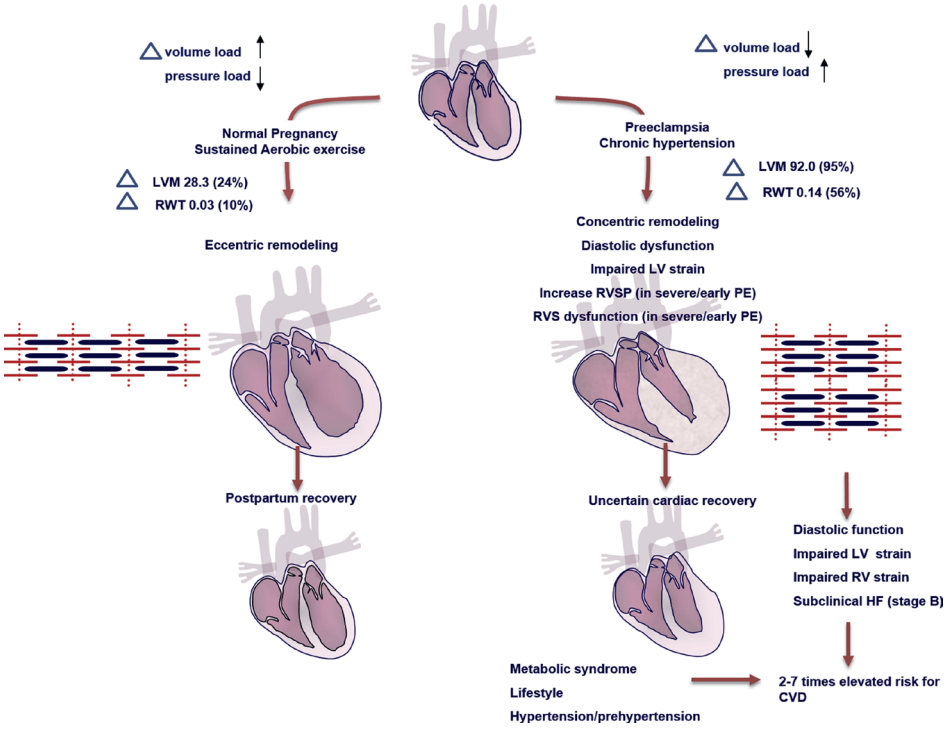

Figure 2. In Normal Pregnancy, Volume Load Increases, Pressure Load Decreases, LVM Increases, and RWT Increases Slightly. Both pregnancy-induced and aerobic–exercise-induced cardiac hypertrophy show similar morphology termed eccentric hypertrophy. In pre-eclamptic pregnancy, the change in volume load is reduced whereas pressure load increases significantly. Pre-eclampsia (PE) is characterized by concentric remodeling, diastolic dysfunction, impaired left ventricular (LV) strain, increased right ventricular systolic pressure (RVSP) and right ventricular (RV) systolic dysfunction (the last 2 mainly in severe early-onset PE). Eccentric remodeling is characterized by sarcomere replication in series, whereas concentric remodeling is by parallel sarcomere replication. The latter concurs with more collagen and fibrosis and extracellular matrix composition leading to reduced cardiac compliance. After PE, the prevalence of diastolic dysfunction, impaired LV strain and RV strain, and subclinical heart failure (HF) (stage B) remains high. These changes may persist or deteriorate, especially in persistence of unfavorable metabolic, lifestyle, or blood pressure factors, and may contribute to the 2 to 7 times elevated risk for cardiovascular disease (CVD), including HF. Abbreviations as in Figure 1.

Global LV systolic function showed contradictory findings in PE, but when corrected for load and heart rate dependency, preserved contractility during PE was suggested.[7, 17] Impaired contractility, measured as decreased ejection fraction, appears in end-stage cardiac disease expression, although early stages of impaired myocardial contractility and relaxation may precede the development of overt systo-diastolic dysfunction. Fewer load-dependent measurement modalities, tissue color Doppler and angle-independent speckle tracking echocardiography (STE), may be capable of assessing more subtle functional myocardial abnormalities in regional and global systolic and diastolic function.[13] STE allows quantification of myocardial deformation in 3 spatial directions (longitudinal, radial, and circumferential). In chronic hypertension, longi-

tudinal strain is mainly impaired, whereas circumferential and radial strain are mostly preserved.[13] In the early phase of hypertension, longitudinal and radial strain are reduced, whereas circumferential strain is increased, indicating a compensatory role for circumferential myocardial function.[13] Cong et al.[18] found that in early-onset severe PE, all strain directions appear to be impaired, whereas in late-onset PE, all but LV radial strain were impaired compared with normal pregnancy. By contrast, Vaught et al.[14] did not find differences in LV longitudinal systolic strain. This may relate to the relative high number of women (24%) with inadequate 2-dimensional imaging, especially because these women had a higher body mass index, introducing not only a power problem, but also the selective loss of individuals in the analysis. The intensive antihypertensive treatment may have also affected cardiac strain. However, Vaught et al.[14] observed, in line with others, higher right ventricular (RV) systolic pressure and decreased RV systolic longitudinal strain, the latter measured for the first time with STE, abnormalities likely to result from a combination of intrinsic subclinical RV dysfunction and increased pulmonary artery pressure.[19] Melchiorre et al.[12] showed earlier that RV dysfunction, measured with tissue Doppler imaging, was only seen in women with moderate-to-severe LV global diastolic dysfunction, which may imply that increased pulmonary resistance may be secondary to higher diastolic ventricular filling pressures in a poorly compliant or failing LV. However, in the absence of increased B-type natriuretic peptide levels in the current study,[14] this theory could not have been supported.

The aberrant cardiac geometry and function seen during PE persist in 25% to 72% of the cases postpartum, especially after preterm PE.[1] Persisting asymptomatic diastolic dysfunction strongly relates to concurrent metabolic syndrome.[20] However, after adjusting for metabolic factors, PE independently associates with subclinical HF.[21] More recently, biventricular myocardial contractility and relaxation, studied by STE, were abnormal in 20% to 50% of patients after early-onset PE.[22] These postpartum abnormalities may be related to the surplus extracellular matrix and subendocardial fibrosis, induced by the gestational afterload-mediated remodeling, resembling alterations seen in hypertensive heart disease, which may not always be reversible. In the persistence of elevated afterload, which is highly prevalent as hypertension or pre-hypertension after PE, contractile dysfunction, dysrhythmia, and HF eventually may occur.[1, 7, 23] Multiple regulatory microRNAs whose up- or down-regulated expression overlaps between PE and concentric LV remodeling suggest a common system biological response, explain, at least partly, the development of HF after PE.[24]

The study of Vaught et al.[14] has highlighted again in an elegant way the occult aberrant cardiac adaptation during severe pre-eclampsia and shows that not only LV diastolic and systolic function may be impaired, but for the first time, also impaired RV longitudinal systolic strain. It supports the concept that pregnancy should be valued as a sex-specific, women-sensitive CV stress test, and the necessity to use novel methods in order to detect early stage abnormalities in the twilight zone between health and disease. Future

studies should focus on the predictive value of cardiac strain abnormalities in pregnancy outcome, long-term CV outcome and the effect of different antihypertensive drug on normalizing cardiac function and with it, short- and long-term female health prognosis.

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Chapter 3

Maternal metabolic syndrome, preeclampsia, and small for gestational age infancy

Mieke C.E. Hooijschuur | Chahinda Ghossein-Doha |
Salwan Al-Nasiry | Marc E.A. Spaanderman

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Abstract

Objective: We sought to explore to what extent the presence of cardiometabolic and cardiovascular risk constitutions differ between pregnancies complicated by small-for-gestational-age (SGA) infancy, preeclampsia (PE), or a combination of both.

Study design: We conducted a cohort study in women after pregnancies complicated by placental syndrome with fetal manifestations (SGA infancy [n=113]), maternal manifestations (PE [n=729]), or both (n=461). Independent sample t test was used to compare cardiometabolic and cardiovascular risk factors between groups. Logistic regression was used to calculate odds ratios and adjusted odds ratios of the prevalence of the metabolic syndrome and its constituents between groups. Adjustments were made for maternal age, parity, smoking, interval between delivery and measurements, and intrauterine fetal demise.

Results: The metabolic syndrome was present in 7.5% of women who delivered SGA infants, 15.6% of former PE women, and 19.8% of women after pregnancy complicated by both SGA and PE. Hypertension was observed in 25% of former PE women and 15% of women with solely SGA. Women who delivered a SGA infant had lower global vascular compliance compared to former PE women without SGA.

Conclusion: Cardiometabolic risk factors consistent with metabolic syndrome relate to the maternal rather than to the fetal presentation of placental syndrome. Nonetheless, highest incidence of metabolic syndrome was observed in women with both PE and SGA. PE relates to chronic hypertension, whereas increased arterial stiffness seems to be associated with women who deliver a SGA infant.

Introduction

Preeclampsia (PE) and small-for-gestational-age (SGA) infancy are common pregnancy-specific diseases referred to as placental syndrome with maternal and fetal clinical manifestations, respectively. They are thought to originate from shallow first-trimester trophoblast invasion, placental damage, and ultimately dysfunction.[1, 2] Both diseases are major causes of maternal and perinatal mortality and morbidity and are characterized by maternal oxidative stress, vascular endothelial excitation, and up-regulation of inflammatory state.[3, 4] Placental syndromes seem to be superimposed upon preexisting maternal conditions that are capable of jeopardizing placental and vascular function.[5, 6] Nonetheless, the clinical presentation of both disease entities of the placental syndrome is completely different. PE is clinically diagnosed as de novo hypertension with co-occurrence of proteinuria developing >20th week of gestation,[7] whereas SGA is defined as a neonate whose weight in reference to a certain population is lower than expected for the gestational age at birth.[8] Although PE is often associated with SGA,[1, 9] SGA can, on the one hand, occur in the absence of maternal features[10] while, on the other hand, PE can also occur without SGA.

Women with a history of PE have a 2- to 7-fold increased risk for developing cardiovascular disease (CVD) later in life compared to women with a history of uncomplicated pregnancies.[11, 12, 13] Women who gave birth to a SGA infant are, independent of PE, also at increased risk for developing CVD, although to a lesser extent.[14] It has been suggested that the increased risk of CVD after placental syndromes comes from cardiovascular and cardiometabolic risk factors that were already present before pregnancy, suggesting that these women are already destined to develop vascular disease.[15] Therefore the American Heart Association suggests including the obstetric history in determining the gender-specific risk of later CVD in women.[16] The metabolic syndrome, an independent risk factor for CVD, tends to be more often present in women after PE rather than after sole SGA.[3, 17] Nonetheless, it may be that the concurrent presence of both SGA and PE relates to the highest risk on cardiovascular jeopardy.

In this study, we tested the hypothesis that combined fetal-maternal presentation of placental syndrome relates strongest to the presence of maternal cardiometabolic and cardiovascular risk factors

Materials and methods

In this cohort study, we selected women with pregnancy complicated by maternal (PE) and/or fetal (SGA infancy) presentation of placental syndrome from 1996 through 2010 that have had our standardized structured cardiovascular and cardiometabolic analysis at least 4 months postpartum. For the study, we only evaluated women with singleton

pregnancies giving birth at gestational age of >22 weeks, without chromosomal abnormalities.[18] In all, 1303 women fulfilled our inclusion criteria. These women had gone through the postpartum cardiovascular assessment with a median postgestation until evaluation interval of 9 months. The protocol for this retrospective cohort study was approved by the medical ethical committee of the Radboud University Medical Center (the Committee on Research Involving Human Subjects 2007/252) and the medical ethical committee board of Maastricht University Medical Center (medical ethical committee 0-4-049).

PE was defined based on the International Society for the Study of Hypertension in Pregnancy (ISSHP) criteria as de novo hypertension with a systolic blood pressure (BP) ≥140 mm Hg and/or diastolic BP ≥90 mm Hg in 2 repeated measurements (at least 6 hours apart) and the co-occurrence of proteinuria (≥0.3 g/24 h or ≥2+ on dipstick analysis) occurring >20 weeks of gestation in previously normotensive women7 or when proteinuria developed >20 weeks of gestation in women with preexisting hypertension. SGA infant was defined as a fetal birthweight <10th percentile according to the Dutch reference standard.[19]

The postpartum screening was performed in 1 run and started at 8:00 AM after an overnight fast. Women were asked to refrain from drinking or eating 10 hours prior to measurements. None of the participants used oral contraceptives or was breast-feeding. Clinical data on obstetric history, medical history, and use of medication were collected from medical files and by self-report.

Height, weight, and BP were measured by an experienced and specialized nurse. Body mass index was calculated by weight (kg) divided by the height (m^2).

After 5 minutes of rest, arterial BP was measured on the right upper arm by a semiautomatic oscillometric device (Dinamap Vital Signs Monitor 1846; Critikon, Tampa, FL). The median value of 11 measurements in a period of 30 minutes was used.

Urine was collected in the 24 hours preceding the measurements. The 24-hour urine sample was assayed for albumin, protein, and creatinine output to calculate (micro) albuminuria corrected for creatinine output (g/mol creatinine) and total protein level (g/24 h).

Glucose, insulin, hemoglobin (Hb)A1c, high-density lipoprotein cholesterol, and triglycerides were collected from fasting blood samples. The homeostasis model assessment (insulin [mU/L] × glucose [mmol/L]/22.5) was used to estimate the degree of insulin resistance (HOMA-ir).[20] HbA1c was expressed as HbA1c [mol]/Hb [mol] × 100%.

Metabolic syndrome was diagnosed based on the World Health Organization criteria[21] as follows: the presence of hyperinsulinemia (fasting insulin ≥9.2 mU/L, fasting blood

glucose ≥6.1 mmol/L, or HOMA-ir ≥2.2) along with ≥2 of the following: (1) body mass index ≥30 kg/m^2, (2) dyslipidemia (triglycerides ≥1.69 mmol/L or high-density lipoprotein cholesterol ≤0.9 mmol/L), (3) hypertension: systolic BP ≥140 mm Hg and/or diastolic BP ≥85 mm Hg or the use of antihypertensive medication, and (4) microalbuminuria (≥2.5 g/mol creatinine) or proteinuria (≥0.30 g/24 h).

Chronic hypertension was categorized in 2 groups: (1) women on antihypertensive medication, and (2) women not using antihypertensive medication but with elevated BP (systolic BP ≥140 mm Hg and/or diastolic ≥90 mm Hg) during evaluation. Prehypertension was defined as a systolic BP between 120–139 mm Hg and/or diastolic BP between 80–89 mm Hg in women who did not use antihypertensive medication.

Echocardiography was performed using a cross-sectional phased-array oscillometric device (Agilent Sonos 5500; Philips Medical System, Eindhoven, The Netherlands; and Hewlett-Packard Sonos 2000 and 2500; Hewlett-Packard Company, Palo Alto, CA). We estimated the mean aortic velocity time integral by averaging the outer edge tracings of 5 consecutive continuous wave Doppler registrations of the left ventricular outflow tract velocity. By taking the product of velocity time integral and the midsystolic cross-sectional area at the level of the left ventricular outflow tract in the parasternal long-axis view, we obtained stroke volume (mL). Heart rate (beats/min) was obtained by taking the reciprocal of the mean of 5 consecutive R-R intervals on the electrocardiogram multiplied by 60. Cardiac output (L/min) was obtained by multiplying stroke volume with heart rate. The assessments were performed offline using EchoPAC PC SW, version 6.1.2; Vingmed Ultrasound, Horten, Norway and Excelera; Philips, The Netherlands. Total peripheral resistance was calculated by dividing mean arterial pressure × 80 by cardiac output (stroke volume × heart rate). An estimate for arterial compliance (mL/mm Hg) was made by dividing the stroke volume by brachial artery pulse pressure.

Statistical analysis

The independent t test was used to analyze continuous data and these variables are presented as mean with SD.[22] Not normally distributed data were analyzed nonparametrically using the Mann-Whitney U test and depicted as median with interquartile range. Categorical data were compared by the χ^2 (if at least 5 cases were present in each group) and presented as percentage. Logistic regression was used to calculate odds ratios (ORs). With multivariate regression analysis adjusted OR (aOR) were calculated. We corrected for maternal age (continuous), smoking (yes/no), primiparity (yes/no), interval between delivery and measurements, and intrauterine fetal demise. A 2-sided p-value <0.05 was considered statistically significant. In multiple comparisons we conducted Bonferroni adjustment to correct for the increased risk of a type 1 error. Consequently, a p-value <0.017 was considered statistically significant. All analyses were performed using SPSS Statistics 20 (IBM Corp, Armonk, NY).

Results

We included all participants with a history of a pregnancy complicated by SGA infancy (n=113), PE (n=729), or both (n=461).

Demographic and obstetric characteristics are presented in Table 1. Women in the PE group were more often primiparous and had a larger interval between delivery and measurements compared to SGA and SGA + PE groups. Women with solely SGA and SGA + PE were more likely to smoke at the time of assessment. In the SGA + PE group >70% of women delivered <34 weeks, which was higher compared to both other groups. The percentage of pregnancies resulting in intrauterine fetal demise was different between all groups and related mostly to the presence of SGA (26.8%, 12.1%, and 2.6% in the SGA, SGA + PE, and PE groups, respectively). Nearly 12% of women in the PE groups had preexisting hypertension, about twice that of solely SGA.

Cardiometabolic and cardiovascular variables of groups are presented in Table 2. We did not observe a significant difference in glucose levels and in HbA1c and lipid profiles between groups. However, insulin levels and HOMA-ir indicating insulin resistance were higher in former PE women compared to women who solely delivered a SGA infant. Systolic BP and diastolic BP were higher in former PE women compared to those with an obstetric history of solely SGA. Moreover, diastolic (but not systolic) BP was also modestly higher in the PE group compared to the SGA + PE group. The prevalence of prehypertension seemed lower in the SGA group (24.8%) compared to the PE group (33.2%, p=0.091) and the SGA + PE group (35.6%, p=0.040) but did not reach the statistical significance threshold accounting for Bonferroni correction. Cardiac output and total peripheral vascular resistance did not differ between groups. Global vascular compliance was lower in PE + SGA group compared to the PE group (p=0.012).

Table 3 shows the presence of the metabolic syndrome and its constituents in groups with corresponding OR and aOR between groups

PE vs SGA and SGA + PE

The prevalence of the metabolic syndrome was not statistically significantly higher in the PE group compared to the SGA group. However, the metabolic syndrome was more strongly associated with the SGA + PE group compared to the PE group (aOR, 1.57; 95% confidence interval [CI], 1.12–2.22). Obesity was comparable between groups. The PE group was, compared to the SGA group, more strongly associated with glucose metabolism problems of hyperglycemia (aOR, 6.26; 95% CI, 1.22–32.05), elevated fasting insulin (aOR, 1.62; 95% CI, 1.03–2.54), and insulin resistance (elevated HOMA-ir aOR, 1.96; 95% CI, 1.21–3.16). Moreover, high insulin levels and high HOMA-ir scores seemed more often present in the SGA + PE group compared to the PE group but without reaching statistical significance. Microalbuminuria related to PE (18.2%) rather than SGA (7.6%)

Table 1. Demographic and obstetric characteristics after pregnancy complicated by SGA, PE, or both

Characteristic	SGA (n=113)	PE (n=729)	SGA + PE (n=461)	p-value		
				PE vs SGA	SGA + PE vs SGA	SGA + PE vs PE
Maternal age, y	31.4 (4.5)	31.8 (4.2)	31.2 (4.4)	0.373	0.646	0.020
BMI, kg/m^2	25.3 (7.0)	25.5 (5.1)	25.9 (5.5)	0.775	0.347	0.178
Smoking, %	20.4	10.3[a]	17.8[b]	0.002[c]	0.527	<0.001[c]
Primiparous, %	72.6	83.8[a]	75.9[b]	0.004[c]	0.459	0.001[c]
GA at delivery, wk	32.6 (5.1)	34.0 (3.6)[a]	31.5 (4.1)[b]	0.004[c]	0.048	<0.001[c]
GA at delivery <34 wk, %	57.5	46.4	70.9[a b]	0.027	0.006[c]	<0.001[c]
Fetal birthweight, g	1258 (781)	2118 (862)[a]	1210 (630)[b]	<0.001[c]	0.544	<0.001[c]
Birthweight percentile <3, %	57 (50.4)	0.0 (0)	105 (22.8)	<0.001[c]	<0.001[c]	<0.001[c]
Birthweight percentile 3–4, %	19 (16.8)	0.0 (0)	91 (19,7)	<0.001[c]	0.509	<0.001[c]
Birthweight percentile 5–9, %	37 (32.7)	0.0 (0)	265 (57.5)	<0.001[c]	<0.001[c]	<0.001[c]
IUFD, %	26.8	2.6[a]	12.1[a b]	<0.001[c]	<0.001[c]	<0.001[c]
Interval between delivery and measurements, mo	7.0 (5.0–20.5)	10.0 (7.0–19.0)[a]	9.0 (6.0–18.0)[b]	0.010[c]	0.316	0.006[c]
Preexisting hypertension, %	6.2	11.8	11.9	0.079	0.083	0.965
Antihypertensive medication, %	8.0	15.2	13.5	0.043	0.118	0.406

Data are expressed as mean (SD), percentage, or median (interquartile range) within group. BMI, body mass index; GA, gestational age; IUFD, intrauterine fetal demise; PE, preeclampsia; SGA, small for gestational age.

[a] Significant difference (p≤0.017) compared to SGA group; [b] Significant difference (p≤0.017) compared to PE group; [c] Significant at p<0.05

Table 2. Metabolic and hemodynamic profile after pregnancy complicated by SGA, PE, or both

				p-value		
Variable	SGA (n=113)	PE (n=729)	SGA + PE (n=461)	PE vs SGA	SGA + PE vs SGA	SGA + PE vs PE
Metabolic						
Glucose, mmol/L	4.9 (0.7)	5.1 (1.1)	5.1 (0.6)	0.077	0.106	0.170
Insulin, mU/L	9.9 (5.5)	11.2 (7.1)[a]	11.8 (6.8)[a]	0.017[b]	0.006[b]	0.151
HOMA-ir	2.2 (1.2)	2.6 (1.9)[a]	2.7 (1.8)[a]	0.004[b]	<0.001[b]	0.293
HbA1c, %	5.3 (0.4)	5.3 (0.5)	5.3 (0.5)	0.597	0.109	0.098
Triglycerides, mmol/L	1.0 (0.6)	1.1 (0.9)	1.1 (0.7)	0.108	0.052	0.994
HDL, mmol/L	1.3 (0.3)	1.3 (0.8)	1.3 (0.3)	0.971	0.825	0.782
Hemodynamic						
Systolic BP, mm Hg	117 (13)	120 (14)	121 (16)[a]	0.034	0.001[b]	0.057
Antihypertensives +	128 (15)	129 (16)	133 (21)	0.838	0.508	0.175
Antihypertensives –	116 (12)	118 (13)	120 (14)[a]	0.134	0.010[b]	0.062
Diastolic BP, mm Hg	70 (9)	73 (10)[a]	74 (11)[a]	0.002[b]	<0.001[b]	0.424
Antihypertensives +	78 (9)	79 (11)	82 (13)	0.802	0.410	0.152
Antihypertensives –	69 (9)	72 (10)[a]	72 (10)[a]	0.007[b]	0.006[b]	0.605
Prehypertension, %	24.8	33.2	35.6	0.091	0.040	0.448
Cardiac output, L/min	5.2 (1.3)	5.3 (1.2)	5.3 (1.2)	0.327	0.425	0.767
TPVR, dynes × s/cm^5	1407 (353)	1407 (327)	1425 (344)	0.998	0.627	0.372
GVC, mL/mm Hg	1.65 (0.42)	1.71 (0.45)	1.65 (0.45)c	0.175	0.909	0.012[b]

Data are expressed as mean (SD) or percentage within group. BP, blood pressure; GVC, global vascular compliance; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; HOMA-ir, homeostasis model assessment–insulin resistance; PE, preeclampsia; SGA, small for gestational age; TPVR, total peripheral vascular resistance.
[a] Significant difference (p≤0.017) compared to SGA group; [b] Significant at p<0.05; [c] Significant difference (p≤0.017) compared to PE group.

Table 3. Metabolic syndrome and its constituents after pregnancy complicated by SGA, PE, or both

Variable	SGA (n=113)	PE (n=729)	SGA + PE (n=461)	OR (95% CI) aOR (95% CI)		
				PE vs SGA	SGA + PE vs SGA	SGA + PE vs PE
Metabolic syndrome	7.5	12.9	19.8	1.82 (0.85–3.86) 1.83 (0.82–4.08)	3.02 (1.41–6.45)[a] 3.31 (1.53–7.17)[a]	1.66 (1.20–2.31)[a] 1.57 (1.12–2.22)[a]
BMI ≥30	15.9	15.6	20.0	0.98 (0.57–1.68) 1.06 (0.58–1.92)	1.32 (0.76–2.29) 1.40 (0.79–2.45)	1.35 (0.99–1.82) 1.29 (0.94–1.77)
Insulin ≥9.2 mU/L	47.2	55.1	62.2	1.38 (0.91–2.07) 1.62 (1.03–2.54)[a]	1.85 (1.20–2.83)[a] 1.94 (1.25–2.99)[a]	1.34 (1.05–1.71)[a] 1.27 (0.99–1.64)
Glucose ≥6.1 mmol/L	1.8	5.0	4.4	2.90 (0.69–12.21) 6.26 (1.22–32.05)[a]	2.53 (0.58–10.98) 2.67 (0.61–11.77)	0.87 (0.50–1.53) 0.79 (0.43–1.43)
HOMA-ir ≥2.2	39.8	50.1	57.7	1.52 (1.00–2.32)[a] 1.96 (1.21–3.16)[a]	2.06 (1.33–3.20)[a] 2.19 (1.40–3.43)[a]	1.36 (1.06–1.73)[a] 1.28 (0.99–1.65)
Triglycerides ≥1.69 mmol/L	8.0	13.8	15.7	1.84 (0.90–3.76) 2.06 (0.96–4.42)	2.15 (1.04–4.44)[a] 2.25 (1.08–4.70)[a]	1.17 (0.84–1.62) 1.13 (0.80–1.59)
HDL ≤0.9 mmol/L	8.1	7.6	9.7	0.93 (0.45–1.94) 0.98 (0.45–2.16)	1.21 (0.58–2.57) 1.21 (0.56–2.58)	1.31 (0.87–1.98) 1.16 (0.75–1.79)
Microalbuminuria ≥2.5 g/mol creatinine	7.6	18.2	23.8	2.70 (1.28–5.70)[a] 2.77 (1.27–6.06)[a]	3.78 (1.78–8.05)[a] 3.83 (1.79–8.20)[a]	1.40 (1.04–1.88)[a] 1.33 (0.98–1.82)
Proteinuria ≥0.3 g/24 h	1.9	3.7	6.8	2.03 (0.48–8.68) 2.17 (0.48–9.89)	3.90 (0.92–16.57) 3.99 (0.93–17.13)	1.92 (1.12–3.29)[a] 1.85 (1.06–3.22)[a]
Hypertension	14.5	25.9	25.4	2.06 (1.18–3.59)[a] 2.67 (1.45–4.94)[a]	2.00 (1.13–3.54)[a] 2.23 (1.24–3.40)[a]	0.97 (0.74–1.27) 0.94 (0.71–1.25)
Systolic BP ≥140 mm Hg	5.0	6.1	9.0	1.26 (0.48–3.28) 1.40 (0.52–3.86)	1.90 (0.73–4.99) 2.01 (0.76–5.32)	1.51 (0.94–2.45) 1.45 (0.88–2.38)
Diastolic BP ≥85 mm Hg	6.9	10.0	11.1	1.49 (0.66–3.35) 1.67 (0.70–3.98)	1.67 (0.73–3.83) 1.82 (0.78–4.23)	1.12 (0.74–1.70) 1.12 (0.73–1.73)
Antihypertensives +	8.0	15.2	13.5	2.06 (1.01–4.19)[a] 2.86 (1.31–6.27)[a]	1.78 (0.86–3.71) 2.03 (0.96–4.29)	0.87 (0.62–1.22) 0.80 (0.56–1.15)

Data are expressed as percentage within group. Adjusted for maternal age, smoking (yes/no), parity (nulliparous yes/no), interval between delivery and measurements, and intrauterine fetal demise (yes/no).
aOR, adjusted odds ratio; BMI, body mass index; BP, blood pressure; CI, confidence interval; HDL, high-density lipoprotein; HOMA-ir, homeostasis model assessment–insulin resistance; OR, odds ratio; PE, preeclampsia; SGA, small for gestational age.
[a] Significant at $p<0.05$.

(aOR, 2.77; 95% CI, 1.27–6.06) but tended to relate more to the SGA + PE group (23.8%) but without reaching statistical significance (aOR, 1.33; 95% CI, 0.98–1.82).

Abnormal lipids did not differ between the PE group and the SGA group or the SGA + PE group. Finally, PE was also more strongly associated with hypertension (aOR, 2.67; 95% CI, 1.45–4.94) than SGA with nearly 2 times as many women from the PE group using antihypertensive medication as compared to the SGA group. The association with hypertension was comparable between the PE group and the SGA + PE group.

SGA vs SGA + PE

We observed a strong association between the metabolic syndrome and the SGA + PE group (19.8%) compared to the SGA group (7.5%) (aOR, 3.31; 95% CI, 1.53–7.17). All other constituents of the metabolic syndrome separately were observed more often in the SGA + PE group than in the SGA group. Moreover, the SGA + PE group significantly more often had hyperinsulinemia and increased HOMA-ir score than the SGA group, whereas the increased prevalence of hyperglycemia did not reach statistical significance. Hypertriglyceridemia was 2 times more often observed in the SGA + PE group compared to the SGA group (aOR, 2.25; 95% CI, 1.08–4.70). Microalbuminuria was >3 times more prevalent in the SGA + PE group compared to the SGA group (aOR, 3.83; 95% CI, 1.79–8.20). When compared to SGA, SGA + PE was more strongly related to hypertension (aOR, 2.23; 95% CI, 1.24–3.40).

Comment

In this study, we explored the underlying maternal cardiometabolic and cardiovascular risk profile after pregnancies complicated by placental syndrome with fetal clinical presentation, maternal clinical presentation, or a combination of both.

Our results show that there is a stepwise increase in association between the metabolic syndrome and the different manifestations placental syndrome in the following order: SGA, PE, SGA + PE. Moreover, chronic hypertension related to an obstetric history of PE rather than SGA but not more often when both PE and SGA were present. Interestingly, reduced arterial compliance suggesting increased arterial stiffness related to SGA rather than an obstetric history of solely PE.

The prevalence of the metabolic syndrome in women with an obstetric history of SGA without PE was comparable to the overall prevalence in Dutch women of similar age (5% for women <40 years of age).[23] In contrast, the prevalence of the metabolic syndrome was almost twice as high in PE and was even higher in women having both fetal and maternal manifestations of placental syndrome. Our findings are consistent with the most unfavorable cardiometabolic and cardiovascular maternal profile in the latter and seem to be in line with the previously found increased CVD risk after PE combined with SGA group compared to sole PE.[11, 14] It has previously been hypothesized that early- and late-onset PE (i.e., delivery ≥34 weeks) may be 2 different disease entities. Early-onset placental syndrome is more strongly associated with metabolic syndrome and relates more strongly to remote CVD compared to late-onset disease.[12, 24] It may be that the observed differences in metabolic profile in the combined group in our study relates at least partly to the higher prevalence of early-onset disease in this group.

We observed a lower global vascular compliance in women who delivered a SGA infant compared to those with merely PE. Decreased vascular compliance indicates increased arterial stiffness and is an independent predictor for remote cardiovascular events.[25] Our results are in line with previous studies in which increased arterial stiffness was found to be highly prevalent in normotensive pregnancies complicated by intrauterine growth restriction and SGA compared to solely PE and uncomplicated pregnancies.[4] Although we do not know whether or not this was already present prior to pregnancy, it is tempting to speculate that these findings may support the concept that fetal involvement in placental syndromes relates to a stiffer maternal arterial system, which, in turn may hamper vascular adaptation to pregnancy.

We found a strong association between chronic hypertension and PE, which is in line with previously reported data.[12] Chronic hypertension seems to be to a lesser extent associated with solely SGA, although the prevalence of chronic hypertension observed in our SGA group was still 3-fold higher compared to that observed in the general Dutch female population of similar age.[26] Chronic hypertension is a major predictor and risk factor for CVD and may originate from altered circulatory function or adverse metabolic factors jeopardizing endothelial function.[27] Therefore, along with the increased prevalence of additional cardiometabolic risk factors and the known association with remote CVD among these women, women after placental syndromes could benefit from tailored cardiovascular screening programs in the upcoming years after pregnancy.

There are some shortcomings that need to be addressed. First, some women were screened at a postpartum interval <6 months after their complicated pregnancy. Therefore, their cardiometabolic state may sometimes not reflect the completely recovered metabolic profile. As we corrected for this interval in the aOR, we assume that our observations still hold. Second, we did not include a healthy parous control group in our analysis. Therefore, we were only able to delineate differences between different placental syndrome groups without being able to generalize our findings to the general population. Moreover, since our study population is included in a tertiary center, women with increased risk for CVD or with severe manifestations of placental syndrome (e.g., a high prevalence of fetal death, severe PE, and/or SGA) might be overrepresented. Therefore, translation to the general population must be done with caution. Because women were screened in 1 session and pregnancy outcome was assessed on the same day, there was no loss to follow-up in our cohort.

In conclusion, the different clinical manifestations of placental syndromes are variously associated with the metabolic syndrome. Women with combined presentation of placental syndrome (i.e., both PE and SGA) are at the highest risk to have underlying cardiovascular and cardiometabolic risk factors. Considering the high incidence of underlying dyslipidemia or insulin resistance, our data support the concept and need for postpartum cardiovascular screening to specify the different risk profiles that can

be used to tailor cardiovascular risk management programs after specified placental syndrome.

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Chapter 4

Metabolic syndrome and pre-eclampsia

Mieke C.E. Hooijschuur | Chahinda Ghossein-Doha |
Abraham A. Kroon | Peter W. de Leeuw | Adrienne A.M. Zandbergen

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Abstract

Objective: To evaluate the association between different pre-eclampsia (PE) phenotypes and the development of metabolic syndrome postpartum, in order to identify the subgroup of formerly pre-eclamptic women with a worse cardiovascular risk profile requiring tailored postpartum follow-up.

Methods: This was a cohort study of 1102 formerly pre-eclamptic women in whom cardiovascular and cardiometabolic evaluation was performed at least 3 months postpartum. Women were divided into four subgroups based on PE resulting in delivery before 34 weeks (early-onset (EO)) or at or after 34 weeks (late onset (LO)) of gestation and whether they delivered a small-for-gestational-age (SGA) neonate. Metabolic syndrome was diagnosed as the presence of hyperinsulinemia along with two or more of: body mass index ≥30 kg/m^2; dyslipidemia; hypertension; and microalbuminuria or proteinuria. Data were compared between groups using ANOVA after Bonferroni correction. Odds ratios (OR) were calculated using logistic regression to determine the association between metabolic syndrome and the four subgroups. We constructed receiver–operating characteristics curves and computed the area under the curve (AUC) to quantify the ability of different obstetric variables to distinguish between women who developed metabolic syndrome and those who did not.

Results: The prevalence of metabolic syndrome was higher in women with EO-PE and SGA (25.8%) than in those with EO-PE without SGA (14.7%) (OR 2.01 (95% CI, 1.34–3.03)) and approximately five-fold higher than in women with LO-PE with SGA (5.6%) (OR 5.85 (95% CI, 2.60–13.10)). In women with LO-PE, the prevalence of metabolic syndrome did not differ significantly between women with and those without SGA. Multivariate analysis revealed that a history of SGA, a history of EO-PE and systolic blood pressure at the time of screening are the best predictors of developing metabolic syndrome postpartum. The AUC of the model combining these three variables was 74.6% (95% CI, 70.7–78.5%). The probability of the presence of metabolic syndrome was calculated as: $P = 1/(1 + e^{-LP})$, where LP is linear predictor $= -8.693 + (0.312 \times \text{SGA (yes} = 1)) + (0.507 \times \text{EO-PE (yes} = 1)) + (0.053 \times \text{systolic blood pressure})$.

Conclusions: The incidence of metabolic syndrome postpartum was associated more strongly with EO-PE in combination with SGA as compared with LO-PE or EO-PE without SGA. Both time of onset of PE and fetal growth affect the risk of metabolic syndrome after a pre-eclamptic pregnancy.

Introduction

Cardiovascular disease (CVD) is the number one cause of mortality in women worldwide.[1] The presence of metabolic syndrome, a cluster of modifiable cardiovascular and cardiometabolic conditions, raises the risk of CVD.[2] In patients with an unfavorable CVD risk profile, targeting individual risk factors using pharmacological and/or lifestyle interventions can prevent or delay the onset of CVD and decrease healthcare costs.[3-13] Therefore, when considering the worldwide health and economic implications of CVD in women, timely detection and treatment prior to the onset of overt CVD is an important and time-sensitive matter.

Pre-eclampsia (PE) is a vascular complication of pregnancy that is associated with high fetal and maternal morbidity and mortality.[14, 15] In addition to its short-term implications, PE is associated with a two- to seven-fold higher risk of developing CVD at a relatively young age,[16, 17] especially in case of early-onset (EO) PE (before 34 weeks' gestation) or the co-occurrence of a small-for-gestational-age (SGA) fetus.[16, 18] In addition to this elevated risk of CVD, PE is also associated with modifiable CVD risk factors defining metabolic syndrome.[19-22] Therefore, PE may be viewed as a transient early warning sign of CVD risk, providing the opportunity for early management and primary prevention of CVD.[23, 24] Nonetheless, lack of understanding of the relationship between different obstetric outcomes and the prevalence of modifiable underlying CVD risk factors hampers the opportunity to identify those women at risk. To this end, we tested the hypothesis that women with EO-PE and a SGA fetus have the most unfavorable cardiovascular and cardiometabolic risk profile as compared with late-onset (LO) PE and/or normal fetal growth. We also evaluated whether obstetric outcome in combination with screening parameters could predict the presence of metabolic syndrome.

Patients and methods

This was a cohort study of women who had had a singleton pregnancy complicated by PE between 1996 and 2010 in The Netherlands. The study protocol was approved by the medical ethics committees of Radboud University Medical Center in Nijmegen (CMO 2007/252) and Maastricht University Medical Center in Maastricht (MEC 0-4-049), The Netherlands.

PE was defined as new-onset hypertension with systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥ 90 mmHg and the presence of proteinuria (≥0.3 g per 24 h or ≥ 2+ on dipstick analysis) occurring after 20 weeks' gestation in previously normotensive women[25] or when proteinuria developed after 20 weeks in women with pre-existing hypertension. EO-PE and LO-PE were defined as PE resulting in delivery

before 34 weeks and at or after 34 weeks, respectively. SGA was defined as an infant with a birth weight ≤ 10th percentile according to the Dutch reference standard.[26]

Women were recruited throughout the country at their regular 6-week postpartum follow-up. They were evaluated for at least 3 months postpartum in the cardiovascular evaluation program at two tertiary referral hospitals in The Netherlands (Radboud University Medical Center and Maastricht University Medical Center). Women who had had a singleton pregnancy complicated by PE and who had given birth after 22 weeks' gestation were included in the study.[27]

Assessment of the women was performed in a single session that started at 8.00 a.m. in a temperature controlled room (20°C). The women were instructed to refrain from drinking and eating 10 h prior to assessment. None of the participants was breastfeeding. Clinical data on obstetric variables of the index pregnancy were collected from medical files or by self-reporting. Additional information on obstetric and medical history, lifestyle and use of medication was retrieved by self-reporting, and body mass index (BMI) was calculated. After 5 min of rest, arterial blood pressure was measured with the woman in a sitting position on the right arm using a semiautomatic oscillometric device (Dinamap Vital Signs Monitor 1846; Critikon, Tampa, FL, USA). The median value of 11 measurements obtained over a period of 30 min was used.

Urine was collected in the 24 h preceding the measurements. The 24-h urine sample was assayed for albumin, protein and creatinine to calculate (micro)albuminuria corrected for creatinine output (g/mol creatinine) and total protein level (g/24 h). Fasting blood samples were collected to measure levels of glucose, insulin, high-density lipoprotein cholesterol (HDL), triglycerides and creatinine. The homeostasis model assessment (HOMA-ir) (insulin (mU/L) × glucose (mmol/L) / 22.5) was used to estimate the degree of insulin resistance.[28]

Metabolic syndrome was diagnosed based on the criteria of the World Health Organization,[29] as the presence of hyperinsulinemia (fasting insulin ≥9.2 mU/L, fasting blood glucose ≥6.1 mmol/L, or HOMA-ir ≥2.2) along with two or more of the following: (1) BMI ≥30 kg/m^2; (2) dyslipidemia (triglycerides ≥1.69 mmol/L or HDL ≤0.9 mmol/L); (3) hypertension (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥85 mmHg, and/or use of antihypertensive medication); and (4) microalbuminuria (≥2.5 g/mol creatinine) or proteinuria (≥0.30 g per 24 h).

From 2003 onwards, high-sensitivity C-reactive protein (hs-CRP) was also measured using a multiarray detection system based on electrochemiluminescence technology (MesoScaleDiscovery, SECTOR Imager 2400, Gaithersburg, MD, USA).

Statistical analysis

Our sample of women who experienced PE was divided into four subgroups based on the time of onset of the disease (EO-PE vs LO-PE) and the co-occurrence of SGA (PE with vs without SGA).

Normally distributed continuous data were compared between groups using analysis of variance (ANOVA). Categorical data were analyzed using the chi-square test if at least five cases were present in each group, and are presented as n (%). Logistic regression was used to calculate odds ratios (OR) to analyze the association between the onset of PE and co-occurrence of SGA and (components of) metabolic syndrome. Multivariate logistic regression analysis was performed to adjust for factors that could influence outcome, including maternal age (continuous), smoking (yes/no), nulliparity (yes/no), interval between delivery and measurements, and intrauterine death (IUD).

To quantify the ability of PE (early/late) and SGA (yes/no), birth-weight centile and gestational age at delivery to discriminate between women who developed metabolic syndrome postpartum and those who did not, we constructed receiver–operating characteristics curves and computed the area under the curve (AUC). AUC can range between 50% (no discriminative ability) and 100% (perfect discriminative ability). In addition, the obstetric history was combined with potential predictors measured at assessment (smoking status, age, BMI and blood pressure) to evaluate the discriminative performance for the presence of metabolic syndrome of a model consisting of all significant predictors. The Akaike Information Criterion, a maximum likelihood-based method that takes model complexity into account, was used to select predictors that contributed significantly to the model. The discriminative performance of this model was quantified as the AUC, and calibration was assessed by visually inspecting the calibration plot.

Spearman's correlation test was used to analyze the association between the prevalence of metabolic syndrome and birth-weight centiles and gestational age; two-sided $p<0.05$ was considered statistically significant. Bonferroni adjustment was performed to correct for multiple testing (i.e. in comparisons between four groups a p-value of $<0.05/4$ (0.0125) was considered to be statistically significant).[30] Statistical analysis was performed using IBM SPSS Statistics version 20 (IBM Corp., Armonk, NY, USA).

Results

A total of 1,102 formerly pre-eclamptic women fulfilled the inclusion criteria and were evaluated for cardiovascular and cardiometabolic risk factors. Of these, 608 (55%) had EO-PE, of whom 295 (49%) had a SGA fetus and 313 (51%) did not, and 494 (45%) women had LO-PE, of whom 125 (25%) had a SGA fetus and 369 (75%) did not.

Table 1. Demographic and obstetric characteristics of women with history of early- or late-onset pre-eclampsia (PE), according to delivery of small-for-gestational-age (SGA) infant

	Early-onset PE		Late-onset PE		
Characteristic	No SGA (n=313)	SGA (n=295)	No SGA (n=369)	SGA (n=125)	Overall p
Maternal age (years)	31.2 (30.8–31.7)	30.9 (30.4–31.4)	32.3 (31.9–32.7)	32.1 (31.3–32.9)	<0.001
Smoker	42 (13.4)	56 (19.0)	28 (7.6)	18 (14.4)	<0.001
Nulliparous	272 (86.9)	228 (77.3)	302 (81.8)	89 (71.2)	0.001
Intrauterine death	12 (3.8)	46 (15.6)	4 (1.1)	5 (4.0)	<0.001
PP interval to assessment (months)	8 [6–15]	7 [6–13]	11 [7–21]	12 [8–31]	<0.001
GA at delivery (weeks)	30.9 (30.7–31.2)	29.4 (29.1–29.7)	36.8 (36.6–37.0)	36.8 (36.5–37.2)	<0.001
Birth weight (g)	1403 (1361–1445)	876 (842–910)	2746 (2681–2810)	2013 (1932–2094)	<0.001
Pre-existing hypertension	43 (13.7)	38 (12.9)	36 (9.8)	12 (9.6)	0.298

Data are presented as mean (95% CI), n (%) or median [interquartile range].
GA, gestational age; PP, postpartum.

Women in the EO-PE with SGA group were approximately 1 year younger, were more likely to be a smoker and had a higher prevalence of IUD compared with women in the other three groups (Table 1). Women with EO-PE without SGA were more likely to be nulliparous than women in the other three groups. Women with EO-PE had their postpartum assessment on average a few months earlier than did those in the LO-PE subgroups.

EO-PE with vs without SGA

In the EO-PE group, all absolute values of metabolic and hemodynamic variables were similar between women with and those without SGA, apart from hs-CRP, which was higher in women with SGA (Table 2). However, the prevalence of metabolic syndrome was higher in the subgroup of women with SGA (25.8%) than in those without (14.7%) (adjusted OR (aOR) 1.93 (95% CI, 1.26–2.93)) (Figure 1). Moreover, women with EO-PE and SGA more often had high fasting insulin levels (aOR 1.66 (95% CI, 1.18–2.34)), high HOMA-ir scores (aOR 1.61 (95% CI, 1.15–2.28)), high triglyceride levels (aOR 1.65 (95% CI, 1.06–2.57)) and microalbuminuria (aOR 1.59 (95% CI, 1.07–2.37)) compared with women with EO-PE without SGA (Table 3). The presence of obesity, hyperglycemia, proteinuria and hypertension did not differ between the two subgroups.

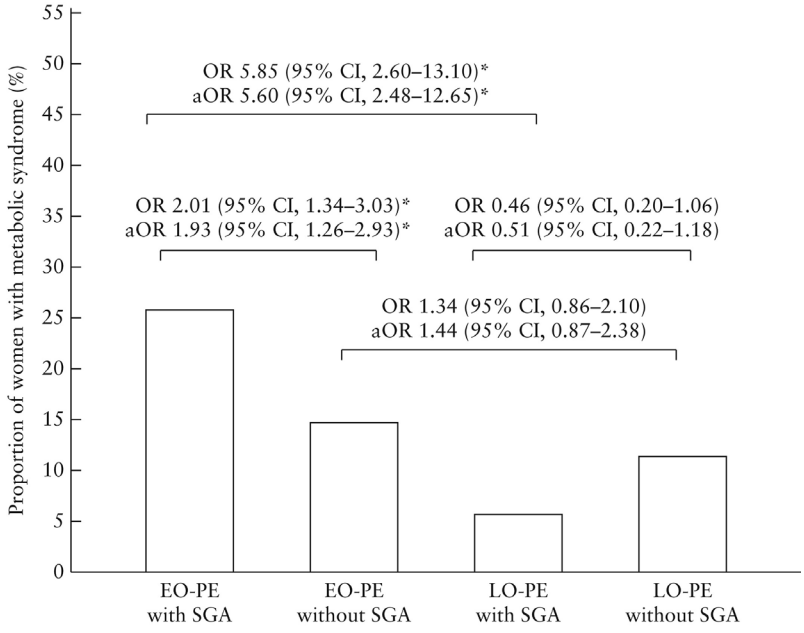

Figure 1. Prevalence of metabolic syndrome after 3 months postpartum in women who had had early-onset (EO) or late-onset (LO) pre-eclampsia (PE), according to whether or not they had delivered a small-for-gestational-age (SGA) infant. Odds ratios (OR) and adjusted OR (aOR) (adjusted for maternal age, smoking (yes/no), nulliparity (yes/no), interval between delivery and measurements, and intrauterine death) are shown.
* Statistically significant difference.

Table 2. Metabolic and hemodynamic variables measured more than 3 months postpartum in women who had had early- or late-onset pre-eclampsia (PE), according to whether or not they had delivered a small-for-gestational-age (SGA) infant

	Early-onset PE		Late-onset PE		
Variable	No SGA (n=313)	SGA (n=295)	No SGA (n=369)	SGA (n=125)	Overall p
Metabolic					
BMI (kg/m^2)	25.7 (25.1–26.3)	26.4 (25.8–27.1)	25.2 (24.7–25.7)*	24.5 (23.7–25.4)*	0.002
Insulin (mU/L)	11.2 (10.5–11.9)	12.6 (11.8–13.4)	10.9 (10.2–11.7)*	9.8 (8.8–10.8)*	0.001
Glucose (mmol/L)	5.1 (5.0–5.2)	5.1 (5.0–5.2)	5.1 (5.0–5.2)	5.0 (4.9–5.0)	0.469
HOMA-ir	2.6 (2.4–2.8)	2.9 (2.7–3.2)	2.5 (2.3–2.8)*	2.2 (2.0–2.4)*	0.002
Triglycerides (mmol/L)	1.2 (1.1–1.3)	1.2 (1.2–1.3)	1.1 (1.0–1.2)	0.9 (0.8–1.0)* †	0.001
Cholt (mmol/L)	4.9 (4.8–5.0)	4.8 (4.7–4.9)	4.8 (4.7–4.9)	4.7 (4.6–4.9)	0.374
HDL (mmol/L)	1.30 (1.26–1.33)	1.32 (1.28–1.36)	1.38 (1.28–1.48)	1.36 (1.30–1.41)	0.355
LDL (mmol/L)	3.1 (3.0–3.1)	3.0 (2.9–3.1)	3.0 (2.9–3.0)	3.0 (2.8–3.1)	0.415
hs-CRP (mg/L)	4.6 (4.1–5.1)*	5.7 (5.1–6.3)	4.5 (4.1–4.9)*	4.1 (3.5–4.7)*	0.001
Hemodynamic					
SBP (mmHg)	122 (120–123)	123 (121–125)	117 (116–119)* †	117 (115–119)* †	<0.001
DBP (mmHg)	75 (74–76)	75 (74–76)	72 (71–73)* †	70 (69–72)* †	<0.001
MAP (mmHg)	92 (90–93)	92 (91–94)	88 (87–89)* †	87 (85–89)* †	<0.001
HR (beats/min)	72 (70–73)	73 (71–74)	71 (70–72)	70 (68–72)	0.068
Proteinuria (g/L)	0.14 (0.09–0.19)	0.16 (0.09–0.23)	0.11 (0.08–0.13)	0.08 (0.07–0.10)	0.232
eGFR (mL/min/1.73m^2)	92 (90–94)	91 (89–93)	93 (90–95)	91 (88–94)	0.776
Creatinine (µmol/L)	67 (66–68)	68 (66–69)	66 (65–68)	67 (65–69)	0.519

Data are presented as mean (95% CI).

* Significant compared with women with early-onset PE and SGA.

† Significant compared with women with early-onset PE without SGA.

BMI, body mass index; Cholt, total cholesterol; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein cholesterol; HOMA-ir, homeostatic model assessment for insulin resistance; HR, heart rate; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein cholesterol; MAP, mean arterial pressure; SBP, systolic blood pressure.

Table 3. Prevalence of determinants of metabolic syndrome after 3 months postpartum, with corresponding odds ratios (OR) and adjusted OR (aOR), in women who had had early- or late-onset pre-eclampsia (PE), according to whether or not they had delivered a small-for-gestational-age (SGA) infant

	Early-onset PE				Late-onset PE			
Variable	No SGA (n=313)	SGA (n=295)	OR (95% CI)	aOR (95% CI)	No SGA (n=369)	SGA (n=125)	OR (95% CI)	aOR (95% CI)
Obesity (BMI ≥30 kg/m^2)	53/313 (16.9)	65/295 (22.0)	1.39 (0.93–2.08)	1.39 (0.92–2.11)	51/369 (13.8)	19/125 (15.2)	1.18 (0.63–1.98)	0.97 (0.53–1.76)
Insulin ≥9.2 mU/L	166/304 (54.6)	193/292 (66.1)	1.62 (1.16–2.26)*	1.66 (1.18–2.34)*	188/359 (52.4)	57/122 (46.7)	0.80 (0.53–1.20)	0.76 (0.49–1.16)
Glucose ≥6.1 mmol/L	11/313 (3.5)	16/291 (5.5)	1.58 (0.72–3.45)	1.67 (0.75–3.76)	17/362 (4.7)	2/125 (1.6)	0.33 (0.08–1.47)	0.34 (0.08–1.64)
HOMA-ir ≥2.2	148/296 (50.0)	171/282 (60.6)	1.54 (1.11–2.14)*	1.61 (1.15–2.28)*	162/350 (46.3)	54/119 (45.4)	0.96 (0.64–1.46)	0.87 (0.57–1.35)
Triglycerides ≥1.69 mmol/L	42/313 (13.4)	60/295 (20.3)	1.65 (1.07–2.54)*	1.65 (1.06–2.57)*	45/369 (12.2)	5/125 (4.0)	0.30 (0.12–0.77)*	0.35 (0.13–0.91)*
HDL ≤0.9 mmol/L	30/313 (9.6)	34/291 (11.7)	1.25 (0.74–2.10)	1.12 (0.65–1.92)	22/369 (6.0)	7/125 (5.6)	0.94 (0.39–2.25)	0.90 (0.36–2.21)
Microalbuminuria	57/300 (19.0)	81/287 (28.2)	1.68 (1.14–2.47)*	1.59 (1.07–2.37)*	62/360 (17.2)	17/123 (13.8)	0.77 (0.43–1.38)	0.81 (0.44–1.48)
Proteinuria ≥0.3 g/24 h	14/304 (4.6)	23/295 (7.8)	1.77 (0.89–3.51)	1.71 (0.85–3.46)	12/369 (3.3)	2/125 (1.6)	0.49 (0.11–2.24)	0.47 (0.10–2.21)
Hypertension	99/309 (32.0)	83/293 (28.3)	0.84 (0.59–1.19)	0.81 (0.56–1.16)	71/368 (19.3)	23/123 (18.7)	0.96 (0.57–1.62)	0.96 (0.56–1.65)
Systolic BP ≥140 mmHg	36/313 (11.5)	40/295 (13.6)	1.21 (0.75–1.95)	1.15 (0.70–1.90)	21/369 (5.7)	9/123 (7.3)	1.30 (0.58–2.91)	1.17 (0.50–2.73)
Diastolic BP ≥85 mmHg	51/313 (16.3)	50/294 (17.0)	1.05 (0.68–1.61)	1.00 (0.64–1.55)	29/369 (7.9)	9/125 (7.2)	0.91 (0.42–1.98)	0.83 (0.37–1.90)
Antihypertensives use	54/309 (17.5)	44/293 (15.0)	0.83 (0.54–1.28)	0.76 (0.48–1.19)	43/369 (11.7)	14/124 (11.3)	0.96 (0.50–1.81)	0.96 (0.49–1.88)

Prevalence data presented as n/N (%).
* With vs without SGA, statistically significant.
aOR adjusted for maternal age, smoking (yes/no), nulliparity (yes/no), interval between delivery and measurements, and intrauterine fetal demise.
BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein cholesterol; HOMA-ir, homeostatic model assessment for insulin resistance.

LO-PE with vs without SGA

In the LO-PE group, the prevalence of metabolic syndrome did not differ significantly between women with and those without SGA (aOR 0.51 (95% CI, 0.22–1.18)) (Figure 1). Continuous metabolic and hemodynamic variables (Table 2) and most determinants of metabolic syndrome (Table 3) did not differ significantly between the two subgroups, except for a lower incidence of high triglyceride levels in women with LO-PE and SGA than in those without SGA (aOR 0.35 (95% CI, 0.13–0.91)).

Early-onset vs late-onset PE

With respect to absolute values of metabolic and hemodynamic variables, BMI and fasting insulin were higher in women with EO-PE and SGA than in the two LO-PE subgroups, and HOMA-ir values were higher in the EO-PE with SGA group than in the LO-PE subgroups (Table 2). Triglycerides levels were higher in both EO-PE subgroups than in the LO-PE with SGA group. Systolic and diastolic blood pressure and mean arterial pressure were higher in women with EO-PE than in those with LO-PE. Levels of glucose, HDL, low-density lipoprotein cholesterol, total cholesterol, creatinine, heart rate, proteinuria and estimated glomerular filtration rate did not differ between the four subgroups. The hs-CRP level was higher in women with EO-PE and SGA than in the LO-PE subgroups, but it did not differ between the EO-PE without SGA group and the LO-PE subgroups.

The prevalence of metabolic syndrome was approximately five-fold higher in women with EO-PE and SGA (25.8%) than in those with LO-PE and SGA (5.6%) (aOR 5.60 (95% CI, 2.48–12.65)), while it did not differ between the EO-PE without SGA (14.7%) and the LO-PE without SGA (11.4%) subgroups (aOR 1.44 (95% CI, 0.87–2.38)) (Figure 1).

Hypertension was associated more strongly with EO-PE than with LO-PE (aOR 1.71 (95% CI, 1.01–2.88) and 1.80 (95% CI, 1.23–2.64) in the groups with and without SGA, respectively). Moreover, compared with women who had LO-PE and SGA, those with EO-PE and SGA more often had high insulin levels (aOR 2.32 (95% CI, 1.49–3.61)), high fasting glucose levels (aOR 5.24 (95% CI, 1.08–25.50)), high HOMA-ir scores (aOR 1.92 (95% CI, 1.23–2.99)), high triglyceride levels (aOR 5.25 (95% CI, 2.20–12.54)) and micro-albuminuria (aOR 2.07 (95% CI, 1.17–3.67)). No differences were observed between women with EO-PE without SGA and those with LO-PE without SGA in the individual indices of metabolic syndrome, except for hypertension.

Prediction of postpartum metabolic syndrome

The combination of onset of PE and fetal growth (presence of SGA) had the highest predictive value for the development of metabolic syndrome postpartum, with an AUC of 63.6% (95% CI, 59.2–68.1%), compared with solely gestational age (AUC 61.6% (95% CI, 57.0–66.3%)), onset of PE (early/late) (AUC 59.6% (95% CI, 55.1–64.0%)), birth-

weight centile (AUC 56.1% (95% CI, 51.3–60.9%)) or SGA (yes/no) (AUC 56.2% (95% CI, 51.4–60.9%)).

Multivariate analysis showed that a history of a SGA newborn, having had EO-PE and systolic blood pressure at the time of screening are the best variables to predict which women will develop metabolic syndrome postpartum (Table 4). The AUC of the model combining these three variables was 74.6% (95% CI, 70.7–78.5%) (Figure 2a). The calibration plot of the model is shown in Figure 2b. All deciles are close to the line of perfect agreement between predicted probabilities and observed probabilities, indicating near-perfect calibration. The probability of the presence of metabolic syndrome was calculated as: P = 1/(1 + e–LP), where LP is linear predictor = –8.693 + (0.312 × SGA (yes = 1)) + (0.507 × EO-PE (yes = 1)) + (0.053 × systolic blood pressure).

Table 4. Prediction model for presence of metabolic syndrome after 3 months postpartum in women who had had pre-eclampsia (PE)

Variable	Regression coefficient	Odds ratio (95% CI)
Intercept	-8.693	NA
SGA (yes)	0.312	1.37 (0.96–1.20)
Early-onset PE (yes)	0.507	1.66 (1.13–2.44)
Systolic BP (mmHg)	0.053	1.05 (1.04–1.07)

Probability of presence of metabolic syndrome (MS) can be calculated as: P(MS) = 1/(1 + e–LP), where LP is linear predictor = –8.693 + (0.312 × SGA (yes = 1)) + (0.507 × early-onset PE (yes = 1)) + (0.053 × systolic BP). BP, blood pressure; NA, not applicable; SGA, small-for-gestational age.

Correlation of metabolic syndrome with birth-weight centile and gestational age

The presence of metabolic syndrome postpartum correlated negatively with birth-weight centile (r=-0.068; p=0.025) in the whole study population of formerly pre-eclamptic women. When considering only women with EO-PE, metabolic syndrome remained negatively correlated with birth-weight centile (r=-0.119; p=0.004). However, when considering only women with LO-PE, a statistically significant positive correlation was observed between metabolic syndrome and birth-weight centile (r=0.108; p=0.016). Moreover, the presence of metabolic syndrome postpartum correlated negatively with gestational age at delivery (r=-0.146; p<0.001). When considering only women with co-occurrence of SGA, metabolic syndrome remained negatively correlated with gestational age at delivery (r=-0.209; p<0.001), whereas, when considering only women without co-occurrence of SGA, there was no correlation with gestational age at delivery (r=-0.039; p=0.308).

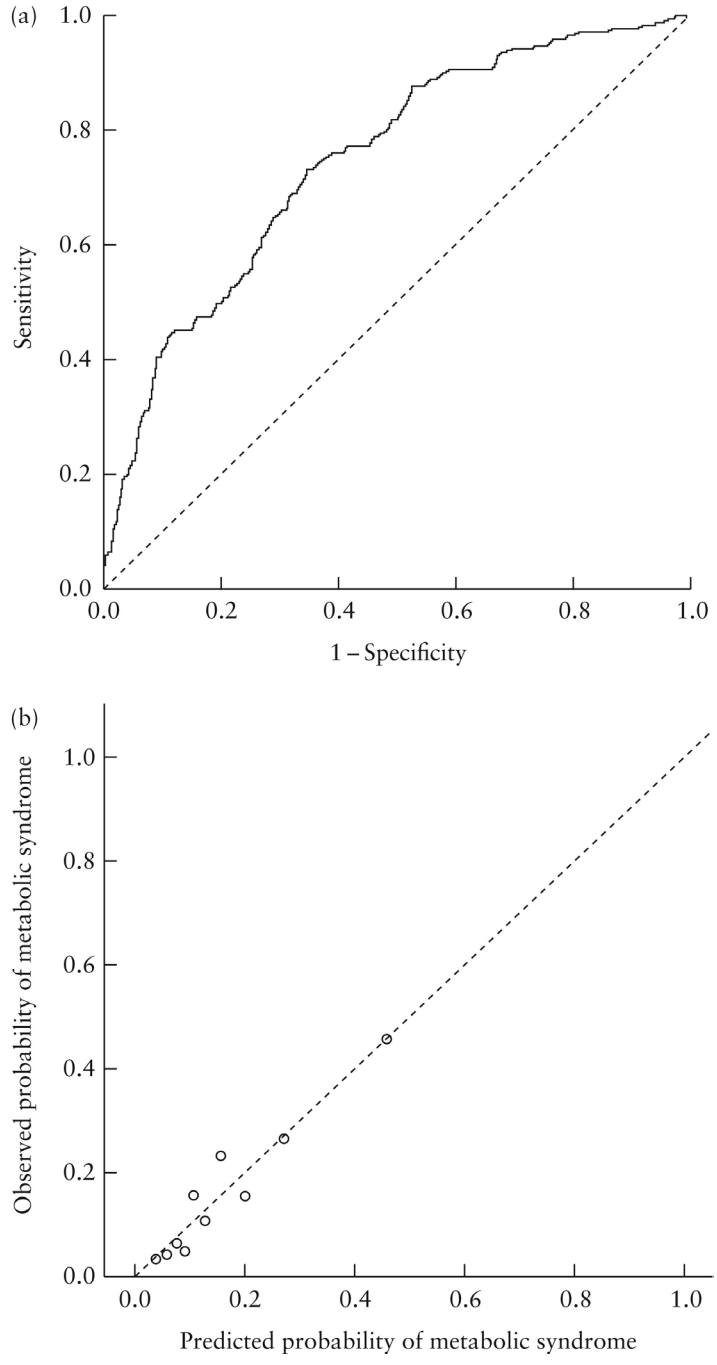

Figure 2. Receiver–operating characteristics curve (a) and calibration plot (b) of multivariate model (including systolic blood pressure at time of screening and obstetric history of small-for-gestational-age (yes) infant and early-onset pre-eclampsia (PE; yes)) to predict presence of metabolic syndrome in women with history of PE. In (a), area under curve is 74.6% (95% CI, 70.7–78.5%). In (b), all deciles are close to line of perfect agreement between predicted probabilities and observed probabilities, indicating near-perfect calibration.

Discussion

The results of this large cohort study show that the incidence of metabolic syndrome after at least 3 months postpartum in formerly pre-eclamptic women is associated more strongly with EO-PE in combination with SGA than with LO-PE or EO-PE without SGA. The prevalence of metabolic syndrome in women with EO-PE and SGA was more than 25%, which is approximately five-fold higher than the prevalence in the general female Dutch population of that age31. Both the time of onset of PE and co-occurrence of SGA affected the risk of metabolic syndrome after a pre-eclamptic pregnancy.

Previous studies have reported a higher prevalence of metabolic syndrome in women who had had EO-PE than in those with LO-PE,[21, 22] and in women with co-occurrence of SGA than in those without SGA.[20] In this study, we considered both the time of onset of PE and fetal growth and observed that, in women who had had EO-PE, the prevalence of postpartum metabolic syndrome was higher when there had been concomitant SGA, while in women with LO-PE, the prevalence was comparable between women with and those without SGA. Moreover, metabolic syndrome correlated progressively and inversely with birth-weight centile in EO-PE, whereas there was a positive correlation when considering only women with LO-PE. These seemingly paradoxical findings can be explained by the theory that the co-occurrence of SGA reflects different disease origins for EO-PE and LO-PE, in which cardiometabolic and cardiovascular characteristics affect placental development and growth and with it placental susceptibility and fragmentation, initiating maternal inflammatory responses and secondary endothelial dysfunction on the one hand and attenuated or fortified fetal growth on the other.[32-36] Large-for-gestational-age (LGA) infants are more common in LO-PE.[33] Different components of the metabolic syndrome are also risk factors for LGA (i.e. obesity, impaired glucose metabolism and hypertriglyceridemia),[34, 37] which therefore could explain the higher prevalence of metabolic syndrome in women with LO-PE without a SGA infant than in those with LO-PE and SGA in our study.

Our finding that women with EO-PE and SGA had the highest prevalence of traditional CVD risk factors is in agreement with epidemiological evidence suggesting that this group of women have the highest chance of developing CVD.[16, 18] Moreover, elevated hs-CRP as well as microalbuminuria were highly prevalent in women with EO-PE and SGA, suggesting persistent endothelial dysfunction and systemic inflammation.[38, 39] Elevated levels of hs-CRP together with markers of metabolic syndrome seem to double the risk for future CVD,[40] emphasizing the extent to which cardiovascular status in this group of previously pre-eclamptic women is impaired. In line with previous studies, we found that chronic hypertension was associated more strongly with EO-PE than with LO-PE,[21] irrespective of the concomitant presence of SGA.

Favorable CVD risk-factor levels in early and middle age are associated with a lower lifetime risk for CVD and prolonged survival.[41, 42] Most of the individual CVD risk factors

evaluated in this study are modifiable, meaning that targeted intervention could prevent or delay the onset of CVD, thus emphasizing the value of this opportunity for the early detection of high-risk women.[3, 4, 43-45] Therefore, our results emphasize the need for close follow-up of these young women, and for normalizing their CVD risk status by initiating healthy lifestyle programs and, when necessary, pharmacological intervention. In order to facilitate identification of previously pre-eclamptic women who are in need of further screening, we developed a model consisting of easily obtainable predictors to calculate the risk of metabolic syndrome after PE. Obstetric history and systolic blood pressure at the time of consultation could help a physician to determine which previously pre-eclamptic women will require further screening for cardiometabolic and cardiovascular risk factors postpartum. Nonetheless, the impact of preventive measures in such women is at present unknown and should be determined in future clinical trials.

In the context of cardiovascular risk management, there are sex differences in how traditional CVD risk factors impact on the development of CVD.[46-52] Guidelines of the American Heart Association[23, 53] recommend that a woman's pregnancy history is a potential factor for guiding cardiovascular monitoring and that, given the relatively young age of these women, not only the 10-year risk score but also the 30-year and lifetime risk scores of CVD should be evaluated, especially as CVD in women occurs on average 10–15 years later than in men.[54] We strongly support the development of female-specific CVD risk scores, which should also be suitable for younger women. To assist the development of such risk scores, this study evaluates how modifiable CVD risk factors relate to different PE subtypes and stresses the importance of focusing on women with a history of EO-PE with concurrent SGA.

There are some limitations of this study that need to be addressed. First, the study population represents that of a tertiary hospital and therefore extrapolation of the findings to the general population should be done with caution. Second, multiple testing may increase the risk of a Type-II error, although Bonferroni correction was used to minimize this effect. Finally, information on the presence of prepregnancy CVD risk factors was not available so, although previous data suggest that these CVD risk factors were presumably already present before pregnancy, we cannot exclude the possibility of a direct influence by complications of pregnancy. However, in the context of the development of tailored management after pregnancy complications, this knowledge is less important.

Despite these limitations, this study is of major clinical importance, since it provides a detailed understanding of the relationship between PE subtypes and postpartum modifiable CVD risk factors in these seemingly healthy women. Such information is essential for the development of tailored disease-modifying strategies for women presenting with this temporary early-warning sign of CVD risk. Moreover, this study highlights the impact of fetal growth and the onset of PE in CVD risk stratification and provides

predictors of metabolic syndrome after PE. Future studies are needed to develop, and determine the effectiveness of, diagnostic and preventive interventions after PE.

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Chapter 5

No accelerated arterial aging in relatively young women after preeclampsia as compared to normotensive pregnancy

Emma B.N.J. Janssen | Mieke C.E. Hooijschuur | Veronica A. Lopes van Balen | Erjona Morina-Shijaku | Julia J. Spaan | Eva G. Mulder | Arnold P. Hoeks | Koen D. Reesink | Sander M.J. van Kuijk | Arnoud Van 't Hof | Bas C.T. van Bussel | Marc E.A. Spaanderman | Chahinda Chossein-Doha

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Abstract

Introduction: Preeclampsia, an endothelial disorder of pregnancy, predisposes to remote cardiovascular diseases. Whether there is an accelerated effect of ageing on endothelial decline in former preeclamptic women is unknown. We investigated if the arterial ageing regarding endothelial-dependent and -independent vascular function is more pronounced in women with a history of preeclampsia as compared to women with a history of solely normotensive gestation(s).

Methods: Data was used from the Queen of Hearts study (ClinicalTrials.gov Identifier NCT02347540); a large cross-sectional study on early detection of cardiovascular disease among young women (≥18 years) with a history of preeclampsia and a control group of low-risk healthy women with a history of uncomplicated pregnancies. Brachial artery flow-mediated dilation (FMD; absolute, relative and allometric) and sublingually administered nitroglycerine-mediated dilation (NGMD; absolute and relative) were measured using ultrasound. Cross-sectional associations of age with FMD and NGMD were investigated by linear regression. Models were adjusted for body mass index, smoking, antihypertensive drug use, mean arterial pressure, fasting glucose, menopausal state, family history of CVD and stress stimulus during measurement. Effect modification by preeclampsia was investigated by including an interaction term between preeclampsia and age in regression models.

Results: Of the 1,217 included women (age range 22 to 62 years), 66.0% had a history of preeclampsia and 34.0% of normotensive pregnancy. Advancing age was associated with a decrease in relative FMD and NGMD (unadjusted regression coefficient: FMD: -0.48%/10 years (95% CI: -0.65 to -0.30%/10 years), NGMD: -1.13%/10 years (-1.49 to -0.77%/10 years)) and increase in brachial artery diameter (regression coefficient = 0.16 mm/10 years (95% CI 0.13 to 0.19 mm/10 years)). Similar results were found when evaluating FMD and NGMD as absolute increase or allometrically, and after confounder adjustments. These age-related change were comparable in former preeclamptic women and controls (p-values interaction ≥0.372). Preeclampsia itself was independently associated with consistently smaller brachial artery diameter, but not with FMD and NGMD.

Conclusion: In young- to middle-aged women, vascular ageing in terms of FMD and NGMD was not accelerated in women after preeclampsia compared to normotensive pregnancies, even though former preeclamptic women consistently have smaller brachial arteries.

Introduction

Arterial ageing is a physiological process that develops gradually over time and increases the risk of cardiovascular diseases (CVD). With advancing age, several structural and functional arterial changes contribute to this increased cardiovascular (CV) risk.[1-3] Age-related vascular dysfunction is characterized by a decline in endothelial function involving impaired vasodilatory capacity of the blood vessel.

Besides age, vascular dysfunction may be accelerated by both conventional and sex-specific CV risk factors.[4, 5] Preeclampsia (PE), a hypertensive vascular complication of pregnancy, is associated with impaired endothelial function, both during pregnancy and in the first years after delivery.[6, 7] Endothelial dysfunction during or after PE might contribute to the subsequently observed two- to seven-fold increased risk of CVD among these women.[8, 9] On top of that, vascular ageing might further be accelerated in former preeclamptic women since conventional risk factors, especially increased blood pressure, are highly prevalent after PE.[10]

The major mediator of vasodilatory capacity of arteries is endogenous nitric oxide (NO) release by the endothelium, which relaxes vascular smooth muscles[11, 12] resulting in flow-mediated vasodilation in healthy conditions. This physiological response is favorable as it keeps local wall shear stress constant.[13] Flow-mediated dilation (FMD) measurement of the brachial artery is a non-invasive method to assess endothelial dysfunction by high-resolution ultrasound imaging. Impaired FMD is used as surrogate measure for CV health as it is strongly associated with and predictive of CVD later in life.[14-17]

Whether PE modifies the age-related decline in endothelial function is unknown. Therefore, we investigated whether the age-related decline in endothelial-dependent and -independent vasodilatory function is more pronounced in women with a history of PE as compared to women with normotensive pregnancies, independent of conventional CV risk factors.

Materials and methods

Study design and population

This study was part of a large cross-sectional study aimed at investigating subclinical CVD in women (Queen of Hearts study; ClinicalTrials.gov Identifier NCT02347540) and was approved by the Medical Ethics Committee of the Maastricht University Medical Centre (METC azM/UM 14-2-20136 NL47252.068.14). All participating women provided written informed consent. Procedures were in conformity with institutional guidelines and adhered to the principles of the Declaration of Helsinki.

We included women aged ≥18 years with a history of PE and a control group of women who had normotensive pregnancies. Women were included within a postpartum interval of 0.5 to 30 years, which was based on delivery of their first (complicated) pregnancy. Women who participated between December 2014 and October 2019 were included in the current study. Women with a history of hypertension, autoimmune disease, or kidney disease prior to their first pregnancy were excluded.

PE was defined as new-onset hypertension (i.e. systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg) along with proteinuria (≥300 mg/24 h) after 20 weeks of gestation, or other maternal organ dysfunction.[18] Diagnosis before 34 weeks was characterized as early onset PE. Uncomplicated pregnancy was defined as normotensive pregnancy in absence of any placenta-associated disease, including HELLP-syndrome, placental abruption, small for gestational age infancy and/or fetal demise.

Cardiovascular assessment

Postpartum cardiovascular assessment was performed following a standardized protocol during one morning study visit at the Maastricht University Medical Centre (MUMC+), including vascular assessment, physical examination of weight and height, blood pressure measurements, fasting blood collection and (obstetrical) medical history taking. All women were instructed to fast for at least ten hours before the study visit.

Height and weight were measured to calculate body mass index (BMI). SBP, DBP, mean arterial pressure (MAP) and heart rate were measured for 30 minutes in sitting position by a semiautomatic oscillometric device (Dinamap Vital Signs Monitor 1846, Critikon, Tampa, FL) with a three-minute measurement interval. The median value of these measurements was used for analyses. Hypertension was defined as antihypertensive drug use or SBP ≥140 and/or DBP ≥90 mmHg, as according to European guidelines.[19] A positive family history of CVD was defined as a (grand)parent or sibling below the age of 65 years with CVD.

Measurements of endothelium-dependent and -independent vasodilation

Endothelium-dependent and -independent brachial artery dilation were evaluated by assessing FMD and the effect of a sublingual dose of nitroglycerine (i.e. nitroglycerine-mediated dilation [NGMD]), respectively. FMD and NGMD measurements were performed sequentially under standardized conditions in a temperature-controlled room (±22°C). Before the measurements, participants rested in supine position on a comfortable bed for at least 15 minutes. The arm was in an extended position at ±80° from the torso. A rapid inflation and deflation cuff (Hokanson, Bellevue, VA 98005) was positioned around the forearm distal to the olecranon. A multi-frequency linear array probe attached to a high-resolution ultrasound machine (Voluson p6, GE Healthcare)

with an operating frequency of five MHz was used to image the brachial artery in the distal third of the upper arm, two to five cm above the antecubital fossa. The probe was fixed during all measurements by a custom-made fixation device made by instrumental services.

For (endothelium-dependent) FMD evaluation, we acquired a three-minute baseline recording of the brachial artery diameter. Thereafter, the forearm cuff was inflated (200 mmHg) for five minutes followed by rapid deflation. The diameter and Doppler spectrum were assessed continuously from three minutes before inflation to five minutes after deflation, but interrupted from 30 seconds after inflation to 30 seconds before deflation.

For (endothelium-independent) NGMD evaluation, we also started with a three-minute baseline recording after which a dose of NG (0.4 mg/dose) was administered sublingually. The recording ended ten minutes after sublingual administration of NG.

Image analysis of the brachial artery diameter was performed off-line with a custom designed edge-detection and wall-tracking software[20] in Matlab (Matlab R2013b, The Mathworks Inc. Natick, MA), which separates the measurements from the analyses and therefore reduced the risk of bias. Peak diameter was automatically detected, as described previously.[20] In a previous pilot, two experienced sonographers performed repeated measurements of FMD in 15 volunteers, to quantify the inter-observer agreement. The corresponding inter-observer intraclass correlation coefficient (ICC) was 0.82, while the intra-observer ICC was 0.83.

FMD and NGMD outcome measures

FMD and NGMD were expressed both as an absolute and relative (i.e. percentage) increase in brachial artery diameter, which were based on the peak change in diameter with respect to baseline. Baseline diameter during FMD referred to the three-minute period before cuff-release. During NGMD, a single value for baseline was measured at the start of the response. Although the baseline brachial artery diameter was separately measured in FMD- and NGMD-assessment, the variability of these measurements was not statistically significant (paired sample t-test; p-value = 0.659).

FMD was also expressed with an allometric scaling to avoid baseline dependency as proposed by Atkinson et al.[21] It aims to compensate for potential differences in vessel diameter. For the allometric FMD, we calculated the regression slope between logarithmically transformed values of both baseline diameter and peak diameter and derived the correct scaling exponent for our dataset.[21] A value of 1 is necessary for appropriate use of FMD%.[22, 23] The regression slope between the logarithmically transformed values of both baseline diameter and peak diameter yielded a 1.014 scaling exponent, which was used to calculate the allometric scaled FMD.

Besides, we calculated the physiologic dilatory response to stress (i.e. FMD) as proportion of maximal dilatory capacity (i.e. NGMD) by (FMD%*100)/NGMD%.

Statistical analysis

Baseline data are presented as mean and standard deviation in case of normal distribution, otherwise as median and interquartile range [IQR]. Categorical variables are presented as number and percentage within group. To analyze between-group differences in baseline characteristics, we used the independent-samples t-test, Mann-Whitney U or Fisher's exact, as appropriate. To ensure no selection bias had occurred due to missing, incomplete or low-quality data on FMD and NGMD, we compared baseline characteristics of women who were excluded to those included in the analyses.

First, differences between age groups (20–30, 30–40, 40–50, ≥50 years) regarding brachial artery diameter, FMD, and NGMD were tested using one-way ANOVA and Kruskal Wallis tests, as appropriate. Subsequently, linear regression analysis was performed to evaluate the association of age with brachial artery diameter, FMD and NGMD, both unadjusted and fully-adjusted for BMI, smoking, anti-hypertensive drug use, MAP, fasting blood glucose level, menopausal state and a positive family history of CVD. When investigating absolute FMD and NGMD, we additionally adjusted for the baseline diameter. In all regression models on FMD and NGMD, we additionally adjusted for the potential effect of stress stimulus by adjusting for the velocity area under the curve (vAUC) as measured by Doppler during FMD and NGMD assessments, as described previously.[20] Effect estimates (β) of the association between age and vascular function were presented per 10 years of advancing age.

Second, the potential interaction effect of age and history of PE was investigated by adding an interaction term between age and history of PE to the linear regression models described above. If the interaction term was not statistically significant (i.e. p-value >0.10), the interaction was omitted from the model and we only evaluated the effect estimate of PE, while adjusting for age.

Finally, sensitivity analyses were performed to evaluate the association of postpartum interval instead of age and the robustness of our findings following the parameters we used to operationalize FMD and NGMD. We repeated the above analyses 1) by replacing age by postpartum interval, 2) by replacing leading baseline by baseline measured at a single point before response, 3) by replacing relative FMD by normalized relative FMD for stress stimulus (i.e. FMD%/stimulus instead of separate adjustment).

Statistical analyses were performed using the statistical software program IBM SPSS (version 24.0). P-values of main effects <0.05 and p-values of interactions <0.10 were considered statistically significant.

Results

Study population

Of the 1,465 participating women, 248 women were excluded from analysis due to 1) missing-, incomplete or low-quality FMD and NGMD measurements or 2) no or uncertain fasting state before the vascular evaluation (Figure 1). Baseline characteristics of in- and excluded women were comparable except for a higher BMI among those excluded (0.6 kg/m^2 higher, p-value = 0.018, Table S1).

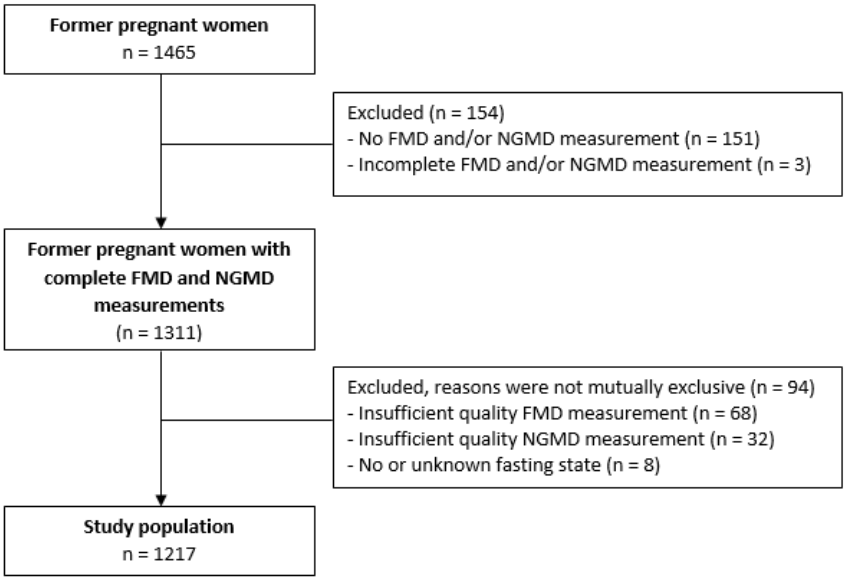

Figure 1. Flowchart of inclusion study population.
Abbreviations: FMD, flow-mediated-dilation; NGMD, nitroglycerine-mediated dilation.

Of the 1,217 eligible participants, 803 (66.0%) had a history of PE and 414 (34.0%) women had a normotensive pregnancy. Baseline characteristics of the total study population and groups are presented in Table 1.

The age of the study population ranged between 22 and 62 years. Women with a history of PE were on average 6 years younger, less often in postmenopausal state, and at a shorter postpartum interval compared to women with normotensive pregnancy. Moreover, BMI, fasting glucose levels, SBP and MAP were higher and DBP level was lower in women with a history of PE.

Prevalence of hypertension (14.2% vs. 7.0%, p<0.001), antihypertensive drug use (11.2% vs. 5.6%, p=0.001), positive CVD family history (61.9% vs. 55.7%, p=0.041) and smoking (5.7% vs. 9.4%, p=0.024) were higher among women with a history of PE.

Table 1. Baseline characteristics of entire study population and stratified for history of preeclampsia

	Total study population (n=1,217)	Women with history of PE (n=803)	Women without history of PE (n=414)	p-value
Age (years)	40.5±8.6	38.5±7.9	44.5±8.4	*<0.001*
Parity	2 [1–2]	2 [1–2]	2 [2–3]	*<0.001*
Early onset PE[a]	411 (33.8%)	411 (51.2%)	N.A.	N.A.
HELLP-syndrome	567 (46.6%)	567 (70.6%)	N.A.	N.A.
Months postpartum	104 [28–198]	71 [17–155]	180 [91–272]	*<0.001*
Postmenopausal[a]	176 (14.6%)	78 (9.8%)	98 (23.9%)	*<0.001*
BMI (kg/m^2)	25.3±4.6	25.7±4.8	24.8±4.1	*0.003*
Current smoking	85 (7.0%)	46 (5.7%)	39 (9.4%)	*0.024*
Positive CVD family history[a]	723 (59.8%)	493 (61.9%)	230 (55.7%)	*0.041*
Diabetes Mellitus	13 (1.1%)	12 (1.5%)	1 (0.2%)	0.072
Hypertension	143 (11.8%)	114 (14.2%)	29 (7.0%)	*<0.001*
Antihypertensive drugs use	113 (9.3%)	90 (11.2%)	23 (5.6%)	*0.001*
Multivitamin use	331 (27.2%)	205 (25.5%)	126 (30.4%)	0.077
Glucose level (mmol/L)[a]	5.1±0.8	5.2±0.9	5.0±0.5	*0.001*
Systolic BP (mmHg)[a]	113 [107–122]	115 [108–123]	111 [105–118]	*<0.001*
Diastolic BP (mmHg)[a]	71 [66–77]	73 [67–79]	69 [64–74]	*<0.001*
MAP (mmHg)[a]	87 [82–94]	89 [83–96]	84 [79–90]	*<0.001*
Baseline brachial artery diameter (mm)	3.53±0.44	3.50±0.43	3.60±0.46	*<0.001*
Absolute FMD (mm)	0.14 [0.09–0.21]	0.14 [0.09–0.20]	0.14 [0.09–0.21]	0.846
Relative FMD (%)	3.9 [2.5–5.9]	3.9 [2.5–5.9]	3.9 [2.4–5.9]	0.514
Allometric FMD (%)	4.0 [2.5–6.0]	4.0 [2.5–6.0]	4.0 [2.4–6.1]	0.514
Absolute NGMD (mm)	0.59±0.18	0.59±0.18	0.59±0.19	0.921
Relative NGMD (%)	17.0±5.5	17.1±5.5	16.8±5.5	0.260
Dilation (FMD) in proportion of maximal dilation (NGMD) (%)[a]	24.3 [14.5–35.8]	23.8 [14.4–35.8]	24.5 [14.6–35.9]	0.962

[a] Variable consisted few missing values (<2.0%), valid percentages are presented. Continuous variables are reported as mean ± standard deviation in case of normal distribution, otherwise as median [IQR]. Categorical variables are reported as number (%). Statistically significant p-values are presented in cursive.
Abbreviations: PE, preeclampsia; BMI, body mass index; CVD, cardiovascular disease; BP, blood pressure; MAP, mean arterial pressure; FMD, flow-mediated-dilation; NGMD, nitroglycerine-mediated dilation.

Baseline brachial artery diameter was lower in women with a history of PE than in those with normotensive pregnancies (p≤0.008). No statistically significant differences in FMD (absolute, relative and allometric), NGMD (absolute and relative) and physiologic response as proportion of maximal dilatory capacity were found between both groups (Table 1).

Association of age with FMD and NGMD

Across age deciles, a significantly increasing trend was found for brachial artery diameter, whereas for all parameters of FMD and NGMD a decreasing trend was found (Table S2). These trends were similar for women with and without a history of PE (Figures 2 and 3, Table S2). The dilation in response to stress stimulus (FMD) as proportion of maximal dilatory capacity (NGMD) decreased with ageing in former preeclamptic women, but did not in controls (Table S2). Though this remained not statistically significant in fully-adjusted regression models, the trend of a decreased ability to maximally dilate among former PE remained (Table 3).

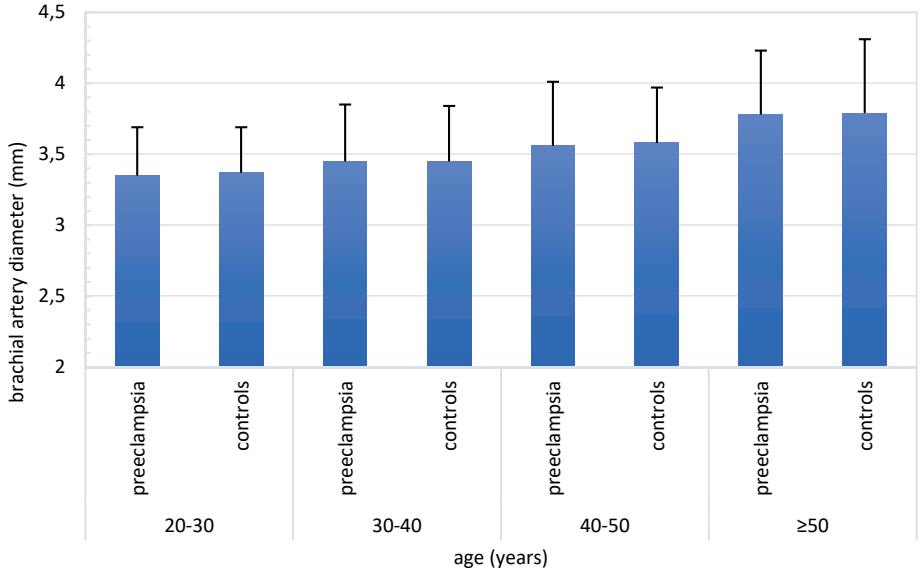

Figure 2. Brachial artery diameter (mm) across age categories stratified for women with a history of preeclampsia-complicated pregnancy (i.e. preeclampsia) and women with a history of normotensive pregnancy (i.e. controls).

Both in women with and without a history of preeclampsia, brachial artery diameter increased with advancing age.

Number of inclusions within groups: 20–30 years: preeclampsia n=103, controls n=16; 30–40 years: preeclampsia n=392, controls n=111; 40–50 years: preeclampsia n=238, controls n=159; ≥50 years: preeclampsia n=70, controls n=128.

Table 2. Trend effect of advancing age on FMD and NGMD

Measurement	20–30 yr (n=119)	30–40 yr (n=503)	40–50 yr (n=397)	≥50 yr (n=198)	p-value of trend
Brachial artery diameter (mm)	3.36±0.34	3.45±0.40	3.57±0.43	3.79±0.50	*<0.001*
FMD					
Absolute FMD (mm)	0.16 [0.11–0.22]	0.15 [0.09–0.21]	0.13 [0.09–0.20]	0.12 [0.07–0.18]	*<0.001*
Relative FMD (%)	4.7 [3.3–6.7]	4.4 [2.6–6.4]	3.6 [2.4–5.7]	3.1 [2.0–5.1]	*<0.001*
Allometric FMD (%)	4.8 [3.3–6.9]	4.5 [2.6–6.6]	3.7 [2.4–5.8]	3.1 [2.0–5.2]	*<0.001*
NGMD					
Absolute NGMD (mm)	0.60±0.16	0.61±0.18	0.58±0.19	0.58±0.20	*0.035*
Relative NGMD (%)	18.1±5.4	17.8±5.6	16.5±5.2	15.4±5.4	*<0.001*
Dilation (FMD) in proportion of maximal dilation (NGMD) (%)	27.7 [19.9–36.6]	24.4 [15.1–36.4]	23.9 [14.3–35.3]	20.5 [12.4–34.1]	*0.007*

Continuous variables are reported as mean±standard deviation in case of normal distribution, otherwise as mean [IQR]. Categorical variables are reported as number (%). Statistically significant p-values are presented in cursive.
Abbreviations: yrs, years; FMD, flow-mediated-dilation; NGMD, nitroglycerine-mediated dilation.

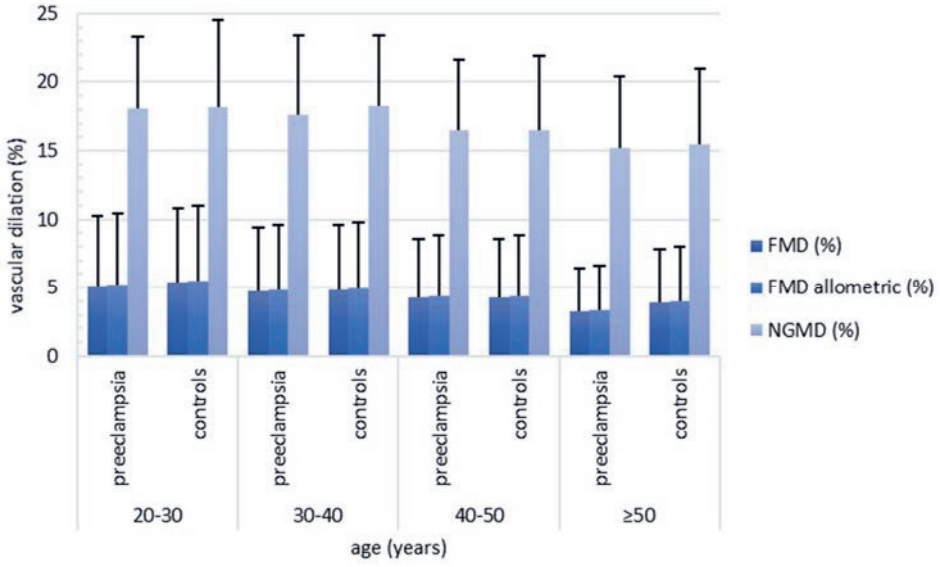

Figure 3. Relative FMD (%), allometric FMD (%) and NGMD (%) across age categories stratified for women with a history of preeclampsia-complicated pregnancy (i.e. preeclampsia) and women with a history of normotensive pregnancy (i.e. controls).
Both in women with and without a history of preeclampsia, FMD (%), allometric FMD and NGMD (%) decreased with advancing age. Between women with preeclampsia and controls no clear differences were found with regard to FMD (%), allometric FMD (%) and NGMD (%).
Number of inclusions within groups: 20–30 years: preeclampsia n=103, controls n=16; 30–40 years: preeclampsia n=392, controls n=111; 40–50 years: preeclampsia n=238, controls n = 159, ≥50 years: preeclampsia n=70, controls n=128.
Abbreviations: FMD, flow-mediated-dilation; NGMD, nitroglycerine-mediated dilation.

In line, unadjusted linear regression models revealed a statistically significant association of advancing age with brachial artery diameter (regression coefficient (95% CI) = 0.16 mm/10 years (0.13–0.19 mm/10 years), p-value <0.001) and all parameters of FMD (absolute: = -0.001 mm/10 years (95% CI -0.002–-0.002 mm/10 years), relative: regression coefficient = -0.48 mm/10 years (95% CI -0.65–-0.30 mm/10 years), allometric: regression coefficient = -0.49 mm/10 years (95% CI -0.68–-0.31 mm/10 years); p-values ≤0.007) and NGMD (absolute: regression coefficient = -0.02 mm/10 years (95% CI -0.03–-0.01), relative: regression coefficient = -1.13 mm/10 years (95% CI -1.49–-0.77 mm/10 years); p-values ≤0.001) (Table S3). This result remained similar after adjustment for confounders (p≤0.018), with exception of the association of age with absolute FMD when adjusting for baseline diameter which became non-significant in multivariable analyses (regression coefficient = -0.01 mm/10 years (95% CI -0.01–0.003), p-value 0.060, Table S3). If not adjusting for baseline, the effect of age on absolute FMD remained statistically significant in the multivariable analysis (regression coefficient = -0.01 mm/10 years (95% CI -0.01–-0.001 mm/10 years), p-value 0.024).

Table 3. Association of age and history of preeclampsia with brachial artery diameter, FMD and NGMD

	Brachial artery diameter (mm)		Absolute FMD (mm)		Relative FMD (%)	
	β (95% CI), mm/10yr	p-value	β (95% CI), mm/10yr	p-value	β (95% CI), %/10yr	p-value
Unadjusted model						
Age (in deciles)	0.16 (0.13–0.18)	*<0.001*	-0.01 (-0.02–-0.003)	*0.003*	-0.50 (-0.69–-0.32)	*<0.001*
History of PE	-0.01 (-0.07–0.04)	0.602	-0.008 (-0.02–0.004)	0.183	-0.15 (-0.49–0.19)	0.381
Fully-adjusted model						
Age (in deciles)	0.14 (0.10–0.17)	*<0.001*	-0.01 (-0.01–0.003)	0.060	-0.42 (-0.63–-0.21)	*<0.001*
History of PE	-0.06 (-0.12–-0.1)	*0.025*	-0.008 (-0.02–0.003)	0.155	-0.09 (-0.43–0.25)	0.598
	Allometric FMD (%)		Absolute NGMD (mm)		Relative NGMD (%)	
	β (95% CI), %/10yr	p-value	β (95% CI), mm/10yr	p-value	β (95% CI), %/10yr	p-value
Unadjusted model						
Age (in deciles)	-0.52 (-0.72–-0.33)	*<0.001*	-0.02 (-0.04–-0.01)	*0.001*	-1.20 (-1.58–-0.81)	*<0.001*
History of PE	-0.16 (-0.51–0.20)	0.384	-0.01 (-0.04–0.01)	0.282	-0.36 (-1.05–0.34)	0.312
Fully-adjusted model						
Age (in deciles)	-0.44 (-0.66–-0.22)	*<0.001*	-0.02 (-0.03–-0.002)	*0.024*	-1.02 (-1.48–-0.56)	*<0.001*
History of PE	-0.09 (-0.44–0.26)	0.602	-0.001 (-0.03–0.02	0.951	0.09 (-0.63–0.81)	0.806
	Dilation (FMD) as proportion of maximal dilation (NGMD) (%)					
	β (95% CI), %/10yr	p-value				
Unadjusted model						
Age (in deciles)	-1.47 (-2.67–-0.27)	*0.016*				
History of PE	-0.85 (-3.01–1.31)	0.441				
Fully-adjusted model						
Age (in deciles)	1.22 (-2.54–0.10)	0.071				
History of PE	-0.87 (-2.97–1.24)	0.417				

Fully-adjusted models adjusted for BMI, smoking, anti-hypertensive drug use, MAP, fasting glucose levels, menopausal state and family history of CVD. Regression on FMD and NGMD was additionally adjusted for stress stimulus and regression on absolute FMD and absolute FMD for baseline diameter. Statistically significant p-values are presented in cursive. Abbreviations: β, unstandardized regression coefficient; FMD, flow-mediated-dilation; NGMD, nitroglycerine-mediated dilation; 95% CI, 95% confidence interval.

No interaction between PE and age on FMD and NGMD

For baseline brachial artery diameter, the interaction term between age and history of PE was not statistically significant, both in unadjusted and fully-adjusted linear regression models (interaction term p-values ≥0.588). Similar non-significant interactions were found for FMD (absolute, relative and allometric; p-values interaction ≥0.360), NGMD (absolute and relative; p-values interaction ≥0.443) and dilation as proportion of maximal dilatory capacity (≥0.224). These statistically non-significant interaction terms did not favor any stratification based on a history of PE.

Accordingly, we further investigated the independent effect of PE in all regression models. Following, for all measures of FMD and NGMD, no effect of a history of PE was found (p-values ≥0.170) (Table 3). For brachial artery diameter, however, after adjustment for age and other confounders the effect of a history of PE on brachial artery diameter was -0.06 mm (95% CI -0.12–-0.10 mm, p-value = 0.025) as compared to history of normotensive pregnancy, indicating smaller brachial arteries in women with PE (Table 3). The results on the association with age remained similar in these models as compared with the regression analyses described above (Table S3).

Sensitivity analyses

Sensitivity analyses on replacing age by postpartum interval did not provide different findings (data not shown), with exception of the confounder-adjusted association between postpartum interval and absolute NGMD which became non-significant (data not shown) in contrast to the reported result for age and absolute NGMD (Table S3). Although the association between years postpartum and dilation as proportion of maximal dilation was not significant in univariable analyses, is was significant in multivariable analyses as in line with the analyses on age. Re-analyzing the data by replacing parameters for FMD and NGMD, as described in our methods section (i.e. replacing leading baseline by single-point baseline, and replacing relative FMD and relative NGMD by normalized relative FMD for stress stimulus instead of separate adjustment for stress stimulus), did also not alter the results (data not shown).

Discussion

In this cross-sectional study we show that the age-related decline in brachial artery vasodilation and increase in diameter was independent of obstetric history, suggesting no additional (accelerating) effect of PE on the decline in endothelial function with ageing. The age-related decline in both endothelium-dependent and –independent brachial artery vasodilation was significant even after adjusting for important confounding factors. PE itself was consistently associated with a smaller brachial artery diameter across ages, but did not affect observed FMD and NGMD.

No accelerated age-effect on FMD and NGMD in former preeclamptic women

In agreement with previous studies, we show an independent decline in FMD and NGMD and increase in arterial diameter with advancing age.[3, 24, 25] This may provide a valuable explanation for the increasing CVD risk with ageing, especially as traditional risk factors do not completely explain the impact of age on CVD. We also showed that women with a history of PE have smaller brachial artery diameters at baseline, but showed similar age-related diameter and NGMD changes compared to women with a history of normotensive pregnancies. Physiologically, our study shows that the known PE-linked endothelial dysfunction does not relate to an accelerated endothelial decline with advancing age in former preeclamptic women. Clinically, the future cardiovascular risk after PE seems less likely attributable to an accelerated age-related decline in FMD or NGMD. The absence of an effect of NGMD in addition to the observed difference in diameter suggests smaller arteries in former preeclamptic women, although one would then expect to find differences in relative changes, which is not the case in our study.

Earlier studies found that FMD was diminished in preeclamptic women, even several weeks before diagnosis.[26, 27] Also, in the first decade after PE, some studies demonstrated diminished FMD, whilst others did not find any difference in later time periods when compared to control groups.[27-32] A meta-analysis of Weissgerber et al.[27] demonstrated a decreased FMD only within the first three years after PE, after which no difference in FMD was found up to 10 years postpartum. Our study did not find any difference across all age groups. Severity and/or time of onset of PE may contribute to these conflicting results. Besides, endothelial (dys)function has many dimensions, of which FMD and NGMD are only two. Other endothelial functions might still be altered in former PE women (both independent as in interaction with age), for example, circulating markers that might represent early endothelial dysfunction, including soluble fms-like tyrosine kinase (sFlt-1) and high-sensitivity C-reactive protein, already are elevated after PE up and until 10 years postpartum.[29, 33]

Arterial ageing in women

With advancing age, arteries demonstrate a systemic, gradual impairment in vascular endothelial function, which is likely due to functional, downregulation of vasodilator pathways (i.e. reduction in endothelial-derived nitric oxide (NO) bioavailability) and/or up-regulation of vasoconstrictor pathways (i.e. increased production of vasoconstrictors like endothelin-1) and structural vessel wall characteristics, amongst diameter and composition.[3] The first functional change might specifically affect endothelium-dependent function (FMD), whereas the latter affects endothelium-independent function (NGMD). A lifetime exposure to (CV) risk factors and the susceptibility of individuals to the harmful consequences of these risk factors combined with ageing itself may result in decreased arterial function.[34] However, as ageing and underlying progressive risk

factors for disease are interrelated, it is a challenge to separate the so-called biological ageing from ageing-associated diseases.

The increase in brachial artery diameter over time may, at least partly, reflect a structural basis for an age-related reduction in dilatory capacity. With ageing, smooth muscle cells undergo changes that may impact the vascular dilatory capability, such as changes in phenotype and senescence.[35-37] As a result of these changes, elastic vessel properties are also altered, shifting the balance from elastin towards collagen. Consequently, arterial mechanical load due to blood pressure is more borne by the stiffer collagen in the arterial wall,[3] at the expense of the relative dilatory capacity in response to endogenous or exogenous NO. The magnitude of (NO-mediated) vascular dilation also depends on the ability of the smooth muscle cells to relax which can be quantified by the maximum dilatory response following sublingual NG.[3] Therefore, we interpret the age-related decline in FMD and NGMD as reflective of an altered smooth muscle phenotype, either by loss of bioavailability of, or sensitivity to NO, increase vasoconstriction activity, stiffer acting extra-cellular matrix and/or an already stretched vessel wall due to luminal enlargement.[36, 38, 39] Unexpectedly, we did not find a fully-adjusted association between age and absolute FMD. Adjusting the absolute FMD by baseline diameter might, however, average out the age-related decline in dilation due to the age-related increase in baseline diameter or suggest that the age-related decline in function is mainly accountable to the age-related increase in brachial artery diameter.

With advancing age the most consistent structural changes include diameter enlargement (i.e. dilation), wall thickening (i.e. remodelling) and changes in wall content (e.g. loss of elastin), with related changes in elastic properties.[3] We observed that the baseline diameter increases with advancing age, even after correcting for influencing factors, is in line with the age-related diameter enlargement described previously.[24, 25] Interestingly, this increase in baseline diameter itself is independently associated with an increased risk of CVD.[14, 40] Since the brachial artery is hardly prone to atherosclerosis, the perceived increase in baseline may more likely be related to age-related structural remodelling of the vessel wall rather than plaque formation. A history of PE was related to a smaller brachial artery diameter compared to normotensive gestation after correcting for confounders. This suggests a so far unknown vascular predisposition after hypertensive-pregnancy complications.

Strengths and limitations

Several strengths and limitations merit attention in the interpretation of our results. Strengths of this study support internal validity of our findings and include 1) consideration of a longer age-interval than currently published studies and 2) our large sample size powering our study to detect even small effects. In addition, multiple operationalisations of FMD (absolute, relative, allometric) and NGMD (absolute, relative) were

included in multivariable analyses and sensitivity analyses, which showed all similar results. This supported the robustness of our findings and further decreased information bias. The most commonly defined measure for FMD and NGMD is the percentage increase in diameter with respect to baseline. Some investigators argue that it is the absolute dilatory response that captures the endothelium-dependent dilatory capacity best, and hence, when using relative FMD, smaller vessels intrinsically show greater FMD.[41] There are assumptions that correcting for this vessel diameter dependency by allometric scaling is the best operationalisation of FMD, though it did not affect our results. We found that allometrically-scaled FMD yielded similar results compared to FMD percentage increase, suggesting that differences in baseline vessel diameter did not fully explain age-related decline in FMD in our study population. Furthermore, the scaling exponent of 1.014 justified the use of FMD percentage increase in current study cohort.

Limitations of this study include the cross-sectional design which made it impossible for us to investigate causal pathways. This may have obscured an effect of PE on FMD and NGMD that might had been revealed with repeated measurements within individuals before and after pregnancy. Second, a decline in vascular function due to PE may only be apparent in a subgroup of women with a specific (CV) predisposition, which we, unfortunately could not distinguish in our study. Third, selection bias might have occurred in our control group, which might mitigated the observed effects. Women who perceived higher risk of CVD might have been more willing to participate in a CV study, in which personal advice on risk factors was given to participants. For example, the prevalence of a positive family history for CVD was higher within our study population than expected based on the general population, in which the prevalence ranges between 10% and 16% being depending on one's age.[42] Finally, FMD and NGMD measurements are considered susceptible for methodological variability. However, in the hands of experienced sonographers and following a strict protocol, variations can be kept to a minimum.[12, 43] Moreover, we used wall tracking software to improve reproducibility and data on the obstetric history was not available for the sonographer.

Conclusion

This study shows that in young- to middle-aged women, vascular ageing with respect to endothelium-dependent and -independent vessel dilation testing was similar in women after PE compared to women with a history of normotensive pregnancies, even though former preeclamptic women consistently have smaller brachial arteries. These findings suggest that the increased CV risk in the first decades after PE do not originate from an accelerated decline in endothelial function as measured by FMD or NGMD in conduit vessels. Different site (microvascular) and mode of endothelial action (hemostatic and inflammatory related integrity) might be involved, which remain subject for further investigation.

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Supplemental material

Table S1. Comparison between included and excluded women due to missing, incomplete or low-quality data on FMD and NGMD, and/or unknown fasting state

	Included (n=1,217)	Excluded (n=248)	p-value
Age (years)	40.5 ± 8.6	40.6 ± 8.7	0.954
History of PE	803 (66.0%)	169 (68.1%)	0.555
Parity	2 [1–2]	2 [1–2]	0.809
Months postpartum	104 [28–198]	100 [25–212]	0.941
Postmenopausal[a]	176 (14.6%)	39 (15.8%)	0.623
BMI (kg/m^2)	25.3 ± 4.6	24.6 ± 4.5	*0.018*
Current smoking	85 (7.0%)	20 (8.1%)	0.589
Positive CVD family history[a]	723 (59.8%)	142 (57.7%)	0.569
Diabetes Mellitus	13 (1.1%)	1 (0.4%)	0.487
Hypertension	143 (11.8%)	33 (13.3%)	0.520
Antihypertensive drugs use	113 (9.3%)	27 (10.9%)	0.409
Multivitamin use	331 (27.2%)	64 (25.8%)	0.695
Glucose level (mmol/L)	5.1 ± 0.8	5.1 ± 0.6	0.665
Systolic BP (mmHg)[a]	113 [107–122]	114 [107–123]	0.266
Diastolic BP (mmHg)[a]	71 [66–77]	72 [66–79]	0.345
MAP (mmHg)[a]	87 [82–94]	88 [82–97]	0.447

[a] Variable consisted few missing values (<1.0%/≤ n=10), valid percentages are presented. Continuous variables are reported as mean ± standard deviation in case of normal distribution, otherwise as median [IQR]. Categorical variables are reported as number (%). Statistically significant p-values are presented in cursive.

Abbreviations: PE, preeclampsia; BMI, body mass index; CVD, cardiovascular disease; BP, blood pressure; MAP, mean arterial pressure.

Table S2. Trend ageing on FMD and NGMD in women a history of PE and normotensive pregnancy

	Women with a history of PE (n=803)	Women without history of PE (n=414)	p-value
Brachial artery diameter (mm)			
20–30 years	3.35 ± 0.34	3.37 ± 0.32	0.884
30–40 years	3.45 ± 0.40	3.45 ± 0.39	0.962
40–50 years	3.56 ± 0.45	3.58 ± 0.39	0.678
≥50 years	3.78 ± 0.45	3.79 ± 0.52	0.851
Age trend	*<0.001*	*<0.001*	
Absolute FMD (mm)			
20–30 years	0.16 [0.11–0.22]	0.17 [0.11–0.23]	0.668
30–40 years	0.15 [0.09–0.21]	0.15 [0.09–0.22]	0.491
40–50 years	0.12 [0.08–0.20]	0.13 [0.09–0.19]	0.442
≥50 years	0.10 [0.07–0.15]	0.12 [0.08–0.20]	0.056
Age trend	*<0.001*	*0.030*	
Relative FMD (%)			
20–30 years	4.6 [3.2–6.8]	4.8 [3.7–6.6]	0.654
30–40 years	4.3 [2.6–6.4]	4.6 [2.8–6.4]	0.607
40–50 years	3.6 [2.4–5.7]	3.7 [2.7–5.7]	0.646
≥50 years	2.9 [1.7–4.1]	3.4 [2.1–5.4]	0.081
Age trend	*<0.001*	*0.001*	
Allometric FMD (%)			
20–30 years	4.7 [3.3–7.0]	4.9 [3.7–6.8]	0.654
30–40 years	4.4 [2.6–6.6]	4.7 [2.8–6.5]	0.607
40–50 years	3.7 [2.4–5.8]	3.8 [2.7–5.8]	0.646
≥50 years	2.9 [1.7–4.2]	3.4 [2.1–5.5]	0.081
Age trend	*<0.001*	*0.001*	
Absolute NGMD (mm)			
20–30 years	0.60 ± 0.16	0.60 ± 0.18	0.988
30–40 years	0.60 ± 0.16	0.62 ± 0.17	0.498
40–50 years	0.58 ± 0.19	0.58 ± 0.19	0.850
≥50 years	0.56 ± 0.16	0.59 ± 0.21	0.396
Age trend	*0.045*	0.263	
Relative NGMD (%)			
20–30 years	18.1 ± 5.2	18.2 ± 6.3	0.928
30–40 years	18.1 ± 5.2	18.3 ± 5.1	0.283
40–50 years	16.3 ± 5.1	16.5 ± 5.4	0.952
≥50 years	15.2 ± 5.2	15.5 ± 5.5	0.690
Age trend	*<0.001*	*<0.001*	
Dilation (FMD) in proportion of maximal dilation (NGMD) (%)			
20–30 years	27.4 [19.9–36.5]	29.5 [20.3–39.8]	0.613
30–40 years	24.5 [14.6–36.6]	24.2 [16.3–35.5]	0.671
40–50 years	23.2 [13.4–34.9]	25.5 [14.7–35.9]	0.575
≥50 years	17.6 [12.2–31.1]	23.8 [12.4–35.2]	0.103
Age trend	*0.003*	0.502	

Number of inclusions within groups: 20–30 years: preeclampsia n=103, controls n=16; 30–40 years: preeclampsia n=392, controls n=111; 40–50 years: preeclampsia n=238, controls n=159; ≥50 years: preeclampsia n=70, controls n=128. Abbreviations: PE, preeclampsia; FMD, flow-mediated-dilation; NGMD, nitroglycerine-mediated dilation.

Table S3. Association of age with FMD and NGMD

	Brachial artery diameter (mm)		Absolute FMD (mm)		Relative FMD (%)	
	β (95% CI), mm/10yr	p-value	β (95% CI), mm/10yr	p-value	β (95% CI), %/10yr	p-value
Unadjusted model						
Age (in deciles)	0.16 (0.13–0.19)	*<0.001*	-0.01 (-0.02–-0.002)	*0.007*	-0.48 (-0.65–-0.30)	*<0.001*
Fully-adjusted model						
Age (in deciles)	0.15 (0.12–0.18)	*<0.001*	-0.01 (-0.01–0.002)	0.130	-0.40 (-0.60–-0.21)	*<0.001*
	Allometric FMD (%)		Absolute NGMD (mm)		Relative NGMD (%)	
	β (95% CI), %/10yr	p-value	β (95% CI), mm/10yr	p-value	β (95% CI), %/10yr	p-value
Unadjusted model						
Age (in deciles)	-0.49 (-0.68–-0.31)	*<0.001*	-0.02 (-0.03–-0.01)	*0.001*	-1.13 (-1.49–-0.77)	*<0.001*
Fully-adjusted model						
Age (in deciles)	-0.42 (-0.62–-0.21)	*<0.001*	-0.02 (-0.03–-0.003)	*0.018*	-1.04 (-1.47–-0.61)	*<0.001*
	Dilation (FMD) as proportion of maximal dilation (NGMD) (%)					
	β (95% CI), %/10yr	p-value				
Unadjusted model						
Age (in deciles)	-1.31 (-2.44–-0.17)	*0.023*				
Fully-adjusted model						
Age (in deciles)	-1.04 (-2.28–0.21)	0.103				

Confounders adjusted for in fully-adjusted model: BMI, smoking, anti-hypertensive drug use, MAP, fasting glucose levels, menopausal state and family history of CVD. Regression on FMD and NGMD was additionally adjusted for stress stimulus and regression on absolute FMD and absolute FMD for baseline. Statistically significant p-values are presented in cursive.

Abbreviations: β, unstandardized regression coefficient; FMD, flow-mediated-dilation; NGMD, nitroglycerine-mediated dilation; 95% CI, 95% confidence interval.

Chapter 6

Prediction model for hypertension in the first decade after preeclampsia in initially normotensive women

Mieke C.E. Hooijschuur | Emma B.N.J. Janssen | Eva G. Mulder | Abraham A. Kroon | Jori M.J. Meijers | Jasper J. Brugts | Bas C.T. van Bussel | Sander M.J. van Kuijk | Marc E.A. Spaanderman | Chahinda Ghossein-Doha

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Abstract

Objective: To develop a prediction model for the development of hypertension in the decade following preeclampsia in women who were initially normotensive shortly after pregnancy.

Methods: We conducted a longitudinal cohort study in 259 formerly preeclamptic women in a University hospital in the Netherlands. We developed a prediction model using multivariable logistic regression analysis. The model was internally validated with bootstrapping techniques.

Results: Of the 259 women, 185 (71%) were normotensive at first visit at a median of 10 months [IQR 6–24] postpartum of which 49 (26%) had developed hypertension at the second visit at a median of 11 years postpartum. The prediction model, based on birth weight centile, mean arterial pressure, total cholesterol, left ventricular mass index and left ventricular ejection fraction, had a good to excellent discriminative ability of AUC-ROC-curve 0.82 (95% CI 0.75–0.89) with an optimism corrected AUC of 0.80. Sensitivity and specificity of our model to predict hypertension was 98% and 65% respectively and positive- and negative predictive values were 50% and 99% respectively.

Conclusions: Based on five variables, we developed a good-to-excellent performing predictive tool to identify incident hypertension following preeclampsia in women that were normotensive shortly after pregnancy. After external validation this model could have considerable clinical utility in tackling the cardiovascular legacy of pre.

Introduction

Hypertension is the leading global risk factor for cardiovascular disease morbidity and mortality and is therefore the most substantial and neglected health burden in women.[1] Women with a history of preeclampsia (PE) have an increased risk to develop hypertension and related cardiovascular diseases (CVD) at a relatively young age.[2-4]

Hypertension is a strong risk factor for CVD. The cumulative effect of prolonged exposure to high blood pressure results in subclinical low-grade inflammation, endothelial dysfunction and progressively irreversible changes in cardiac- and vascular structure and -function, continuously increasing the risk of overt clinical cardiovascular (CV) events.[5,6] When diagnosed before irreversible cardiovascular dysfunction has occurred, blood pressure can be modified by lifestyle adjustments or medication in order to prevent CV adverse events.[7-12] Therefore, timely detection of hypertension is of utmost importance especially in formerly preeclamptic individuals, who are at 2–7 fold increased risk for CVD later in life.[3]

Current guidelines recommend counseling and follow up for cardiovascular disease risk modification after preeclampsia[4] although hampered by the lack of prediction tools. Current prediction models for hypertension are not applicable for this relatively young female population, as they are often designed in cohorts dominated by middle-aged men or postmenopausal women. Computed predicted risk for the diagnosis of hypertension after PE may result in intensified follow-up for those at risk or tempered follow-up for low-risk individuals. To this end, we developed a prediction model for remote hypertension in former preeclamptic women who were normotensive after giving birth.

Methods

The manuscript was written following the Transparent Reporting of a multivariable model for Individual Prognosis Or Diagnosis (TRIPOD) guideline.[13] This study was conducted in the Maastricht University Medical Centre (MUMC) between 1996 and December 2019. The Medical Ethical Committee of the MUMC approved the study protocols (METC azM/UM 14-4-118 and 14-2-013). Since 1996, an extensive postpartum CV assessment was offered to women with a history of PE at least six months postpartum. This clinical service was accessible to all women in the Netherlands. Women were referred either by their obstetrician or general practitioner. All women that attended the cardiovascular assessment between October 1996 and October 2014 from whom contact details (either postal address or email address) were available were invited for a second CV assessment. This second assessment was conducted from 2015 onwards as part of the Queen of Hearts study. For our analysis, we included women attending

the second visit who were normotensive at the first as visit. The cohort was divided into two groups based on whether or not they developed incident hypertension in the time between the first and second visit (i.e. a normotensive/normotensive group and a normotensive/hypertensive group).

Outcome and definitions

We defined hypertension as a systolic blood pressure (SBP) ≥130 mmHg and/or diastolic blood pressure (DPB) ≥80 mmHg and/or the use of antihypertensive medication. These cutoff values are classified as high-normal by the European society of cardiology (ESC) guidelines[14] and as grade 1 hypertension based on the 2018 guidelines of the American Heart Association.[15] Hypertension present at second visit was the main outcome. PE and Hemolysis Elevated Liver enzymes and Low Platelets (HELLP) syndrome were defined according to the criteria of International Society for the Study of Hypertension in Pregnancy.[16] Women with chronic hypertension before pregnancy were excluded. Early onset PE was defined as PE before 34 weeks of gestation.

Assessments

Measurements at both postpartum visits were performed in standardized environmental conditions at a morning clinic according to an identical protocol. Clinical data on obstetric- and medical history and the use of medication were collected from medical files, discharge letters and by direct patient enquiry. Blood pressure was measured in a sitting position by a semiautomatic oscillometric device (Dinamap Vital Signs Monitor 1846; Critikon, Tampa, Fl at the first visit and the GE Dinamap V100 at the second visit) with a cuff size appropriate for arm circumference. Blood pressure was measured based on a predefined standardized protocol at a 3-minute interval for a period of 30 minutes. The median systolic-, diastolic- and mean arterial pressure value of 11 measurements was reported. Systolic and diastolic blood pressure was used to diagnose hypertension. The operator was blinded for blood pressure values at visit 1, when performing measurements at visit 2.[17] Glucose, insulin, total cholesterol, high-density lipoprotein cholesterol (HDL) and triglyceride levels were obtained from fasting blood samples. Insulin resistance was estimated using the Homeostatic Model Assessment ($HOMA_{IR}$) by the formula (glucose [mmol $\times$ l^{-1}] $\times$ insulin [mU $\times$ l^{-1}] $\times$ 22.5^{-1}).[18] Low-density lipoprotein cholesterol (LDL) was calculated by the Friedewald Equation.[19] Body mass index (BMI) was calculated by dividing the body weight in kilograms by the squared height in meters. Obesity was defined as a BMI ≥30 kg $\times$ m^{-2}. Body surface area (BSA) was calculated using the formula of DuBois and Dubois.[20]

Echocardiographic measurements

Cardiac function was evaluated during the first postpartum visit with the participant in dorsal recumbence using a phased-array echocardiographic Doppler system (Hewlett-Packard Sonos 2000 and 2500; Hewlett-Packard Company, Palo Alto, California at the first visit and iE33 system with S5-1 or X5-1 transducers, Philips Medical Systems, Best, the Netherlands at the second visit). Imaging data were analyzed offline using specific software (Excelera, Philips, The Netherlands). To allow assessment of left ventricular mass and relative wall thickness, we measured left ventricular end-diastolic diameter (LVEDd, mm) left ventricular end-systolic diameter (LVESd, mm), and the end-diastolic thickness of both the inter-ventricular septum (IVST, mm) and the posterior wall (PWT, mm) by two-dimensional (2D) echocardiography. We used the Devereux-formula to estimate left ventricular mass (LVM) both as an absolute figure (g) and indexed for BSA.[21] We calculated relative wall thickness (RWT) as follows: RWT = [PWTx2] / LVEDd. The heart rate (HR, beats $\times$ min^{-1}) was obtained by taking the reciprocal of the mean of 5 consecutive RR intervals on the electrocardiogram multiplied by 60 seconds. We estimated the mean aortic Velocity Time Integral (VTI) by averaging the outer edge tracing of Continuous Wave Doppler registrations of the aortic flow at the level of the aortic valve.

Stroke volume (SV, mL) was obtained by taking the product of VTI and the cross-sectional area at the level of the aortic annulus in the parasternal long axis view. Finally, cardiac output (CO, L $\times$ min^{-1}) was obtained by multiplying SV with HR, and cardiac index (CI, L $\times$ min^{-1} $\times$ m^{-2}) was calculated dividing CO by BSA. Left ventricular end-diastolic volume (EDV, mL) and end-systolic volume (ESV, mL) were estimated using the Teichholz formula.[22] Left ventricular (LV) ejection fraction (EF) was calculated by LVEF(%) = [[EDV-ESV] $\times$ [EDV]$^{-1}$] $\times$ 100%. Total peripheral vascular resistance (TPVR, dynes $\times$ sec $\times$ cm^{-5}) was obtained by (80 $\times$ mean arterial pressure [mmHg]) $\times$ CO^{-1}.

By measuring the trans-mitral flow pattern by pulsed-wave (PW) Doppler echocardiography from the apical 4-chamber view, we derived the early diastole (E)/atrial contraction (A) ratio, which provides a crude estimate for diastolic function and corresponds with the ratio of peak-mitral flow velocity during early diastole and that during atrial contraction. The PW Doppler sample volume (5 mm) was carefully positioned at the tip of the mitral valve leaflets. The sweep rate was set at 50 mm $\times$ s^{-1}.[23, 24]

Statistical analysis

We performed all statistical analyses using IBM SPSS Statistics version 25 (version 25, IBM Statistics, Armonk, NY, USA) and R version 3.6.1. Baseline characteristics were expressed as median and interquartile range for continuous variables, and count and percentage for categorical variables. The Mann-Whitney U-test and Kruskal-Wallis were employed for comparison of quantitative variables. Cross-tabulation significance levels

were based on Pearson's chi-square test and Fisher's exact for the categorical variables. A two-sided p-value of <0.05 was considered as statistically significant.

We used univariate logistic regression analysis to estimate the association between single predictors and outcome (hypertension), quantified as odds ratios (ORs) and 95% confidence intervals (95% CI). Only parameters available at the first visit were included. For the initial model, we selected parameters with a p-value of <0.10 and the final prediction model was developed with multivariable logistic regression using backward stepwise selection. All potential predictors that contributed to the model based on Akaike's Information Criterion were selected into the final model. Variance inflation factor (VIF) was used to exclude collinearity. Moreover, we aimed to develop an additional model that would be applicable in primary care (i.e. increasing accessibility by reducing parameters that require additional tests).

To derive a prediction model, we used the regression coefficients, including the model intercept, to formulate a prediction formula. We computed the predicted probabilities and assessed measures of discrimination and calibration. Discrimination is the model's ability to separate those who develop the outcome from those who do not. We used classification tables for risk stratification accuracy evaluation of the adjusted score. Discriminative ability was quantified as the area under the receiver operating characteristic (ROC) curve, or AUC, and interpreted as non-informative (AUC≈0.5), poor discrimination (0.5>AUC<0.6), moderate discrimination (0.6≥AUC<0.7), good discrimination (0.7≥AUC<0.8), good-to-excellent (0.8≥AUC<0.9) or excellent (AUC≥0.9).[25] For the internal calibration plot, we split the study sample into quintiles based on the predicted probability. This plot shows the comparison of the mean predicted probability in each quintile with the proportion positive for the outcome. Ideally, all points are situated on the 45-degree reference line. A point above this line indicates underestimation of risk, a point below the line indicates overestimation.

The model was internally validated using bootstrapping. The bootstrap routine yields a shrinkage factor between 0 and 1 that is subsequently used to penalize (i.e., shrink towards 0) the regression coefficients. This step ensures fewer extreme predictions when applied to new participants to counteract the effect of overfitting (i.e., the phenomenon that a model works better on the data that were used to develop it, but less so on data outside the development cohort). Subsequently, the model intercept was re-estimated to make sure that the average predicted probability of the penalized model was exactly the same as the observed frequency of hypertension. In addition, the bootstrap routine yields a measure of optimism, which is the expected difference in discriminative ability between the development cohort and future patients.

Results

Baseline characteristics

From 1996 until 2014, 1200 women with a history of PE underwent a postpartum cardiovascular assessment in the MUMC. From January 2015 until December 2019, of the 1200 women that attended the first visit, 823 women (69%) were invited for a second visit, of which 259 (31%) consented to participate. Cardiovascular and metabolic characteristics of women who responded to the invitation compared to the women who did not respond are presented in Table S1. The study sample consisted mainly of white women from Northern Europe, except for five women (with a South-American-, Asian-, African-, Asian-Northern European- and African-Northern European ancestry). The first visit took place at a median interval of 10 months [IQR 6–24] postpartum. At this evaluation, 74 women (29%) were considered hypertensive, of whom 45 women had an SBP ≥130 mmHg or DBP ≥80 mmHg, and 29 women were using antihypertensive

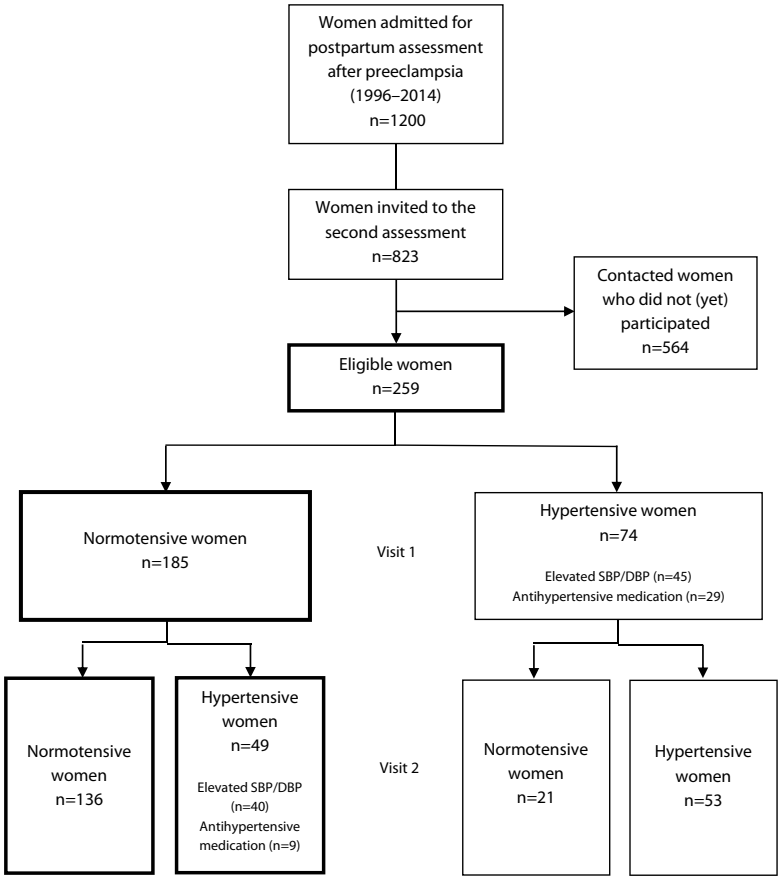

Figure 1: Flowchart. Flowchart shows enrolment of study participants and blood pressure grouping. SBP indicates systolic blood pressure; DBP diastolic blood pressure.

Table 1: Baseline characteristics and cardiovascular and cardiometabolic parameters in women. Groups are based on normotensive or hypertensive at second visit.

	Visit	Total (n=185)	Normotensive (n=136)	Hypertensive (n=49)	p-value
Delivery to 1st visit, months		9 [6–22]	10 [6–21]	8 [7–27]	0.914
1st to 2nd visit, years		11 [6–14]	9 [5–13]	13 [9–16]	<0.001
Delivery to 2nd visit, years		12 [7–15]	11 [7–14]	14 [10–19]	<0.001
Maternal age, years	1	31.8 (4.4)	31.5 (4.0)	32.5 (5.4)	0.316
	2	42.0 (6.4)	40.9 (5.8)	44.9 (7.1)	<0.001
BMI, kg×m^{-2}	1	23.1 [21.4–26.0]	23.1 [21.2–25.9]	23.4 [21.6–26.9]	0.607
	2	24.7 [22.6–27.1]	24.4 [22.2–26.8]	26.0 [23.2–28.7]	0.012
No (%) Obesity	1	20/185 (11)	14/136 (10)	6/49 (12)	0.706
	2	21/185 (11)	12/136 (9)	9/49 (18)	0.071
Index pregnancy					
No (%) Primiparous		158/185 (85)	118/136 (87)	40/49 (82)	0.383
Birthweight centile, %		20.0 [9.0–47.0]	25.0 [10.0–49.5]	12.0 [7.0–31.0]	0.012
No. (%) Early onset PE		107/185 (58)	75/136 (55)	32/49 (65)	0.217
No. (%) HELLP syndrome		143/185 (77)	109/136 (80)	34/49 (69)	0.123
No (%) recurrent PE and/or HELLP	2	32/185 (17)	20/136 (15)	12/49 (25)	
SBP, mmHg	1	110 [107–116]	109 [105–113]	117 [110–122]	<0.001
	2	113 [106–123]	111 [105–115]	131 [122–136]	<0.001
DBP, mmHg	1	70 [65–73]	68 [65–72]	73 [70–76]	<0.001
	2	71 [67–77]	70 [66–73]	81 [77–85]	<0.001
MAP, mmHg	1	84 [81–89]	83 [79–87]	90 [84–93]	<0.001
	2	87 [83–95]	85 [81–88]	100 [96–106]	<0.001
PP, mmHg	1	42 [37–47]	41 [37–47]	43 [38–48]	0.099
	2	42 [38–49]	41 [36–46]	48 [41–57]	<0.001
Heart rate, bpm	1	69 [64–76]	68 [63–75]	70 [66–78]	0.338
	2	66 [60–73]	65 [60–72]	69 [63–79]	0.004
Total cholesterol, mmol×L^{-1}	1	4.7 [4.1–5.4]	4.5 [4.1–5.3]	5.0 [4.4–5.6]	0.012
HDL, mmol×L^{-1}	1	1.4 [1.2–1.6]	1.4 [1.2–1.6]	1.4 [1.2–1.5]	0.540
LDL, mmol×L^{-1}	1	2.8 [2.4–3.5]	2.8 [2.3–3.4]	3.1 [2.6–3.6]	0.032
Triglycerides, mmol×L^{-1}	1	0.81 [0.62–1.15]	0.78 [0.59–1.07]	0.84 [0.67–1.33]	0.098
Glucose, mmol×L^{-1}	1	5.1 [4.8–5.4]	5.0 [4.8–5.3]	5.1 [4.8–5.5]	0.190
Insulin, mU×L^{-1}	1	8.1 [5.5–12.0]	7.4 [5.2–11.5]	8.5 [6.5–13.0]	0.216
$HOMA_{IR}$	1	1.80 [1.20–2.64]	1.70 [1.15–2.59]	1.89 [1.33–2.77]	0.208
HbA1c, %	1	5.3 [5.0–5.5]	5.3 [5.0–5.5]	5.3 [4.9–5.5]	0.575

Data are depicted as median and interquartile range [IQR] or mean (SD).
BMI: body mass index; kg: kilograms; DBP: diastolic blood pressure; GA: gestational age; HDL: high-density lipoprotein; HELLP: Hemolysis Elevated Liver enzymes and Low Platelets; HOMA-IR: Homeostatic Model Assessment for Insulin Resistance; LDL: low-density lipoprotein; MAP: mean arterial pressure; PE: preeclampsia; PP: pulse pressure; SBP: systolic blood pressure.

medication. Characteristics of these women are presented in Table S2. For our analysis, 185 women (71%) who were normotensive at the first visit were included. The second visit was performed at a median interval of 11 years [IQR 6–14] after the first evaluation. Of the 185 initially normotensive women, 136 women (74%) remained normotensive and 49 women (26%) developed hypertension during this period, of whom 40 women had an SBP ≥130 mmHg or a DBP ≥80 mmHg, and nine women were taking antihypertensive medication (Figure 1).

Women who remained normotensive vs women who became hypertensive

The baseline characteristics of the normotensive women at the initial visit are presented in Table 1 according to categories of incident hypertension or not. Women with incident hypertension had their second visit 4 years later than those who remained normotensive. At the initial visit, there were no differences in age or BMI between both groups. At the second visit, women with incident hypertension were on average 4 years older and had higher BMI compared to women who remained normotensive. With respect to the index pregnancy, the incidence of early onset PE and concomitant HELLP syndrome was comparable between the groups, although women with incident hypertension delivered on average 22 days earlier at lower offspring birth weight centile compared to those remaining normotensive.

Table 2: Cardiac geometry and function at the first visit. Groups based on normotensive or hypertensive at second visit.

	Total (n=185)	Normotensive (n=136)	Hypertensive (n=49)	p-value
LAD, mm	35 [32–37]	34 [32–37]	35 [33–38]	0.168
Cardiac output, L×min^{-1}	4.9 [4.2–5.6]	4.8 [4.2–5.5]	5.2 [4.5–5.9]	0.112
Cardiac index, L×min^{-1}×m^{-2}	2.8 [2.5–3.1]	2.7 [2.5–3.1]	2.9 [2.5–3.2]	0.171
TPVR, dynes×s×cm^{-5}	1364 [1200–1559]	1363 [1215–1549]	1367 [1187–1647]	0.685
E/A ratio	1.4 [1.3–1.7]	1.5 [1.3–1.7]	1.4 [1.2–1.7]	0.247
LV ejection fraction, %	64 [61–67]	64 [61–67]	65 [63–68]	0.062
LVM, g	130 [115–150]	128 [112–150]	139 [125–151]	0.018
LVM index, g×m$^{-2,7}$	74 [65–83]	73 [63–81]	77 [72–85]	0.009
RWT	0.33 [0.30–0.36]	0.32 [0.30–0.35]	0.33 [0.32–0.36]	0.050

Data are depicted as median [IQR].
LV, left ventricular; LVM, left ventricular mass; RWT, relative wall thickness; TPVR, total peripheral vascular resistance.

Cardiovascular and cardiometabolic parameters

Women with incident hypertension had higher blood pressure, higher total cholesterol and LDL, at the first evaluation, compared to woman that remained normotensive. At the second assessment, women with incident hypertension had higher heart rate and

pulse pressure in addition to higher blood pressure (Table 1). At first evaluation, cardiac parameters were comparable between both categories, besides higher left ventricular mass and left ventricular mass index in the women with incident hypertension (Table 2).

Prediction model derivation and performance

The association between single variables and incident hypertension, accompanying odds ratios and 95% CI, and number of missing variables that were imputed, are presented in Table 3. Univariable logistic regression analysis showed an association with incident hypertension for gestational age at delivery and birth weight centile of neonate in the index pregnancy and the following variables measured at the first visit: mean arterial blood pressure, total cholesterol and LDL, LVM(i), left ventricular EF and RWT. After multivariable logistic regression with stepwise backward selection, the final model included birth weight centile, mean arterial pressure, total cholesterol, LVMi and left ventricular EF.

The Hosmer and Lemeshow goodness of fit test yielded a p-value of 0.4116. The outcome of the model was the individual risk estimate, which ranged from 0% to 98%

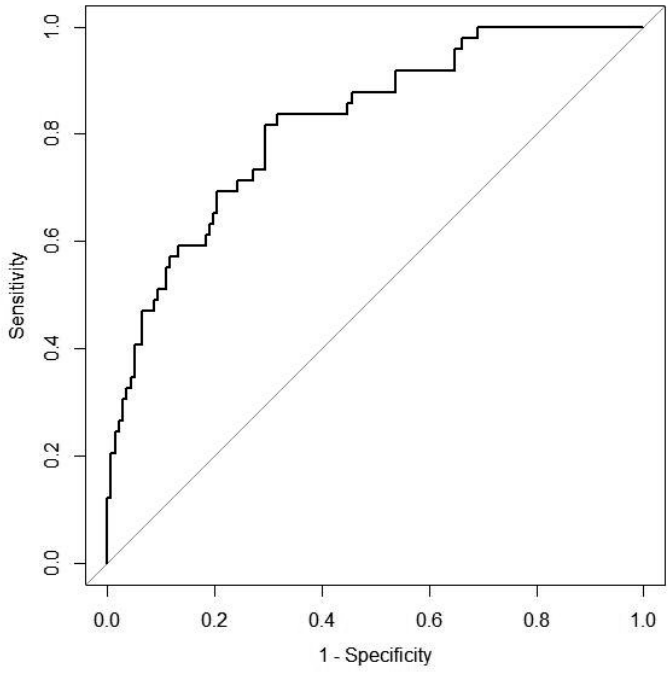

Figure 2. Receiver operating characteristic (roc) curve.
AUC = 0.82 (95% CI 0.75–0.89). Probability incident hypertension (%/10 year) = 1/(1+ exp-linear predictor); linear predictor = -28.521 – 0.003 × birth weight centile(%) + 0.176 × mean arterial pressure (mmHg) + 0.390 × fasting total cholesterol (mmol × L-1) + 0.044 × left ventricular mass index (g × m-2) + 0.113 × ejection fraction (%).

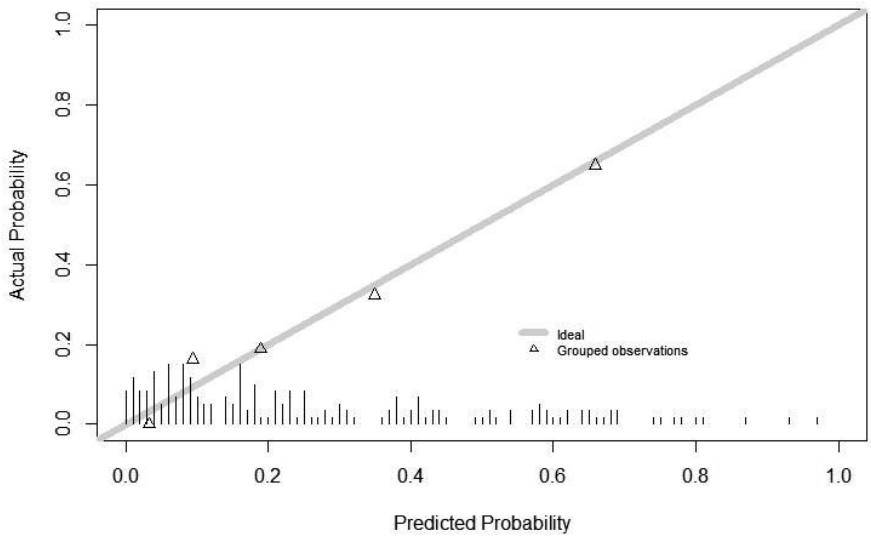

Figure 3. Internal calibration curve.
Internal calibration curve shows predicted probability and observed incident hypertension. Patients are grouped in quintiles.

in our population. The area under the receiver operating characteristic curve of the model was 0.82 (95% CI 0.75–0.89) (Figure 2). The quintile internal calibration curve (Figure 3) showed adequate risk estimates all along the range of estimated predictions.

Considering the broad variation in time between first- and second visit we additionally adjusted our model for the study design by including time between visits. Performance was comparable (AUC 0.85 (95% CI 0.79–91), Hosmer and Lemeshow goodness of fit test: p-value 0.838).

Moreover, additional models were developed that require less tests and therefore might increase applicability 1) a model without echocardiographic- and laboratory parameters and 2) a model without echocardiographic parameters. Predictive performance of both models only slightly decreased, but calibration became less accurate. (See Figure S1 and S2 respectively).

Internal validation

The internal validation yielded a shrinkage factor of 0.87, which was used to multiply the regression coefficients with to adjust for overfitting in another population. Subsequently, the model intercept was re-estimated (Table 3). The optimism in the estimation of the AUC was 0.024. Hence, the expected discriminative performance in future patients, expressed as the AUC is 0.82–0.02=0.80.

Table 3. Regression coefficients and odds ratios (95% CI) to estimate risk of developing hypertension

Variables	Missing variables	Univariable analysis			Multivariable analysis
		β	p-value	OR (95% CI)	β*
Intercept		-	-	-	-28.521
Maternal age	-	0.051	0.171	1.05 (0.98–1.13)	
BMI	-	0.025	0.552	1.03 (0.94–1.11)	
Early onset PE	-	0.426	0.219	1.53 (0.78–3.07)	
HELLP syndrome	-	-0.577	0.126	0.56 (0.27–1.19)	
Birthweight centile (%)		-0.014	<0.070	0.987 (0.972–1.001)	-0.003
MAP	-	0.174	<0.001	1.19 (1.12–1.28)	0.176
Heart rate	2	0.009	0.576	1.01 (0.98–1.04)	
Total cholesterol	1	0.439	0.021	1.55 (1.07–2.27)	0.390
HDL	1	-0.274	0.591	0.76 (0.27–2.03)	
LDL	2	0.499	0.024	1.65 (1.07–2.56)	
Triglycerides	1	0.160	0.292	1.17 (0.87–1.69)	
Glucose	4	0.439	0.202	1.55 (0.79–3.07)	
Insulin	9	0.042	0.159	1.04 (0.98–1.11)	
$HOMA_{IR}$	11	0.177	0.140	1.19 (0.94–1.51)	
HbA1c	9	-0.207	0.604	0.81 (0.37–1.78)	
LVM	1	0.017	0.024	1.02 (1.00–1.03)	
LVM index	1	0.036	0.016	1.04 (1.01–1.07)	0.044
E/A ratio	3	-0.626	0.239	0.53 (0.18–1.47)	
Cardiac output	2	0.168	0.301	1.18 (0.86–1.63)	
Cardiac index	2	0.319	0.292	1.38 (0.75–2.49)	
TPVR	2	0.001	0.349	1.00 (1.00–1.00)	
LV ejection fraction	9	0.084	0.052	1.09 (1.00–1.19)	0.113
RWT	1	0.010	0.026	1.01 (1.00–1.02)	

* Regression coefficients adjusted for shrinkage factor and re-estimated intercept.
BMI, body mass index; CI, confidence interval; GA, gestational age; HELLP, Hemolysis Elevated Liver enzymes and Low Platelets; HDL: high-density lipoprotein; $HOMA_{IR}$, homeostatic model assessment insulin resistance; MAP: mean arterial pressure; LDL, low-density lipoprotein; LV, left ventricular; LVM, left ventricular mass; OR, odds ratio; PE, preeclampsia; RWT, relative wall thickness; TPVR, total peripheral vascular resistance.

Prediction

The risk of incident hypertension in the 10 years following pregnancy complicated by PE can be calculated according to the formula: $1/(1+ \exp^{-\text{linear predictor}})$, and the linear predictor = $-28.521 - 0.003 \times$ birth weight centile (%) $+ 0.176 \times$ mean arterial pressure (mmHg) $+ 0.390 \times$ fasting total cholesterol (mmol $\times L^{-1}$) $+ 0.044 \times$ left ventricular mass index (g $\times m^{-2}$) $+ 0.113 \times$ ejection fraction (%).

Sensitivity, specificity and positive- and negative predictive values
Aiming to detect all women with 10% risk of developing hypertension in the decade following pregnancy, the current model has a specificity of 65% and a sensitivity of 98%. Moreover, positive- and negative predictive values are 50% and 99% respectively (Table S3).

Discussion

In this longitudinal follow-up study, we developed a good-to-excellent performing diagnostic prediction model for incident hypertension after PE in women that were initially normotensive shortly after delivery. The final model includes birth weight centile, mean arterial pressure, total cholesterol, left ventricular mass (LVM) index and left ventricular ejection fraction (LVEF).

Over the past decades, the strong relationship between PE and incident hypertension has been well established.[3, 26] As such, pregnancy outcome offers an unique indicator to detect women at risk. Nevertheless, even after decades of awareness, regular blood pressure checks have not been implemented in aftercare for these women. The exact reasons are unclear, but may relate to the large variability of CVD risk after PE. Personalized aftercare including applying this current prediction model, could be used to temper or intensify aftercare. As the prediction model has a high sensitivity, it offers opportunity to distinguish high- from low-risk women and possibly optimize utility of health care resources.

Untreated hypertension, even before the age of 40, is a strong but modifiable risk factor for CVD.[27] Every SBP increment of 20 mm Hg or DBP 10 mmHg from a blood pressure of 115/75 mmHg onwards results in roughly doubled risk of vascular mortality.[28] In women specifically, CVD risk is associated with elevations from lower SBP ranges as when compared to men (e.g. risk for myocardial infarction for women with SBP 110 tot 119 mmHg was comparable to risk for men with SBP ≥160 mmHg).[29]

Prolonged exposure to elevated blood pressure accelerates vascular aging, as structural- and functional changes of the vascular wall seen in young individuals with hypertension are comparable to those in old normotensive individuals.[6, 8, 9, 30] These changes are still reversible if blood pressure is normalized, but eventually extends towards hypertension related end-organ damage.[9, 31]

Lowering blood pressure reduces the risk of CV events; for every decrease in SBP of 10 mmHg, the risk for coronary heart disease, stroke, heart failure and all-cause mortality declines 17%, 27%, 28% and 13%, respectively.[32, 33] Moreover, the likelihood of successful CVD risk reduction relates to the duration of the treatment intensity and period of

elevated blood pressure (i.e. prolonged blood pressure lowering result in a stronger reduction of CV events).[34] These findings underscore the merit of early detection and treatment of hypertension. Treating traditional risk factors in former preeclamptic women is likely to reduce their elevated CVD risk, as their future risk for CVD becomes substantially higher when more risk factors are present. Especially forceful treatment of elevated blood pressure seems of the upmost importance, as hypertension seems to explain most of the excess CVD risk after PE.[35, 36] However, initiation of treatment of hypertension following current guidelines is based on predicted 10 year risk for CVD, which is often low in formerly PE women because of their young age. However, actual lifetime risk in these young women is likely to be underestimated because currently available CVD risk calculators do not include female specific risk factors like PE which are considered major risk factors for CVD.[4] Therefore, this could result in insufficient treatment. This current risk assessment tool is one of the first to be applied in this specific high-risk female populations.

In the first years after gestation, LVM was higher in women with incident hypertension in the next decade. Elevated LVM is indicative for increased afterload, and predicts CV events, even below the 'cut-off'-value for left ventricular hypertrophy.[37-39] Reduction of LVM, as a result of the treatment of hypertension and with it, lowering cardiac pressure load, relates to strong reduction in cardiovascular events.[38, 40] Moreover, in former PE women, early treatment with ace-inhibitors after pregnancy improved left ventricular remodeling (LVM, RWT) and – diastolic function six months after pregnancy.[41] These findings indicate that early detection and treatment could, at least partly, lead to regression of cardiac abnormalities, overall resulting in improved cardiovascular outcome after PE.

In line with others,[42] 21/74 (28%) women of our studied population have been considered hypertensive at first evaluation, but have recovered some time later. A possible explanation could be that regression from hypertension to normal BP after pregnancy takes longer than timing of the first visit. These women were not included in our study as they were assigned to the hypertensive subgroup. From a clinical point of view, because of the diagnosis of hypertension, these women were already under surveillance and therefore in care.

There are some limitations that need to be addressed. First, we used different devices to measure blood pressure at the first and the second visit, possibly resulting in slightly different measurements between visits. However, the rest of the study was conducted in the same hospital under similar conditions- and protocol, resulting in overall low risk of measurement bias. Secondly, our model includes two echocardiographic parameters, which could make the model less applicable in areas with less resources. Third, women that did not respond to our invitation for the second visit showed a slightly worse cardiovascular risk profile at the first visit compared to the responders which

might have caused underestimation of the number of women with hypertension at the first visit. However, we do not think that this influenced the validity of the prediction model because women with hypertension at the first visit were excluded. Moreover, this current prediction model was developed without a 'fixed time interval' between the first and second visit. This should be incorporated when the model is externally validated. Finally, our cohort included a large proportion of high-risk PE pregnancies (i.e. early onset PE, HELLP syndrome). Therefore, external validation in term-PE women is warranted to test the generalizability of the model in this subgroup.

In conclusion, we developed a good to excellent prediction model to predict remote hypertension in the decade following PE in women that were normotensive shortly after delivery. After external validation, this model could contribute to risk-guided follow-up after hypertensive complicated pregnancies, aiming at timely diagnosis and treatment of elevated blood pressure to reduce overall cardiovascular disease burden.

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Supplemental material

Table S1. Characteristics of non-responders and responders to the invitation for a second cardiovascular visit

	Non-responders (n=564)	Responders (n=259)	p-value
Characteristics at evaluation			
Maternal age, years	31.6 (4.4)	31.8 (4.2)	0.843
Delivery to 1st visit, months	11 [6-26]	9 [6–22]	0.058
Primiparous women	469/564 (83%)	218/259 (84%)	0.331
BMI, kg×m^{-2}	24.9 [22.0–28.6]	23.4 [21.4–26.9]	0.002
Glucose, mmol×L^{-1}	5.1 [4.8–5.4]	5.1 [4.8–5.4]	0.570
Insulin, iU×L^{-1}	9.1 [6.3–13.0]	8.3 [5.5–13.0]	0.077
HOMA-IR	2.04 [1.39–3.08]	1.86 [1.24–3.03]	0.070
HbA1c, %	5.3 [5.1–5.6]	5.3 [5.0–5.5]	0.022
Total cholesterol, mmol×L^{-1}	4.8 [4.3–5.4]	4.7 [4.1–5.3]	0.101
HDL, mmol×L^{-1}	1.3 [1.1–1.5]	1.4 [1.2–1.6]	0.014
LDL, mmol×L^{-1}	3.0 [2.5–3.6]	2.8 [2.4–3.4]	0.018
Triglycerides, mmol×L^{-1}	0.91 [0.66–1.26]	0.82 [0.62–1.16]	0.019
SBP, mmHg	116 [108–125]	113 [108–122]	0.085
DBP, mmHg	72 [67–78]	72 [67–77]	0.585
MAP, mmHg	88 [83–96]	87 [82–94]	0.171
Heart rate, bpm	72 [66–78]	70 [64–78]	0.020
Use of antihypertensive medication	101/564 (18%)	29/259 (11%)	0.014
LVM, g	134 [115–152]	130 [115–150]	0.402
LVM index, g×m^{-2}	74 [65–82]	74 [65–83]	0.971
Relative wall thickness	0.33 [0.30–0.35]	0.33 [0.30–0.36]	0.826
E/A ratio	1.4 [1.2–1.6]	1.4 [1.2–1.7]	0.199
Cardiac output, L×min^{-1}	5.1 [4.6–5.8]	5.0 [4.4–5.6]	0.010
TPVR, dynes×sec×cm^{-5}	1396 [1200–1568]	1415 [1265–1636]	0.096
LV ejection fraction, %	64 [61–67]	64 [62–67]	0.832

Data are presented as median [interquartile range] or number/valid measurements (percentage within group).
BMI: body mass index; DBP: diastolic blood pressure; HDL: high-density lipoprotein; HOMA-IR: Homeostatic Model Assessment for Insulin Resistance; LDL: low-density lipoprotein; LVM: left ventricular mass; MAP: mean arterial blood pressure; SBP: systolic blood pressure; TPVR: total peripheral vascular resistance.

Table S2. Characteristics of women who were normotensive and hypertensive at first visit

	Normotensive (n=185)	Hypertensive (n=74)	p-value
Characteristics at evaluation			
Maternal age, years	31.8 (4.4)	31.8 (3.7)	0.988
Delivery to 1st evaluation, months	10 [7-24]	11 [6–27]	0.930
Primiparous women	118/136 (87%)	40/49 (82%)	0.383
BMI, kg×m^{2}	23.1 [21.4–26.0]	24.9 [21.4–28.7]	0.088
Glucose, mmol×L^{-1}	5.1 [4.8–5.4]	5.4 [4.8–5.4]	0.553
Insulin, iU×L^{-1}	8.1 [5.5–12.0]	9.2 [5.9–15.3]	0.066
HOMA-IR	1.80 [1.20–2.64]	2.27 [1.31–3.51]	0.076
HbA1c, %	5.3 [5.0–5.5]	5.2 [5.0–5.5]	0.561
Total cholesterol, mmol×L^{-1}	4.7 [4.1–5.4]	4.7 [4.1–5.2]	0.962
HDL, mmol×L^{-1}	1.4 [1.2–1.6]	1.4 [1.2–1.6]	0.796
LDL, mmol×L^{-1}	2.8 [2.4–3.5]	2.8 [2.4–3.3]	0.758
Triglycerides, mmol×L^{-1}	0.81 [0.62–1.15]	0.82 [0.60–1.21]	0.753
SBP, mmHg	110 [107–116]	127 [119–134]	<0.001
DBP, mmHg	70 [65–73]	82 [79–85]	<0.001
MAP, mmHg	84 [81–89]	99 [94–104]	<0.001
Heart rate, bpm	69 [64–76]	73 [63–79]	0.112
Use of antihypertensive medication	0/185	29/74 (39%)	<0.001
LVM, g	130 [115–150]	135 [117–152]	0.332
LVM index, g×m^{-2}	74 [65–83]	73 [65–83]	0.966
Relative wall thickness	0.33 [0.30–0.36]	0.33 [0.30–0.35]	0.711
E/A ratio	1.4 [1.2–1.7]	1.2 [1.1–1.7]	0.006
Cardiac output, L×min^{-1}	4.9 [4.2–5.6]	5.1 [4.6–5.6]	0.211
TPVR, dynes×sec×cm^{-5}	1365 [1200–1559]	1539 [1389–1759]	<0.001
LV ejection fraction, %	64 [61–67]	64 [62–67]	0.692

Data are presented as median [interquartile range] or number/valid measurements (percentage within group).
BMI: body mass index; DBP: diastolic blood pressure; HDL: high-density lipoprotein; HOMA-IR: Homeostatic Model Assessment for Insulin Resistance; LDL: low-density lipoprotein; LVM: left ventricular mass; MAP: mean arterial blood pressure; SBP: systolic blood pressure; TPVR: total peripheral vascular resistance.

Table S3. Sensitivity, specificity and negative- and positive predictive values (after internal validation)

% risk of developing hypertension	10	25
Sensitivity	98	74
Specificity	65	28
Positive predictive value	50	27
Negative predictive value	99	75

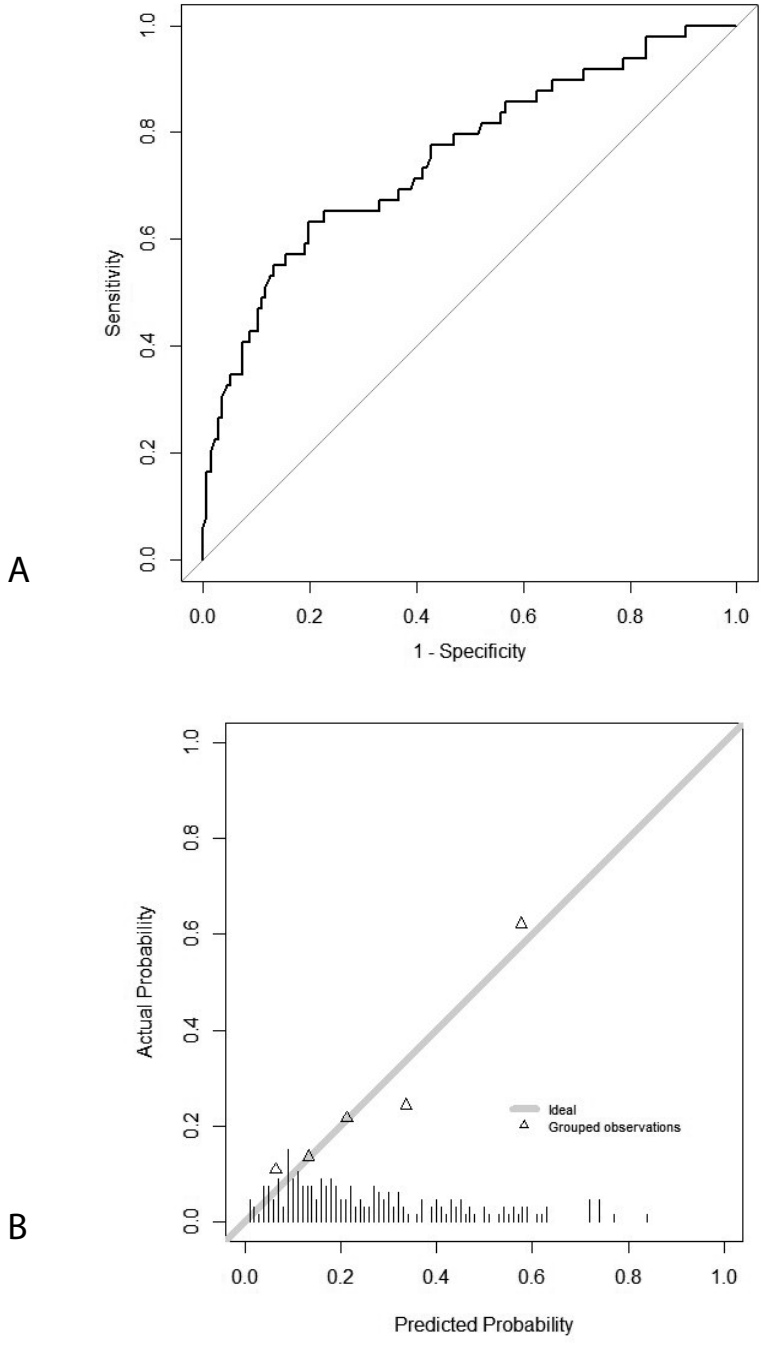
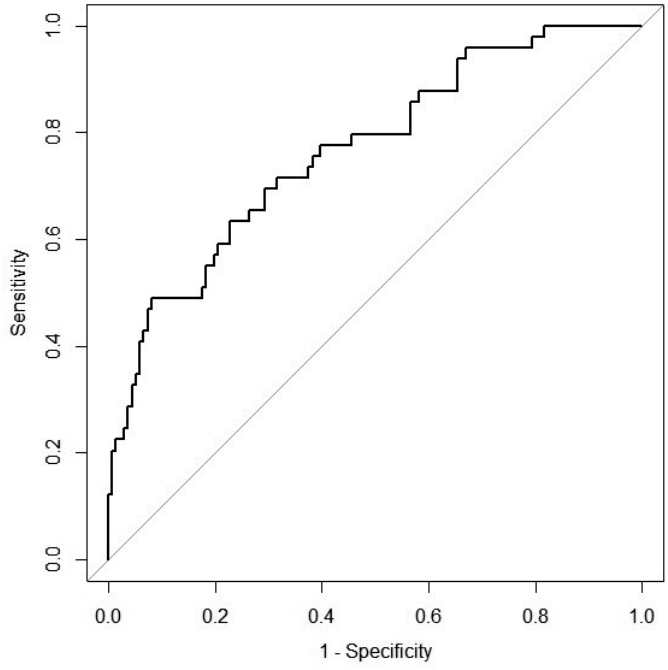


Figure S1. Additional Model 1 including birth weight centile and MAP.
(A) Receiver operating characteristic (ROC) curve. AUC 0.75 (95% CI 0.67–0.84). (B) Internal calibration curve. Internal calibration curve shows predicted probability and observed incident hypertension. Patients are grouped in quintiles. Hosmer and Lemeshow goodness of fit: p-value 0.879, predicted probability range 1%–85%.

A



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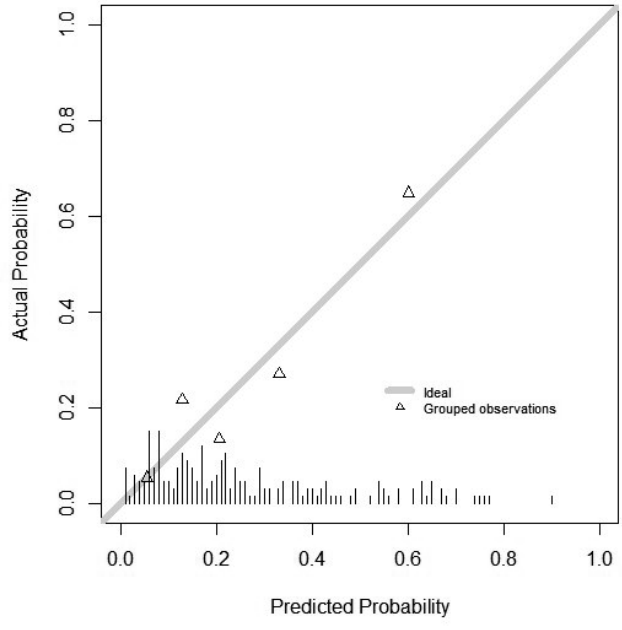

Figure S2. Additional Model 2 including birth weight centile, MAP and fasting cholesterol.
(A) Receiver operating characteristic (ROC) curve. AUC=0.77 (95% CI 0.69–0.84). (B) Internal calibration curve. Internal calibration curve shows predicted probability and observed incident hypertension. Patients are grouped in quintiles. Hosmer and Lemeshow goodness of fit: p-value 0.3456, predicted probability range 1%–90%.

Chapter 7

Cardiovascular risk assessment throughout ageing after preeclampsia

Emma B.N.J. Janssen | Mieke C.E. Hooijschuur | Eva G. Mulder | Veronique M.M.M. Schiffer | Robert Jan Alers | Laura Jorissen | Gwyneth Janssen | Arnoud W.J. van 't Hof | Jasper J. Brugts | Trang Dinh | Marc E.A. Spaanderman | Chahinda Ghossein-Doha

Abstract

Background and aims: Despite the long-term risk for cardiovascular disease after preeclampsia, guidelines do not include recommendations on how to apply structural cardiovascular (CV) screening. Insight in the prevalence of conventional CV risk factors at different age intervals may guide the necessity of timely CV risk assessment. We evaluated age-related patterns in the prevalence of conventional CV risk factors in former preeclamptic women as compared to women with a history of normotensive pregnancy.

Methods: Data was used from the cross-sectional Queen of Hearts study, including parous women six months to thirty years post-delivery with a history of preeclampsia and a control group of women with a history of uncomplicated pregnancy. We assessed the prevalence of hypertension, diabetes mellitus, hypercholesterolemia, insulin resistance, chronic kidney disease and albuminuria as measures of increased CV risk. Age-related effects of a history of preeclampsia on CV risk prevalence was evaluated by Odds Ratio's (ORs), Kaplan Meier curves and Cox Proportional Hazard Ratio's (HRs).

Results: We included 1040 (39 ± 8 years) women who had suffered preeclampsia and 518 women who experienced normotensive pregnancy (44 ± 8 years). In both groups, the prevalence of hypertension and hypercholesterolemia increased statistically significantly with advancing age (p for trend <0.001). For hypertension, this age-related increase was larger in former preeclamptic women as compared to controls. Across all age groups, former preeclamptic women suffered more often hypertension, diabetes mellitus or hypercholesterolemia than controls (<30 years: 20.7% vs. 12.5% respectively, OR 1.7 (95% CI 0.5–6.4); 30-39 years: 26.1 % vs. 11.4%, respectively, OR 2.6 (95% CI 1.6–4.4); 40–49 years: 26.1% vs. 11.4% respectively, OR 2.6 (95% CI 1.6–4.4); ≥50 years: 65.7% vs. 45.7% respectively, OR 2.3 (95% CI 1.3–3.7)), consistent with a cumulative proportions increased HR of 2.6 (95% CI 1.3–15.1). The age of first presence of CV risk factors was on average 8 years younger in former preeclamptic women than controls (39 ± 9 vs. 47 ± 8 years, respectively).

Conclusions: The (cumulative) prevalence of CV risk factors is significantly higher in former preeclamptic women than controls, already below the age of 40 and increasing with age. Predominantly the age-related increase in hypertension was larger among former preeclamptic women than controls. Awareness on the high prevalence of CV risk factors already at young age in women after preeclampsia should be taken into account when developing screening guidelines.

Introduction

The outcome of pregnancy offers a unique opportunity to timely detect women at risk for cardiovascular disease (CVD). It is well established that women who develop preeclampsia during pregnancy, are at increased risk to develop CVD later in life.[1, 2] Although European and American cardiovascular (CV) prevention guidelines acknowledge this specific high-risk female population, they remain inconcrete about strategies to apply CV screening after hypertensive pregnancy complications when traditional risk factors remain unidentified in the first decades after pregnancy.[3, 4]

The CVD risk after preeclampsia is largely mediated by conventional CV risk factors, either pre-existing, persisting from pregnancy onwards or developing after delivery. Former preeclamptic women have a four- to ten-fold increased risk for hypertension,[1, 2, 5-8] an up to three-fold increased risk for diabetes mellitus[6, 7, 9] and two-fold increased risk for hypercholesterolemia.[7] These risks are mostly reported within the first five years after delivery, and higher if the preeclampsia was more severe.[2] Detecting these risk factors is pivotal in CV risk modification as it is well established that lowering blood pressure, blood glucose and Low Density Lipoprotein (LDL) cholesterol significantly reduces CV risk.[10-12]

Lack of clear evidence on when these modifiable risk factors develop, hampers concrete advice on when to apply CV screening after preeclampsia and in what frequency follow-up should be implemented. Empirical evidence on the prevalence of conventional CV risk factors at different age intervals may guide towards risk factor-based advice in structured follow-up.

In this study, we evaluated age-related patterns in the prevalence of hypertension, diabetes mellitus, hypercholesterolemia, chronic kidney disease and albuminuria in former preeclamptic women compared to women with a history of normotensive pregnancy within the first three decades after delivery.

Methods

Study design and population

Data was obtained from a large cross-sectional study designed to investigate early detection of heart failure in women (Queen of Hearts study; ClinicalTrials.gov Identifier NCT02347540). Parous women (≥18 years) with a history of preeclampsia and a control group of women with a history of normotensive pregnancy were included within a postpartum period of six months to thirty years. The study was approved by the Medical Ethics Committee of Maastricht University Medical Centre+ (azM/UM identifier NL 47252.068.14, 2014) and conducted according to institutional guidelines and the Declaration of Helsinki. All participants provided written informed consent.

Given the remote history, preeclampsia was traditionally defined as new-onset hypertension (i.e. SBP ≥140 mmHg and/or DBP ≥90 mmHg) along with de novo proteinuria (≥300 mg/24 h) after 20 weeks of gestation. Normotensive pregnancy was defined as the absence of foetal or maternal placental syndrome (including intrauterine growth restriction (IUGR, p<10), intrauterine foetal death, pregnancy-induced hypertension, preeclampsia, HELLP syndrome, placental abruption) with no preterm delivery (i.e. <37 weeks of gestation). Women who were pregnant at time of inclusion or were diagnosed with chronic hypertension, auto-immune disease or renal disease prior their first (complicated) pregnancy were excluded. We also excluded women in non-fasting state, those who had been diagnosed with diabetes mellitus or hypercholesterolemia prior their first (complicated) pregnancy and those with missing values on the parameters used for de novo detection of CV risk factors.

Cardiovascular assessments

All participants received an extensive CV assessment during one study visit performed by experienced clinical researchers using a standardized study protocol at Maastricht University Medical Centre+ (MUMC+). This CV assessment included history taking (medical, obstetric, family); physical examination; 30-minutes blood pressure measurement; and laboratory analyses of venous blood and 24-hours urine.

Medical history taking

During medical history taking, we examined self-reported prior known diagnoses of hypertension (elevated blood pressure and/or antihypertensive drug use), diabetes mellitus (type 1 or type 2), and hypercholesterolemia. Based upon family history taking, a positive family history of hypertension or CVD (i.e. myocardial infarction, cerebral infarction, stroke) was defined as a first- or second-degree parent or sibling having (had) hypertension or CVD, respectively, below the age of 65 years.

Cardiovascular measurements

Cardiovascular measurements were performed to *de novo* detect cardiovascular risk factors, based on current prevention guidelines of the European Society of Cardiology (ESC).[3]

Height and weight were measured to calculate body mass index (BMI). Obesity was defined as BMI ≥30 kg/m^2. After at least 15 minutes of acclimatization, systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate were measured for 30-minutes in upright sitting position by a semiautomatic oscillometric device (Dinamap Vital Signs Monitor 1846, Critikon, Tampa, FL) with a 3-minute measurement interval. Median values were taken for statistical analyses. De novo hypertension was defined as SBP ≥140 mmHg and/or DBP ≥90 mmHg.[3, 13]

Venous blood sampling was performed to measure levels of metabolic and renal biomarkers, including fasting plasma glucose, HbA1c, insulin, total cholesterol, LDL, HDL, apolipoprotein A and B (Apo A and Apo B) and creatinine. Homeostatic assessment of insulin resistance (HOMA-IR) was calculated based on insulin and glucose levels, as appropriate. Glomerular filtration rate was estimated (eGFR) following the Modification Diet in Renal Diet (MDRD) formula, as appropriate. All participants collected 24-hours urine, which was used to measure micro-albumin. Undetectable micro-albumin levels were considered as 0 mg/L.

De novo diabetes mellitus was defined as one fasting glucose level ≥7.0 mmol/L.[14] Insulin resistance as HOMA-IR >2.9.[15] Hypercholesterolemia was defined as ≥3.5 mmol/L.[16] Chronic kidney disease (CKD) was defined as an impaired MDRD <60 ml/min/1.73 m^2.[3] Albuminuria was defined as micro-albumin ≥3.0 g/mol creatinine.[3] A composite endpoint was defined as having either hypertension, diabetes mellitus and/or hypercholesterolemia.

Statistical analyses

Continuous variables are expressed as mean and standard deviation (SD) when normally distributed, or as median and interquartile range (IQR) when non-normally distributed. Categorical variables are presented as number and percentage. Between-group differences were statistically tested using Independent Samples T Test, Mann Whitney U or Fisher's Exact, as appropriate.

Prevalence of conventional CV risk factors was evaluated based on obstetric history and age categories (i.e. <30 years, 30–39 years, 40–49 years, ≥50 years), combining both prior detected and de novo identified risk factors. Trends across cross-sectional age categories were tested using univariable logistic regression, and Odds Ratios (ORs) were calculated to identify potential risk differences between women with former preeclampsia and controls. Multivariable logistic regression was performed to adjust ORs for family history of CVD. Besides, effect modification between age and obstetric history of preeclampsia on the risk of suffering CV risk factors was evaluated by adding an interaction term between both to the logistic regression model.

To consider the cumulative proportion of cardiovascular risk factors, we constructed Kaplan Meier curves stratified for obstetric history of preeclampsia, and established corresponding Log Rank test p-values to test for between-group differences. In order to enable a more powered evaluation of the age-specific cumulative proportional prevalence of CV risk factors, we rounded age to a consecutive five-point scale (i.e. 25 years, 30 years, 35 years, etc.). Cox proportional hazard models were applied to establish unadjusted and adjusted (i.e. for family history CVD) Hazard Ratios (HRs) with corresponding 95% CI.

To evaluate potential residual effects of pregnancy after 6 months postpartum on the presence of CV risk factors, we performed a sensitivity analysis by excluding women within 12 months postpartum.

Statistical analyses were performed using the statistical software programs R (version 4.0.2) and IBM SPSS (version 28.0). General p-values <0.05 and interaction p-values <0.10 were considered statistically significant.

Results

Study population

Baseline characteristics are presented in Table 1. A total of 1558 women were included (age 22 to 62 years), of which 1,040 women (66.8%) had suffered a preeclamptic pregnancy in the past and 518 (33.2%) had experienced merely normotensive pregnancies. Of the former preeclamptic women, 12.8% experienced recurrent preeclampsia and 53.9% early-onset preeclampsia at least once.

As a group, former preeclamptic women were on average 5 years younger than controls (39 ± 8 years vs. 44 ± 8 years, respectively, p-value <0.001) and had a longer postpartum interval. Former preeclamptic were more often obese than controls (17.2% vs. 10.2%, p-value <0.001), and had more often a positive family history of hypertension and CVD (p-values 0.001 and 0.003, respectively). Levels of SBP, DBP, fasting glucose, insulin, HOMA-IR, eGFR and micro-albumin were statistically significantly higher amongst former preeclamptic women compared to the control group. Mean levels of LDL and Apo B were similar between both groups (p-value 0.330 and 0.755, respectively), whereas former preeclamptic women had lower Apo A levels than controls (166.8 ± 29.4 vs. 175.1 ± 32.0, respectively, p-value <0.001).

Total cross-sectional prevalence of conventional CV risk factors

Prevalence of CV risk factors for both study groups are presented in Table 2. Of these total prevalence rates, 21.8% of hypertension cases were identified first during the study visit (51/234), 40.9% of diabetes mellitus cases (9/22), and 75.6% of hypercholesterolemia cases (226/299) (Supplementary File 1).

Overall, the odds of developing hypertension (OR 2.8 (95% CI 1.9–4.0)), insulin resistance (OR 1.6 (95% CI 1.2–2.2) and albuminuria (OR 2.1 (95% CI 1.2–3.7)) was statistically significantly higher among former preeclamptic women than controls (Table 1). Former preeclamptic women were more often identified with the composite outcome (33.5%) (i.e. hypertension, diabetes or hypercholesterolemia) compared to controls (23.9%) (aOR of 1.6 (95% CI 1.2–2.0)).

Table 1. Baseline characteristics entire study population and stratified for obstetric history

	Women with prior preeclampsia (n=1,040)	Women with prior normotensive pregnancy (n=518)	p-value
Demographics			
Years postpartum	7 [2–14]	13 [6–21]	**<0.001**
Caucasian ethnicity[a]	1,014 (97.5%)	504 (97.5%)	1.000
CV risk factors			
BMI (kg/m^2)	24.6 [22.3–27.7]	23.8 [21.6–26.7]	**<0.001**
Obesity	179 (17.2%)	53 (10.2%)	**<0.001**
Current smoking	69 (6.6%)	44 (8.5%)	0.213
Postmenopausal[a]	114 (11.0%)	105 (20.5%)	**<0.001**
Positive HT family history[a]	681 (66.2%)	260 (50.5%)	**<0.001**
Positive CVD family history[a]	631 (61.3%)	276 (53.4%)	**0.003**
Cardiovascular assessment			
SBP (mmHg)	117 ± 13	112 ± 12	**<0.001**
DBP (mmHg)	74 ± 9	69 ± 7	**<0.001**
Heart rate (bpm)	68 ± 10	66 ± 9	**<0.001**
Metabolic assessment			
Fasting glucose (mmol/L)	5.1 [4.8–5.4]	5.0 [4.7–5.3]	**<0.001**
HbA1c (mmol/mol)	33.0 [31.0–35.0]	34.0 [32.0–36.0]	**0.010**
Insulin (pmol/L)	44.9 [29.7–70.3]	36.1 [22.8–57.5]	**<0.001**
Total cholesterol (mmol/L)	4.7 ± 0.9	4.9 ± 0.9	**0.012**
HDL (mmol/L)	1.6 ± 0.4	1.7 ± 0.4	**<0.001**
LDL (mmol/L)	2.7 ± 0.8	2.7 ± 0.8	0.330
Triglycerides (mmol/L)	0.9 [0.7–1.2]	0.8 [0.7–1.1]	**0.009**
HOMA-IR	1.5 [0.9–2.4]	0.7 [1.2–1.9]	**<0.001**
Apo A[b] (mg/dL)	166.8 ± 29.4	175.1 ± 32.0	**<0.001**
Apo B[b] (mg/dL)	88.3 ± 23.1	88.7 ± 22.0	0.755
Renal assessment			
eGFR (mL/min/1.73m^2)	86.0 ± 14.6	83.6 ± 14.8	**0.003**
Microalbumin (g/molcreat)	0.4 [0.0–0.9]	0.0 [0.0–0.7]	**<0.001**

Continuous variables are presented as mean ± SD when normally distributed and median (IQR) when non-normally distributed. Categorical variables are presented as number (%). [a] Variables consisted missing values, with a maximum of 1% missing values. [b] Variables consisted 292 (19%) missing values. Missing values were deleted pairwise, valid percentages are presented. Statistically significant p-values are presented in bold.

Abbreviations: n, number; BMI, body mass index; HT, hypertension; CVD, cardiovascular disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HOMA-IR, homeostatic model assessment of insulin resistance; Apo A, apolipoprotein A; Apo B, apolipoprotein B.

Mean age of CV risk diagnosis in former preeclamptic women versus controls

As a group, preeclamptic women were diagnosed on average 9 years earlier with hypertension compared to the control group (38 ± 9 years vs. 47 ± 7 years, p-value <0.001), 7 years earlier with diabetes mellitus (38 ± 10 years vs. 45 ± 7 years, p-value >0.05) and 6

years earlier with hypercholesterolemia (41 ± 9 years, vs. 47 ± 8 years, p-value <0.001) (Table 2). Also for insulin resistance, CKD and albuminuria, the age of diagnosis was on average 7, 4 and 6 years younger after preeclampsia (Table 2).

Table 2. Prevalence and age of diagnosis of CV risk factors

	Entire study population (n=1,588)	History of preeclampsia (n=1,040)	Controls (n=518)	aOR (95% CI), or p-value
Hypertension	234 (15.0%)	195 (18.8%)	39 (7.5%)	**2.8 (1.9–4.0)**
Age at diagnosis	40 ± 9	38 ± 9	47 ± 7	**<0.001**
Diabetes Mellitus	22 (1.4%)	19 (1.8%)	3 (0.6%)	2.8 (0.8–9.6)
Age at diagnosis	39 ± 10	38 ± 10	45 ± 7	0.304
Hypercholesterolemia	299 (18.8%)	203 (19.5%)	96 (18.5%)	1.1 (0.8–1.4)
Age at diagnosis	43 ± 9	41 ± 9	47 ± 8	**<0.001**
Insulin resistance	226 (14.5%)	171 (16.4%)	55 (10.6%)	**1.6 (1.2–2.2)**
Age at diagnosis	39 ± 9	37 ± 8	44 ± 10	**<0.001**
CKD	45 (2.9%)	28 (2.7%)	17 (3.3%)	0.8 (0.4–1.5)
Age at diagnosis	47 ± 7	46 ± 7	50 ± 7	**0.048**
Albuminuria	88 (5.6%)	71 (6.8%)	17 (3.3%)	**2.1 (1.2–3.7)**
Age at diagnosis	40 ± 9	38 ± 8	44 ± 11	0.056
≥1 CV risk factor	472 (30.3%)	348 (33.5%)	124 (23.9%)	**1.6 (1.2–2.0)**
Age at diagnosis	40.9 ± 9.1	38.9 ± 8.6	46.7 ± 7.9	**<0.001**

Age at diagnosis is presented as mean ± standard deviation. ORs are adjusted for family history of CVD. Composite endpoint of ≥1 CV risk factors included the presence of hypertension, diabetes mellitus and/or hypercholesterolemia. Statistically significant ORs and p-values are presented in bold.
Abbreviations: n, number; aOR, adjusted Odds Ratio; 95% CI, 95% confidence interval; CKD, chronic kidney disease.

Age-stratified cross-sectional prevalence of CV risk factors

Both in former preeclamptic women and controls, the prevalence of hypertension, hypercholesterolemia and CKD increased with advancing age (p-values <0.001, Table 3 and 4).

Hypertension was more often observed in former preeclamptic women than controls across all age groups. Moreover, age-related increase in elevated blood pressure was larger in women with a history of preeclampsia than in the control group (p-value interaction <0.05) reaching up to 38.2% in women aged ≥50 years after preeclampsia whereas up to 15.7% in controls (Table 3).

Table 3. Prevalence of hypertension, diabetes mellitus and hypercholesterolemia based on medical history taking and de novo findings

		20–29 years (n=145)	30–39 years (n=665)	40–49 years (n=506)	≥50 years (n=242)	*p-value trend*
Hypertension	Total	10 (6.9%)	71 (10.7%)	92 (18.2%)	61 (25.2%)	*<0.001*
	Former PE	10 (8.3%)	67 (13.4%)	79 (24.8%)	39 (38.2%)	*<0.001*
	Controls	0 (0%)	4 (2.4%)	13 (6.9%)	22 (15.7%)	*<0.001*
	aOR (95% CI)	*n.a.*	*6.0 (2.2–16.8)*	*4.4 (2.4–8.2)*	*3.3 (1.8–6.1)*	***p-interaction 0.044***
Diabetes Mellitus	Total	3 (2.1%)	7 (1.1%)	7 (1.4%)	5 (2.1%)	*0.542*
	Former PE	3 (2.5%)	7 (1.4%)	5 (1.6%)	4 (3.9%)	*0.409*
	Controls	0 (0%)	0 (0%)	2 (1.1%)	1 (0.7%)	*0.323*
	aOR (95% CI)	*n.a.*	*n.a.*	*1.4 (0.3–7.3)*	*5.6 (0.6–51.4)*	***p-interaction 0.521***
Hypercholesterolemia	Total	19 (13.1%)	88 (13.2%)	96 (19.0%)	96 (39.7%)	*<0.001*
	Former PE	16 (13.2%)	73 (14.6%)	69 (21.7%)	45 (44.1%)	*<0.001*
	Controls	3 (12.5%)	15 (9.0%)	27 (14.4%)	51 (36.4%)	*<0.001*
	aOR (95% CI)	*1.0 (0.3–3.8)*	*1.6 (0.9–3.0)*	*1.6 (1.0–2.7)*	*1.4 (0.8–2.3)*	***p-interaction 0.208***
≥1 CV risk factor	Total	28 (19.3%)	149 (22.4%)	164 (32.4%)	131 (54.1%)	*<0.001*
(hypertension, diabetes mellitus, hypercholesterolemia)	Former PE	25 (20.7%)	130 (26.1%)	126 (39.6%)	67 (65.7%)	*<0.001*
	Controls	3 (12.5%)	19 (11.4%)	38 (20.2%)	64 (45.7%)	*<0.001*
	aOR (95% CI)	*1.7 (0.5–6.4)*	*2.6 (1.6–4.4)*	*2.6 (1.7–3.9)*	*2.3 (1.3–3.7)*	***p-interaction 0.161***

Abbreviations: n, number; PE, preeclampsia, aOR, adjusted Odds Ratio; 95% CI, 95% confidence interval; CV, cardiovascular.

Table 4. Prevalence of insulin resistance, chronic kidney disease and albuminuria based on the cardiovascular assessment

		20–29 years (n=145)	30–39 years (n=665)	40–49 years (n=506)	≥50 years (n=242)	*p-value trend*
Insulin resistance	Total	37 (25.5%)	97 (14.6%)	56 (11.1%)	36 (14.9%)	*0.004*
	Former PE	33 (27.3%)	81 (16.2%)	42 (13.2%)	15 (14.7%)	*0.003*
	Controls	4 (16.7%)	16 (9.6%)	14 (7.4%)	21 (15.0%)	*0.487*
	aOR (95% CI)	*1.9 (0.6–6.0)*	*1.7 (1.0–3.1)*	*1.8 (1.0–3.5)*	*0.9 (0.4–1.9)*	***p-interaction 0.026***
CKD	Total	0 (0%)	9 (1.4%)	17 (3.4%)	19 (7.9%)	*<0.001*
	Former PE	0 (0%)	7 (1.4%)	13 (4.1%)	8 (7.8%)	*<0.001*
	Controls	0 (0%)	2 (1.2%)	4 (2.1%)	11 (7.9%)	*0.002*
	aOR (95% CI)	*n.a.*	*1.2 (0.2–5.6)*	*2.0 (0.6–6.2)*	*1.0 (0.4–2.5)*	***p-interaction 0.794***
Albuminuria	Total	15 (10.3%)	35 (5.3%)	24 (4.7%)	14 (5.8%)	*0.265*
	Former PE	12 (9.9%)	31 (6.2%)	21 (6.6%)	7 (6.9%)	*0.531*
	Controls	3 (12.5%)	4 (2.4%)	3 (1.6%)	7 (5.0%)	*0.761*
	aOR (95% CI)	*0.7 (0.2–3.2)*	*2.7 (0.9–7.7)*	*4.5 (1.3–15.3)*	*1.3 (0.5–4.0)*	***p-interaction 0.573***

Abbreviations: n, number; PE, preeclampsia, aOR, adjusted Odds Ratio; 95% CI, 95% confidence interval; CKD, chronic kidney disease, CV, cardiovascular.

Hypercholesterolemia occurred more often in former preeclamptic women between 40-49 years of age, but not in the other age groups. The age-related change in hypercholesterolemia was similar in both groups. CKD was comparably identified in both groups among all age intervals and increased with age in both groups comparably.

Diabetes mellitus occurred similarly in both groups for all age intervals (p-values >0.05, Table 3), and did not change significantly over time in both groups.

Insulin resistance occurred more frequently amongst former preeclamptic women compared to controls in the age groups ranging from 30 to 49 years. In both former preeclamptic women and controls, the prevalence of insulin resistance was highest among women aged 20–29 years and remarkably lower in subsequent age groups (Table 4). This decrease in insulin resistance across age groups was more pronounced in former preeclamptic women than controls (p-value interaction <0.05).

Albuminuria prevalence was comparable in former preeclamptic women and controls, expect for women aged 40–49 years in whom the prevalence was higher after preeclampsia. The prevalence of albuminuria was highest in women aged 20–29 years old in both groups and was lower for subsequent age groups. Changes over time were not different between groups (p-value interaction >0.1).

The composite outcome (i.e. hypertension, diabetes mellitus or hypercholesterolemia) increased with advancing age in both former preeclamptic women and controls. The prevalence of the clinical composite was higher amongst former preeclamptic women compared to controls, from 30 years onwards. In former preeclamptic women, this prevalence increased from 26.1% <40 years to 65.7% >50 years of age, whereas in controls from 11.4% to 45.7%. For the presence of at least one risk factor, the age-related increase seemed larger in women after preeclampsia, though the interaction term was non-significant (p-value >0.1).

Cumulative prevalence of CV risk factors: effect of former preeclampsia

Cumulative proportions of CV factors were statistically significantly higher amongst former preeclamptic women than controls (Log Rank p-values ≤0.05), with exception of CKD (Log Rank p-value >0.05) (Figure 1 and Figure 2). Thereby indicating that former preeclamptic women develop more often CV risk factors over time. Differences in cumulative proportions of hypertension, hypercholesterolemia, insulin resistance and albuminuria seemed to appear from as early as 30 years of age. For diabetes mellitus, differences only seemed apparent in women above 50 years of age.

Correspondingly, the hazard for developing CV risks was significantly increased in women after preeclampsia with women after normotensive pregnancy (Figure 1 and Figure 2). The adjusted hazard of developing at least hypertension, diabetes mellitus

or hypercholesterolemia (composite risk factor) was 2.6 (95% 2.1–3.2) times higher in former preeclamptic women than controls (Figure 1).

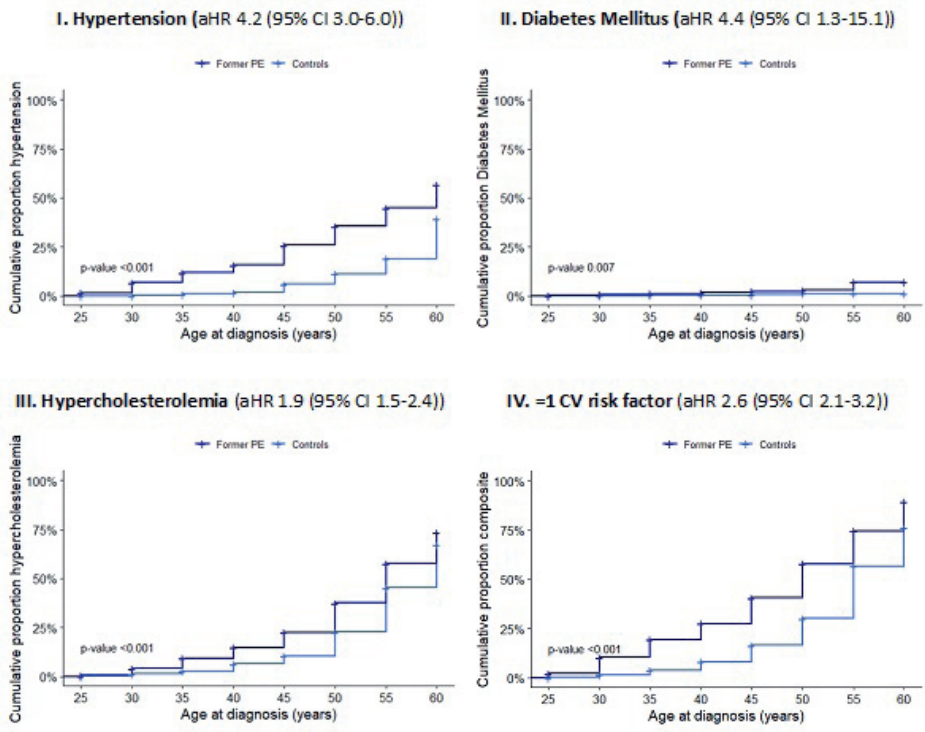

Figure 1. Cross-sectional cumulative proportion of hypertension, diabetes mellitus and hypercholesterolemia stratified on obstetric history.
For power purposes, age was rounded to a five-point scale with corresponding sample sizes: 25 years: n=50, 30 years: n=264, 35 years: n=326, 40 years: n=298, 45 years: n=263, 50 years: n=199, 55 years: n=122, 60 years: n=36. Abbreviations: PE, preeclampsia; aHR, adjusted Hazard Ratio; 95% CI, 95% confidence interval.

Sensitivity analysis

The sensitivity analysis on the potential residual effect of pregnancy did not alter the cross-sectional nor cumulative prevalence of CV risk factors within age groups and thereby did not alter the results (Supplementary File 2–4). Only the proportion albuminuria was twice as lower among women with a history of normotensive pregnancy below the age of 30 when excluding those within 12 months post-delivery.

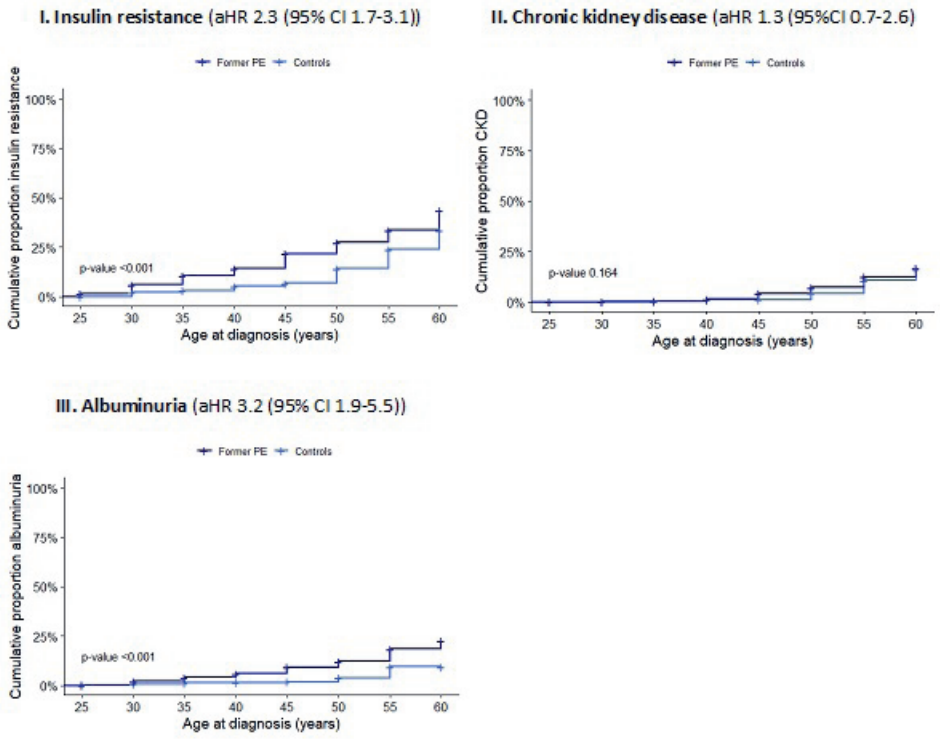

Figure 2. Cross-sectional cumulative proportion of insulin resistance, chronic kidney disease and albuminuria stratified on obstetric history.
For power purposes, age was rounded to a five-point scale with corresponding sample sizes: 25 years: n=50, 30 years: n=264, 35 years: n=326, 40 years: n=298, 45 years: n=263, 50 years: n=199, 55 years: n=122, 60 years: n=36. Abbreviations: PE, preeclampsia; aHR, adjusted Hazard Ratio; 95% CI, 95% confidence interval.

Discussion

In this study we observed that one third of women after preeclampsia had at least one cardiovascular risk factor (hypertension, diabetes mellitus or hypercholesterolemia) compared to a quarter of women who had normotensive uncomplicated pregnancy. Former preeclamptic women were on average eight years younger than controls when conventional CV risk factors emerged. The prevalence of CV risk factors increased significantly with age in both groups, but seemed more pronounced in the former preeclamptic group. That is, the prevalence almost doubled from 35% below the age of 40 years to almost 70% over the age of 50 after preeclampsia, primarily driven by development of hypertension.

Prevalence of conventional CV risk factors after preeclampsia and the effect of ageing

Preeclampsia is considered as a marker of future CVD risk including cardiac atherosclerotic events, heart failure, cerebral vascular accidents, peripheral vascular disease, atrial fibrillation and cardiac death, with the highest risk occurring after early-onset preeclampsia. Much of the increased CV risk in the setting of preeclampsia is attributable to co-existence/-development of CV risk factors,[1, 17-22] especially hypertension.[23] Women with preeclampsia demonstrate unfavourable profiles in CV risk as early as one year postpartum including higher levels of blood pressure, LDL cholesterol, markers of insulin resistance and BMI.[24, 25] Women with a history of preeclampsia have a pooled risk ratio of 3.13 (95% CI 2.51–3.89) for subsequent development of hypertension[22] which explained 64% of the increased risk of coronary artery disease (CAD) and 49% of the increased risk of heart failure in these women.[18] The increased risk of CAD, atherosclerosis, and arrhythmia after preeclamptic pregnancies are less well elucidated. A better understanding of the prevalence of conventional CV risk factors after preeclampsia and how this evolves with ageing is essential in unraveling long-term health risks.

In line with others,[1, 2, 5-8] our study shows that CV risk factors develop more often women with a history of preeclampsia. We observed that former preeclamptic women develop CV risk factors almost a decade earlier compared to women who had a normotensive pregnancy. This indicates that affected women are exposed for longer time to increased mechanical and biochemical vascular strain, which may explain the earlier development of CVD disease after PE compared to women after normotensive pregnancies. It also suggests a promising benefit from timely intervention, especially when vascular changes are still in an asymptomatic phase susceptible to deconditioning. This is supported by the finding that ACE inhibition after early-onset preeclampsia leads to significantly lower diastolic blood pressure, and more accurate cardiac diastolic function and LV remodelling 6 months after delivery compared to those with expectant (placebo) management.[26]

Recent insights in the effect of ageing on CV risk factors after pregnancy are mainly derived from studies assessing women after hypertensive pregnancy disorders (HDP) as a composite. The longitudinal PREVED study,[27] following more than 2800 parous women up to 15 years, revealed that 10-year CV risk scores according to the Pooled Cohort Equations, are consistently higher among women with a history of HDP starting from as early as 28 years until 75 years of age. In line with this study, a Danish nationwide study among 482,972 former pregnant women showed that the cumulative incidence of post-pregnancy hypertension within the first decade after delivery rises up to 32% among women with former HDP as compared to 11% in women with former normotensive pregnancy.[8] Rates of post-pregnancy hypertension in women with HDP in their first pregnancy were 12-fold to 25-fold higher in the first year postpartum and up to 10-fold higher in the decade after delivery and remained more than doubled more than 20 years later compared to women without HDP.[8]

Evidence-based recommendations might guide preeclampsia aftercare

The key management strategy is to recognize that preeclampsia is a first vascular event that relates to subsequent early-onset CVD providing an urgent call for (secondary) CVD prevention. Improved access to care in order to analyse underlying CV risk factors, and if present, targeted but multidimensional treatment including lifestyle, diet or medication with additional attention to concurrent mental aspects, may alter the currently reported CVD risks.[28]

We show that CV risk factors are already highly prevalent at one year postpartum and continue to exist up to three decades later. This indicates that a single postpartum evaluation will not meet changes in CV risks over time, especially since the prevalence of hypertension emerged more steeply with advancing age after preeclampsia than in women with normotensive pregnancies.

Although this urgency of CV risk management after preeclampsia is emphasized in guidelines,[3, 4] these fail to provide uniform and structured guidance on when and how to start CV risk assessment due to lacking empirical evidence within this regard. As a result, recommendations by national guidelines are highly divergent and implementation of preeclampsia aftercare in clinical practice is lacking. Consequently, the clinical work-up provided by clinicians is often insufficient and inconsistent.[29] This is supported by a large retrospective study using insurance data, showing only a small proportion of women to be referred to any specialized outpatient care provider, which failed to match the early and rapid increase in the incidence of hypertension and long-term morbidity after preeclampsia.[30] Moreover, patients express a clear desire for intensified follow-up with specific focus on both physical and psychosocial consequences after preeclampsia.[29] Therefore, routine CVRM in the first year after preeclampsia and subsequent follow-up along with targeted interventions, especially those that lower blood pressure including lifestyle modifications, seem reasonable and likely benefits reducing the incidence of CVD in these women.[31, 32]

Critical steps forward towards personalized follow-up

Recent and current insights could guide towards an evidence-based and coordinated guideline for preeclampsia follow-up, probably being initiated shortly after delivery and focused on both physical and mental consequences.[33] Unfortunately, inclusion of a history of preeclampsia in an established CV risk score does not substantially improve discrimination or reclassification of CVD risk prediction.[34, 35] Current CVD risk calculators have not been designed for women of reproductive age who have a low CVD risk, highlighting the urgent need to develop models to assess long-term CVD risk which include sex-specific risk factors such as HDP or specifically preeclampsia. On the one hand, it might be helpful to primary target CV risk factors, amongst hypertension, obesity, diabetes, dyslipidaemia, instead of weighing modelled CVD risk to determine

treatment strategies. On the other hand, viewing HDP as first vascular event implicates secondary preventive measures, in which treatment thresholds are more tightly compared to primary preventive boundaries.[28]

Limitations

Several limitations merit attention within the interpretation of the results. First, the cross-sectional study design hampered within-individual follow-up of the development of CV risk factors over time. This resulted in a high proportion of censoring in established cumulative proportions. Longitudinal data should verify whether relatively young women within the current cohort that are not identified with CV risk factors at time of their study visit eventually developed CV risk factors and at what age. Besides, we were unable to verify whether the presence of CV risks changes over time due to, for example, lifestyle interventions. This forced us to assume that, once identified, CV risks remained present over time. However, a recent study showed that the presence of metabolic syndrome remained unchanged in 90% of formerly preeclamptic women within the first years after preeclampsia, suggesting only limited misclassification bias in current study.[32]

Second, participant inclusion was based on self-referral, which probably resulted in certain levels of selection bias as women who were more aware of their CV risk could internally be more motivated to participate in this study. As all participants received their own test results and based on the high proportion of family history of hypertension and CVD, we expect that our control group suffered more often from CV risks than the general female population. These types of selection bias could have resulted in underestimated between-group differences, and thereby bias towards the null. Third, we investigated CV risk factors in a relatively young female population. Although relevant clinical insights have been revealed, absolute prevalence and incidence rates of CV risks remained relatively low, probably resulting in the lack of power to detect statistically significance among subgroups. Fourth, our study population consisted nearly completely of women of Caucasian ethnicity, which limits generalizability towards other ethnic groups.

Conclusion

The prevalence of CV risk factors is higher in women with a history of preeclampsia compared to women with a history of normotensive pregnancy, and is already observed almost a decade earlier. Especially hypertension was more prevalent in former preeclamptic women and rose steeper with advancing age. Considering the epidemiological observed increased risk in early-onset CVD, the increased prevalence in traditional CVD risk factors and the differences in time-course with advancing age between former preeclamptic women and controls, we suggest CV risk management including tailored follow-up to start as soon as six months post-delivery.

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Supplementary File 1. Prevalence of CV risk factors distinguished by a piori known diagnoses and de novo identification

	Entire study population (n=1,588)	History of preeclampsia (n=1,040)	Prior normotensive pregnancy (n=518)	OR (95% CI)/p-value
Hypertension	234 (15.0%)	195 (18.8%)	39 (7.5%)	2.8 (2.0–4.1)
Age at diagnosis	40 ± 9	38 ± 9	47 ± 7	<0.001
Known diagnosis	183 (11.7%)	156 (15.0%)	18 (3.5%)	<0.001
with ATH drug use	135 (8.7%)	117 (11.3%)	18 (3.5%)	<0.001
Age at diagnosis	38 ± 8.6	37 ± 8	46 ± 6	<0.001
De novo diagnosis	51 (3.7%)	39 (3.8%)	12 (2.3%)	<0.001
Age at diagnosis	45 ± 8	43 ± 7	51 ± 7	0.004
Diabetes Mellitus	22 (1.4%)	19 (1.8%)	3 (0.6%)	3.2 (0.9–10.8)
Age at diagnosis	39 ± 10	38 ± 10	45 ± 7	0.304
Known diagnosis	13 (0.8%)	11 (1.1%)	2 (0.4%)	0.240
Age at diagnosis	35 ± 8	34 ± 8	41 ± 6	0.285
De novo diagnosis	9 (0.6%)	8 (0.8%)	1 (0.2%)	0.070
Age at diagnosis	45 ± 8	41 ± 8	49 ± 3	0.201
Hypercholesterolemia	299 (18.8%)	203 (19.5%)	96 (18.5%)	1.1 (0.8–1.4)
Age at diagnosis	43 ± 9	41 ± 9	47 ± 8	<0.001
Known diagnosis	73 (4.7%)	58 (5.6%)	15 (2.9%)	0.021
Age at diagnosis	41 ± 8	40 ± 8	45 ± 8	0.032
De novo diagnosis	226 (14.5%)	145 (13.9%)	81 (15.6%)	0.663
Age at diagnosis	44 ± 9	42 ± 9	48 ± 8	<0.001

Supplementary File 2. Prevalence and age of diagnosis of CV risk factors after excluding women between 6 and 12 months postpartum: sensitivity analysis

	Entire study population (n=1,357)	History of preeclampsia (n=864)	Controls (n=493)	aOR (95% CI), or p-value
Hypertension	217 (16.0%)	178 (20.6%)	39 (7.9%)	3.0 (2.1–4.4)
Age at diagnosis	40 ± 9	38 ± 9	47 ± 7	<0.001
Diabetes Mellitus	20 (1.5%)	17 (2.0%)	3 (0.6%)	3.3 (1.0–11.2)
Age at diagnosis	40 ± 10	39 ± 10	45 ± 7	0.377
Hypercholesterolemia	266 (19.6%)	175 (20.3%)	91 (18.5%)	1.1 (0.8–1.5)
Age at diagnosis	44 ± 9	43 ± 9	48 ± 8	<0.001
Insulin resistance	188 (13.9%)	137 (15.9%)	51 (10.3%)	1.6 (1.2–2.3)
Age at diagnosis	41 ± 9	39 ± 8	45 ± 9	<0.001
CKD	45 (3.3%)	28 (3.2%)	17 (3.4%)	0.9 (0.5–1.7)
Age at diagnosis	47 ± 7	46 ± 7	50 ± 7	0.034
Albuminuria	62 (4.6%)	49 (5.7%)	13 (2.6%)	2.2 (1.2–4.1)
Age at diagnosis	42 ± 9	41 ± 9	48 ± 9	0.009
≥1 CV risk factor	424 (31.2%)	305 (35.3%)	119 (24.1%)	1.7 (1.3–2.1)
Age at diagnosis	42 ± 9	40 ± 9	39 ± 7	<0.001

Chapter 8

General discussion

Cardiovascular disease (CVD) is the leading cause of mortality in women worldwide.[33] Awareness on the magnitude of the burden of CVD in women has increased. However, after decades of overall decline in CVD related mortality, recent data suggests stagnation in women and even a slight increase of CVD related mortality in young women.[34] Nevertheless CVD remains the number one reason for mortality in women.

There are differences between women and men in how traditional CVD risk factors (e.g. hypertension, diabetes, dyslipidemia) impact CVD risk.[35] Moreover, there are non-traditional women-specific risk factors, including hypertensive disorders of pregnancy like preeclampsia (PE), that are strongly associated with increased CVD risk. A better understanding of sex-specific CVD risk factors, may play a significant role in improving cardiovascular health in women.

Pregnancy can provide much information on a women's cardiovascular resilience and offers a unique opportunity of early identification of women at high CVD risk that can benefit from screening and follow up. Hypertensive pregnancy complications occur in 2–10% of pregnancies and are the major cause of maternal morbidity and mortality. In this spectrum of hypertensive pregnancy disorders, PE is associated with the highest risk of developing CVD later in life. It is defined as maternal hypertension after 20 weeks gestation in combination with proteinuria and/or end organ dysfunction. Women with a history of PE have substantial higher CVD risk later in life than women without this complication. Several clinical pregnancy-related variables seem associate to the magnitude of CVD risk after PE, with higher risk in those with severe PE, early onset of PE in pregnancy (EOPE i.e. before 34 weeks of gestation) and co-occurrence of compromised fetal growth or fetal death.

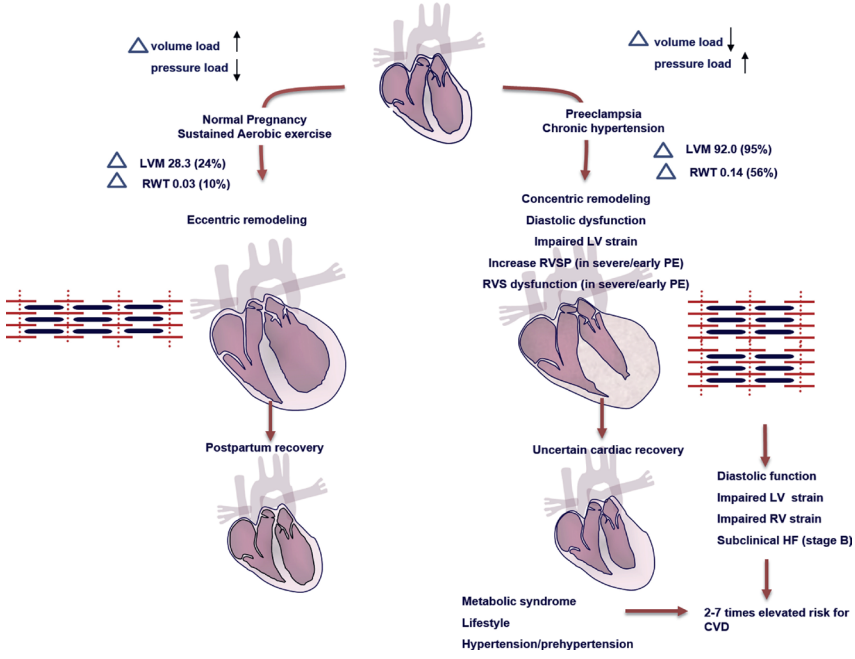
In this thesis, we elaborate on cardiovascular alterations during and after PE. We provide insight in prevalence of modifiable CVD risk factors in different PE subgroups and developed a model to predict hypertension after PE. Altogether, aiming at working towards structural and tailored follow up programs in this group of young women at high risk for future CVD.

Cardiovascular alterations during- and after preeclampsia

The maternal cardiovascular system is exposed to major hemodynamic alterations in pregnancy. The gestational major initiator of circulatory stress, a substantial drop in peripheral vascular resistance, unavoidably increase demands of the maternal cardiovascular system. The ability of the maternal cardiovascular system to adapt to these extensive changes offer a unique opportunity to reveal information about maternal cardiovascular resilience.[36]

In Chapter 2 we give an overview of cardiovascular and cardiac alterations during- and after PE pregnancy. In contrast to normotensive pregnancy, PE pregnancy is a state

of high pressure after-load usually accompanied by low volume pre-load, reflecting a substantial burden to the heart. As a response, left ventricular (LV) alterations occur to compensate for these cardiovascular changes. During PE pregnancy, maternal LV mass (LVM) and relative wall thickness (RWT) increase disproportionally (95% and 56%, respectively) resulting in concentric LV remodeling.[37] This is substantially different compared to women during a normotensive pregnancy (24% increase in LVM and only a slight increase in RWT of 10%) were cardiac alterations are comparable to that seen in athletes (i.e. eccentric pattern). LV remodeling in PE is asymmetrical, predominantly involving the basal anteroseptum, which is comparable to that seen in early hypertension.[38] It is often accompanied by diminished LV compliance resulting in diastolic dysfunction, especially when PE occurs early in pregnancy.



LV ejection fraction (LVEF) is often used when assessing LV function. However, a decrease in LVEF appears in end-stage cardiac disease expression. Early stages of impaired myocardial contractility and relaxation may precede the development of overt cardiac failure. In echocardiography, strain describes local shortening, thickening and lengthening of the myocardium (which often are assessed from 3 spatial directions: longitudinal, radial, and circumferential). Strain can be used to detect subtle functional myocardial abnormalities in systolic and diastolic ventricular function. Global longitudinal strain measurements is more sensitive than LVEF in detecting (sub-clinical) ventricular dysfunction. When compared to measuring LVEF, strain appears to be superior in predicting

cardiac events.[39, 40] Detection and treatment of cardiac impairment in this early and subclinical phase, before it progresses to a symptomatic stage, improves long-term prognosis. Therefore, this way of assessment of cardiac function during- and after PE can detect abnormalities in an early stage where they might be reversible by timely intervention. In women with PE, all strain measurements were significantly lower during PE pregnancy compared to normotensive pregnancy, with the exception of global *radial* strain in late onset PE (LOPE i.e. PE at or after 34 weeks of gestation).[41] Moreover, with the exception of global longitudinal strain, all strain measurements were lower in women with EOPE vs LOPE while measurements in EOPE were performed over 7 weeks earlier in pregnancy as when compared to LOPE (28.9- and 36.4 weeks at gestation in EOPE and LOPE, respectively) suggesting earlier and more severe decline in cardiac function in EOPE. This is supported by a study that found that, at mid-gestation, cardiac diastolic dysfunction and impaired myocardial relaxation were only seen in women with preterm PE (i.e. requiring delivery before 37 weeks) but not in term PE.[42] LV hypertrophy seen in normotensive pregnancy resolves after delivery.[43] On the contrary, abnormalities in cardiac geometry and function seen during PE persist in 25% to 72% of the cases postpartum, especially after preterm PE.[44, 45] Persisting diastolic dysfunction after PE strongly relates to presence of metabolic syndrome.[46] However, even after correcting for metabolic variables, PE stayed independently associated with asymptomatic heart failure 4–10 years postpartum.[47]

Endothelial (dys)function

Systemic endothelial dysfunction is thought to play an important role in the development of PE.[48] This process can be accompanied by impaired spiral artery remodeling after poor trophoblast invasion (especially in EOPE), making the placenta much more vulnerable to perfusion related damage, and/or as a response of maternal constitutional factors to changes in pregnancy.[49] Flow mediated dilatation (FMD) is a well-established, non-invasive method to measure endothelial function and impaired brachial FMD is associated with future CVD events.[50, 51] A meta-analysis showed that for every 1% increase in brachial artery FMD, the relative risk of cardiovascular events was 0.87 after adjusting for confounding risk-factors.[51] Although data of these studies should be interpreted with caution due to inclusion of heterogeneous studies, altogether results are indicative that brachial artery FMD is associated with future CVD risk. PE women have lower FMD prior to-, during-, and up to 3 years after pregnancy suggesting that persistent endothelial dysfunction in these women might contribute to excess CVD risk after PE.[52] Endothelial function can be modulated by traditional CVD risk factors (e.g. obesity, diabetes, hypertension), but decline in endothelial function is also independently associated with advancing age.[53] In Chapter 5 we tested the hypothesis that this age-related decline in vascular function was more pronounced in former PE women compared to women with normotensive pregnancy. Endothelial-dependent vasodila-

tory function was measured by FMD and endothelial-independent vasodilatory function was tested using sublingually administered nitroglycerine-mediated dilation (NGMD). In line with previous studies, there was decline in FMD and NGMD with advancing age, even after correcting for traditional CVD risk factors. Interestingly, although former PE women had smaller brachial artery's compared to normotensive controls, but their vasodilatory abilities were comparable with advancing age (both with- and without adjusting for traditional CVD risk factors). These findings suggest no additional effect of PE on the age-dependent decline in endothelium-dependent flow-mediated assessed vascular function. However, the cross-sectional design of the study limits the ability to compare vascular function before- and after pregnancy and we therefore can't exclude (significant) changes over time in former PE women (e.g. before- and after pregnancy). Moreover, this not excludes endothelial dysfunction as a contributing factor for the excess CVD risk after PE, as not all of its sides (microvascular) or mode of endothelial actions can be measured by FMD and NGMD. Another variable might be onset of PE as there may be differences in vascular function after EOPE vs LOPE. Nonetheless, the effect of PE on the age-related decline in vascular function measured by FMD and NGMD don't seem to fully explain the substantial increased CVD risk after PE.

Cardiovascular disease- and impact of cardiovascular disease risk factors after preeclampsia

Women with a history of PE have a 2–7 times higher risk of developing CVD, including ischemic heart disease, cerebrovascular accidents, arrhythmias, heart failure, and diastolic dysfunction, compared to women with uncomplicated pregnancies.[4, 5, 54] Moreover, they develop CVD at a younger age.[5] Cardiovascular outcome seems to relate to time of onset of PE in pregnancy were women with early onset PE have higher CVD risk than those with late onset PE. In addition, also co-occurrence of fetal complications (e.g. fetal growth restriction, fetal death) increases future CVD risk, both when occurring on its own as well as in co-occurrence with PE.[4, 5, 54]

PE is also independently associated with future cardiovascular disease related death. In a large prospective cohort study of over 14,000 women, women with a history of PE have double the risk of CVD related death when compared to women without PE.[55] In women with EOPE this risk was substantially higher (i.e. over nine times higher as when compared to women without PE), resulting in cardiovascular death in 14.1% after 30 years of follow up at a median age of 56 years in this group. This was substantially higher compared to CVD mortality in women with LOPE (1.7%) and without PE (0.7%) and underlines the severity of cardiovascular burden in women with EO PE.

Metabolic syndrome

Metabolic syndrome (MS) is a condition that defines the existence of a cluster of CV risk factors including impaired glucose metabolism, obesity, dyslipidemia, hypertension and proteinuria. MS increases the risk for CVD two-fold in the general population.[56] Interestingly, a cohort study of over 1 million former pregnant women showed that the magnitude of impact of CVD risk factors of MS on CVD risk were more pronounced when present in women with a history of 'maternal placental syndrome' (i.e. preeclampsia, gestational hypertension, placental abruption, or placental infarction).[5] MS in women with a history of PE resulted in more than 11-fold increased risk of CVD compared to women that have neither circumstance. Moreover, persisting asymptomatic diastolic dysfunction after PE strongly relates to presence of post-partum metabolic syndrome.[46] Altogether, MS therefore seems to mediate, at least partly, the increased CVD risk after PE.

CVD risk factors are often present for years before the development of overt CVD. Most of the individual risk factors of MS are modifiable. As most of these risk factors are often asymptomatic, many stay undiagnosed and untreated. In young women (18 to 39 years of age) without CVD, favorable CVD risk-factor levels are associated with lower CVD mortality.[57] Moreover, in women at age of 45, optimal risk factor levels were associated with lower CVD mortality and substantial longer time to onset of CVD (i.e. lower CVD morbidity).[58, 59] Early detection and treatment of these risk factors at young(er) age is likely to decrease CVD risk and could play an important role in reducing the CVD burden after PE.

Aiming to elucidated which former PE women are at risk for developing MS postpartum, in Chapter 3 and Chapter 4 we provided insight in presence of the postpartum MS after different PE phenotypes (i.e. weighing onset of PE and whether or not pregnancy was also complicated by delivery of a small for gestational age (SGA) infant).

Prevalence of MS was higher in women with a history of pregnancy complicated by PE and SGA (19.8%) compared to those with solely PE (15.6%) or solely SGA (7.5%). The high prevalence in the PE + SGA group related to onset of PE; in women with EOPE and SGA prevalence of MS was substantially higher (25.8%) compared to those with LOPE and SGA (5.6%). Previous studies found higher prevalence of MS in women with EOPE compared to those with LO PE.[60, 61] Our results add important information that high prevalence of MS relates to poor fetal growth as in women with EO PE without SGA prevalence was substantially lower.

In women with LOPE, prevalence of MS was higher in those without SGA compared to those with SGA. Moreover, in women with EOPE, there was a negative correlation between birth weight centile of the fetus, whereas in LOPE this correlation was reversed. A possible explanation could be that large for gestation age (LGA) infancy is more

common in women with LOPE.[62] Risk factors for fortified fetal growth (e.g. diabetes, dyslipidemia) overlap with MS.[63, 64] Prevalence of MS in women with a history of solely SGA was comparable to that of the overall prevalence of MS in Dutch women of similar age (i.e. women <40 years of age), suggesting a different mechanism responsible for their higher CVD risk. A possible explanation is the lower vascular compliance in women with a history of SGA, which is an independent predictor for cardiovascular events. This observation connects to the finding that by using conventional cardiovascular risk models currently used in cardiovascular risk management, primarily formerly preeclamptic women with concurrent hypertension are at increased modelled risk for future cardiovascular disease.[18]

There is no one-size-fits-all in the etiology of PE. Moreover, the mechanism of- and impact on future CVD health seems to relate to phenotype of PE in pregnancy. Our findings suggest a link with postpartum present MS and increased CVD risk in women with EOPE with SGA, as the prevalence of MS was over 5 times higher compared to that of overall prevalence of MS in Dutch women of similar age. Studies on CVD risk after PE showed that risk is higher after EO PE vs LO PE and PE with SGA vs PE without SGA.[5] It is likely that CVD risk is highest in women with a history with EOPE and SGA, but this hypothesize has yet to be tested. Nonetheless, our results warrant follow up of cardiovascular and cardiometabolic risk factors after EO PE with SGA.

Hypertension

Asymptomatic cardiovascular alterations occur earlier in women than previously thought. From early age i.e. the third decade, throughout life, BP increases steeper in women compared to men.[65] Especially at young age, there is a more pronounced association between blood pressure (BP) and CVD risk in women, were on the contrary, there seems to be no association with age in magnitude of effect of BP on CVD risk in men.[35] More than half of the mortality and disability from CVD occur in women with hypertension.[66] Untreated hypertension is a strong but modifiable risk factor for CVD. Prolonged exposure to elevated blood pressure will result in structural vascular and cardiac adjustments that all relate to increased risk of CVD.[67] Even before the age of 40, presence of hypertension strongly increases risk for subsequent cardiovascular events,[68] even after correction for multiple additional cardiovascular risk factors (hazard ratio for cardiovascular events was 1.75 (95% CI 1.22–2.53) in those with stage 1 hypertension (i.e. systolic BP (SBP) 130–139 mmHg and/or diastolic BP (DBP) 80–89 mmHg) and 3.49 (95% CI 2.42–5.05) in those with stage 2 hypertension (i.e. SBP ≥140 and/or DBP ≥90) as when compared to those with normal BP (<120/80 mmHg)). Moreover, threshold in BP for which risk for CVD risk increases in lower in women compared to men;[69] risk for myocardial infarction with SBP 110 to 119 mmHg in women was comparable to the risk with SBP ≥160 mmHg in men. This was also observed in the risk for heart failure (risk SBP 110 to 119 mmHg in women = risk SBP 120 to 129 mmHg in men) and risk

for stroke (risk SBP 120 to 129 mmHg in women = risk SBP 140 to 149 mmHg in men). Timely detection and treatment of elevated BP can reduce the risk for cardiovascular events. For every 10 mmHg reduction in SBP, risk for major cardiovascular events (coronary heart disease (CHD), stroke or heart failure(HF)) was reduced by 20% and all-cause mortality by 13%.[70]

Chronic hypertension explains most of the increased risk for CVD after PE as it accounts for half- up to two-third of the excess CVD risk after hypertensive complicated pregnancy.[17, 71] In a large prospective cohort study in over 23,000 women with a medial follow up of 18 years, BP in combination with BMI accounted up to 77% of the excess risk after hypertensive pregnancy complications.[71] Up to over half of women with a history of PE meet the criteria for stage 1 hypertension in the first period postpartum.[72, 73] However, normalization of BP occurs in up to half of these women in the following years.[73] Nonetheless, up to one third of women with a hypertensive disorder of pregnancy may stay- or develop hypertension within a decade after pregnancy.[20]

In our cohort, women with EOPE more often met the criteria for hypertension (i.e. approximately 30%) compared to LOPE (approximately 20%). Moreover, after pregnancy complicated by solely SGA (but not PE), prevalence was around 15%. Although these results suggest, in line with others, that risk for hypertension is highest after PE, more detailed identification of which women are at risk for chronic hypertension after PE seems to hamper structural follow up. Screening all former PE women in the years after pregnancy would have an enormous impact on health care capacities (as this would mean screening women of up to 8% of all pregnancies) and result in overmedicalization in a large proportion of these women. In Chapter 6 we developed a good to excellent performing model to predict risk for hypertension in the decade following PE pregnancy. The model was developed in a 259 women with a history of PE who underwent a first cardiovascular assessment after 10 months postpartum and a second assessment at a median of 11 years later. Women who were hypertensive at the first visit were excluded, as they are likely to stay under control of a physician. In the remaining normotensive group we developed a good- to excellent performing tool to predict chronic hypertension after PE. By determining fetal birth weight centile, mean arterial pressure, total cholesterol, left ventricular mass (LVM) index and left ventricular ejection fraction (LVEF) in the first months postpartum risk for hypertension can be assessed and used in stratifying follow up and screening for elevated BP after PE. The model has a high sensitivity (i.e. 98% when aiming at detecting women with 10% risk of hypertension in the decade following pregnancy) could make it suitable to distinguish low- from high risk women.

Of note with these findings is that in our first studies (Chapter 3 and Chapter 4) hypertension was defined according to the WHO definition of MS as SBP ≥140 and/or DBP ≥85 and/or use of antihypertensive medication. More recent studies result in the under-

standing that CVD risk is elevated from lower BP resulting in redefining hypertension by the American Heart Association to a lower threshold. Subsequently, in Chapter 6 we used SBP ≥130 and/or DBP ≥80 and/or use of antihypertensive medication as cut-off for defining hypertension.

Diabetes mellitus

Diabetes mellitus (DM) seems to be a more potent risk factor for CVD and CVD-related mortality in women than in men; risk for coronary heart disease in women with DM is over 40% higher compared to that in men with DM.[74] Moreover, in women, DM is associated with 50% higher relative risk for fatal coronary artery disease compared to men.[75] The effect of DM on CVD risk is most pronounced in young women (i.e. <40 years of age), underling the importance of early detection and treatment.[76] Both lifestyle interventions and pharmacological interventions that target DM and other CVD risk factors (e.g. hypertension, dyslipidemia) in individuals with DM2 decrease risk for CVD and CVD related mortality.[77] Women with DM more often have unfavorable cardiovascular risk factor profile as when compared to men (i.e. more cardiovascular risk factors like elevated BP and dyslipidemia present).[75] However, women with type 2 DM receive less treatment for modifiable CVD risk factors compared to diabetic men[78] which is likely to contribute to increased impact of DM on development of CVD in women.

Women who develop PE are more often insulin resistant before-, during- and after pregnancy compared to normotensive pregnancy.[79] Insulin resistance at mid gestation, especially when other constituents of the MS are present, seems to be an independent predictor of subsequent development of PE.[80, 81] However, before pregnancy, the relation between insulin resistance and the development of PE seems to be driven by other risk factors for the development of PE are also associated with insulin resistance (obesity, advanced maternal age, chronic hypertension) rather than it being a risk factor on its own.[82] In our cohort of postpartum women, hyperinsulinemia and high HOMA-ir values were highly prevalent after PE (up to over 60%), but only a small proportion of women met the criteria for elevated fasting glucose levels. Hyperinsulinemia seems to reflects a cardiometabolic and cardiovascular imbalance associated with obesity, hypertension and dyslipidemia, but not (yet) resulting in overt DM. The intermediate metabolic state between normal glucose metabolism and diabetes (i.e. prediabetes), increases risk for type 2 DM and CVD.[83] Normalizing glucose regulation by lifestyle interventions and antidiabetic drugs in individuals with prediabetes decrease the risk of type 2 DM and CVD.[83, 84] Although we did not evaluate presence of prediabetes, the high prevalence of insulin resistance in our cohort suggests that lifestyle intervention could improve cardiovascular outcome after PE.

Hypercholesterolemia

The relation between dyslipidemia and CVD risk has been well established. In particular lipocarriers of cholesterol (low-density lipoproteine (LDL) and very low-density lipoproteine (VLDL)) have strong atherogenic effects and are a primary cause of atherosclerosis.[85] Moreover, apolipoproteine B (apoB), the main protein of LDL and VLDL, can be measured to detect atherogenic cholesterol.

Before menopause, women tend to have a favorable lipid profile compared to men. However, after menopause, cholesterol levels rise to higher levels than in men suggesting that menopause has an unfavorable effect on lipid metabolism.[86] Large meta-analysis show that lowering cholesterol decreases CVD risk substantially; 5-year incidence of major cardiovascular events is reduced over 20% per mmol/L reduction in LDL, irrespective of initial cholesterol level, other CVD risk factors and whether or not participants had previous CVD.[87] Moreover, at middle age, 1 mmol/L lowering of total cholesterol results in halving risk of death from ischemic heart disease in both men and women.[88]

In primary prevention, current guidelines primarily use LDL-cholesterol to identify- and guide treatment for dyslipidemia.[85] With the exception of individuals with very high LDL-levels (>190 mg/dl, >4.9 mmol/l) and those with diabetes, initiation of pharmacological intervention (i.e. statin) in primary prevention is based on overall predicted CVD risk (including weighing factors like blood pressure, smoking), rather than solely cholesterol-levels. In young adults (20–39 years of age), pharmacological intervention should be considered for those with LDL-levels >160 mg/dl (>4.1 mmol/l) plus a positive family history for premature CVD, and for the remainder estimation of lifestyle CVD risk and if necessary lifestyle interventions should be advised. A previous study showed that lifetime CVD risk was elevated in approximately 40% of former PE women around 30 years of age (compared to approximately 18% in controls) which would make them candidates for lifestyle intervention.[89] For those aged 40 to 75 years and LDL-cholesterol 70–189 mg/dl, (1.8–4.9 mmol/L) predicted 10-years CVD risk drives the motivation for pharmacological treatment, where in those 'borderline'- and intermediate' 10-year CVD risk (i.e. 5 to 20%), presence of 'risk enhancers', including metabolic syndrome and a history of preeclampsia, favor initiation of treatment. In our cohort we found high prevalence of metabolic syndrome, making 2 risk enhancing factors in this group of young women. However, as maternal age was around 30 years of age in our cohort, a history of PE would not be weighing in treatment decision making according to current guidelines. Moreover, as age is an important factor in predicted 10-year CVD risk, this risk will be often low in former PE women >40 years of age in the years following pregnancy, but likely underestimating their lifetime risk.

In our cohort, lipid levels were comparable between different PE subgroups with the exception of triglyceride levels, which were lowest in women with LOPE with SGA

(lower compared to women with EO PE with SGA). This is in line with overall favorable cardiovascular and cardiometabolic profile in this subgroup.

There is room for improving diagnosis and initiation of treatment for dyslipidemia in women; a study (2021) showed that in a primary care setting, 18% of adults meeting the criteria for dyslipidemia were not diagnosed and did not receive treatment, especially in young women (20.1% of women compared to 15.8% of men).[90]

Obesity

Overweight defined as body mass index (BMI) ≥25 and <30 kg/m^2 and obesity as BMI ≥30 kg/m^2 are associated with higher risk for CVD morbidity and -mortality.[91] Alternatively, also high waist circumference can be used as an indicator of abdominal/central obesity with clinical cardiovascular consequences, even when BMI is in normal range.[92] The impact of obesity on the development of CVD seems greater in women than in men; obesity increased age-adjusted relative risk for CVD with 64% in women was and with 46% in men.[93]

Obesity results in endothelial dysfunction and acceleration of atherosclerotic changes in the vessel wall through several mechanisms, including systemic and vascular inflammation and insulin resistance. [94, 95] Obesity is associated with CVD including coronary heart disease, and particularly, heart failure (HF).[91, 96, 97] In a study with a median follow up of 14 years, incidence of HF in women increased with 7% for every 1-unit BMI increase (adjusted for other CVD risk factors).[97] In a cohort including middle aged women, women with obesity had over 2 times higher risk of congestive HF and those with morbid obesity (i.e. BMI ≥40) over 4 times higher risk compared to women with normal BMI (i.e. 18.5–24.9).[91] Obesity has impact on the heart function through several mechanisms, including hemodynamic changes including higher blood pressure and higher bit still less compensatory blood volume through hormonal- and neural activation, a direct effect of adiposity on the myocardium and inflammation resulting in cardiac stress and -injury leading to concentric LV remodeling and subsequent diastolic- and systolic HF.[95] The effect of obesity seems in particular associated with HF with preserved ejection fraction (HFpEF).[98] Cardiac structure and -function in HFpEF differ between individuals with normal BMI and those with obesity, with more pronounced cardiac abnormalities in obese individuals.[99] Altogether, these findings warrant focusing on weight management strategies for HF prevention. This is especially the case for women after PE, who are, as described above, at high risk for postpartum HF. Obesity in our cohort was highest (over 20%) in women with prior pregnancy complicated by PE with SGA.

Obesity often clusters with other traditional risk factors. In contrary to HF, were obesity is also independently associated with CVD risk, excess risk for (atherosclerotic) coronary artery disease by obesity was for almost 50% explained by these other risk factors.[100]

Prevention of development of these risk factors is likely to reduce overall CVD risk. The effect of weight loss by lifestyle intervention can reduce risk of type 2 diabetes, improve lipid profile (i.e. decrease of low-density lipoprotein cholesterol levels and increase of high-density lipoprotein cholesterol) and lower blood pressure.[101, 102] This is of great importance to former PE women, with high risk of multiple concurrent CVD-risk factors consistent with metabolic syndrome.[103-105] Moreover, middle-aged women with a healthy life style (not smoking, maintaining BMI <25 kg/m^2, a healthy diet, half-hour per day of vigorous or moderate activity and limiting alcohol consumption) have over 80% lower risk for coronary heart disease compared to women who did not meet all these criteria, underlining the importance of these interventions.[106]

Towards risk-guided cardiovascular follow up in women

Pregnancy offers a unique opportunity to early detect women at risk for CVD. Although the cardiovascular sequelae after PE have been known for decades, no structural cardiovascular follow up programs after these high risk pregnancies have been implemented. Guidelines recognize PE as an early indicator of CVD risk and advise appropriate follow up after pregnancy for monitoring and control of CVD risk factors, but remain vague about specific strategies to do this. Structural longitudinal cardiovascular assessment of all former preeclamptic women would implicate a novel additional burden on health care facilities. As not all former preeclamptic women have high risk for CVD, unselected longitudinal follow up of all women would result in over medicalization for a large proportion of them. Structured analysis of all formerly PE women in the first year after delivery along with personalized risk modeling for future hypertensive disease and suited individualized cardiovascular risk management strategies may be an effective answer to meet the clinical care demand by being purposeful at the same time.

Postpartum cardio-vascular and -metabolic risk factors of MS seem to play an important role in the increased risk of CVD after PE. As elaborated on in the previous paragraph, both pharmacological and non-pharmacological interventions for prevention- and treatment of CVD risk factors lowers CVD risk. The overall impact of screening for these risk factors in young women after PE has to be established. Lack of (large) trials on structural screening of risk factors in young adults (i.e. from around 30 years of age) and in particular young women result in insufficient data of the exact health benefits of such preventive interventions in the general population. Nevertheless, studies show that favorable CVD risk profile in women at a young age is associated with decreased CVD risk. This effect is likely to be even more pronounced in former PE women, that have a substantial higher CVD risk compared to women of comparable age without PE. We strongly support implementation of structural assessment for modifiable risk factors after PE, towards evaluating the overall health benefits of such interventions, but especially aiming at reducing overall CVD burden after PE. This thesis provides, on top of pre-existing literature, a good starting point towards such screening programs.

First, women with EOPE and SGA have, in line with their highest CVD risk, substantial high risk for postpartum MS (i.e. over 5 times compared to women of comparable age in the general population) that warrants priority of screening in this subgroup. Second, after external validation, the prediction model for development of hypertension as dominant driver of increased CVD risk in formerly PE women in the decade following pregnancy can provide the ability to distinguishing high- from low risk women. Early detection and treatment of elevated BP after PE is of great importance, as hypertension seems to explain most of the excess risk after PE. Finally, we support counseling shortly after pregnancy emphasizing the importance of maintaining a healthy lifestyle and its benefits for all PE women, not only in those with (excess) high risk with indication for tight follow up.

CVD risk prediction in (young) women

Current guidelines for the prevention of CVD advise use of the 10-year CVD risk estimate to guide decision-making for the intensity of preventive interventions.[102] The impact of sex-specific risk factors on CVD risk has increasingly recognized and guidelines consider PE as a risk-enhancing factor in guiding cardiovascular therapy (e.g. presence of PE in a women with borderline- or intermediate 10-year risk could be used as an argument to initiate statin treatment or reduce blood pressure at lower thresholds).[102] However, more detailed, sex-unique approaches seem mandatory to reduce CVD in women including sex-specific weighing of traditional CVD risk factors and including non-traditional risk factors like preeclampsia in current risk prediction tools. When using PE as a risk-predictor, if available, including pregnancy related variables like onset of disease and co-occurrence of compromised fetal growth could contribute to more accurate CVD risk estimation. Moreover, for young women after PE, estimating 30- or lifetime CVD risk instead of 10-year CVD risk, were age is an important factor, is likely to provide a better reflection of their cardiovascular status.

Conclusions and future perspectives

The extensive cardiovascular disease burden after preeclampsia warrants tailored cardiovascular risk management strategies and women specific treatment thresholds of cardiovascular risk factors in the years following pregnancy. Current CVD risk stratification tools are insufficient to detect those women at risk subsequently resulting in lack of follow up and insufficient treatment of risk factors.

In this thesis, we elaborated on cardiovascular alterations during- and after PE (Chapter 2 and Chapter 5). Asymptomatic cardiovascular alterations can persist after PE and seem to relate to presence of traditional cardiovascular risk factors. Aiming at detecting PE subgroups at risk (i.e. those for which structural screening is indicated), in Chapter 3 and Chapter 4 we provide insight which PE subgroups have highest risk for post-partum

metabolic syndrome and its individual risk factors. Moreover, in Chapter 6, we developed a prediction model for the development of hypertension after PE in women that were normotensive shortly after delivery. After external validation, implementation could be an important first step towards tailored cardiovascular risk management programs to timely detect those women for who CVD prevention measures are indicated without over-medicalization of women for who follow up is not indicated. Further research is necessary to determine the impact of these preventive strategies.

In general, we advocate implementation of women-specific clinical guidelines for cardiovascular disease prevention that include weighing female-specific risk factors like preeclampsia.

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Chapter 9

Valorisation

In this chapter, the relevance and possible impact of this thesis on society will be addressed.

Over the past decades, it has been well established that preeclampsia (PE) is associated with increased cardiovascular disease (CVD) risk. Research has shifted from the association between PE and CVD towards exploring what drives this excess CVD risk. Remaining cardiovascular changes inflicted by the hypertensive pregnancy itself and the present concurrent cardiometabolic and cardiovascular risk factors seem to promote the development of early-onset CVD. Especially emerging high blood pressure as one of the constituents of traditional CVD risk factors seem to play a dominant role and therefore pregnancy could offer unique opportunity to identify women at risk aiming at early detection and treatment of hypertension amongst the other CV risk factors before overt CVD. For over more than a decade, CVD prevention guidelines advise weighing PE in CVD risk assessment and follow up of CVD risk factors after pregnancy, but in absence of comparative trials, differences in how to reach this still exists. Subsequently, no widely supported follow up programs have been implemented to decrease the substantial CVD sequela after PE.

In this thesis, we provide additional understanding in cardiovascular- and cardiac alterations that drive excess CVD risk after PE, and the development of a predictive tool for the development of hypertension to distinguish high- from low risk women. Overall, aiming to contribute in the process towards developing stratified follow up after these complicated pregnancies.

CVD prevention

CVD is the leading cause of morbidity and mortality in women. Besides its clinical impact, the economic impact is substantial and still increasing; in the United States alone, it is estimated that total CVD cost will rise up to over 1 trillion dollar in 2035. (1) All together, prevention before overt clinical CVD is mandatory. Initiation of preventive interventions in CVD risk management are currently based on predicted 10-year CVD risk scores. Existing guidelines on primary CVD prevention advise weighing PE as a 'risk enhancer' to guide initiation of preventive interventions in women with intermediate predicted 10-year CVD risk. On the one hand, this advice is only applicable to women from 40 years of age onwards as below that age, predicted CVD risk and predictions on the effect on lifetime health by CVD risk factor treatment are imprecise. (2) On the other hand, even in middle-aged women, according to current guidelines, preventive interventions are likely not be indicated as age is the major determinant in predicted 10-year CVD risk (e.g. a non-smoking women below 50 years will almost always have low predicted risk and subsequently receive no treatment of CVD risk factors, even when multiple known CVD risk factors are present). An alternative approach could be that PE is viewed upon as first cardiovascular event with consequently an indication

for secondary prophylaxis. The accepted treatment boundaries are than much more tight than in primary prevention.

In this thesis, we provided detailed insight in prevalence of metabolic syndrome (MS) and its components. As these CVD risk factors that are found in the first year after gestation often persist later in life, this provides guidance in detecting high risk women. (3) One of our major findings was that women with early onset PE in combination with compromised fetal growth have most severely affected cardiovascular- and cardiometabolic profile with prevalence of MS of over 25%. This was higher compared to other PE subgroups and women with a history of solely compromised fetal growth. Moreover, this is substantially higher than the prevalence of MS in women of comparable age in the Dutch general population (approximately 5%). This finding, in addition to the steeper rise in high blood pressure development in former PE women, underscores that tight follow up of risk factors of this subgroup of women is mandatory.

Prediction model for hypertension

Elevated blood pressure (BP) is the main force driving excess CVD risk after PE.(4) Moreover, BP in women in general CVD risk increases from a lower BP threshold when compared to men. These findings together strongly indicate that in the prevention of CVD initiation of treatment of BP should be considered at a lower threshold in (former PE) women. Therefore, in women, risk stratification tools to CVD should give more weight to (risk on) elevated blood pressure (BP). In our cohort, in the first year postpartum, approximately 30% of women with early-onset PE and 20% of women with late onset PE met the criteria for hypertension. This is substantially higher compared than the 3.8% of women aged 18-34 years with hypertension in the general Dutch population. However, it is less clear which PE women will develop chronic hypertension (i.e. some that are hypertensive in the first months postpartum will become normotensive in the following years and vice versa). The prediction model for chronic hypertension in the decade following PE in those women who are normotensive in the first months postpartum can, after external validation, be used as the first concrete tool to stratify follow up after PE. The high sensitivity of the model offers great opportunity to distinguish high- from low-risk women and possibly optimize utility of health care resources.

Presence of CVD risk factors in combination with a history of PE increase CVD risk substantially more compared to presence of either alone (5), suggesting higher impact of these risk factors on overall CVD risk after PE. More forward treatment of CVD risk factors, in line with secondary prevention guidelines, should be considered. Besides a lower threshold for BP treatment, effect of a lower threshold for initiation of lipid lowering therapy and more attention to the highly prevalent insulin resistance in primary prevention after PE should be evaluated. Expanding statin eligibility also seems cost-effective; a recent study from Scotland (6) predicted that lowering threshold for

statin use in primary prevention (i.e. from lower predicted 10-year CVD risk and based on absolute risk reduction) will likely result in a higher cost-effectiveness ratio. But also more structured attention and support in life style, weight management and diet should would be a logical consequence of our findings.

Desire for aftercare

An evaluation in Dutch former PE women showed that there is a clear desire for cardiovascular aftercare after PE. (7) However, as former PE women may be at variable risk for future CVD, much more tailored cardiovascular risk management is mandatory to come to purposeful care. Towards a more stratified approach, we support, largely in line with current Dutch guidelines, cardiovascular assessment after allowing recovery performed in second half of the year after giving birth (i.e. after cardiovascular- and metabolic derangements of pregnancy itself have 'normalized') to determine the intensity and individual specific addressed heath threatening issues within the cardiovascular follow up. From a cardiovascular risk management point of view, based on existing literature and findings from this thesis, this assessment should at least include measuring traditional CVD risk factors (e.g. BMI, lipid spectrum, glucose metabolism, blood pressure and kidney function) and preferably echocardiography to detect (subclinical) cardiac alterations to enable predicting risk for future hypertension. Information on future CVD risk and options for lifestyle modification when applicable should be provided in all former PE women. As these findings also affect PE recurrence rate, the most logical primary care giver should be the gynecologist, and when observed risk factors necessitate, further specialized care should be set in motion. Although early onset PE or growth restriction divergently affect the prevalence of CVD risk factors, the increased prevalence after PE in general supports the view that all former PE women qualify for initial cardiovascular risk assessment.

Follow up program

As we are only informed about cardiovascular and cardiometabolic risk factors and not effectiveness of treatment protocols, we can only make careful but logical recommendations weighing the impact of these risk factors along with obstetric history. We recommend cardiovascular assessment in all former preeclamptic women 6 to 12 months postpartum. When cardiovascular risk factors and/or (subclinical) abnormalities in cardiac function or structure are present at the postpartum assessment, the clinical consequences should be weighed to determine follow up sequence with or without referral to specialized care. Decreased kidney function and/or (persistent) micro-albuminuria and/or proteinuria also warrants also follow up and treatment by a medical specialist, regardless of other risk factors. Obesity, dyslipidemia or pre-diabetes could all first indicate weight management, lifestyle and diet attention. Blood pressure treatment is recommended at lower threshold in women, especially when slightly elevated blood pressure is accompanied by concentric or eccentric cardiac hypertrophy.

Further cardiovascular risk management (CVRM) could be determined by weighing the obstetric history and 10-year high blood pressure risk assessment. Considering their overall highest CVD risk and highest risk to develop CVD risk factors and cardiac abnormalities, it seems defendable to recommend CVRM of women with EO PE with concurrent compromised fetal growth in pregnancy. For women without CVD risk factors or cardiac abnormalities at the postpartum assessment, further risk stratification could be based on predicted 10-year risk to develop chronic hypertension. When risk is low (i.e. <10%), follow up of blood pressure could be considered every 5 years, but when 10-year high blood pressure risks exceed 10%, blood pressure follow up could be considered every year. When cardiac abnormalities are present, especially those consistent with subclinical heart failure, follow up could be considered every two years to evaluate progression to clinical heart failure or regression to healthy functioning.

It is without saying that future studies are necessary to determine the (cost-)effectiveness of implementation of this follow up after pregnancy.

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Chapter 10

Summary

Preeclampsia is associated with a substantially increased remote risk of early onset cardiovascular disease risk, and may be viewed upon as the 'twilight zone' between health and disease. Often, clinical obstetric characteristics of pregnancy complications are weighed in determining short and long term health sequelae in affected women. In **Chapter 2** we give an overview of the cardiac alterations during- and after preeclamptic pregnancy in comparison to normotensive pregnancy. In normotensive pregnancy, as a response to the extensive hemodynamic changes, remodeling of left ventricle shows alterations comparable to aerobic-exercise induced hypertrophy (i.e. eccentric remodeling). In preeclampsia, mainly as a result of increased pressure load in conjunction with reduced volume load, left ventricular hypertrophy develops in a concentric way with disproportional increase in left ventricular mass and relative wall thickness. Moreover, abnormalities in diastolic- and subclinical systolic function are often found, especially in relation to early onset- or severe preeclampsia, and persist in 25% to 72% of affected women in the years after delivery. These cardiac alterations are often subclinical during- and shortly after pregnancy, but may prelude remote clinical cardiovascular disease. In this group of young women, measuring strain by tissue color Doppler and angle-independent speckle tracking echocardiography is a promising method to detect subtle myocardial abnormalities that precede development of overt ventricular dysfunction.

in **Chapter 3** we studied the presence of metabolic syndrome in women with a history of preeclampsia, small for gestational age infancy, and those with a combination of both. Metabolic syndrome is a cluster of cardiovascular disease risk factors. As these risk factors are modifiable, early detection and treatment can reduce overall cardiovascular burden after preeclampsia. In this chapter, we provide better insight which former preeclamptic women are at highest risk for postpartum metabolic syndrome for whom monitoring and control of risk factors could be beneficial. Prevalence of postpartum metabolic syndrome was higher in women with a history of both preeclampsia in combination with small for gestational age infancy (19.8%) compared to those with solely preeclampsia (15.6%) or solely small for gestational age infancy (7.5%). Hypertension was more often observed in former preeclamptic women (25%) compared to women with solely small for gestational age infancy (15%).

In **Chapter 4**, we evaluated the association between postpartum metabolic syndrome and different preeclampsia phenotypes (weighing onset of disease and co-occurrence of small for gestational age infancy) in a cohort of over 1,100 women. Time of onset of preeclampsia relates to long-term cardiovascular disease risk after preeclampsia (i.e. higher risk in those with early-onset preeclampsia (<34 weeks of gestation) compared to those with late-onset preeclampsia). Moreover, also co-occurrence of small for gestational age infancy in preeclampsia elevates cardiovascular disease risk. We found that the prevalence of metabolic syndrome was highest in women with a history of early-onset preeclampsia in combination with small for gestational age infancy (25.8%)

compared to those with early-onset preeclampsia without small for gestational age infancy (14.7) and late onset preeclampsia (5.6% and 11.4% in those with- and without small for gestational age infancy respectively). In late onset preeclampsia, prevalence of metabolic syndrome was higher in women without small for gestational infancy compared to late onset with small for gestational age infancy. In this group, there was a positive correlation between fetal birth weight and metabolic syndrome. A likely explanation for this finding is that in late onset preeclampsia fortified fetal growth is common, which has risk factors that overlap with potentially growth stimulating constituents within the metabolic syndrome (e.g. diabetes, dyslipidemia).

In **Chapter 5** we investigated if preeclampsia is associated with accelerated age-related decline in vascular function by assessing vascular function in a substantial group of women with a history of preeclampsia and women with a history of normotensive pregnancy at different age intervals. Women were between 20 and 60 years old. Arterial ageing is a phenomenon that develops gradually over time and increases cardiovascular disease risk. Endothelial-dependent vasodilatory function was measured by flow mediated dilatation of the brachial artery and endothelial-independent vasodilatory function was tested using sublingually administered nitroglycerine-mediated dilation. Advancing age was associated with a decline in endothelial-dependent and -independent vascular function. However, there were no differences between women with a history of preeclampsia compared to those with normotensive pregnancy in this age related vascular decline. Although the cross-sectional study design limits the ability to fully exclude an effect of preeclampsia on vascular ageing over time, these results suggest that the excess cardiovascular disease risk after preeclampsia cannot fully be explained by accelerated peripheral vascular ageing after preeclampsia.

Hypertension is considered the strongest modifiable risk factor in the development towards cardiovascular disease. Timely detecting is mandatory to institute preventive measures. In **Chapter 6** we developed a good- to excellent performing model for development of chronic hypertension in the decade following preeclampsia. The model was developed in a longitudinal cohort of 259 former preeclamptic women that underwent a first cardiovascular assessment after 10 months postpartum and a second assessment at a median of 11 years later. We excluded women who were hypertensive at the first visit, as they are likely to stay under control of a health care physician. By determining fetal birth weight centile, mean arterial pressure, total cholesterol, left ventricular mass index and left ventricular ejection fraction in the first year postpartum, future risk for hypertension can be predicted. The high sensitivity of the model (i.e. 98% when aiming at detecting women with 10% risk of hypertension in the decade following pregnancy) allows distinguishing low- from high risk women and therefore can be used to stratify monitoring of blood pressure after preeclampsia.

In **Chapter 7** we evaluate the prevalence of conventional cardiovascular risk factors in former pregnant women with or without a history of preeclampsia at different age intervals. Despite the long-term risk for cardiovascular disease after preeclampsia, guidelines do not include specific recommendations on how to apply structural cardiovascular screening after complicated pregnancy. Insight in the prevalence of conventional cardiovascular risk factors at different age intervals may provide logical view upon the necessity of timely cardiovascular assessment. Data was used from the cross-sectional Queen of Hearts study, which includes relatively young women with a history of preeclampsia and a control group of women with a history of uncomplicated pregnancy. Based on history taking we established the prevalence of known diagnoses of hypertension, diabetes mellitus and hypercholesterolemia. We included 1040 (39 ± 8 years) women who had suffered preeclampsia and 518 who experienced normotensive pregnancy (44 ± 8 years). The prevalence of hypertension, diabetes mellitus and hypercholesterolemia is significantly higher in former preeclampsia women as compared to controls, already below the age of 40 and increasing with age. The age-related increase in risk was larger amongst former preeclamptic women than controls. Awareness on the high prevalence of cardiovascular risk factors at young age in former preeclamptic women should be taken into account when developing screening guidelines.

Chapter 8 elaborates on the findings of this manuscript.

Chapter 11

Nederlandse samenvatting

Vrouwen die pre-eclampsie hebben doorgemaakt, hebben een sterk verhoogd risico op het ontwikkelen van hart- en vaatziekten, vaak al op een jonge leeftijd. Van pre-eclampsie spreken we wanneer er in de zwangerschap hoge bloeddruk optreed en orgaanschade na de 20 weken van de zwangerschap. Een klinische voorgeschiedenis vermeldend pre-eclampsie kan daarom gezien worden als een 'schemergebied' tussen gezondheid en ziekte. Kenmerken van de zwangerschap worden vaak meegewogen om een inschatting te maken van de gevolgen voor de gezondheid van deze vrouwen op korte en lange termijn. In **hoofdstuk 2** geven we een overzicht van de veranderingen van het zowel de functie als geometrie van het hart van vrouwen tijdens- en na pre-eclampsie en van met vrouwen met een normale bloeddruk tijdens de zwangerschap (normotensieve zwangerschap). Als reactie op hemodynamische veranderingen in de zwangerschap ontstaat er bij normotensieve zwangerschap hermodellering van de linker ventrikel. Deze veranderingen zijn het meest vergelijkbaar met de excentrische linkerventrikelhypertrofie die ontstaat als gevolg van (langdurige) aerobe inspanning. Daartegenover ontwikkelen vrouwen met pre-eclampsie als gevolg van de verhoogde drukbelasting in combinatie met een verminderde volumebelasting concentrische linkerventrikelhypertrofie. Hierbij is er sprake is van een onevenredige toename van de linkerventrikelmassa ten opzichte van de inhoud van het ventrikel, de relatieve wanddikte. Daarnaast worden er vaak (subklinische) afwijkingen gezien in diastolische- en systolische functie van het hart, vooral bij vrouwen die een vroege en/of ernstige pre-eclampsie ontwikkelen. Deze afwijkingen blijven bestaan bij 25% tot 72% van de vrouwen in de jaren na de bevalling. Tijdens en kort na de zwangerschap zijn deze hartafwijkingen vaak subklinisch, maar kunnen een voorbode zijn voor het ontwikkelen van symptomatisch hartfalen. Naast de conventionele methoden is het meten van strain middels echocardiografie is een veelbelovende nieuwe techniek om in deze groep jonge vrouwen in een vroeg stadium subtiele afwijkingen van het myocard te detecteren zodat tijdig interventie ingezet kan worden om verdere achteruitgang in hartfunctie te voorkomen.

In **hoofdstuk 3** hebben we gekeken naar de prevalentie van het metabool syndroom na een zwangerschap gecompliceerd door pre-eclampsie, groeivertraging van het kind of een combinatie van beide. Het metabool syndroom is een cluster van risicofactoren voor hart- en vaatziekten. Omdat deze risicofactoren beïnvloedbaar zijn met verandering van leefstijl en/of medicatie, kan vroege detectie en behandeling ervan zorgen voor het verlagen van het risico op hart- en vaatziekten na pre-eclampsie. In dit hoofdstuk geven we beter inzicht in welke vrouwen na pre-eclampsie het grootste risico hebben op het ontwikkelen van het metabool syndroom na de zwangerschap en voor wie monitoring en eventuele behandeling van risicofactoren aanwezen is. De prevalentie van het metabool syndroom was het hoogste bij vrouwen na een zwangerschap met pre-eclampsie in combinatie met groeivertraging van het kind (19,8%) vergeleken met vrouwen met uitsluitend pre-eclampsie (15,6%) of alleen groeivertraging van het kind

(7,5%). Hypertensie werd meer gezien bij vrouwen met pre-eclampsie (25%) dan bij vrouwen waarbij er alleen sprake was van groeivertraging bij het kind (15%).

In **hoofdstuk 4** hebben we de associatie tussen de het metabool syndroom postpartum en verschillende fenotypes van pre-eclampsie onderzocht in een cohort van meer dan 1100 vrouwen. Hierbij werden het moment van ontstaan van pre-eclampsie in de zwangerschap (vroeg: <34 weken/ laat: ≥34 weken) en of er wel- of geen sprake was van groeivertraging van het kind meegewogen. Het moment waarop vrouwen pre-eclampsie ontwikkelen (vroege pre-eclampsie) in de zwangerschap is gerelateerd aan een hoger risico op hart- en vaatziekten in vergelijking met vrouwen met een late pre-eclampsie). Daarnaast is er sprake van een hoger risico op hart- en vaatziekten als er naast pre-eclampsie ook sprake is van groeivertraging bij het kind. Onze studie laat zien dat de prevalentie van het metabool syndroom het hoogste is bij vrouwen met een vroege pre-eclampsie in combinatie met groeivertraging bij het kind (25,8%). Dit was hoger in vergelijking met vrouwen met een vroege pre-eclampsie, maar waarbij er geen groeivertraging bij het kind was (14,7%) en bij vrouwen met een late pre-eclampsie (5,6% en 11,4% bij respectievelijk bij degenen met en zonder groeivertraging van het kind). Bij late pre-eclampsie was de prevalentie van metabool syndroom hoger bij vrouwen waarbij er geen sprake was van groeivertraging van het kind. Ook was er in deze groep een positieve correlatie tussen het geboortegewicht van het kind en het metabool syndroom. Een mogelijke verklaring voor deze bevinding is dat er bij late pre-eclampsie vaak juist sprake is van versterkte groei van het kind, waarvoor de cardiometabole risicofactoren overlappen met het metabool syndroom (bijvoorbeeld insuline resistentie en verhoogd cholesterol).

In de loop van het leven treedt er geleidelijke veroudering op van bloedvaten, wat het risico op hart- en vaatziekten verhoogd. In **hoofdstuk 5** hebben we onderzocht of dit proces bij vrouwen die een pre-eclampsie hebben doorgemaakt versneld optreedt door op verschillende leeftijdsintervallen de vaatfunctie te testen bij vrouwen met een voorgeschiedenis met pre-eclampsie en deze te vergelijken met vrouwen die een normotensieve zwangerschap hadden doorgemaakt. De vrouwen waren tussen de 20 en 60 jaar oud. De vaatfunctie werd getest door te kijken naar het vermogen van het bloedvat om te verwijden (vasodilatatie). Het endotheel-afhankelijke- als endotheel-onafhankelijke vermogen van een bloedvat om dit te doen werd getest doormiddel van respectievelijk 'flow mediated dilatation' van de arteria brachialis en met behulp van sublinguaal toegediende nitroglycerine. Bij het ouder worden zagen we dat er afname was van de endotheel-afhankelijke en endotheel-onafhankelijke vaatfunctie. Hierbij vonden wij er geen verschillen tussen vrouwen na pre-eclampsie en vrouwen na een normotensieve zwangerschap. Doordat de opzet van de studie cross-sectioneel was kunnen we niet volledig uitsluiten dat pre-eclampsie invloed heeft op de snelheid van veroudering van de bloedvaten, maar de resultaten van dit onderzoek suggereren wel dat het verhoogde risico op hart- en vaatziekten na pre-eclampsie hier niet volledig door verklaard wordt door functie verlies van het endotheel.

Hypertensie is de sterkste beïnvloedbare risicofactor voor hart- en vaatziekten. Het tijdig ontdekken en behandelen van een verhoogde bloeddruk is van groot belang om dit risico te verminderen. In **hoofdstuk 6** hebben we een predictiemodel ontwikkeld met een goede tot uitstekende voorspellende functie voor het ontwikkelen van hypertensie in de eerste 10 jaar na een zwangerschap gecompliceerd door pre-eclampsie. Het model werd ontwikkeld in een 259 vrouwen die gevolgd werden over de jaren en een uitgebreide analyse van hart- en vaten kregen 10 maanden na de zwangerschap en een tweede analyse gemiddeld 11 jaar later. Vrouwen die al hypertensie hadden bij de eerste beoordeling werden niet meegenomen in de studie, omdat deze vrouwen waarschijnlijk al onder controle blijven van een arts. Door middel van het bepalen van het percentiel van het geboortegewicht van het kind, de gemiddelde bloeddruk, het totale cholesterol, de linkerventrikelmassa-index en de ejectiefractie van het linkerventrikel in het eerste jaar na de bevalling, kan het toekomstige risico op hypertensie worden voorspeld. De hoge sensitiviteit van het model (d.w.z. 98% bij het opsporen van vrouwen met 10% risico op hypertensie in de eerste 10 jaar na de zwangerschap) maakt het mogelijk om vrouwen met een laag risico te onderscheiden van vrouwen met een hoog risico wat bij kan dragen aan het maken van een inschatting hoe intensief de bloeddruk na pre-eclampsie gemonitord moet worden.

Ondanks dat vrouwen na pre-eclampsie een verhoogd risico hebben op het ontwikkelen van hart- en vaatziekten geven richtlijnen geen specifieke aanbevelingen voor het toepassen van structurele screening na de zwangerschap. Inzicht in de prevalentie van traditionele risicofactoren voor hart- en vaatziekten na pre-eclampsie op verschillende leeftijdsintervallen kan een beter beeld geven wanneer screening naar risicofactoren nodig is. In **hoofdstuk 7** bekijken we het voorkomen van traditionele risicofactoren bij voormalige zwangere vrouwen met of zonder een voorgeschiedenis van pre-eclampsie op verschillende leeftijdsintervallen. Hiervoor werden data gebruikt van de Queen of Hearts studie, waarbij cross-sectioneel gekeken werd naar deze risicofactoren bij vrouwen na pre-eclampsie en bij vrouwen na een ongecompliceerde zwangerschappen. De prevalentie van hypertensie, diabetes mellitus en hypercholesterolemie voor aanvang van de studie werd vastgesteld middels anamnese. In de studie werden 1040 vrouwen die pre-eclampsie hadden doorgemaakt geïncludeerd en 518 met een normale zwangerschap in het verleden. De prevalentie van hypertensie, diabetes mellitus en hypercholesterolemie was significant hoger bij vrouwen die pre-eclampsie doormaakten, ook onder de leeftijd van 40 jaar. De prevalentie van deze risicofactoren nam toe met het oplopen van de leeftijd, wat meer uitgesproken was bij vrouwen na pre-eclampsie in vergelijking met vrouwen na een normotensieve zwangerschap. Bewustwording van de hoge prevalentie van risicofactoren voor hart- en vaatziekten op jonge leeftijd na pre-eclampsie moet meegewogen worden in het ontwikkelen van richtlijnen voor de screening na deze zwangerschappen.

In **hoofdstuk 8** worden de bevindingen van dit proefschrift bediscussieerd.

Chapter 12

Curriculum vitae

Mieke Hooijschuur werd op 24 april 1988 geboren in Groningen. Ze behaalde haar Vwo-diploma aan het Zernike college in Haren. Daarna studeerde zij geneeskunde, waarvan ze haar bachelor behaalde aan de Rijksuniversiteit Groningen. Haar master deed zij aan de Universiteit van Maastricht, waar ze haar MSc ontving in 2014.

Na haar afstuderen werkte zij als arts niet in opleiding tot specialist in het Ikazia ziekenhuis te Rotterdam op de afdeling interne geneeskunde. In 2017 begon zij de opleiding tot specialist Interne Geneeskunde (primair in het Ikazia ziekenhuis, sinds 2019 in het Erasmus Medisch Centrum). Momenteel is zij bezig met het laatste deel van deze opleiding; de differentiatie tot internist-infectioloog. Parallel aan haar opleiding tot medisch specialist deed zij een promotietraject onder begeleiding van Marc Spaanderman en Chahinda Ghossein-Doha.

Chapter 13

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