Cardiovascular risk at intermediate term in women after hypertensive pregnancy diseases

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Cardiovascular risk at intermediate term in women after hypertensive pregnancy diseases

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CHAPTER 1

General introduction and outline of this thesis

INTRODUCTION

Over the last three decades there has been a decline in cardiovascular disease (CVD) mortality worldwide in all age groups and for both sexes.[1] Despite this improvement, CVD is still the leading cause of death worldwide (Figure 1).[1,2] There are important differences between men and women in the development of CVD and the impact of the traditional risk factors. For the risk of acute coronary syndromes, smoking in young women (<55 years) is relatively more important than in similarly aged men[3,4], whereas smoking-associated risk for stroke is comparable between both genders.[5] Diabetes has a relatively higher CVD mortality risk in women than in men.[6] In young men, hypertension is more prevalent than in women; however, the opposite is true in females after menopause.[7]

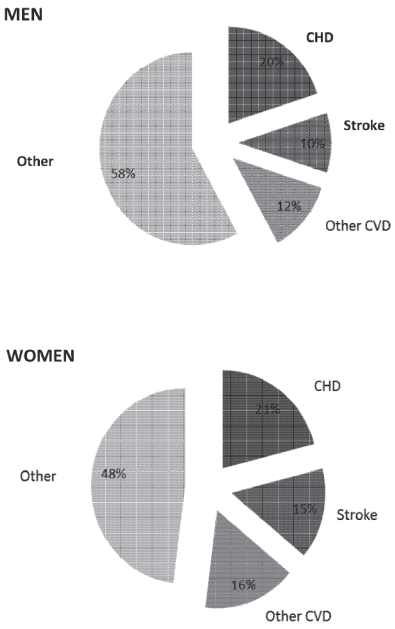

Figure 1: Death by cause in Europe for men (top) and women (bottom), from Nichols et al.[1] CHD, coronary heart disease; CVD, cardiovascular disease.

Beside these gender differences in classic CVD risk factors, several female-specific risk factors have been identified, mostly related to reproductive factors. Circulating estrogens are important for maintaining normal endothelial and vascular function in premenopausal women. Hormonal dysfunction or estrogen deficiency, which develops during menopausal transition, is associated with the development of vascular dysfunction and an adverse CVD risk profile.[8-10] Early menopause is associated with an increased CVD risk and emerging data indicate that menopausal age and vasomotor symptoms in menopausal transition reflects vascular health status.[11,12] On the other hand, a premenopausal harmful CVD risk factor profile is also associated with early menopause.[13]

Earlier in women's lives, pregnancy-related complications may be the first manifestation of an increased predisposition to CVD.[14,15] Hypertensive pregnancy disorders (HPD) complicate about 10% of all pregnancies and cover a spectrum of conditions: gestational hypertension (GH), chronic hypertension and preeclampsia (PE). Women with a history of HPD, especially preeclampsia are at increased risk for earlier manifestation of various CVD risk factors post pregnancy, such as an elevated BMI, higher blood pressure and unfavourable lipid values.[16] Besides the importance of preeclampsia as a cause of pregnancy-related disease and death[17,18], it is therefore also important for health later in life. Several population-based studies have shown that decades later the prevalence of CVD is at least doubled in women post PE compared to women with uncomplicated pregnancies.[14,19,20] More severe and recurrent HPD are associated with a higher risk of CVD (Figure 2).[21,22]

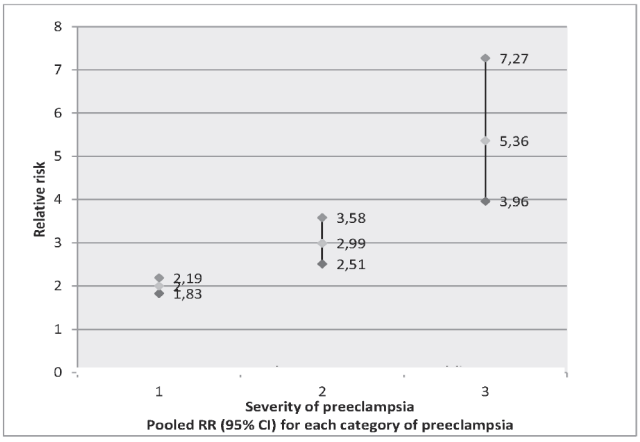

Figure 2: Graded relation between severity PE and cardiac disease and death, from McDonald 2008.[20]

Despite our knowledge on adverse long-term prognosis, data on the course of the development of CVD risk factors from pregnancy onwards are relatively scarce. Knowledge on intermediate-term CVD risk factors are necessary to understand the disease process in these young women and to determine at what moment postpartum preventive actions should be undertaken. In the latest 2011 guidelines of the American Heart Association on CVD prevention in women, it has been emphasized that HPD are important female specific cardiovascular risk factors.[23] It is recommended to monitor emerging CVD risk factors carefully in this subset of women, although concrete preventive measures are lacking. Currently, the follow-up of women with a history of PE is insufficient in primary care.[24] To develop more detailed preventive guidelines in these potential high risk women, additional information on the pathophysiological mechanism of CVD development and evaluation of the effectiveness of postpartum (lifestyle) interventions is needed.[25]

OBJECTIVES

The main aim of this thesis is to investigate the development of CVD risk in women with a history of the various manifestations of HPD, i.e., preeclampsia and gestational hypertension, at intermediate term postpartum. We will focus on the presence of traditional CVD risk factors, but also on first diagnostic signs of existing CVD. Furthermore, we are interested in the timing and (cost)-effectiveness of routine follow-up and treatment of CVD risk parameters in women post HPD.
As described, female-specific CVD risk factors are involved in the development of CVD in women. Our second purpose is to evaluate the presence of various female-specific risk parameters next to the traditional CVD risk factors in women.

OUTLINE OF THIS THESIS

In CHAPTER 2, we summarize the clinical spectrum of the various manifestations of HPD, and summarize the current knowledge on the etiology of PE and future risk to develop chronic hypertension. The longitudinal differences in traditional CVD risk factors between women with and without a history of gestational hypertension in a large population based cohort study (Doetinchem Cohort Study) are described in CHAPTER 3. Prevalence of CVD risk factors in a specific population of women post

early PE, based on the PREVFEM (Preeclampsia Risk EValuation in FEMales) cohort, are described in CHAPTER 4. In CHAPTER 5 we analyze ECG parameters at 10 years post index pregnancy and in unaffected controls from the PREVFEM-study. In CHAPTER 6 we evaluate a subset of novel cardiovascular and inflammatory biomarkers in the PREVFEM cohort. Subsequently, in CHAPTER 7 we describe the cost-effectiveness of screening for hypertension in women with a history of early pre-eclampsia.

In CHAPTER 8 we make a side-step to the female-specific CVD risk factors and describe the association between a history of HPD and presence, frequency, severity and intensity of vasomotor symptoms.

CHAPTERS 9 and 10 contain the general discussion and summary of the above-mentioned chapters.

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CHAPTER 2

Preeclampsia as a female-specific risk factor for chronic hypertension

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ABSTRACT

Preeclampsia is a complication of pregnancy that has also long-term effects on maternal health. Several epidemiologic studies have shown an increased risk for cardiovascular morbidity (relative risk [RR] 2.3) and mortality (RR 2.3) in women after a history of preeclampsia. The chance to develop chronic hypertension afterwards is 2-fold to 10 times higher in affected women, compared with women after normotensive pregnancies. As hypertension is a major cardiovascular risk factor, early detection and treatment is mandatory to reduce the risk of future cardiovascular disease. Data on (cost)-effectiveness of cardiovascular screenings programs in women after preeclampsia are currently lacking and there are no recommendations yet for prevention in the guidelines. We recommend regularly preventive blood-pressure measurements after high-risk pregnancies. More research is needed to identify women who will profit most of early intervention.

INTRODUCTION

Hypertensive disorders complicate 10% of all pregnancies and cover a spectrum of conditions including chronic (essential) hypertension, gestational hypertension, preeclampsia and the HELLP (Haemolysis, Elevated Liver enzymes and Low Platelets) syndrome.

Of these conditions, preeclampsia is the most important in absolute numbers of maternal and fetal morbidity and mortality. Besides the perinatal complications, preeclampsia has also long-term consequences for maternal health. Several epidemiological surveys have shown an association between preeclampsia and an increased risk for the development of hypertension and cardiovascular disease (CVD) later in life.[1-7] The underlying etiology of preeclampsia and future cardiovascular consequences is still debated, although both conditions share similar risk factors such as hypertension, elevated insulin resistance and dyslipidemia.[8-10]

In this review we discuss the hypertensive disorders of pregnancy, especially preeclampsia, and the current knowledge for their consequences on future maternal blood pressure.

Table 1: Definitions of hypertensive pregnancy disorders

Type of disorder	Blood pressure	Duration of gestation	Other symptoms
Chronic hypertension	≥140/90 mmHg	Before pregnancy, òr in first 20 weeks of gestation	–
Gestational hypertension	≥140/90 mmHg	>20 weeks of gestation until 12 weeks postpartum	–
Preeclampsia	≥140/90 mmHg	>20 weeks of gestation until 12 weeks postpartum	Proteinuria ≥0.3 g/24 h
HELLP syndrome	Not defined	>17 weeks of gestation until 1 week postpartum	hemolysis liver failure trombopenia proteinuria

CLINICAL SPECTRUM OF HYPERTENSIVE DISORDERS IN PREGNANCY (TABLE 1)

Chronic hypertension

Chronic hypertension complicates approximately 3% of all pregnancies and is defined as a blood pressure ≥140/90 mmHg that already exists before gestation or arises before the 20th week of pregnancy. Chronic hypertension is more prevalent in women with advanced age (>35 years) during pregnancy and in obese women.[9,11] It has a benign course, with often normalisation of blood pressure during midpregnancy. Antihypertensive medication is indicated when systolic blood pressure is higher than 150 mmHg or a diastolic pressure above 100 mmHg or when signs of hypertensive end-organ damage (nephropathy, left ventricular hypertrophy, retinopathy) are present. It is unknown whether adequate treatment of chronic hypertension in pregnancy may prevent the superposition of preeclampsia. Excessive lowering of blood pressure however may result in placental hypoperfusion and induce an adverse fetal outcome.[9,12]

Gestational hypertension

Gestational hypertension is defined as a systolic blood pressure ≥140 mmHg or a diastolic blood pressure ≥90 mmHg, occurring in the second half of pregnancy in previously normotensive women. Blood pressure has to be normalized at 12 weeks

postpartum. If hypertension does not resolve postpartum the condition is diagnosed as chronic hypertension.[9,1] Gestational hypertension occurs in about 8-10% of pregnancies. In about one third of these women, gestational hypertension will progress into preeclampsia.[11] The relative risk of future hypertension is between 1.7 and 7.2, depending on the years of follow-up and the severity of gestational hypertension.[7,13,14] Fetal consequences are mainly dependent on duration of pregnancy at delivery and birth weight.[15]

Preeclampsia

Preeclampsia, occurring in 3-5% of pregnancies, is defined as hypertension ≥140/90 mmHg and proteinuria ≥0.3 g/24 h occurring after the 20th week of gestation. Remission of symptoms of preeclampsia (hypertension and proteinuria) is induced by delivery, although in a small portion of women symptoms do persist postpartum. Sub-classifications can be made into mild preeclampsia (hypertension ≥140-159/90-99 mmHg and proteinuria ≥0.3-2.9 g/24 h) and severe preeclampsia (hypertension ≥160/100 mmHg or proteinuria ≥3.0 g/24 h). Preeclampsia can also be divided in early and late onset, referring at the gestational age when symptoms reveal. In early preeclampsia symptoms appear before 28 weeks of gestation. Fetal consequences of preeclampsia are preterm birth and growth retardation with low birth weight, which are both important causes of neonatal death. Globally preterm birth (<37 weeks of gestation) accounts for a quarter of neonatal deaths, which is defined as death in first 28 days after delivery. Low birth weight, is an important indirect cause of 60-80% of neonatal deaths.[15,16] The risk of ischemic heart disease and mortality is at least 2-fold higher in women with a history of preeclampsia compared with women with normotensive pregnancies.[1-3,6] Preeclampsia occurs most often in first pregnancies, however, the risk of recurrence is high estimated at 30-50%. In women with a history of early preeclampsia (symptoms before 28 weeks of gestation) the recurrence rate is even higher.[16,17]

Eclampsia is the convulsive form of preeclampsia and affects approximately 0.1% of all pregnancies. Seizures are most plausibly caused by hypertensive encephalopathy.[17] The risk of recurrent eclampsia is low, while the recurrence rate of preeclampsia remains high.[18]

HELLP syndrome

The HELLP syndrome is a severe form of preeclampsia with the clinical syndrome of renal failure, liver failure, disseminated intravascular coagulation and central nervous dysfunction (cerebral edema, seizures, headaches). It occurs in 10-20% of women with

signs of preeclampsia and leads to urgent delivery with a high maternal and fetal mortality rate (7-20%).[11,19] Blood pressure levels are not typically very high, but can be moderately elevated, sometimes even without proteinuria.[9] Recurrence of the HELLP syndrome is low, approximately 2-5%. However, up to 50% of these women will develop hypertension in subsequent pregnancies.[20] Data on future cardiovascular (CV) risk post HELLP syndrome is scarce, the chance to develop chronic hypertension after 3-5 years of follow-up varies from 6-33%.[21-23]

ETIOLOGY OF PREECLAMPSIA IN PREGNANCY

There are many theories about the etiology of preeclampsia, it is therefore called the 'disease of theories'.[24] Mechanisms involved in its pathophysiology are an abnormal placentation, constitutional factors of the mother (CV risk factors and familiar occurrence of pregnancy-related complications) and an exaggerated metabolic response on pregnancy. Inadequate trophoblast invasion of the spiral arteries in the placenta bed leads to hypoperfusion and ischemia of the placenta. This causes an activation and dysfunction of the maternal endothelium with vasoconstriction and an enhanced vascular permeability of the maternal blood vessels. This results in clinical signs of preeclampsia in the mother with the development of hypertension, proteinuria and oedema.[8,9,25] Several metabolic components in the maternal circulation further contribute to the activation of the endothelium. Many serum levels of inflammatory markers such as cytokines, leucocytes and a variety of cellular adhesion molecules (TNFα,IL-2, IL-6, VCAM-1, ICAM-1, E-selectin) are up-regulated. During normal pregnancy coagulation factors (factor V, VII, VIII, von Willebrand, X, XII) and platelets are elevated while fibrinolysis is suppressed. In preeclampsia however this response is exaggerated, leading to a hypercoaguability state. The occurrence of micro-vascular thrombi in different organs (e.g., kidney, cerebrum) is therefore very common. Triglycerides, low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) rise to very high levels during preeclampsia, while high-density lipoprotein (HDL) levels are very low. These changes in serum lipid levels may further contribute to the endothelial damage in the mother.[8]

Oxidative stress

The vascular lesions in the placenta bed, due to ischemia, are called 'acute atherosis' and are characterized by fibrosis, foam cells, fibroblast proliferation and a mononuclear

cell perivascular infiltrate. These lesions are comparable with early atherosclerotic plaque formations in CVD disease. Oxidative stress plays an important role in the aetiology of atherosclerosis and may also be involved in the maternal response to placental ischemia. The release of free oxygen radicals, like superoxide aniones or lipid hydroperoxides, damages the endothelium and contributes to the development of atherosclerotic plaques.[8,26] It is hypothesized that oxidative stress and acute atherosis may be the main causative factors in the increased CV risk in women with a history of preeclampsia.[24]

Other triggers for preeclampsia

Besides the abnormal placental vascularisation other triggers may be involved in the activation of the endothelium in preeclampsia. Infections (urinary tract infections) and pre-existent auto-immune diseases or coagulation disorders (like disseminated lupus erythematosus or hyperhomocysteinemia) have been mentioned.[9,17,25] These underlying conditions may change the maternal responsiveness to pregnancy and provoke the clinical signs of preeclampsia.[25]

Genetics

Genetic factors are involved in the development of preeclampsia, both by the maternal and fetal genotype. A positive family history of preeclampsia (mothers and sisters) triples the risk of occurrence.[27] Maternal susceptibility for preeclampsia may also be influenced by paternal antigens. This is in line with observations that primipaternity and a changed paternity in multiparous women are also risk factors for preeclampsia.[24,28] Currently, investigations aim at the candidate gene theory (single genes only expressed in pregnancy), linkage genes (involved in maternal-fetal interaction) and associations with specific immunological genes (like the HLA system).[24]

RAS (renin-angiotensin system)

During pregnancy the RAS is activated in the uteroplacental unit by hypoperfusion of the placenta and this may mediate in the pathophysiology of hypertensive pregnancy disorders. In normal pregnancy levels of renin, angiotensin and aldosteron are elevated with less sensitivity to angiotensin II. Paradoxically, in preeclampsia sensitivity to angiotensin II is increased, resulting in a higher peripheral resistance and blood pressure. This leads to vasoconstriction in the kidneys and a deterioration of renal function with proteinuria.[29,30]

Table 2: Risk of chronic hypertension after preeclampsia/ hypertensive pregnancy

Study	Study design	Patients	Matching	N	Follow-up (years)	Relative risk (95% CI)/percentage	Adjustment
Sibai, 1986[18]	PC	PE vs NT	age, race, age of delivery	406 vs 409	7.3	2.63 (1.66-4.17)	–
Hannaford, 1997[48]	PC	PE vs NT	–	2371 vs 14,831	12.5*	2.35 (2.08-2.65)	age, smoking, socioeconomic status
Marin, 2000[13]	PC	PE vs NT	–	80 vs 86	16.2	3.7 (1.7-7.9)	BMI, DM II, hypercholesterolemia, socioeconomic status, follow-up time
		GH vs NT		111 vs 86		7.2 (3.4-14.8)	
Forest, 2005[32]	PC	PE vs NT	–	63 vs 168	7.8	12.5 (2.9-54.1)**	–
		GH vs NT		105 vs 168			
Adams and Macgillivray, 1961[44]	RC	PE vs NT	–	53 vs 185	–	5.91 (3.89-8.98)	–
Carleton, 1988[46]	RC	PE vs NT	age	23 vs 23	10	1.50 (0,28-8,16)	BMI
Nisell, 1995[47]	RC	PE vs NT	–	45 vs 44	7	8.80 (1.16-66.59)	–
Shammas and Maayah, 2000[49]	RC	PE vs NT	–	47 vs 46	10	7.50 (2.42-23.28)	–
Wilson, 2003[7]	RC	PE vs NT	age	443 vs 206	32	2.62 (1.77-3.86)	age, BMI, socioeconomic status, smoking
		GH vs NT		343 vs 206		1.70 (1.13-2.56)	
Sattar, 2003[31]	RC	PE vs NT	date index- partus, BMI, smoking	40 vs 40	20	3.50 (0.77-5.87)	–
Lykke, 2009[14]	RC	GH vs NT	–	7449 vs 741,012	14.6	5.31 (4.90-5.75)	age, year of delivery, DM II, preterm delivery, stillbirth, SGA offspring, placental abruption
		Mild PE vs NT		26,810 vs 741,012		3.61 (3.43-3.80)	
		Severe PE vs NT		7016 vs 741,012		6.07 (5.45-6.77)	
Bellamy, 2007 [2]	Meta	PE vs NT	–	3658 vs 16,086	14	3.70 (2.70-5.05)	–

PC, prospective cohort; RC, retrospective cohort; Meta, meta-analysis; PE, preeclampsia; NT, normotensive during pregnancy; GH, gestational hypertension.

* Calculated from total number of women years as reported in Bellamy et al.[2].

** Preeclampsia and gestational hypertension groups combined.

PREECLAMPSIA AND ATHEROSCLEROSIS, ASSOCIATED BY THE INSULIN RESISTANCE SYNDROME?

Traditional CV risk factors like hypertension, dyslipidemia, obesitas and diabetes are more often pre-existent in women who develop hypertensive disorders in pregnancy. Postpartum the prevalence of these CV risk factors further increases.[13,27,31-36] Clustering of various risk factors in the metabolic syndrome is associated with an even higher risk of future CVD.[37] In the CHAMPS-study (Cardiovascular Health After Maternal Placental Syndromes - study) an almost 12-fold increased risk of premature CVD was found in women with the combination of preeclampsia and the metabolic syndrome.[3] Elevated insulin resistance is a common factor in both preeclampsia and atherosclerosis.[38-42] The time of onset of preeclampsia (early vs late) is also important for the development of the metabolic syndrome. At 1 year postpartum the metabolic syndrome is two times more present in women with early-onset preeclampsia than in women with late-onset preeclampsia.[43] Probably the metabolic syndrome is important in the development of both preeclampsia and cardiovascular disease on future age, however the exact mechanisms are not clear.

DEVELOPMENT OF CHRONIC HYPERTENSION AFTER PREECLAMPSIA

Several case-control and cohort studies have shown a higher risk of chronic hypertension after preeclampsia (Table 2).[2,7,13,14,18,31,32,44-49] Mild and severe preeclampsia may have a different impact on the risk of chronic hypertension. Lykke et al.[14] have made a subclassification into mild preeclampsia (hypertension and proteinuria) and severe preeclampsia, including signs of the HELLP syndrome. The relative risk (RR) of hypertension was 6.07 for severe preeclampsia compared with 3.61 for mild preeclampsia.
Gestational hypertension is generally considered a more benign condition in terms of perinatal morbidity and mortality in comparison with preeclampsia and the HELLP syndrome. Some studies however have reported a higher risk on chronic hypertension after gestational hypertension than with preeclampsia.[13,47,48] Differences in definition of exposure in these studies may have caused this inconsistency. Others speculate on the heterogeneous expression of hypertensive diseases in pregnancy with a different pathophysiology.[10,50] While early preeclampsia may be caused by placental dysfunction, late-onset preeclampsia may be the expression of a hypertensive condition

without placenta dysfunction. However, this does not explain the differences in prevalence of chronic hypertension later in life.

RECOMMENDATIONS FOR PREVENTION OF CHRONIC HYPERTENSION AFTER PRE-ECLAMPSIA

Hypertension is a major risk factor for the development of CVD in women. The worldwide prevalence of hypertension in all age-groups is estimated at about 26% and will rise up to 30% in the coming years.[45] In the USA 75% of postmenopausal women develop hypertension that has to be medically treated.[51,52] Antihypertensive treatment translates in significant reductions of cardiovascular morbidity and mortality, comparative in men and women.[53] In the latest USA guidelines for CVD prevention in women there are no recommendations yet for women with a past history of preeclampsia.[54] These are not formulated either in the latest European guidelines for the management of arterial hypertension.[53] In current clinical practice monitoring of blood pressure post-partum is performed until clinical signs recover, usually several weeks post-partum. As the risk for chronic hypertension can be 1.50 to 12 times higher (see Table 2) in these women compared with normotensive women in pregnancy, regular controls of blood pressure are advisable. Lifestyle modifications are the first step in treatment of elevated blood pressure.[53-55] Additional medical treatment of hypertension should be according to the current guidelines. So far there are no published follow-up data on the (cost)-effectiveness of cardiovascular screening/ monitoring programs in women after preeclampsia. Until further evidence confirms benefit of cardiovascular screening in women with a history of preeclampsia, there seems to be no place for preventive interventions other than lifestyle modification.

PREVENTION OF PREECLAMPSIA

Reducing the occurrence of preeclampsia will improve long-term maternal health. A healthy lifestyle is of primary importance, especially in women with a positive family history and the presence of several CV risk factors such as obesity. Other known risk factors for the development of preeclampsia are pre-existing auto-immune disease (antiphospholipid antibodies) and increased maternal age. Weight loss and adequate treatment of pre-existing cardiovascular risk factors can be effectuated in

preconception care. In pregnancy the women with identified high-risk for development of preeclampsia should be monitored more carefully in antenatal care for the development of symptoms (e.g., hypertension and proteinuria).[27,55] Unfortunately, there is not one single diagnostic test (hormone markers or markers of placental insufficiency) which predicts the development of preeclampsia adequately. In the absence of a golden standard the search for a predictive test is even more difficult. Uterine artery Doppler assessment can be used to demonstrate inadequate trophoblast invasion in women at risk, but is of limited ability in screening, although a positive result increases the likelihood ratio by six. Genetic research may probably reveal some distinct features in the future to predict preeclampsia at an earlier stage.[56,57]
In pregnant women with a history of preeclampsia prevention with aspirin can be considered, starting after the first 12 weeks of gestation, but the benefits are minor. Antihypertensive medication in pregnancy can be given conform the current obstetric guidelines.[55-57] Calcium supplementation is only useful in women on low calcium intake.[58] There is no evidence that other nutritional interventions or supplements (antioxidants, fish oil, sodium restriction) are effective to prevent (re-)occurrence of preeclampsia.[55,56]

CONCLUSION

Preeclampsia complicates about 3-5% of pregnancies, with serious consequences on maternal lifetime cardiovascular health. The risk to develop chronic hypertension later in life is high and guidelines for blood-pressure management post preeclampsia are currently lacking. Future research should focus on cost-effectiveness of CV screening programs in women afterwards. Physicians should be triggered by a history of hypertensive pregnancy disorders and provide surveillance for blood pressure with adequate lifestyle measurements in these potential high-risk women.

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CHAPTER 3

Longitudinal analysis of cardiovascular risk parameters in women with a history of hypertensive pregnancy disorders: the Doetinchem Cohort Study

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ABSTRACT

Objective: Women with hypertensive pregnancy disorders (HPD) are at increased risk of developing hypertension and cardiovascular disease later in life; however, it is unknown how cardiovascular risk develops throughout life. We evaluated the longitudinal trends in cardiovascular risk factors in women after hypertensive pregnancy disorders compared to women with normotensive pregnancies.
Design and population: All women of the Doetinchem Cohort Study (1987-1991), a population-based cohort study, were included.
Methods: Women were examined (questionnaires and physical examination) four times at 5-year intervals. History of HPD was assessed from questionnaires. We compared 5-year changes in risk factors between women with and without HPD, by analysing longitudinal trends using generalized estimating equation analysis to estimate the effects of HPD and mean age, adjusting for treatment, body mass index (BMI), smoking and social economic status.
Main outcome measures: Change over time in traditional cardiovascular risk factors, including systolic blood pressure (SBP) and diastolic blood pressure (DBP), BMI, total and high-density lipoprotein (HDL) cholesterol for women with and without history of HPD.
Results: A total of 2703 women with normotensive pregnancies (mean age 40.5 years, SD10.4) and 689 women with a history of HPD (mean age 38.4 years and SD 9.5) were included. Compared to normotensive women, in women with a history of HPD, SBP was 2.8 mmHg higher (95%CI 1.7; 3.9), DBP 2.3 mmHg higher (95%CI 1.6; 3.0) and BMI 0.7 kg/m^2 higher (95%CI 0.4; 1.1). Total cholesterol (-0.05; 95%CI -0.1; 0.0) and HDL cholesterol (0.02; 95%CI -0.0; 0.1) were similar in both groups. No difference in annual change in blood pressure or in the other risk factors was observed between women with and without a history of HPD.
Conclusion: Women with a history of HPD have higher levels of SBP, DBP and BMI compared to normotensive women, but the increase with ageing is similar in both groups.

INTRODUCTION

In the last decade differences in cardiovascular disease (CVD) between men and women have been extensively studied. Well-known cardiovascular risk factors such as

hypertension, hypercholesterolemia and diabetes mellitus are important for both genders. In addition, several female-specific risk factors have been identified, mostly connected with reproductive history.[1-3] A history of complications in pregnancy, such as gestational diabetes, hypertensive pregnancy disorders (gestational hypertension, preeclampsia and HELLP [hemolysis, elevated liver enzymes and low platelet count] syndrome) and placental dysfunction have been associated with increased cardiovascular risk. The severity of pregnancy disorders is related to future cardiovascular risk.[4-8] Women with a history of preeclampsia, defined as hypertension and proteinuria in the second half of pregnancy, have at least a two times higher risk of cardiovascular disease at older age.[9-11] Gestational hypertension is more benign in terms of pregnancy outcome and long-term maternal health; however, risk of chronic hypertension and coronary artery calcification is also increased in these women.[12-14] Several hypotheses about the mechanism between hypertensive pregnancy disorders (HPD) and CVD have been postulated, and endothelial dysfunction seems to play a crucial role in the development of future CVD.[15-19]

Until now there has been a gap in information on the development of cardiovascular risk between the ages of 40 and 60 years in women after HPD. A recent study showed an increased 10-year cardiovascular risk in women with a history of HPD 18 years postpartum compared to women with normotensive pregnancies or previous gestational diabetes.[8] However, longitudinal follow-up data are not available. Current guidelines identify women with a history of gestational diabetes, GH and PE at risk for future cardiovascular disease, although there are no specific recommendations on timing of monitoring or prevention in these high-risk women;[20] neither is there evidence on cost-effectiveness of preventive measures in this target group.[21-22]

The objective of this study is to gain more insight into the presence and development of cardiovascular risk factors over time in women with a history of HPD. In this study we investigate in a population-based cohort, the Doetinchem Cohort Study, the longitudinal trends in the cardiovascular risk factors blood pressure, body mass index (BMI), total cholesterol and high density lipoprotein (HDL) cholesterol in a subgroup of women with and without a history of HPD.

METHODS

Study population

The Doetinchem Cohort Study is a prospective population-based study, set up to study the impact of (changes in) lifestyle factors and biological risk factors on health.

Between 1987 and 2007, four measurement rounds were completed. At baseline (R1: 1987-1991), 12 405 inhabitants aged 20-59 years of Doetinchem, a town in a rural area of The Netherlands, were examined as part of the Monitoring Project on Cardiovascular Disease Risk Factors (MP-CDRF). From the first round, a random sample of 7769 participants was re-invited for a second examination (R2: 1993-1997), and again 5 and 10 years later for a third (R3: 1998-2002) and fourth (R4: 2003-2007) examination. A detailed description of the sampling and data collection procedures has been published previously.[23] The study protocol was approved by the external Medical Ethics Committee of The Netherlands Organization of Applied Scientific Research Institute (TNO), and all participants provided written informed consent. To evaluate the effects of HPD we only selected the women in Doetinchem Cohort study (n=3392); throughout the study there were 2703 women without a history of HPD and 689 women with a history of HPD (i.e., a positive answer on the question 'Did you ever have high blood pressure in pregnancy.').

Outcome variables

Biological risk factors: The biological risk factors of interest for the present study that were collected in each round included (1) systolic blood pressure (SBP) and diastolic blood pressure (DBP), (2) total and HDL cholesterol and (3) height and weight. Body weight and height were measured in light indoor clothing with emptied pockets and without shoes. Height was measured with a wall-mounted stadiometer to the nearest 0.5 cm. Body weight was measured with a balance beam scale to the nearest 0.5 kg. BMI was calculated as weight (kg) divided by height (m) squared. Blood pressure was measured twice, with the participant in sitting position. The mean value of the two measurements was used in the analysis. In R1-3 blood pressure (BP) was measured with a random zero sphygmomanometer (Hawksley & Sons, Lancing, UK) and the first and the fifth phase Korotkoff sounds are the criteria for SBP and DBP, respectively. In examination R4, BP was measured by means of an automated Speidel-Keller meter (Welch Allyn, Skaneatelles Falls NY, USA). In all rounds, a 30-ml non-fasting serum blood sample was drawn. Total and HDL cholesterol were determined at the Lipid Reference Laboratory of the Erasmus Medical Center in Rotterdam, using an automated enzymatic procedure.

Cardiovascular risk factors: Hypertension was defined as a SBP $\geq$140 mmHg and/or a DBP of $\geq$90 mmHg and/or use of antihypertensive medication. Presence of diabetes mellitus (DM) was defined as self-reported treatment for DM; hypercholesterolemia as

non-fasting total cholesterol ≥6.5 mmol/l and/or use of statins. Smoking was defined as current smoking, ex-smoking or no smoking.

Other variables: In each round, participants completed a questionnaire on demographic characteristics, lifestyle characteristics and presence of chronic diseases or risk factors thereof. Use of antihypertensive medication and cholesterol lowering therapy was classified into yes/no. Educational level was assessed as the highest level of completed education during follow-up and classified into three categories: low (intermediate secondary education or less), medium (intermediate vocational or higher secondary education) and high (higher vocational education or university). A history of HPD was defined by self-reported history of hypertensive pregnancy disease. This was based on a positive answer of the question 'Did you ever have high blood pressure in pregnancy' at one of the four rounds. A history of gestational diabetes was also based on self-reported history.

Data analysis

Baseline characteristics were described as mean with standard deviation for continuous data, and as percentages for categorical data. Differences between women with and without HPD for continuous data were analyzed by Student's *t*-test for independent groups and for categorical data with Chi-square or Fisher exact test when appropriate.

To evaluate the effect of HPD and age on blood pressure, cholesterol measurements and BMI over the follow-up time we used generalized estimating equation analyses (GEE) with the GENMOD procedure in SAS software (SAS Institute, Cary, NC, USA). The GEE procedure extends the generalized linear model to allow for analysis of repeated measurements at different time points. The intercept of this model is an estimate of the difference in risk factor between women with and without HPD. For this analysis we modeled HPD time-dependently, which means that women were defined as having had HPD from the moment on they reported first HPD. The regression coefficient is an estimate of the annual change in risk factor. Whether presence of HPD yes or no modifies the age-related increase in risk factors was evaluated by including the interaction term 'HPD x age' into the model. Adjustments for use of antihypertensive medication, statins, BMI, smoking and social-economic status (SES) were made. All p values were two-sided, statistical significance was assumed when two tailed probability value was <0.05.

RESULTS

Table 1 shows characteristics of the Doetinchem women at all four follow-up rounds. Table 2 shows the regression analysis of the different continuous cardiovascular risk factors (SBP and DBP), BMI and cholesterol (total and HDL) for presence of HPD, ageing and interaction between HPD and age.

Blood-pressure levels were significantly higher in the women with a history of HPD compared to those without HPD. SBP was 3.10 mmHg (95%CI 1.95; 4.25) higher and DBP 2.58 mmHg (95%CI 1.87; 3.29) higher in women with HPD compared to women without history of HPD. Adjustment for use of antihypertensive medication, statins, BMI, smoking and SES in the model slightly decreased the blood-pressure differences between both groups, but differences remained statistically significant, SBP 2.78 mmHg (95%CI 1.69; 3.87) higher and DBP 2.30 mmHg (95%CI 1.62; 2.98). No interaction effect for the presence of HPD and age-related increase in blood pressure was observed: the increase in blood pressure was 0.84 mmHg (95%CI 0.80; 0.88) per year for SBP and 0.29 mmHg (95%CI 0.26; 0.31) per year for DBP in both groups.

Body mass index was also significantly different between both groups, 0.64 kg/ m^2 higher (95%CI 0.29; 0.99) in women with a history of HPD; the yearly BMI increase was not different according to HPD (0.10 m^2/kg (95%CI 0.09; 0.11) per year. Adjustment for potential confounders did not change the BMI differences between the groups nor the annual BMI increases in women.

At rounds 1 and 2, total cholesterol was higher in women without history of HPD, later this difference disappeared. HDL levels were similar at each round. After full adjustment, total and HDL cholesterol levels did not differ between women with and without history of HPD (difference between groups -0.05 mmol/l; 95%CI -0.13; 0.03 for total cholesterol, and 0.02 mmol/l; 95%CI -0.01; 0.05, for HDL cholesterol). A history of HPD also did not influence yearly changes of total and HDL cholesterol.

Prevalences of other traditional cardiovascular risk factors are described in Table 1. Smoking prevalence was lower in women with HPD at rounds 1 to 3. Prevalence of hypertension was not different between both groups, although use of antihypertensive medication was more prevalent in women without history of HPD at rounds 1 to 3. Prevalence of hypercholesterolemia, DM and family history of myocardial infarction was similar in both groups of women. Women with a history of HPD had more often previous gestational diabetes compared to women without hypertensive pregnancy complications (6% for women with HPD and 3% in women without HPD at round 4).

Table 1: Baseline characteristics of the women in the Doetinchem Cohort

Variable	Doetinchem Cohort women Mean (SD)							
	Round 1		Round 2		Round 3		Round 4	
	Without HPD n = 2851	History HPD n = 541	Without HPD n = 2851	History HPD n = 541	Without HPD n = 2750	History HPD n = 642	Without HPD n = 2703	History HPD n = 689
Age (years)	40.5 (10.4)	38.4 (9.5) *	44.4 (9.5)	46.7 (10.4) *	49.3 (9.4)	50.8 (10.2) *	55.4 (10.1)	54.1 (9.2)
Parity (n)	2.3 (1.0)	2.3 (1.0)	2.3 (1.0)	2.4 (0.9)	2.3 (1.1)	2.4 (0.9)	-	-
Smoking (%)	34.9	29.5 *	31.0	26.0 *	26.7	21.3 *	21.2	21.3
Ex-smoking (%)	58.1	57.7	31.4	36.4 *	32.9	36.5	37.8	41.6
SBP (mmHg)	117 (15.0)	118 (13.5)	122 (17.5)	123 (15.9)	125 (18.4)	128 (17.9) *	132 (20)	134 (18.8) *
DBP (mmHg)	75 (10.5)	76 (9.3)	78 (10.7)	79 (10.6) *	79 (10.6)	81 (10.9) *	83 (10.3)	85 (10.2) *
Hypertension (%)	14.8	11.8 *	23.0	22.8	30.9	31.8	47.3	51.4
Antihypertensive medication (%)	4.9	1.6 *	8.3	0.2 *	12.6	5.4 *	18.2	14.6
Total cholesterol (mmol/l)	5.4 (1.1)	5.3 (1.0) *	5.5 (1.1)	5.4 (1.0) *	5.7 (1.1)	5.7 (1.0)	5.6 (1.0)	5.7 (1.0)
HDL cholesterol (mmol/l)	1.4 (0.3)	1.4 (0.3)	1.5 (0.4)	1.5 (0.4)	1.5 (0.4)	1.5 (0.4)	1.6 (0.4)	1.6 (0.4)
Ratio Tot/HDL	4.2 (1.3)	4.1 (1.4) *	3.8 (1.2)	3.7 (1.1) *	4.0 (1.3)	4.0 (1.3)	3.8 (1.2)	3.8 (1.2)
Hypercholesterolemia (%)	15.0	12.5	16.8	12.8	22.1	20.6	20.3	19.4
Statin use (%)	0.2	0	1.2	0.6	3.4	2.1	9.1	6.1
BMI (kg/m^2)	24.2 (3.8)	24.4 (3.8)	25.2 (4.2)	25.6 (4.3)	25.8 (4.3)	26.3 (4.3) *	26.1 (4.6)	26.9 (4.7) *
Diabetes mellitus (%)	0.6	0.9	1.6	1.6	2.2	0.9	4.0	3.5
Gestational diabetes (%)	-	-	2.5	4.2 *	3.8	7.0 *	3.4	6.3 *

* p<0.05 compared to women without hypertensive pregnancy disease (HPD) at the same visit, unadjusted.

Table 2: Difference and annual change of cardiovascular risk factors (RF) for women with history of HPD and women without HPD (GEE analysis)

CVD risk factor	Unadjusted		Adjusted for antihypertensive medication and statins		Adjusted for antihypertensive medication, statins, BMI, smoking, SES	
	Difference in RF between women with and without HPD (intercept)	Annual change in RF for women with and without HPD (β) *	Difference in RF between women with and without HPD (intercept)	Annual change in RF for women with and without HPD (β) *	Difference in RF between women with and without HPD (intercept)	Annual change in RF for women with and without HPD (β) *
SBP (mmHg)	3.10 (1.95;4.25)	0.84 (0.80;0.88)	3.39 (2.26;4.52)	0.80 (0.76;0.85)	2.78 (1.69;3.87)	0.72 (0.68;0.77)
DBP (mmHg)	2.58 (1.87;3.29)	0.29 (0.26;0.31)	2.76 (2.06;3.45)	0.26 (0.24;0.29)	2.30 (1.62;2.98)	0.22 (0.19;0.24)
BMI (kg/m^2)	0.64 (0.29;0.99)	0.10 (0.09;0.11)	0.69 (0.34;1.03)	0.09 (0.07;0.10)	0.72 (0.38;1.06)	0.07 (0.06;0.09)
Total cholesterol (mmol/l)	-0.03 (-0.10;0.05)	0.034 (0.031;0.037)	-0.04 (-0.12;0.04)	0.040 (0.037;0.043)	-0.05 (-0.13;0.03)	0.039 (0.036;0.042)
HDL cholesterol (mmol/l)	0.01 (-0.02;0.04)	0.000 (-0.001;0.002)	0.01 (-0.03;0.04)	0.001 (0.000;0.002)	0.02 (-0.01;0.05)	0.003 (0.002;0.004)

* Interaction term 'HPD x age' for none of the risk factors statistically significant, indicating that the annual change in RF was similar for women with and without HPD.

DISCUSSION

Main findings

In this longitudinal population-based cohort study we observed that in women with a history of HPD mean SBP is 3 mmHg higher, mean DBP 2 mmHg higher and mean BMI 0.7 kg/m^2 higher, compared with women without history of HPD. Increases in blood pressure and BMI with age did not differ between the two groups. Mean levels of total and HDL-cholesterol did not differ between women with and without a history of HPD.

Strengths and weaknesses

Our study has several limitations that have to be taken into account. An important limitation is the assessment of the self-reported history of hypertensive pregnancy disorders, based on the questionnaire. This precluded us from differentiating between mild and severe conditions. Furthermore, mild conditions may have been under-reported, resulting in misclassification. This misclassification of mild cases of HPD as normotensive women will however only have led to an underestimation of the true magnitude of the associations, and could be a good explanation for the modest changes in blood pressure and BMI we found in our study compared with other studies in literature.[8,19] Besides this, we lack information on the timing of the affected pregnancy and the severity of the reported HPD, that may vary from limited GH to full-blown severe preeclampsia or HELLP syndrome. Previous studies have shown that this has important consequences for future cardiovascular risk.[7] In the women with a history of HPD in our analysis the complete spectrum of hypertensive pregnancy disorders will be present. Data in women with severe preeclampsia only will result in larger effects, as we previously demonstrated.[24]

Important strengths of our study are that we had data from almost 3400 young women from the general population with an extensive follow-up and high response rates during follow-up, between 75 and 80%. Additionally, risk factors were measured four times over a period of 20 years, with direct contact with the participants at each round. We were able, for the first time, to study the role of HPD in CVD risk factor patterns over time. As intermediate cardiovascular follow-up data in affected women are scarce, our study adds valuable information to the field of cardiovascular risk in women with history of hypertensive diseases of pregnancy.

Interpretation

Several studies identified the increased risk of CVD for women with a history of hypertensive pregnancy diseases, especially preeclampsia.[4-8] Prevalence of chronic hypertension, an important risk factor for CVD, is also high in this subset of women.[13] As we have underlined before, little is known about the course of development of cardiovascular risk factors after having experienced gestational hypertension. A recent study identified an increased 10-year cardiovascular risk (based on Framingham risk score) in women with a history of pregnancy disorders (18 years post partum).[8] To our knowledge our study is the first analysis of longitudinal data on cardiovascular risk factors in women with previous HPD. We observed that blood pressures and BMI levels in these women are significantly higher at all time periods during follow-up, which is consistent with the literature.[17-19] However, the impact on clinical significance of the observed differences is limited and further research should confirm our data. The established differences between both groups do not further increase during follow-up. This information might shed some light on the different hypotheses about the relation between hypertensive pregnancy disorders and future cardiovascular disease. From round 1 onwards, the exposed women are different, giving support to the hypothesis that the endovascular system of affected women has changed before pregnancy. In this study we were not able to evaluate the effect of prepregnancy factors, because we do not know the exact timing of the HPD in these women.

For other traditional cardiovascular risk factors, like lipids, we did not find a difference between women with a history of HPD compared to women with normotensive pregnancies. This is unexpected, as other studies have found a more unfavorable lipid profile in women with a history of HPD compare to reference women.[17,25] The possibly more limited severity of the previous HPD in our cohort could be the reason for these findings. Women with a history of HPD were less often smokers, while previous smoking was similar within both groups. These factors therefore do not explain the known increased cardiovascular risk for women with a history of HPD. Blood pressure and BMI seem to be the most important factors for future cardiovascular risk in this subset of women. Unfortunately, our study was not powered to evaluate differences in cardiovascular events over time for women with and without history of HPD.

The latest American Heart Association guidelines for CVD prevention in women mention pregnancy disorders as risk factor for future CVD and advise taking a detailed obstetric history in women and monitoring their risk factors carefully.[20] This is not yet common daily practice however, so more efforts are needed to create awareness among clinicians and their patients. According to our present data, measurements of blood

pressure and lifestyle advice are to be recommended for women with a history of HPD between 40 to 55 years of age. The clinical impact in the long-term is unclear.
To further elucidate the relation between hypertensive pregnancy disorders and CVD risk we suggest that future research should focus on lifetime development of risk factors with additional pre-pregnancy measurements, careful registration of pregnancy disorders and long-term follow-up postpartum. In parallel, the effects of possible preventive measures should be evaluated.

CONCLUSION

In this longitudinal population-based cohort study we observed that women with a history of HPD have significantly higher blood pressure and BMI compared with women without a history of HPD. During follow-up both blood pressure and BMI increase similarly with age in both groups. Based on these data we could not advise long-term monitoring of cardiovascular risk factors post partum for women with a history of HPD. Future research should focus on careful registration of pregnancy disorders, preferably with information on pre-pregnancy risk factor levels and evaluation of lifetime development of cardiovascular risk factors.

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CHAPTER 4

Cardiovascular risk factors in women 10 years post early preeclampsia: the Preeclampsia Risk EValuation in FEMales study (PREVFEM)

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ABSTRACT

Introduction: Preeclampsia is a complication of pregnancy and a known risk factor for cardiovascular disease (CVD) later in a women's life. The best approach for prevention of CVD in affected young women is yet unclear. We sought to investigate the prevalence of cardiovascular risk factors in women at 10 years post preeclampsia in comparison with a reference group.

Methods: Women with a history of early preeclampsia (exposed), DBP ≥90 mmHg with proteinuria ≥0.3 g/24 h before 32 weeks of gestation, and an equal number of women after uncomplicated pregnancy (non-exposed) from the obstetric database of 1991-2007, were sent a questionnaire and invited for a cardiovascular screening program.

Results: 339 exposed women and 332 non-exposed women, 10 years post index-pregnancy, were included in the current study. Systolic and diastolic blood pressures (SBP/DBP) were 127/86 versus 119/79 mmHg in the exposed and reference group respectively ($p<0.001$). Exposure to early preeclampsia was associated with a 3-fold increased prevalence of hypertension (adjusted odds ratio (OR) 3.59, 95%CI 2.48; 5.20). BMI and waist circumference were 26.9 kg/m^2 and 86.5 cm in exposed group and 26.2 kg/m^2 ($p=0.07$) and 83 cm ($p=0.001$)in non-exposed group. We found no differences in levels of glucose, lipids and CRP. Adjusted OR for the metabolic syndrome in women post preeclampsia was 2.18 (95%CI 1.34; 3.52) compared with women in the reference group.

Conclusion: We found a high prevalence of hypertension in young women at 10 years post early preeclampsia. More research on the timing of cardiovascular screening in these high-risk women is needed.

INTRODUCTION

Preeclampsia occurs worldwide in 3-5% of all pregnancies, in The Netherlands the prevalence is about 1%.[1] Preeclampsia is defined as *de novo* blood-pressure elevation ≥140/90 mmHg with proteinuria ≥0.3 g/ 24 h occurring after the 20th week of gestation. Symptoms of early preeclampsia arise between 20-32 weeks of pregnancy.[2,3] An increasing number of reports over the past decade have shown that preeclampsia may serve as a risk factor of future cardiovascular disease (CVD) in women.[4-10] The risk of premature CVD is strongly related to the severity of the metabolic disturbances

that have occurred during pregnancy.[5] The difficulty in studying future maternal health risks is related to the heterogeneity of the patients within most study cohorts.[4-10]
Although the aetiology of preeclampsia is still debated and incompletely understood, it has been acknowledged that preeclampsia that occurs early in pregnancy (between 20-32 weeks) has a different pathophysiology to late preeclampsia (symptoms after 32 weeks of gestation).[11,12] A key factor in the onset of early preeclampsia is an abnormal inflammatory response in the maternal circulation, provoked by placental arterial insufficiency as a consequence of failure of trophoblast invasion in the spiral arteries. This leads to vasoconstriction and activation of the thrombotic system in the mother.[3] The specific lesions in the vascular bed of the placenta that occur in preeclampsia show similarities with the initial process of atherosclerosis.[13]
After delivery symptoms usually recover within 1 week and most women are dismissed from further obstetric follow-up after a control visit to the outpatient clinic (about 6 weeks postpartum).[11] A few decades later, however, CVD event rate is at least doubled in women after preeclampsia compared to women with uncomplicated pregnancies.[4-10] Since intermediate prospective follow-up data after preeclampsia are relative scarce, it is not known at which time interval cardiovascular (CV) risk factors appear and need to be targeted for prevention. The 2011 American Heart Association (AHA) guidelines on cardiovascular prevention in women recommend careful monitoring of risk factors following preeclampsia, without mentioning when monitoring and preventive measurements should be started.[14] Furthermore, in subsets of women with early preeclampsia there may be identifiable patients who would benefit from early risk factor intervention more than others. In our present study we aimed to evaluate the occurrence of CV risk factors in young women at 10 years post early preeclampsia in comparison with an age-matched reference group.

METHODS

Population

At the department of obstetrics at the Isala klinieken in Zwolle, The Netherlands, all pregnant women have been registered in a database since 1991. Early preeclampsia was defined (according to the International Society for the Study of Hypertension in Pregnancy (ISSHP) definition) as having had an elevated diastolic blood pressure $\geq$90 mmHg with proteinuria ($\geq$0.3 g/24 h) between 20 and 32 weeks of gestation during index pregnancy, almost always followed by premature delivery (Caesarean section).

We invited all women registered in the early preeclampsia database as well as an equal number of age-matched females without preeclampsia from the regular obstetric database in the same time-period (1991-2007) to participate in the Preeclampsia Risk EValuation in FEMales (PREVFEM) study. Participants were included in the study after signing an informed consent form and were invited for a CV screening program at the department of Cardiology. Pregnant or lactating women were excluded from participation (n=10). Approval for the study was obtained from the institutional review board of the Isala klinieken in Zwolle.

Measurements

After inclusion, participants were asked to fill in a questionnaire on obstetric history, family history, other medical history (especially CVD and known presence/awareness of CV risk factors), life style behavior, current medication use and current health complaints. Cardiovascular familiar risk was in the questionnaire defined as CVD or treatment of cardiovascular risk factors (hypertension, DM and hypercholesterolemia) in a first degree family member before the age of 60 years.

At a scheduled visit in the outpatient clinic of the Department of Cardiology a physical examination was performed by trained vascular nurses, consisting of measurements of length, weight, waist and hip circumferences, pulse rate and blood pressure. Blood pressure (Omron M7 machine) was measured after a period of 10 minutes rest at both arms, three times, in a sitting position and with the appropriate cuff size. We report the mean value of these blood-pressure measurements. A resting ECG (Welch Allyn appliance) was taken and fasting blood and urine samples were collected for local laboratory testing. We measured cholesterol profiles (Roche Modular P800), glucose (Roche Modular P800), Hb1Ac (Primus Ultra 2), CRP (Roche Modular P800) and fibrinogen (Sysmex CA-1500). In urine we screened for (micro-)albuminuria. All data were collected in an electronic case report form, provided by Diagram BV.

Definition of cardiovascular risk factors

Cardiovascular risk factors were defined as follows: hypertension as a systolic blood pressure (SBP) $\geq$140 mmHg, a diastolic blood pressure (DBP) $\geq$90 mmHg or use of antihypertensive medication. Adequate control of blood pressure was defined as SBP <140 mmHg and DBP <90 mmHg for women on antihypertensive medication. The presence of DM was defined as diagnosed DM with treatment (diet or medication) or fasting glucose $\geq$7.0 mmol/l and hypercholesterolemia as total cholesterol $\geq$5.0 mmol/l or current use of statins. The metabolic syndrome (MetS) is defined according to the ATP III criteria.[15]

Data analysis

Characteristics of pregnancy and cardiovascular risk factors were compared between exposed women and non-exposed women in the reference group. For normally distributed variables we used an independent *t*-test and for categorical variables a Chi-Square test. In the CRP value, which was not normally distributed, we performed a log transformation. Values greater than 20 mg/l were excluded from further analysis. We conducted ANOVA analysis to adjust the continue measurements for differences in age, years postpartum and current smoking. For the differences in development of cardiovascular risk factors between both groups we computed odds ratios (OR) with 95% confidence intervals (95%CI) and used logistic regression analyses to adjust for influence of age, years post-partum and current smoking. Data were analysed by using SPSS version 16.0 software.

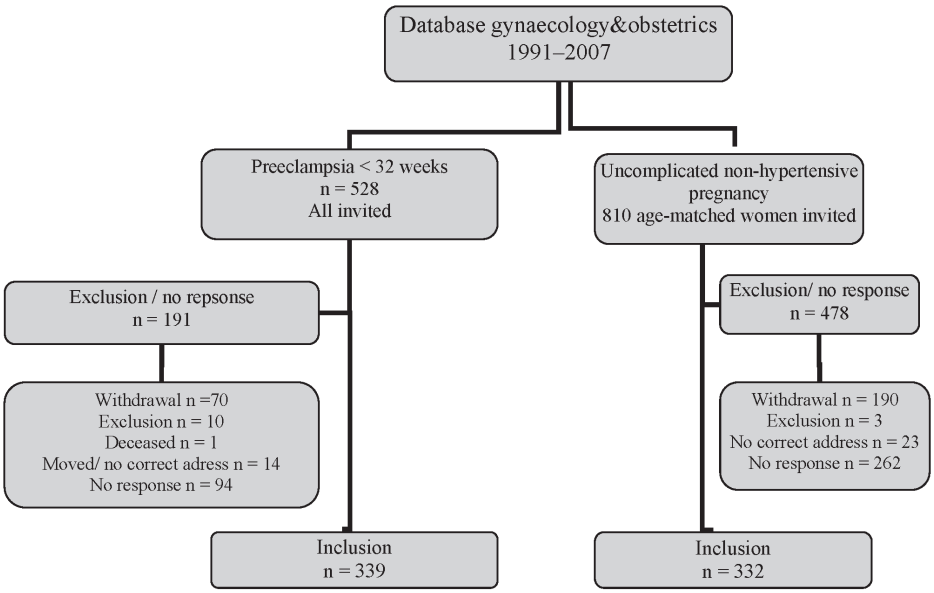

Figure 1: Inclusion and exclusion criteria for PREVFEM cohort.

Table 1: Characteristics of the study population at index delivery

Variable	Preeclampsia n = 339 (± SD)	Non-preeclampsia n = 332 (± SD)
Age at index partus (years)	29.8 (3.8)	28.6 (4.1) [a]
Index pregnancy as first pregnancy (%)	79.6	70.2 [a]
Amenorrhea duration (weeks)	31.0 (3.9)	39.6 (2.1) [a]
Birthweight index partus (g)	1438 (791)	3408 (647) [a]
Stillborn child index-pregnancy (%)	14.8	3.9 [a]
Smoking index pregnancy[b] (%)	11.2	16.6
Pregnancies (n)	2.7 (1.4)	3.1 (1.4) [a]

[a] Significant unadjusted differences (p value < 0.05).

[b] Smoking index-pregnancy is defined as smoking on most days during whole pregnancy.

RESULTS

A total number of 339 out of 515 invited women (response rate 64%) were willing to participate and 332 of 810 non-exposed women (response rate 41%) served as a reference group (Figure 1). Characteristics of the index pregnancies for both groups are shown in Table 1. Women in the exposed group were approximately 1 year older than women in the reference group at delivery with a higher percentage of first pregnancies (79.6% and 70.2%, respectively). Amenorrhea duration was significantly shorter in the exposed group with lower birth weights and more stillbirths (14.8% and 3.9% respectively), reflecting the impact of early preeclampsia on the fetus in the exposed group. The occurrence of gestational diabetes mellitus was not different between both groups (4.1% for the exposed group and 6.3% for the reference group). Self-reported data on family history revealed that gestational hypertension was more frequently present in mothers or sisters of the exposed women (39.5%) compared with mothers or sisters in the reference group (25.3%, $p<0.001$), while there were no reported differences in family history of gestational diabetes.

Table 2: Characteristics of study population at screening visit outpatient clinic

Characteristic	Preeclampsia n = 339 Mean (± SD)	Non-preeclampsia n = 332 Mean (± SD)
Age (years)	38.9 (4.9)	39.3 (4.4)
Years post index partus (years)	9.1 (3.7)	10.7 (3.0) [a]
Current smoking (%)	15.6	17.5
Previous smoking (%)	29.5	30.4
Hypertension (%)	43.1	17.2[a]
Awareness (%)	30.1	9.0[a]
Antihypertensiva (%)	20.6	2.1[a]
Adequate control of women on medication (%)	38.6	14.3
Diabetes Mellitus (%)	2.4	1.5
Oral antidiabetics (%)	0.9	0.3
Insulin (%)	0.3	0.3
Hypercholesterolemia (%)	38.6	42.5
Statin use (%)	1.2	0.3
Metabolic syndrome (%)	18.0	9.0 [a]
Family history of cardiovascular risk (%)	75.5	63.9[a]

[a] Significant unadjusted differences (p value <0.05).

Population characteristics at the screening visit in the outpatient clinic are described in Table 2. While mean age of participants was comparable between both groups, the number of years elapsed since delivery was 16 months less in the exposed group than in the reference group (p<0.001). Unadjusted mean systolic (SBP) and diastolic (DBP) blood pressures were significantly higher in women after preeclampsia compared with women in the reference-group, 127 (SD 17.3) mmHg versus 119 (SD 13.8) mmHg for SBP and 86 (SD 11.6) mmHg versus 79 (SD 10.0) mmHg for DBP, respectively, both p values <0.001. After adjustment for age, years post index pregnancy and current smoking these differences did not change (Table 3). Hypertension was present in 43.1% of exposed women and in 17.2% of women in the reference group (adjusted OR 3.59, 95%CI 2.48; 5.20). Only 38% of all women with elevated blood pressure were treated with antihypertensive medication. Data on awareness of elevated blood pressure, use of antihypertensive medication and control of blood pressure with antihypertensive medication are also mentioned in Table 2. Although body mass index (BMI) was not significantly different between both groups, obesity (BMI >30 kg/m^2) was more often present in women after preeclampsia (26.8% vs 20.2%, p=0.04). Waist

circumference (adjusted), as measure of central obesity, was 86.5 cm in women post preeclampsia compared with 83.2 cm in the reference women (p=0.001).
Fasting levels of glucose, cholesterol, hsCRP and fibrinogen were not significantly different between both groups (Table 3). Prevalence and treatment of DM and hypercholesterolemia was also not significant different between both groups (Table 2). The MetS was more prevalent within women post preeclampsia (18%) compared with 9% of women with a normal pregnancy in history (adjusted OR 2.18, 95%CI 1.34; 3.52, p<0.001).

Table 3: Adjusted data at screening visit outpatient clinic (adjusted for age; years post index partus and current smoking)

Risk factor	Preeclampsia n = 339 Mean (95%CI)	Non-preeclampsia n = 332 Mean (95%CI)	p value
Systolic blood pressure (mmHg)	127 (125.2; 128.5)	119 (117.6; 121.0)	<0.001[a]
Diastolic blood pressure (mmHg)	86 (84.4; 86.7)	79 (78.1; 80.4)	<0.001[a]
Body mass index (kg/m^2)	26.9 (26.4; 27.5)	26.2 (25.5; 26.7)	0.066
Waist circumference (cm)	86.5 (85.2; 87.8)	83.2 (81.9; 84.5)	0.001[a]
Total cholesterol (mmol/l)	4.86 (4.78; 4.95)	4.85 (4.76; 4.94)	0.85
LDL (mmol/l)	2.89 (2.81; 2.98)	2.90 (2.81; 2.98)	0.95
HDL (mmol/l)	1.52 (1.48; 1.56)	1.53 (1.49; 1.57)	0.77
Triglycerides (mmol/l)	1.00 (0.95; 1.06)	0.95 (0.89; 1.06)	0.18
Ratio HDL/total cholesterol	3.40 (3.29; 3.51)	3.35 (3.23; 3.46)	0.54
Glucose (mmol/l)	4.86 (4.76; 4.95)	4.85 (4.75; 4.94)	0.92
HbA1c (%)	5.27 (5.22; 5.31)	4.24 (5.19; 5.28)	0.37
CRP (mg/l) [b]	3.55 (3.05; 4.05)	3.19 (2.68; 3.69)	0.33
CRP log transformation	0.79 (0.69; 0.88)	0.74 (0.66; 0.84)	0.57
Fibrinogen (g/l)	2.85 (2.79; 2.92)	2.84 (2.77; 2.91)	0.75
	OR (95%CI)	OR (95%CI)	
Hypertension	3.59 (2.48; 5.20)	1.0	<0.001[a]
Diabetes Mellitus	1.72 (0.54; 5.48)	1.0	0.36
Hypercholesterolemia	0.94 (0.68; 1.30)	1.0	0.70
Metabolic syndrome	2.18 (1.34; 3.52)	1.0	0.002 [a]

[a]Significant differences p value <0.05.
[b]CRP values >20 mg/l excluded.

DISCUSSION

In this study we found a prevalence of hypertension (adjusted OR 3.59) before the age of 40 years over three times higher in women with previous early preeclampsia in comparison with an age-matched reference group after uncomplicated pregnancy. Less than half of these hypertensive women were treated adequately with anti-hypertensive medication. Although hypercholesterolemia (total cholesterol $\geq$5.0 mmol/l or use of statins) could be demonstrated in almost 40% of women, we found no differences in the prevalence of hypercholesterolemia or diabetes between both groups and the use of statins and antidiabetic medication was comparable. Other studies have shown more unfavorable levels of lipids and glucose in women post preeclampsia. However, in the study of Berends et al. significant differences for glucose and blood pressure were found, but not for lipids.[16] In this study women with a mean of 7 years post index pregnancy were included while in other studies, which found differences in lipids as well, women were 16-17 years post partum.[17-18] As lipid levels rise gradually in relation to alterations in hormonal status in women during middle-age, and menopausal transition induces an accelerated increase of lipids this could be an explanation for the lack of abnormalities in lipids within our still relatively young group of females.[19]
MetS was twice more prevalent in exposed women as in the reference group, respectively 18% and 9%. As the MetS is a frequently occurring consequence of obesity it has important implications for the development of future CVD.[20] The relatively high occurrence of the MetS in our study population was merely driven by hypertension and central obesity. After adjustment for hypertension and waist circumference the OR for the development of the MetS in women post early preeclampsia was no longer significant. As it was shown in the Framingham Offspring study the trajectory of entering the MetS with hypertension and central obesity confers a high risk for future CVD, especially in women.[21] The elevated waist ratios in exposed women demonstrate a known correlation between central fat distribution and hypertension.[22] In the EPIC-Norfolk study a linear increase of blood pressure (SBP and DBP) across the range of waist-hip ratio in both men and women was found, whereas waist circumference per se was also independently of differences in age and BMI related to SBP and DBP in females.[23] Both BMI and waist circumference are predictive of fatal and non-fatal CVD risk.[24] Obesity-related hypertension may be more resistant to medical treatment than hypertension with normal weight. Lifestyle changes are the primary important preventive measures in obesity-related hypertension.[25]

In our present study we found that almost 76% of exposed women had a positive family history for CVD, compared with 64% of non-exposed women (p=0.006). As family history was assessed by questionnaire it may contain uncertainties. It is currently still debated whether hypertensive disorders in pregnancy alone lead to a higher susceptibility for CVD risk or whether a common genetic predisposition is causative for both the metabolic disturbances during pregnancy and the elevated CVD risk.[26,27] Romundsen et al. found higher pre-pregnancy levels of blood pressure and BMI in women who developed preeclampsia or gestational hypertension compared with women with non-hypertensive pregnancies.[28] Although their cohort consisted of a heterogeneous group of women after gestational hypertension as well as women with early and late preeclampsia, they suggest a relation between pre-pregnancy cardiovascular risk factors and future CVD risk. A limitation of our study is that we had no data on pre-pregnancy values of blood pressure, BMI and waist/hip measurements. In the questionnaire at the outpatient clinic 5% of exposed women and 7.5% of women from the reference group reported hypertension before index pregnancy. However, with these data we cannot reject or confirm a relation between pre-pregnancy hypertension and current hypertension.

It has been suggested that early and late preeclampsia may represent heterogeneous expressions of one common disease, while others assume a different pathophysiology of both conditions.[12,29,30] While early preeclampsia may be caused by severe placental dysfunction through impairment of trophoblast invasion, placental damage in late-onset preeclampsia is less severe with fewer maternal consequences. The timing of the onset of preeclampsia may therefore interfere with long-term consequences of maternal health. In a retrospective cohort study Stekkinger et al. found a higher incidence of the MetS in women with a history of early-onset preeclampsia (delivery before 32 weeks) compared with women after late-onset preeclampsia (delivery at/beyond 32 weeks) at 36-52 weeks post index-delivery.[31] In our study we included only women after early preeclampsia (symptoms and delivery before 32 weeks of gestation). Therefore, as a limitation of our study we cannot extrapolate our findings to all women with preeclampsia. Another limitation is the use of the obstetric database of our hospital to establish the reference cohort. In The Netherlands about 30-35% of uncomplicated pregnancies were delivered at home during our time period, indicating that our reference group may contain higher risk pregnancies that were referred to hospitals.[32] Further, differences in response rate of participants within our study groups arouse concern. Bias may have been introduced by the higher response rate for participation in the exposed group than in the reference group (64% vs 41%). Despite our repeated efforts with letters and telephone calls, women in the reference group were less

motivated than exposed women to take a day off and to travel to our outpatient clinic. Young women after serious health problems in pregnancy had a higher concern for future disease risk than women with uncomplicated pregnancies.

CONCLUSION

Women after early preeclampsia have a 3.59 times higher risk of hypertension and a 2.18 times higher risk for development of the metabolic syndrome in women post early preeclampsia at 10 years post index pregnancy. The aetiology of preeclampsia is yet unresolved. Research on genetics and metabolic biomarkers is needed for a better understanding of its pathogenesis.[33] Additional research should focus on the cost-effectiveness of cardiovascular screening programs and the timing of treatment of cardiovascular risk factors in women with previous preeclampsia. Further, identification of subsets of patients at higher risk is needed.

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CHAPTER 5

Electrocardiographic parameters in women 10 years post early preeclampsia

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ABSTRACT

Objective: Women with a history of preeclampsia are at increased risk to develop cardiovascular disease (CVD) later in life, especially hypertension is common. In this study we aimed to evaluate electrocardiographic parameters as a proxy for detrimental hypertensive effects and later CVD.
Methods: The Preeclampsia Risk EValuation study in FEMales (PREVFEM) study is a prospective cohort study consisting of 339 women with a history of early-onset pre-eclampsia (EOP) and 332 age-matched women without a history if EOP as reference. At 10 years post index pregnancy a 12-lead electrocardiogram recording was made.
Results: There were no significant differences in ECG parameters between both groups at 39 years of age. In our cohort of young women SBP (OR_{mmHg} 1.04; 95%CI 1.2; 1.06) as well as DBP (OR_{mmHg} 1.04; 95%CI 1.01; 1.07) and stage 2 hypertension (OR 3.35; 95%CI 1.16; 9.63) were significantly associated with ECG criteria for LVH, but not for other ECG abnormalities. EOP gives no significant adjusted risk on ECG abnormalities compared to women without EOP.
Conclusion: EOP is no significant predictor of non-specific ECG abnormalities. Routine ECG screening in young women after preeclampsia is not recommended in non-hypertensive women, but may be useful when hypertension is present.

INTRODUCTION

Women with a history of hypertensive pregnancy disorders are at increased risk to develop cardiovascular disease (CVD) later in life. Meta-analyses of population-based studies have shown that in women with a history of preeclampsia, defined as hypertension with proteinuria, CVD risk is more than two times higher than in unaffected women.[1-3] In the latest guidelines from the American Heart Association on CVD prevention in women, careful monitoring of cardiovascular risk factors in this subset of women at elevated risk is recommended.[4] However, validated tools to assess the future cardiovascular risk in these young women are yet not available. First signs of increased CV risk in women after preeclampsia are elevated systolic (SBP) and diastolic (DPB) blood pressures and a higher prevalence of hypertension compared to women with uncomplicated pregnancies.[5] Several studies have identified electro-cardiographic (ECG) screening as an adequate tool to improve risk prediction in hypertensive populations.[6,7] Prognostic ECG abnormalities in hypertensive patients are

voltage-criteria of left ventricular hypertrophy (LVH) and repolarization abnormalities.[8,9]

In population-based studies non-specific ECG changes have also been shown to be important in evaluating future CVD morbidity and mortality.[10-18] The frontal T axis reflects abnormalities in ventricular repolarization and a deviated T axis may be an important predictor of cardiovascular risk.[11,12,16] The spatial QRS-T angle reflects both depolarisation and repolarization and is an even stronger predictor of future CVD events, whereas a wider angle is associated with a higher risk of CVD events (coronary heart disease, congestive heart failure and mortality).[11,17-19] Methods to derive the spatial QRS-T angle are not widely available as it requires vector transformation of the 12-lead ECG. The frontal QRS and T axis are available in most electrocardiographic ECG reports and are often used in clinical practice as a suitable substitute for the spatial QRS-T angle.[10]

Thus far, only one study has evaluated the presence of ECG abnormalities in women with a history of early and late preeclampsia. In 443 women after previous preeclampsia, at a mean age of 60 years the presence of any ECG abnormalities, according to the Minnesota code, was two times higher in comparison with a control group (adjusted odds ratio (OR) 1.96, 95%CI 0.96; 2.98).[20] It is not known however at which age first signs of ECG abnormalities appear in females after hypertensive pregnancy disorders and if standard ECGs are useful in this target population. The objective of our study therefore is to identify ECG changes related to elevated blood pressure in women 40 years of age and to evaluate the effect of early-onset preeclampsia (EOP) in females on the identified ECG changes.

METHODS

Population

Since 1991 the obstetric department of the Isala klinieken in Zwolle, The Netherlands, registers all in-hospital deliveries. We invited consecutively all women registered as having had EOP (n=528) as well as an equal number of age-matched females with a non-hypertensive, uncomplicated, pregnancy during the same time-period (1991-2007) to participate in the Preeclampsia Risk EValuation in FEMales (PREVFEM) cohort study. This study was set up to evaluate the presence of cardiovascular risk factors in young women 10 years post pregnancy complicated by EOP. Early preeclampsia was defined as an elevated diastolic blood pressure $\geq$90 mmHg with proteinuria ($\geq$0.3 g/24

h) between 20 and 32 weeks of gestation. Approval for the study was obtained from the institutional review board of the Isala klinieken in Zwolle. Participants were included in the study after signing an informed consent form and were invited for a cardiovascular screening program at the Department of Cardiology on average after 10 years post index pregnancy. The detailed protocol of the screenings procedure has been described elsewhere, as well as the used definitions of cardiovascular risk factors.[5]

ECG analysis and interpretation

A standard 12-lead electrocardiogram was recorded in lying position using Welch Allyn CardioPerfect equipment and ECGs were stored digitally. With CardioPerfect software ECG measurements were computed for a representative averaged beat for each of the 12 different leads. Welch Allyn Cardioperfect provides data on conduction (ms); amplitude (μV); frontal P, QRS and T axis (°); ST segment and T wave deviation (μV) and heart rate (bpm).

The Minnesota Code (MC) Classification System for Electrocardiographic Findings was used to define ECG abnormalities.[21] Major repolarization abnormalities were coded as ST deviation according to MC 4-1-1, 4-1-2 and 4-2 or negative T wave coded as 5-1 and 5-2. Minor repolarization abnormalities were coded as MC 4-3 and 5-3. Left ventricular hypertrophy (LVH) was assessed by presence of either the gender-specific Cornell product (R aVL + S V3 >2.0 mV in women) or the Solokow-Lyon voltage criteria (S V1 + R V5/V6 >38 mm). Frontal T axis and frontal QRS-T angle were divided in two classes, normal and abnormal. Normal T axis was defined as 25-65° and normal frontal QRS-T angle was defined as an angle between 0 and 90°.[13,14,16]

Data analysis

Participant characteristics at the screening visit were described for women with and without EOP at baseline using means and standard deviations for continuous normally distributed variables and frequencies and percentages for categorical variables.

To evaluate the effect of blood pressure on different ECG abnormalities, we performed logistic regression analyses per unit of increment arterial blood pressure to compute odds ratios (OR) with 95% confidence intervals (95%CI) in all women, and to adjust for potential confounders (age, current smoking and waist circumference). Blood pressure was classified into four categories according to the Joint National Committee report 7.[22] Different categories were normal blood pressure (SBP <120 mmHg and DBP <80 mmHg); prehypertension (SBP 120-139 mmHg or DBP 80-89 mmHg); stage 1 hypertension (SBP 140-159 mmHg or DBP 90-99 mmHg); stage 2 hypertension (SBP $\geq$160 mmHg or DBP $\geq$100 mmHg). Women on antihypertensive medication were

classified in 'stage 2 hypertension'. Odds ratios (95%CI) on the ECG abnormalities were computed for all hypertension categories, whereas 'normal blood pressure' served as the reference category.
To quantify the effect of EOP on development of ECG abnormalities between both cohort groups we reported ECG abnormalities as percentage in both groups, differences in prevalence between both groups were tested with Chi-Square test or Fisher's exact test. Finally, we calculated OR (95%CI) on development of ECG abnormalities in women with history of EOP. Women without history of EOP served as reference. Adjustments were done for age, current smoking and waist circumference. Data were analysed by using SPSS version 16.0 software.

RESULTS

A total number of 671 women were included in the PREVFEM- study, 339 in the EOP group (response rate 64%) and 332 in the reference group (response rate 41%). Baseline characteristics of women are shown in Table 1. Mean age of participants in both groups was 39 years and they were on average 10 years post index-pregnancy. As described elsewhere SBP was 127 mmHg in women with history of EOP and 119 mmHg for women without ($p<0.05$) and DBP was 86 mmHg and 79 mmHg, respectively ($p<0.05$). Hypertension was significant more prevalent in women with history of EOP compared to the reference groups (43% versus 17%, $p<0.05$) and this difference remained significant after adjustment for potential confounders.[5] Of all participants an ECG at baseline visit was available for analysis. Mean heart rate was 70 ±12.6 bpm and abnormal ECG parameters were present in both groups, although only in a small percentage of women (Table 1). Presence of LVH was equal in women with history of EOP (6%) in comparison with women without EOP (5%), p value 0.64.
Analysis of blood pressure as continuous variable and ECG characteristics in all 671 women shows significantly increased risk of the presence of LVH for raised SBP (OR_{mmHg} 1.04; 95%CI 1.02; 1.06) and raised DBP (OR_{mmHg} 1.04; 95%CI 1.01; 1.07). After adjustment for age, smoking and waist these data remain unchanged. Other ECG characteristics were non-significant. Table 2 shows the OR for the different stages of hypertension on the presence of ECG abnormalities. Only stage 2 hypertension (SBP $\geq$160 mmHg or DBP $\geq$100 mmHg or use of antihypertensive medication) was associated with a significantly increased risk of presence of LVH, after adjustment for confounders (OR 3.35 (95%CI 1.16; 9.63).

Table 1: Characteristics of study population at cardiovascular screenings visit

Characteristic	Preeclampsia n = 339 mean (±SD)	Non-preeclampsia n = 332 mean (±SD)
Age (years)	38.9 (4.9)	39.3 (4.4)
Years post index partus (years)	9.1 (3.7)	10.7 (3.0)[a]
Current smoking (%)	15.6	17.5
Systolic blood pressure (mmHg)	127 (17.3)	119 (13.8)[a]
Diastolic blood pressure (mmHg)	86 (11.6)	79 (10.0)[a]
Body mass index (kg/m^2)	26.9 (5.7)	26.2 (4.9)
Waist circumference (cm)	86.6 (14.2)	83.4 (10.7)[a]
Total cholesterol (mmol/l)	4.8 (0.8)	4.9 (0.8)
LDL (mmol/l)	2.9 (0.8)	2.9 (0.8)
HDL (mmol/l)	1.5 (0.4)	1.5 (0.3)
Triglycerides (mmol/l)	1.0 (0.5)	0.9 (0.5)
Ratio HDL/total cholesterol	3.4 (1.0)	3.4 (1.0)
Glucose (mmol/l)	4.9 (1.1)	4.8 (0.6)
Hypertension (%)	43.1	17.2[a]
Diabetes mellitus (%)	3.5	2.1
Hypercholesterolemia (%)	38.6	42.5
Metabolic syndrome (%)	18.0	9.0[a]
ECG parameters		
Heart rate (bpm)	69.8 (12.1)	70.4 (13.2)
Abnormal T axis (%)	21.5	19.6
Abnormal frontal QRS-T angle (%)	2.1	3.9
Major repolarization abnormalities (%)	6.8	6.6
Minor repolarization abnormalities (%)	31.3	34.6
LVH (%) Cornell or Solokow	5.7	4.9

[a]Significant unadjusted differences (p value <0.05).

OR for development of different ECG abnormalities in women with history of EOP compared to women without history of EOP were all non-significant (adjusted for age, smoking and waist).

Table 2: Hypertension and ECG parameters

ECG Parameter	Normal BP (n = 232)		Prehypertension (n = 236)		Stage 1 HT (n = 92)		Stage 2 HT or anti-hypertensive medication (n = 111)	
	Odds ratio (95% CI) unadjusted	Odds ratio (95% CI) adjusted age, smoking, waist	Odds ratio (95% CI) unadjusted	Odds ratio (95% CI) adjusted age, smoking, waist	Odds ratio (95% CI) unadjusted	Odds ratio (95% CI) adjusted age, smoking, waist	Odds ratio (95% CI) unadjusted	Odds ratio (95% CI) adjusted age, smoking, waist
Abnormal T axis (%)	1.00	1.00	1.09 (0.69; 1.71)	1.08 (0.68; 1.71)	0.94 (0.51; 1.75)	0.95 (0.51; 1.80)	1.34 (0.78; 2.30)	1.38 (0.77; 2.46)
Abnormal frontal QRS-T angle (%)	1.00	1.00	1.15 (0.38; 3.46)	1.14 (0.37; 3.47)	1.26 (0.31; 5.14)	1.40 (0.33; 5.90)	1.42 (0.39; 5.15)	1.26 (0.29; 5.47)
Major repolarization abnormalities (%)	1.00	1.00	1.39 (0.67; 2.91)	1.37 (0.61; 2.91)	0.77 (0.24; 2.41)	0.75 (0.23; 2.42)	1.67 (0.71; 3.93)	1.62 (0.64; 4.10)
Minor repolarization abnormalities (%)	1.00	1.00	1.21 (0.82; 1.78)	1.25 (0.84; 1.86)	1.10 (0.65; 1.84)	1.17 (0.69; 1.99)	1.18 (0.73; 1.91)	1.33 (0.79; 2.23)
LVH (%) Cornell or Solokow	1.00	1.00	1.33 (0.55; 3.21)	1.67 (0.67; 4.14)	1.72 (0.59; 4.97)	2.42 (0.81; 7.24)	1.93 (0.72; 5.14)	3.35 (1.16; 9.63) [a]

DISCUSSION

To the best of our knowledge, this is the first study to evaluate the prevalence of ECG abnormalities in young women, mean age 39 years, with a history of early preeclampsia. We found no significant differences in the occurrence of ECG abnormalities in women at 10 years post preeclampsia in comparison with similar aged women after uncomplicated pregnancy.

However, we confirmed a significant relation between continuous level of both SBP (OR 1.04; 95%CI 1.2; 1.06) and DBP (OR 1.04; 95%CI 1.01; 1.07) with ECG criteria for LVH. Within different stages of hypertension only stage 2 hypertension (SBP ≥160 mmHg or DBP ≥100 mmHg or the use of antihypertensive medication) was predictive for LVH criteria (OR 3.35 (95%CI 1.16; 9.63).

Although hypertension (SBP ≥140 mmHg or DBP ≥90 mmHg or use of antihypertensive medication) is the most frequent occurring early risk factor after preeclampsia and already present in 43% of EOP women before the age of 40 years in the PREFVEM-study, first signs of electrocardiographic parameters for LVH are yet uncommon at this age (5.7%). Even in elderly women in the raloxifen use for the heart (RUTH) study (mean age 68 years), criteria for LVH on ECG recordings were met in only 35% of the large proportion (78%) of participating hypertensive women.[23] The sensitivity of ECG criteria for LVH is therefore low to detect detrimental effects of hypertension, although its specificity is high.[24] In young women the premenopausal estrogens status prohibits the development of LVH, while after menopause progression to LVH occurs more frequently.[25] This may also be an explanation for the low occurrence of electrocardiographic signs of LVH in our study. Non-specific ECG abnormalities are yet uncommon in previously affected EOP women at the age of 40 years. Most studies on prognostic value of ECG criteria in the development of CVD have been undertaken in populations that were older (between 48 and 75 years).[12-15,20]

However, our study showed that even young females with stage 2 hypertension (SBP ≥160 mmHg or DBP ≥100 mmHg or use of antihypertensive medication) are at increased risk for electrocardiographic criteria for LVH (OR 3.41, 95%CI 1.10; 10.60; p value 0.03) compared to young women with normal blood pressures. As ECG recordings are currently easily available in primary health care they should be part of the routine assessment in all subjects with high blood pressure according to the European guidelines on arterial hypertension.[26]

One of the limitations of our study is the use of the frontal QRS-T angle instead of the spatial QRS-T angle, as the evidence on use of the frontal angle as a substitute for the

spatial angle is limited.[10] To define an abnormal frontal T axis we used the definition of Atsma et al.[16] Others have applied different criteria for defining categories of normal and abnormal T axis, but small changes of thresholds did not essentially change their results.[12] Another limitation is the use of electrocardiographic criteria for LVH. A recent review concluded that ECG criteria cannot rule out LVH.[27] Further research with echocardiographic data of LVH in young women post preeclampsia is recommended.

In conclusion, we do not recommend routine ECG assessment for CVD risk prediction in young non-hypertensive women after EOP. In young females, however, with grade 2 hypertension, ECG recordings are useful to detect early signs of LVH.

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CHAPTER 6

Novel cardiovascular biomarkers in women with a history of early preeclampsia

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ABSTRACT

Women with a history of preeclampsia are at increased risk for future cardiovascular disease. Determination of cardiovascular biomarkers may be useful to understand the pathophysiological mechanism of cardiovascular disease development in these women.
We performed an analysis in the Preeclampsia Risk EValuation in FEMales study (PREVFEM), a retrospective cohort consisting of 339 women with a history of early preeclampsia and 332 women after normotensive pregnancy, who attended a follow-up visit 10 years after the index pregnancy. A subset of eight different cardiovascular biomarkers was investigated, reflecting inflammatory, metabolic, thrombotic and endothelial function markers. Associations between PE and these novel biomarkers were analyzed by linear regression analysis and adjusted for traditional cardiovascular risk factors.
Mean age of 671 women of the PREVFEM cohort was 39 years and women were on average 10 years post index pregnancy. Women post preeclampsia had significantly higher levels of SE-selectin (adjusted difference 4.55, 99%CI 0.37; 8.74) and PAPPA (adjusted difference 19.08; 99%CI 13.18; 24.99), whereas ApoB (adjusted difference -0.23 99%CI -0.32; -0.14) was inversely associated with preeclampsia, compared to women with a previous normotensive pregnancy. Adiponectin, leptin, sICAM-1, sVCAM-1 and PAI-1 were not different between both groups.
In this retrospective cohort analysis we demonstrated an independent association of preeclampsia with SE-selectin and PAPPA (markers of vascular dysfunction), which may contribute to future cardiovascular events in women post preeclampsia. However, ApoB (a lipoprotein) was significantly lower and could point at a protective mechanism in our PE study women.

INTRODUCTION

Hypertensive disorders of pregnancy (HPD), like gestational hypertension (GH) and preeclampsia (PE), occur in about 10% of pregnancies.[1,2] These syndromes have important consequences for maternal health during pregnancy and the postpartum period, but also for future cardiovascular disease (CVD) risk.[3-5] Dependent on the type of HPD, the risk of future CVD is 1.4-3.0 times higher in women with a history of HPD compared to women with previous normotensive pregnancies .[6] The severity and timing of HPD importantly determines the impact of long-term CVD risk, with early

PE as one of the most hazardous conditions.[3,7] The increased CVD risk in women with a history of PE can be partly attributed to the increased prevalence of classic CVD risk factors like hypertension, hypercholesterolemia and the metabolic syndrome (MetS).[8-10] Although the underlying pathophysiological mechanism of the increased prevalence of cardiovascular risk factors in these women is not completely understood, endothelial dysfunction seems to play an important role, although not consistently.[11,12] Novel genetic evidence indicates potentially shared mechanisms of both preeclampsia and CVD, in particular for oxidative stress and inflammation.[13]

In the last decade(s) several novel biomarkers associated with CVD have been identified.[14,15] Some of these biomarkers, like cytokines (e.g. interleukins); angiogenic factors (endoglin); cell adhesion molecules (soluble fms-like tyrosine kinase 1) and coagulation factors (plasminogen activator inhibitor, PAI-1), are upregulated during preeclamptic pregnancies.[16-18] Data of these novel biomarkers in young women with a history of preeclampsia may unravel the pathophysiological mechanisms of the increased CVD risk in these women. However, study data on biomarkers in this subset of females are not consistent. Sattar et al. found increased levels of intercellular adhesion molecule (ICAM) in women post PE; however, no differences in lipids, vascular cellular adhesion molecule (VCAM), E-selectin and leptin were reported.[11] In the study of Girouard et al. it was shown that women with a history of PE and GH, have significant differences in lipid profile and several miscellaneous markers (TNF-α, Interleukin-6, leptin, adiponectin and homocysteine) at 8 years post index pregnancy compared with control subjects.[19] Wolf et al. demonstrated increased levels of soluble fms-like tyrosine kinase and insulin resistance in women after PE compared to women with normotensive pregnancies within 18 months postpartum.[20] However, several other studies did not find any differences in biomarker profiles between women with and without a history of HPD.[21-23]

In this retrospective cohort study we measured levels of various novel cardiovascular biomarkers in women with and without prior preeclampsia and adjusted the associations for traditional cardiovascular risk markers. Of the many available biomarkers we selected apolipoprotein B (ApoB), a lipid-associated marker, and leptin and adiponectin as cardiometabolic risk markers. We also studied the following endothelial function markers: soluble intercellular adhesion molecule (sICAM-1), soluble vascular adhesion molecule (sVCAM-1), soluble endothelial selectin (SE selectin), and a thrombotic marker, plasminogen activator inhibitor (PAI-1). Furthermore, we evaluated pregnancy associated plasma protein A (PAPPA), a metalloproteinase, which is associated with vulnerable atherosclerotic plaques.[24]

METHODS

Population

Since 1991, the obstetric department of the Isala klinieken in Zwolle, The Netherlands, has registered all in-hospital deliveries. We invited consecutively all women registered as having had early-onset preeclampsia, n=528, in the time period (1991-2007) to participate in the Preeclampsia Risk EValuation in FEMales (PREVFEM) cohort-study. For the reference group we invited an equal number of age-matched females with a non-hypertensive, uncomplicated, pregnancy during the same period. They were selected from the obstetric database after selection based on age and date of delivery, and aiming for an equal distribution of these two variables (range ±2 years).

The study was initiated to evaluate the presence of cardiovascular risk factors in young women at 10 years post pregnancy complicated by early-onset PE. This was defined as an elevated diastolic blood pressure ≥90 mmHg with proteinuria (≥0.3 g/24 h) between 20 and 32 weeks of gestation. Approval for the study was obtained from the institutional review board of the Isala klinieken in Zwolle. Participants were included in the study after signing an informed consent form and were invited for a cardiovascular screening program at the Department of Cardiology. The protocol, definitions of cardiovascular risk factors and baseline data have been described elsewhere.[10]

Biomarker analysis

At the scheduled screening visit an overnight fasting venous blood sample was taken. Blood lipid profile, glucose, CRP and fibrinogen were locally analyzed and the results have been described previously.[10]

Assessment of all novel biomarkers was performed at the laboratory of experimental medicine, at the department of Internal Medicine, Radboud University Medical Center, Nijmegen, The Netherlands. All markers were analysed with a Luminex assay, a multi-analyte technology, based on the principles of flow cytometry.[25] As a consequence of the use of a multi-assay kit, some samples were out of the detection range, for sICAM-1 the lower detection level was 8 ng/ml (n=1 out of range), for PAPPA the lower limit was 0.69 ng/ml (n=28) and for leptin the lower limit was 0.8 ng/ml (n=2). These values were fixed at the lower detection level.

Data analysis

Baseline characteristics were expressed as mean (SD) or number (percentage). Biomarker levels were expressed as continuous variables, mean with SD. Differences in variables between women with and without PE for continuous data were analysed by Student's *t*-test for independent groups and for categorical data with Chi-square or Fisher exact test. Univariate analysis was performed with a two-sided probability value of <0.05.

Association between PE and biomarkers was analysed using linear regression analysis and stepwise adjusted according to four different models. Model 1 adjusted for age; model 2 for age, years postpartum and smoking; model 3 included the variables of model 2 and presence of hypertension; and in model 4 we added the presence of MetS (dichotomous) to the aforementioned variables. Data were expressed as the differences (β) in biomarkers of women with a history of PE compared to the reference women, with 99% confidence interval (99%CI). All p values were two-sided.

As levels of the different biomarkers were not normally distributed (according to the Kolmogorov-Smirnov test), we additionally performed a natural log transformation on the biomarkers and repeated the above-mentioned analysis. Since the results of these natural log transformed analyses did not differ from the original analysis, we prefer to present the original untransformed data to facilitate interpretation of our data in clinical use.

Data analyses were performed with SPSS software version16.0.

RESULTS

A total number of 671 women were included in the PREVFEM-study, 339 in the early-onset PE group and 332 in the reference group. Mean age of participants in the cohort was 39 years and women were on average 10 years post index-pregnancy. Baseline characteristics of the PREVFEM-cohort have been described elsewhere.[10] Hypertension was more prevalent in women post PE (43%) than in reference women (17%), as was the MetS (18% in PE women versus 9% in reference women). Prevalence of diabetes mellitus, levels of different lipid markers and levels of the inflammatory markers (CRP and fibrinogen) were not different between both groups (Table 1).

Table 1: Characteristics of study population at cardiovascular screenings visit

Characteristics	Early preeclampsia n = 339 Mean (±SD)	Reference n = 332 Mean (±SD)
Age (years)	38.9 (4.9)	39.3 (4.4)
Years post index partus (years)	9.1 (3.7)	10.7 (3.0) [a]
Current smoking (%)	15.6	17.5
Systolic blood pressure (mmHg)	127 (17.3)	119 (13.8) [a]
Diastolic blood pressure (mmHg)	86 (11.6)	79 (10.0) [a]
Hypertension (%)	43.1	16.7 [a]
Body Mass Index (kg/m^2)	26.9 (5.7)	26.2 (4.9)
Waist circumference (cm)	86.6 (14.2)	83.4 (10.7) [a]
Total cholesterol (mmol/l)	4.8 (0.8)	4.9 (0.8)
LDL cholesterol (mmol/l)	2.9 (0.8)	2.9 (0.8)
HDLcholesterol (mmol/l)	1.5 (0.4)	1.5 (0.3)
Triglycerides (mmol/l)	1.0 (0.5)	0.9 (0.5)
Ratio HDL/total cholesterol	3.4 (1.0)	3.4 (1.0)
CRP (mg/l) [b]	3.6 (5.4)	3.1 (3.8)
Fibrinogen (g/l)	2.9 (0.6)	2.8 (0.6)
Glucose (mmol/l)	4.9 (1.1)	4.8 (0.6)
Diabetes mellitus (%)	1.2	0.6
Metabolic syndrome (%)	18.0	9.1[a]

[a] Significant unadjusted differences (p value <0.05).
[b] CRP values >20 mg/l excluded.

Table 2: Mean biomarker levels according to history of early-onset preeclampsia

Biomarker	Early preeclampsia n= 339 Mean (SD)	Reference n = 329 Mean (SD)
Adiponectin (µg/ml)	57.9 (36.8)	57.7 (36.1)
PAI-1 (ng/ml)	27.2 (16.6)	27.1 (16.4)
Leptin (ng/ml)	26.3 (19.5)	24.2 (17.9)
sICAM-1 (ng/ml)	94.2 (69.5)	105.6 (63.4) [a]
sVCAM-1 (ng/ml)	910.0 (176.2)	907.0 (173.0)
SEselectin (ng/ml)	48.9 (22.3)	45.3 (18.5) [a]
PAPPA (ng/ml)	38.7 (32.2)	22.5 (23.2) [a]
ApoB (g/l)	0.92 (0.30)	1.15 (0.52) [a]

[a] Significant unadjusted differences (p value < 0.05).

Table 3: Adjusted differences in levels of biomarkers in Women post early-onset pre-eclampsia compared to reference women

Biomarkers	Crude	Model 1	Model 2	Model 3	Model 4
	β (99% CI)	β (99% CI)	β (99% CI)	β (99% CI)	β (99% CI)
Adiponectin (µg/ml)	0.18 (-7.11; 7.47)	0.36 (-6.94; 7.65)	-0.48 (-8.02; 7.06)	1.29 (-6.53; 9.12)	1.65 (-6.02; 9.32)
PAI-1 (ng/ml)	0.08 (-3.22; 3.39)	0.20 (-3.11; 3.50)	-0.22 (-3.62; 3.19)	-2.72 (-6.15; 0.70)	-2.97 (-6.22; 0.29)
Leptin (ng/ml)	2.12 (-1.63; 5.87)	2.11 (-1.65; 5.87)	2.29 (-1.60; 6.18)	0.01 (-3.96; 3.97)	-0.26 (-4.05; 3.52)
sICAM-1 (ng/ml)	-11.37 (-24.68; 1.95)	-11.89 (-25.18; 1.41)	-10.91 (-24.58; 2.76)	-13.78 (-27.97; 0.42)	-13.92 (-28.12; 0.28)
sVCAM-1 (ng/ml)	3.00 (-32.08; 38.07)	4.24 (-30.78; 39.25)	-1.31 (-37.28; 34.66)	5.71 (-31.68; 43.11)	6.56 (-30.71; 43.82)
SEselectin (ng/ml)	3.61 (-0.49; 7.71)	3.97 (-0.06; 8.00)	5.46 (1.33; 9.59)	4.78 (0.48; 9.07)	4.55 (0.37; 8.74)
PAPPA (ng/ml)	10.29 (10.66; 21.91)	16.68 (11.12; 22.25)	19.39 (13.72; 25.08)	19.19 (13.30; 25.08)	19.08 (13.18; 24.99)
ApoB (g/l)	-0.23 (-0.31; -0.14)	-0.22 (-0.31; -0.14)	-0.20 (-0.29; -0.11)	-0.23 (-0.32; -0.14)	-0.23 (-0.32; -0.14)

p value <0.01.
Model 1, adjusted age,
Model 2, adjusted age, years postpartum, smoking.
Model 3, adjusted age, years postpartum, smoking, hypertension.
Model 4, adjusted age, years postpartum, smoking, hypertension, metabolic syndrome.

Blood samples for biomarker analysis were unavailable for three women in the reference group. Table 2 shows levels of biomarkers in women with PE and the reference group. In Table 3 we describe the adjusted differences in biomarkers for women with a history of PE compared to women with a history of uncomplicated pregnancy (reference group). After adjustment for traditional cardiovascular risk factors, women with PE had significantly higher levels of SE-selectin (β 4.55, 99%CI 0.37; 8.74) and PAPPA (β 19.08, 99% CI 13.18; 24.99) compared to women with a healthy pregnancy. Levels of ApoB were significant lower for women post PE compared to reference women, also after adjustment for traditional CVD risk factors (smoking, hypertension, MetS (model 4)), adjusted difference β -0.23, 99%CI -0.31; -0.14. Levels of sICAM-1 were lower in PE women (94.2, SD 69.5 ng/ml) compared to reference women (105.6, SD 63.4 ng/ml) at crude analysis ($p<0.05$); however, after multiple adjustment with a probability level of 0.01, results attenuated to non-significant (β -13.92, 99%CI -28.12; 0.28). In accordance with the crude results, adjustment for potential confounders did not show any significant association between PE and consecutively adiponectin (β 1.65, 99%CI -6.02; 9.32), leptin (β -0.26, 99%CI -4.05; 3.52), sVCAM-1 (β 6.56, 99%CI -30.71; 43.82) and PAI-1 (β -2.97, 99%CI -6.22; 0.29).

DISCUSSION

In this cross-sectional analysis of the PREVFEM study, we evaluated the associations between various novel CVD biomarkers in women with and without a history of PE. Our data show that women 10 years after PE have higher levels of SE-selectin and PAPPA compared to women without previous PE, after adjustment for traditional CV risk factors (smoking, hypertension, MetS). The increased levels of SE-selectin and PAPPA may contribute to the higher cardiovascular risk in these women.[3-5]

SE-selectin, a marker of endothelial dysfunction, is associated with an increased risk of type 2 diabetes mellitus, but higher levels are also related to CVD events.[26,27] The elevated levels of SE-selectin in our cohort of women, 10 years after PE, may be an expression of (persistent) endothelial dysfunction. In contrast with our results, other studies like those of Sattar et al. and Gaugler-Senden et al. could not demonstrate increased levels of SE-selectin in women post PE.[11,21] One of the explanations of this inconsistency may be the heterogeneity of included participants in different studies. Whereas in our cohort only women with early-onset PE were included, Sattar et al.[11] investigated the whole spectrum of PE. Gaugler-Senden et al. did also include women

with severe and early-onset preeclampsia, but their cohort was very small (n=16), limiting the power to detect an association.[21] In addition, both studies did not correct for the potential influence of traditional cardiovascular risk factors on biomarker levels, which might explain another part of the inconsistency between data.

Pregnancy-associated plasma protein A (PAPPA) is a metalloproteinase which is associated with the presence of vulnerable atherosclerotic plaques.[24] Elevated levels of PAPPA and other metalloproteinases during pregnancy have been shown to be associated with worse obstetric outcomes and risk of PE.[28,29] Metalloproteinases may be the link between placental alterations in pregnancy and harmful cardiovascular effects later in life as increased levels of PAPPA are also associated with risk of (recurrent) acute coronary syndromes.[30-32] We therefore hypothesize that the vascular alterations in PE lead to persistent vascular damage and early development of vulnerable atherosclerotic plaques, as shown by increased levels of PAPPA in women post PE. This can subsequently contribute to premature cardiovascular events.

One of the other remarkable results in our study was the lower levels of ApoB in women post PE compared to reference. ApoB is a very potent cardiovascular risk marker and these lower levels suggest protection against future CV events for women post PE.[33] We do not understand the pathophysiological mechanism of the decreased levels of ApoB. As LDL-cholesterol and triglyceride levels do not differ and 90% of ApoB is associated with LDL particles[33], the lower ApoB levels in women post PE suggest the presence of large, buoyant LDL particles, which are associated with decreased cardiovascular risk. On the other hand, the study of Girouard et al. demonstrates increased levels of ApoB for both women with a history of GH and PE compared to control subjects.[19] We do know that hormonal factors, like use of oral anticonceptiva and postmenopausal status, can increase levels of ApoB.[34,35] However, the same is true for LDL cholesterol[34,35], in which we did not find a difference between PE and reference women. Besides, postmenopausal status and length of hormonal anticonceptive use was equal in both groups of our cohort. But current oral anticonceptive use is higher in reference women (40%) compared to former preeclamptic women (31%), additional adjustment for current use of oral anticonceptiva did not change the ApoB results in our study.

All other biomarkers, including the previously measured CRP and fibrinogen, did not show any difference between women with and without a history of PE. This is consistent with several other studies[21-23], with the exception that Sattar et al.[11] did demonstrate increased levels of s-ICAM1 in women post PE and Girouard et al.[19] demonstrated significant differences in leptin, adiponectin and CRP in a combined cohort of GH and PE. Considering the conflicting results in literature, mechanistic

studies are necessary to explain the associations between different endothelial dysfunction biomarkers and PE.

Strengths and limitations

Studies on the levels of CVD biomarkers in women after PE are relatively scarce and inconsistent.[11,19-23] An important reason for this inconsistency is the heterogeneity of the included patients in the studies, which varies from gestational hypertension up to severe and early PE. There is also a great variety of biomarkers, and in each study a different subset of biomarkers was included.[11,19-23] One of the strengths of our cohort is the well-defined population of women after early onset PE, all between 20-32 weeks of gestation, and the relatively long follow-up period of 10 years post index pregnancy. We further composed a set of biomarkers that are involved within various stages of endothelial dysfunction and cover the complete spectrum of early atherosclerosis development.

For the analyses of biomarkers in our cohort the Luminex assay was used, which has the advantage to enable simultaneously measures up to 100 analytes and uses only very small sample volumes.[26] However, dilution for different analyses may be different and may have influenced the cut-off values for the biomarkers as described in the Methods section.

Future perspectives

Our data indicate that particular CVD biomarkers, SE-selectin and PAPPA, are significantly associated with early-onset PE and these associations persist after adjustment for traditional CV risk factors (smoking, hypertension and metabolic syndrome). These markers express the presence of endothelial dysfunction in women post PE and might contribute to their increased cardiovascular risk. Especially PAPPA, which is also associated with worse pregnancy outcome and risk on PE,[30] could be of interest in elucidating the underlying mechanisms between PE and CVD. On the other hand, we did find significantly lower levels of ApoB. Future research should focus on the role of these novel biomarkers in the pathophysiological process of CVD in women post PE.

The recent 2012 European guidelines on CVD prevention do recommend the use of biomarkers in cardiovascular risk prediction in intermediate risk individuals.[35] More research on the prognostic impact and utility of these biomarkers in general cardiovascular screening programmes, but especially in subgroups of high-risk individuals such as women with a history of PE, is needed.

CONCLUSION

In this cross-sectional cohort analysis we demonstrated an independent association of SE-selectin and PAPPA (markers of vascular dysfunction) with PE, which may contribute to future cardiovascular events in women post PE. However, ApoB a lipid-marker was significantly lower and could be protective in these women. Our results show that despite correction for traditional cardiovascular risk factors vascular dysfunction, as measured by biomarkers, is ongoing in women post PE. The mechanisms by which these biomarkers are involved in the increased cardiovascular risk warrant further investigation.

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CHAPTER 7

Cost-effectiveness analysis of a yearly hypertension screening in women with a history of pre-eclampsia

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Submitted

ABSTRACT

Objective: Women with a history of preeclampsia (PE) are at increased risk for future hypertension and cardiovascular disease (CVD). Until now it is not clear whether preventive measures are needed in these high-risk women. In the present study we evaluated the cost-effectiveness of a simple hypertension screening strategy in women post PE.

Design and setting: A decision-analytic Markov model was constructed to evaluate health care costs and effects of screening for hypertension post PE based on available literature.

Participants: Women with a history of preeclampsia with and without (treated) hypertension.

Intervention: Screening consisted of a postpartum annual blood pressure measurement during a timeframe of 20 years.

Main outcomes: Cardiovascular events and CVD mortality were defined as health states. Outcomes were measured in absolute costs, events, life-years and quality-adjusted life-years (QALYs). Sensitivity and threshold analyses were performed to address uncertainty.

Results: Over a 20 year time horizon events occurred in 0.072% of the population after screening, and in 0.085% of the population without screening. QALYs increased from 16.38 (no screening strategy) to 16.41 (screening strategy), an increment of 0.03 (95%CI 0.01; 0.05) QALYs (12 days in perfect health). Total expected costs were €7,834 in the screening strategy, and €9,038 in the no screening strategy, an expected saving of €1,203 (95%CI -3223; -247) per person.

Threshold analysis demonstrated that screening remained cost saving up to annual screening costs of €166 per year.

Conclusion: Annual hypertension screening in women with a history of PE may save costs, for at least similar quality of life and survival due to prevented CVD compared with standard care.

INTRODUCTION

It has been well established that women with a history of preeclampsia (PE) are at increased risk of future cardiovascular disease (CVD) morbidity and mortality.[1] Preeclampsia is defined as de novo hypertension (>140/90 mmHg) with proteinuria

(>0.3 g/24 h) occurring in the second half of pregnancy.[2] It complicates about 2-8%[3] of all pregnancies, which emphasizes the magnitude of the problem. Despite the abundant evidence on the increased CVD risk in these women later in life,[4-6] intermediate follow-up data are still relatively scarce and it is undefined yet whether preventive measures are needed.[7]

In the Preeclampsia Risk EValuation in FEMales (PREVFEM) cohort, consisting of 339 women with a history of early PE (before 32 weeks of pregnancy), we previously identified hypertension as the most important CVD risk factor at a cardiovascular screening 10 years post-partum. At this screening, participating women were on average 40 years of age.[8] As hypertension is an established CVD risk factor[9], early detection and treatment of hypertension seems to be important for this category of young women. Obstetric guidelines on treatment of hypertensive disease of pregnancy (HPD) recommend that women with a history of HPD should pursue a healthy lifestyle and might benefit from assessment of CVD risk factors.[10] However, screening onwards from pregnancy is labour-intensive and may be costly. It is unknown whether these costs are outweighed by the potential improvements in quality of life and long-term prognosis, as the CVD event-rate in young women is low. Currently, no data on cost-effectiveness of preventive interventions in women after PE are available. We performed a model-based cost-effectiveness analysis to estimate the health care costs and potential effects of screening for hypertension in women with a history of (early) PE.

METHODS

Overview

A decision-analytic Markov model was constructed to evaluate costs and effects of screening for hypertension from a health care perspective in women post PE. In each cycle of the model patients were transferred to a certain health state according to the calculated transition probabilities as described in the section transition probabilities. As health states (Figure 1) we defined hypertension (treated and untreated) and the most common CVD events, namely ischemic heart disease, stroke, heart failure and end-stage renal failure (ESRD). Final states were defined as CVD mortality and mortality of other causes.

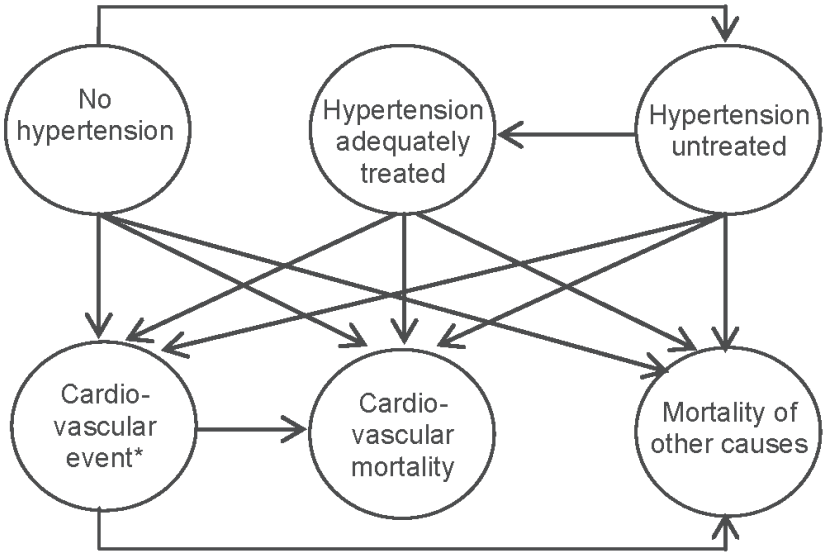

Figure 1: Schematic representation of the Markov model. *The 'cardiovascular event' health state is subdivided into 'ischemic heart disease', 'stroke', 'heart failure' and 'renal failure'.

The cycle length was 1 year. We used time horizons of 10 and 20 years because of the time needed to develop cardiovascular events in young women. Our starting point was at 30 years of age.

We choose to limit the time horizon to 20 years as we are especially interested in potential health gain of prevention in young women starting directly postpartum. During these 20 years before menopause women normally have limited healthcare contacts without routinely cardiovascular risk assessment, while after menopausal transition CVD prevention is already recommended in current guidelines.[11]

Outcomes were measured in number of events, life-years, quality-adjusted life-years (QALYs) and absolute costs. The Markov model was built and analyzed in Microsoft Office Excel 2010.

MODEL CONSTRUCTION

Patient characteristics

As target population we used the PREVFEM cohort, comprising women with a history of early-onset PE, defined as an elevated diastolic blood pressure ≥90 mmHg with proteinuria (≥0.3 g/ 24 h) developing between 20 and 32 weeks of gestation.[12] In this study we evaluated the presence of CVD risk factors in women at 10 years after index pregnancy compared to a reference cohort of age-matched women with uncomplicated pregnancy. We consecutively invited all women registered with early-onset PE at the hospital department of obstetrics during the time-period 1991-2007 to participate in this cohort study (n=528). Approval for the study was obtained from the institutional review board of the Isala klinieken in Zwolle. The detailed protocol of the screening procedure has been described elsewhere, as well as the used definitions of CVD risk factors.[8]

Comparators

We introduced a hypothetical annual blood pressure screening at the general practitioner (GP) for women after PE starting in the first year postpartum. The comparative strategy existed of care as usual: standard obstetric care and no specific arranged blood pressure check-ups. If hypertension (repeated measurements with a systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg) was detected, in any of the strategies, this involved three additional GP visits, an ECG recording and prescription of medication. In the two comparative strategies the probability of developing CVD was equal. The only difference between the strategies was in detecting and therefore treating hypertension.

Transition probabilities

Risk of hypertension and presence of adequate treatment for women after PE was based on the PREVFEM cohort.[8] We made the assumption that women in the screening group with established hypertension will be recognized at the screening and treated adequately. For women in the non-intervention group we based the probability of detected hypertension and adequately treated hypertension on the PREVFEM data.[8] As the follow-up in this cohort is relatively short (10 years) we used published literature to assess the risk of future CVD in women post PE (early as well as late PE) (Table 1).[4,13,14]

Table 1: Risk of cardiovascular health outcome in women with a history of preeclampsia

Health outcome	Risk (%) / (events / total n)	Follow-up (years)	Ref.
Hypertension (screening-strategy)	43.1 (146/339)	10	8
Hypertension (non-intervention strategy)			8
On medication	20.6 (70/339)	10	
Adequately treated	8.0 (27/339)	10	
Ischemic heart disease	1.8 (458/25,148)	14.6	14
Stroke	1.6 (412/25,184)	14.6	14
Heart failure	0.5 (123/25,184)	14.6	14
End-stage renal disease	0.8 (2/242)	40	13
Cardiovascular mortality	1.0 (167/26,168)	10-42	4

Table 2: Relative risk of cardiovascular outcome in participants with untreated hypertension

Health outcome	Relative risk (95% confidence interval)	Distribution	Ref.
Ischemic heart disease	1.32	Fixed	15
Stroke	1.49	Fixed	15
Heart failure	1.47 (1.35-1.61)	Normal	16
End-stage renal disease	2.57 (2.06-3.22)	Normal	17
Cardiovascular mortality	1.61 (1.35-1.92)	Normal	16

Probabilities of developing CVD for each cycle (Table 2) were derived from meta-analyses on cardiovascular disease. We assumed that women with a history of PE and well treated hypertension (intervention group) are at comparable risk of CVD as published in the various cohort studies post PE.[4,13,14] Risk reduction in the development of ischemic heart disease and stroke were based on the effects of blood pressure lowering, starting with a pretreatment SBP of 140 mmHg (as described in the hypertensive women of the PREVFEM cohort) and one drug standard dose.[15] As Law et al did not described the effects of blood pressure lowering on heart failure and mortality we used hazard ratio's (per 20 mmHg SBP increasement) on CVD mortality and total CVD events in a Dutch cohort study (35-65 years of age) to estimate the effects on these health states.[16] The use of a 20 mmHg SBP increasement was based on the difference of SBP in women post PE with and without hypertension in the PREVFEM cohort.[8] Estimation of the relative risk for the development of ESRD was also based on a SBP difference of 20 mmHg in a American cohort of 37 years of age.[17]

Table 3: Health care costs

Health outcome	Event -related costs (€)	Long -term treatment, cost / year (€)	Distribution	Ref.
Hypertension				
Screening/year	29.73	-	Fixed	
Treatment	129.52	34.89	Fixed	19, 20
Ischemic heart disease	16,570	1,007	Fixed	18
(Major) Stroke	34,585	20,194	Fixed	18
Heart failure	3,707	1,550	Fixed	21, 22
End-stage renal disease	-	53,961	Fixed	22
Cardiovascular mortality	4,000	-	Fixed	21

Costs

Costs (Table 3) were presented in the European currency 'Euro' (€). Price indices were used to convert costs to the 2012 price level. Estimation of costs in the intervention strategy was based on a single screening visit at the GP of €30 (Dutch reference price, as established by the Dutch Health Care Insurance Board).[18] Costs for detection of hypertension in both strategies were based on three GP visits and an ECG recording (€130) and yearly costs for treatment of hypertension and medication use according to current Dutch GP guidelines.[19,20] Costs associated with the potential health outcomes and yearly ongoing cost thereafter were derived from published Dutch cost studies.[11,21] If these data were not available (for event-related costs of heart failure and treatment associated with ESRD), we used other European studies.[22] As advised in the Dutch guideline, future expenditures were discounted to their present value by a rate of 4%.[18]

Effects

Quality-adjusted life years (QALYs) were used as outcome measure in the model. These are defined as a combination of survival and health-related quality of life. To measure health-related quality of life we used a single index utility, on a scale from 0 (death) to 1 (perfect health). Utility data (Table 4) were derived from recent population-based literature.[11,23-27] Utility for healthy women and women with (treated and untreated) hypertension were equalized, due to the high utility of hypertensive patients.[11,23] Future effects were discounted to their present value by a rate of 1.5%, according to Dutch guidelines.[18]

Table 4: Health outcome associated utility

Health outcome	Utility (SD)	Distribution	Ref.
No hypertension	As hypertension		
Hypertension	0.98 (0.005)	Beta	23
Ischemic heart disease	0.837 (0.17)	Beta	24
Stroke	0.70 (0.27)	Beta	25
Heart failure	0.47 (0.32)	Beta	26
End-stage renal disease	0.71 (0.05)	Beta	27

Analysis

Total event rates, life years, QALYs and expected costs were calculated for both strategies. If one strategy was more effective and less costly, this strategy was deemed cost-effective. To see if screening was more costly and more effective, or the opposite, incremental cost-effectiveness ratios (ICERs) were calculated by dividing the incremental costs by the incremental QALYs. Whether screening is cost-effective depends on whether this ICER is below the societal willingness to pay for a QALY. The informal willingness to pay in the Netherlands is € 80,000 per QALY for diseases with a high burden.[18]

Sensitivity analysis

To reflect the uncertainty of the parameter estimates in the model probabilistic sensitivity analyses were performed.[28] For this purpose distributions were assigned to the model parameters. Parameter values were drawn at random from the assigned distributions, using Monte Carlo simulation with 1000 iterations. Based on these simulations, mean values and 95% confidence intervals surrounding the costs and effects were calculated. The results of this probabilistic analysis are demonstrated in a cost-effectiveness plane and cost-effectiveness acceptability curve (CEAC). The CEAC shows the probability that screening is cost-effective over a range of willingness to pay thresholds.[29]

In addition, a threshold analysis was performed to determine the maximum costs of the screening strategy. In this threshold analysis the maximum costs of screening are determined to establish which screening is the most effective and least expensive strategy.

One-way deterministic sensitivity analyses were performed to evaluate changes in quality of life of women with hypertension. First, we decreased the utility score of treated and untreated hypertension to 0.95 and 0.90. Second, we analyzed two different scenarios with a lower utility of untreated hypertension compared to treated hypertension.

Table 5: Cost-effectiveness results, based on the probabilistic analysis

	Screening strategy Mean (95% CI)	No screening strategy Mean (95% CI)	Increment Mean (95% CI)
Expected health care costs (€)			
10 year horizon	2,987 (1,826; 5,434)	3,062 (1,738; 5,751)	-75 (-424; 91)
20 year horizon	7,834 (4,492; 14,793)	9,0.38 (4,764; 17,703)	-1,203 (-3,223; -247)
Expected life years			
10 year horizon	9.1715 (9.1674; 9.1750)	9.1700 (9.1657; 9.1739)	0.0015 (0.0008 0.0023)
20 year horizon	16.9525 (16.9397; 16.9652)	16.9423 (16.9267; 16.9574)	0.0102 (0.0049; 0.0157)
Expected QALYs			
10 year horizon	8.93 (8.82; 9.02)	8.92 (8.81; 9.02)	0.0046 (0.0021;0.0077)
20 year horizon	16.41 (16.17; 16.65)	16.38 (16.13; 16.63)	0.0315 (0.0140; 0.0537)

RESULTS

Base case analysis

Screening for hypertension was found to be slightly more effective than no screening (Table 5). Over a 10 year time horizon, screening for hypertension results in 0.037% of the population having an event (either ischemic heart disease, stroke, heart failure, ESRD or CVD mortality), while this is 0.041% without screening. Screening provides an expected efficacy of 9.1715 life years and 8.93 QALYs, whereas for the no-screening strategy these results were 9.1700 life years and 8.92 QALYs. The increment of the screening strategy over 10 years was 0.0015 (95%CI 0.0008; 0.0023) life years and 0.005 (95%CI 0.0021; 0.0077) QALYs. With an extended time horizon of 20 years these differences became larger. Events occurred in 0.072% of the population after screening, and in 0.085% of the population without screening. Life years in the screening strategy were 16.9525 versus 16.9423 in the no screening strategy, an increment of 0.0102 (95%CI 0.0049; 0.0157) life years. QALYs increased to 16.38 for the no screening strategy and to 16.41 for the screening strategy, an increment of 0.0315 (95%CI 0.0140; 0.0537) QALYs, which equals 12 days in perfect health quality.

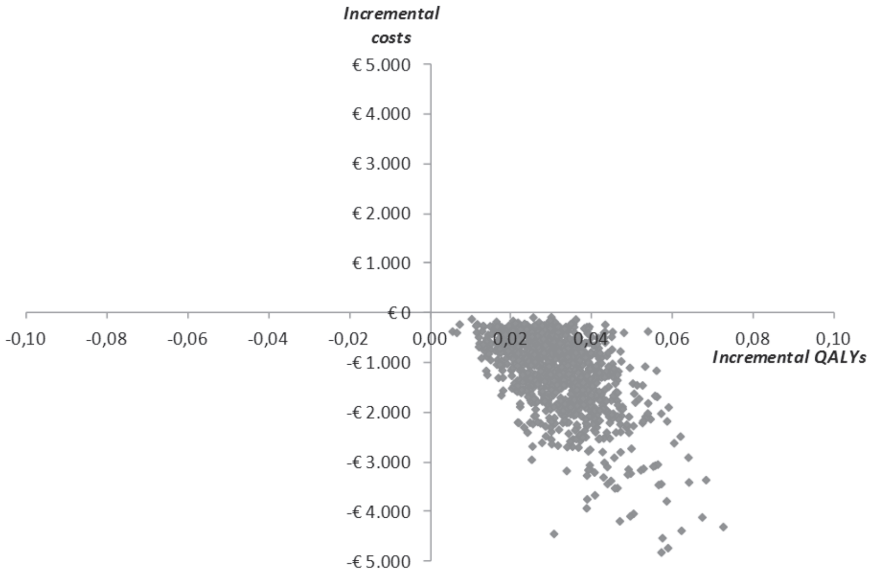

Figure 2: Effectiveness of screening for hypertension post preeclampsia according to the probabilistic analysis in 20 year time horizon.

Screening was also found to be less expensive than no screening. Estimated expenditures over a 10 year time horizon were €2,987 for the screening strategy and €3,062 for the no screening strategy, a saving of €75 (95%CI -424; 91) per person in ten years. Over a 20 year time horizon total costs in the screening strategy increased to €7,834, whereas in the no screening strategy to €9,038. This further increases the savings to €1,203 (95%CI -3223; -247) per person.

Sensitivity analysis

The results of the probabilistic sensitivity analysis showed that despite considerable uncertainty, in almost all simulations the screening strategy is less costly and more effective than the no screening strategy over 20 years (Figure 2). From the CEAC it is clear that regardless of the willingness to pay for a QALY, screening has a probability of being cost-effective over 99% (Figure 3).

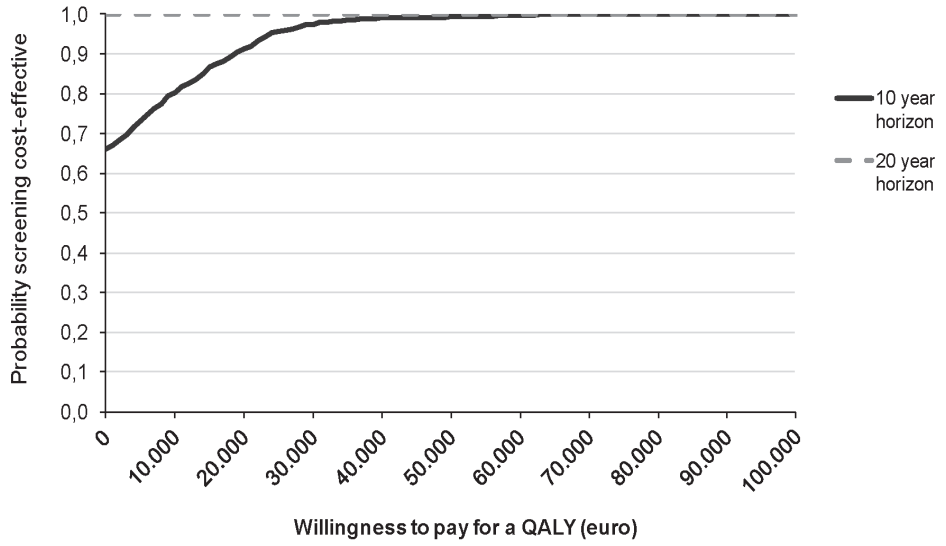

Figure 3: Cost-effectiveness acceptability curves for hypertension screenig in women post preeclampsia, combined results for 10 and 20 year time horizon.

In the threshold analysis, screening remained the least costly strategy over 20 years up to costs of screening of €166 per year.

Table 6 shows the one-way sensitivity analysis on utility. Lowering the utility of both treated and untreated hypertension reduced the QALYs gained in the screening strategy. But on the opposite, if we decreased the utility of untreated hypertension, with unchanged utility of treated hypertension, the QALY gain of screening increased. By using a combination of lower utility of treated hypertension (0.97) compared to a healthy state (0.98) and a utility of 0.95 for untreated hypertension, incremental QALYs of screening raised to 0.132. For each variation in utility the screening strategy remained the most effective strategy.

Table 6. Results of the deterministic threshold and sensitivity analysis (over 20 years)

	Incremental costs screening (€)	Incremental QALYs screening	Incremental costs per QALY gained
Base case analysis	-1195	0.03	Screening dominates
Costs of screening €166	-5	0.03	Screening dominates
Utility hypertension 0.95	-1195	0.03	Screening dominates
Utility hypertension 0.90	-1195	0.03	Screening dominates
Utility untreated hypertension 0.95	-1195	0.18	Screening dominates
Utility untreated hypertension 0.90	-1195	0.44	Screening dominates
Utility untreated hypertension 0.90, treated hypertension 0.95	-1195	0.28	Screening dominates
Utility untreated hypertension 0.95, treated hypertension 0.97	-1195	0.13	Screening dominates

DISCUSSION

In this model-based analysis we assess the expected cost-effectiveness of a hypertension screening strategy in women after PE. We found that a relatively simple preventive strategy, consisting of a yearly blood pressure measurement at the GP after index pregnancy, is less expensive and more effective than current standard care without regular control. Over 20 years, screening for hypertension gives an expected saving of €1,203 per person and a slight increment of 0.03 QALY, i.e. an increase of 12 days living in perfect health per screened person.

Cardiovascular risk and preeclampsia

Several studies have clearly demonstrated the increased risk for CVD in women with a history of PE.[1,4,5] Especially women after early and severe PE are at higher risk for future CVD.[1,14] The 2011 AHA guidelines on cardiovascular disease prevention in women do recognize pregnancy as a unique chance to predict women's lifetime cardiovascular risk, as pregnancy-related complications may unmask premature vascular of metabolic diseases.[7] Therefore appropriate monitoring of CVD risk factors in these high risk women is recommended.[7] The 2012 ESC guideline on CVD prevention also indicates that prevention of CVD in women ideally starts during pregnancy and lasts until end of life.[9] However, in standard primary care obstetric

history is not yet routinely incorporated.[30] The NICE guideline 'Hypertension in pregnancy' recommend physicians to inform women with a history of HPD about the future risk of hypertension and associated complications.[31] The Dutch multidisciplinary guideline on cardiovascular risk management advises cardiovascular risk assessment in postmenopausal women who previously had pregnancy-related hypertensive complications.[11] However, in our analysis we showed that an important preventive effect may already be reached in women before menopause.

Strenghts and limitations

In our Markov model analysis we demonstrated cost-effectiveness of cardiovascular prevention in women with a history of preeclampsia. The power of this model is founded in combining the available evidence on CVD post preeclampsia. Our model could be of help in making evidence-based decisions on prevention post preeclampsia, without performing complex and costly long-term follow-up studies.

However, our model has some limitations. To estimate risk of hypertension in women after PE we used the PREVFEM cohort, a well-defined cohort of women with a history of early PE. As this hypertensive pregnancy disorder confers the highest future CVD risk[1,14], the used risk on future hypertension and therefore the effectiveness of our Markov model might be overrated for women with a later occurrence of PE and other HPD. However, as prospective data in women after early PE are relatively scarce, we also used future CVD risk data of patients with less severe forms of PE to estimate risk on future CVD post PE. This may have underestimated the net effect in our model. Nonetheless the presented data are convincing and underline the need for preventive measures in these high-risk women.

In our model we used mainly Dutch costs. As costs in other jurisdictions will be different from the Dutch situation, our results could be less generalizable to other health systems. However, in general costs in the US tend to be higher than in the Dutch health care system, so savings in the US will probably turn out to be larger. On the other hand, the Dutch well-structured GP system can adopt our intervention strategy easily, whereas this might be more difficult in other countries with a less developed GP system. Given our detailed presentation of the model and its input parameters, interested readers can assess the transferability of the results to their specific situation.[32]

To perform our model we made some assumptions. First, we assumed that women with non-treated hypertension in the non-intervention strategy had a 20 mmHg higher SBP than women with adequate treated hypertension in the intervention strategy, based on our PREVFEM data. This seems reliable if women in the intervention strategy are

directly well controlled and treated, but in current daily practice this is still disappointing.[33,34] In our model partcipants were all compliant in taking antihypertensive medication, in realilty a quarter of women on blood pressure medication does not take them regularly, which will reduce the calculated preventive effects.[35]

Second, to estimate the increase in CVD risk in the presence of increased blood pressure we used a meta-analysis and two cohort studies, these studies consisted of men and women with an age distribution between 35 and 65 years old. Our Markov model focuses on women between 30 and 50 years old. Use of data based on both men and women might have overrated over effects as men have higher CVD rates at younger ages.36

Finally, we assumed that women with and without hypertension have the same utility score and only adapted utility if one of the defined health states was achieved. The study of Stein et al. indicates that patients with hypertension do not experience the lower quality of life which is expected by healthy individuals and clinicians.[23] However, we can imagine that both treated hypertension (with use of medication and lifestyle adaptations) and untreated hypertension (with potential health complaints) influence utility. We evaluated potential adaptation of utility in the sensitivity analyses and demonstrated that screening remains less costly and more effective in each variation (Table 6).

Clinical implications and future perspective

In our model we demonstrated that a yearly blood pressure measurement at the GP post preeclampsia is less expensive and more effective than current standard care without regular blood pressure control in prevention of CVD. However, in a time horizon of 20 years we found only a slight gain in QALYs (15 days living in perfect health per screened person). Although this gain is associated with cost savings, the clinical relevance of this small gain in QALYS can be discussed. Besides the relevance of this health effect we also need to consider the willingness of young, healthy women to use blood pressure medication, with potential side effects, for a 15 days longer life in perfect health. Further, before considering to incorporate a screening strategy into new primary care guidelines, it should be investigated if the used strategy is attainable for GPs. Despite the cost-effectiveness of hypertension screening postpartum, it gives a potential burden for GPs and women post PE. This may be decreased by starting screening at 10 years postpartum or by reducing the frequency of the screening to once in 2 years. More research is needed to establish the best time-schedule for hypertension screening. For the future, there might be an interesting role for e-health medicine in

prevention of CVD in young high-risk women post PE. This also needs to be investigated.

CONCLUSION

Annual hypertension screening in primary care in women after PE is cost-effective in preventing future CVD.

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CHAPTER 8

More vasomotor symptoms in menopause among women with a history of hypertensive pregnancy disorders compared with women with normotensive pregnancies

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ABSTRACT

Objective: Cardiovascular disease is the major cause of mortality in women worldwide. In recent years, several female-specific cardiovascular risk factors, such as hypertensive pregnancy diseases (HPD) and vasomotor menopausal symptoms (VMS), have been identified. In this study, we evaluated the association between a history of HPD and the presence of VMS.
Methods: We consecutively included 853 women (mean age 55.5 years) who visited the outpatient cardiovascular clinic for women in Kampen between 2003 and 2010. The visit included a questionnaire on history of HPD, demographic characteristics and VMS; a physical examination; and blood sampling. Logistic regression analysis was used to analyse the data.
Results: A history of HPD was reported by 274 women (32%) and VMS were reported by 83% of women with HPD in history and 75% of women without HPD in history. In adjusted models, VMS were more often present (odd ratio [OR] 1.62; (95%CI 1.00; 2.63), and more frequently persisted for longer than 1 year (OR 2.05; 95%CI 1.08; 3.89) among women with a history of HPD than among women with normotensive pregnancies. VMS were more often severe in women with history of HPD, but this did not reach significance (adjusted OR 1.28; 95%CI 0.92; 1.80). The frequency and intensity of VMS did not differ between both groups.
Conclusion: In our 'Kampen women cardiology clinic' cohort, women with a history of HPD report VMS during the menopausal transition significantly more often than women with normotensive pregnancies.

INTRODUCTION

Cardiovascular disease is one of the most important causes of death in men and women.[1] For women, several female-specific risk factors have been identified.[2] Hypertensive pregnancy diseases (HPD), especially early preeclampsia, are important female specific risk factors that affect future cardiovascular health.[3-5] Other pregnancy-related complications, such as placental syndrome (abruption or infarction) or gestational diabetes mellitus, also contribute to an increased cardiovascular risk.[6,7] Although the underlying mechanisms are not clear yet, endothelial dysfunction and an exaggerated systemic inflammation after a complicated pregnancy are likely to play a role in the increased cardiovascular disease (CVD) risk.[8] The presence of vasomotor

menopausal symptoms (VMS), another characteristic of reproductive health and commonly referred to as night sweats and hot flushes, is also associated with a less favorable cardiovascular risk profile and an increased CVD risk.[9,10] VMS reflect reduced vascular reactivity, manifested by oxidative stress and endothelial dysfunction, and are also associated with increased carotid intima media thickness.[11,12]

Despite the fact that HPD and VMS are both associated with an increased cardiovascular risk that seems to be mediated through endothelial dysfunction HPD and VMS have never been evaluated to be related. Vascular dysfunction in women with a history of hypertensive diseases in pregnancy may lead to an increase in VMS as a sign of reduced vascular reactivity during menopause transition. More information on the association between HPD and VMS may lead to a better understanding of both phenomena and result in possible preventive measures.

In the present study we examined whether a history of HPD is associated with the presence, duration, severity, frequency and intensity of VMS

METHODS

Population

The study included consecutively all 1179 women who visited the weekly outpatient cardiology clinic for women in Kampen (Zwolle area, The Netherlands) between 2003 and 2010. Reasons for visiting the clinic consisted of cardiac complaints, cardiovascular screening for an increased family risk or second opinion. Women were referred by their primary care physician or other specialist, but also presented on their own initiative. Women were aged between 40 and 70 years at consultation. Between 2009 and 2010, all women were sent an additional questionnaire on presence, duration, severity and frequency of VMS. Of 1179 women, 931 returned the questionnaire. Of those, 853 women provided data on previous pregnancies and presence of HPD and were therefore included in the present analysis.

Measurements

First intake at consultation was performed by a specialty nurse with a detailed questionnaire on demographic characteristics, physical complaints, lifestyle risk factors, medication use, cardiovascular history and obstetric history.

Information on socio-economic status (SES) of the neighborhood has been derived from the Social Cultural Planning Office, The Netherlands. The Social Cultural

Planning Office uses average income, unemployment, and education as indicators for the social status. Three SES deprivation categories were formed: low, moderate and high. Alcohol consumption was categorized as never; 1-3 units (U)/week; 1-3 U/day and >3 U/day. Smoking was defined as current smoking, past smoking or non-smoking. Sedentary lifestyle was defined as low energy expenditure during daily activities and sports activities for 20 min/week or less.
Menopausal status was defined as follows: women were 'pre- or perimenopausal' if they reported having menses, and 'postmenopausal' if they reported not having menses. Women with incomplete questionnaire data or who reported current use of oral contraceptives or hormones were classified as pre- or perimenopausal if they were between 40 and 55 years of age, and postmenopausal if they were older than 55 years of age. Hormone use was defined as ever use of oral anti-conceptive medication, hormone therapy, or both. A history of HPD, defined as high blood pressure in one of the previous pregnancies or gestational diabetes was based on self-reported history.

Cardiovascular risk parameters

Physical examination was performed. Weight (kg) and height (m) were measured and body mass index (BMI) was calculated as weight in kilograms divided by height per meters squared. Waist circumference (cm) was measured with a tape measure at a level midway the lowest rib and the iliac crest. All women were measured in underwear and barefoot. Furthermore, measurements of blood pressure on both arms and of resting heart rate were taken at rest in sitting position. Hypertension was defined as a systolic blood pressure of 140 mmHg or higher and/or a diastolic blood pressure of 90 mmHg or higher and/or use of antihypertensive medication. Baseline electrocardiogram was recorded. A fasting blood sample was taken to analyse glucose, total cholesterol, high-density lipoprotein cholesterol, cholesterol/high-density lipoprotein cholesterol ratio, low-density lipoprotein cholesterol and triglycerides levels (analysed by Roche Modular P800). Presence of diabetes mellitus was defined as self-reported treatment for diabetes mellitus or a fasting glucose higher than 6.9 mmol/l. Hypercholesterolemia was defined as self-reported use of lipid-lowering medication or a fasting total cholesterol higher than 5 mmol/l. CVD was defined as a composite endpoint of history of myocardial infarction, percutaneous coronary intervention (PCI), coronary artery bypass graft or cerebrovascular accident. Family history of CVD was based on self-report of premature CVD (CVD or multiple cardiovascular risk factors before age of 60 years in first-degree family members) in the questionnaire.

Vasomotor menopausal symptoms

Presence of VMS was assessed via the additional questionnaire using the following question: "Do you currently have or have you had hot flushes and/or night sweats?"- with the choices being (a) none; (b) only hot flushes; (c) only night sweats; (d) both hot flushes and night sweats. Women were also asked to report the duration of VMS, response options ranged from less than 6 months to more than 20 years. Based on this answer, duration of symptoms was divided into two classes: symptoms for 1 year or less, and symptoms for longer than 1 year.

Frequency of hot flushes was based on the number of symptomatic days per week (range 1-7), multiplied with the number of hot flushes per day (range 1-10 or more). The resulting hot flushes frequency score ranged from 1 to 70 and was categorized as low ($\leq$21); moderate (22-36) or high ($\geq$37). Women with missing data on both number of symptomatic days and number of hot flushes per day were classified as not having had hot flushes. To determine the frequency of night sweats, we combined the data on number of symptomatic nights per week (range 1-7) and number of nights sweats per night (range 1-14). Based on the resulting night sweats frequency score (range 1-98) we created 3 frequency categories: low ($\leq$8); moderate (9-15); high ($\geq$16) night sweats per week. Women with missing data were again classified as not having had night sweats. The frequency category of hot flushes was multiplied with the frequency category of night sweats, resulting in a total frequency score for VMS (range 1-9). VMS frequency categories were formed: low (score of 1-2), moderate (score of 3-4) or high (score of $\geq$5). Severity of hot flushes and nights sweats was indicated by the participants and divided into four categories: (0) no symptoms, (1) symptoms not disturbing day/night activities, (2) symptoms disturbing activities day/night, and (3) severe symptoms interrupting with activities. We defined symptoms as severe if the criteria fulfilled the last two categories. Women with either severe hot flushes, severe night sweats or both where defined as having severe VMS or as having had severe VMS.

Finally, we determined the intensity of VMS based on a combination of frequencies of VMS, as described before; severity of VMS was determined as indicated by the participants. For hot flushes, we multiplied the frequency category (1-3) with the severity of symptoms (0-4). Based on this score, we divided the intensity into three categories: low (score of 1-2); moderate (score of 3-4); high (score of $\geq$5). For night sweats, we did the same (frequency category x severity) to determine intensity and divide them into three categories. We combined intensity data of hot flushes and nights sweats in a new parameter, 'intensity VMS': low intense VMS (score of 1-2); moderate intense VMS (score of 3-4), and high intense VMS (score of $\geq$5).

Table 1: Baseline characteristics of the study population (n = 853) by presence of hypertensive pregnancy disease

Variables	With hypertensive pregnancy disease n = 274 Mean (SD) or n (%)	Without hypertensive pregnancy disease n = 579 Mean (SD) or n (%)
Age visit outpatient clinic (years)	56.5 (7.3)	54.5 (9.3)*
Cardiac complaints as reason visit clinic	147 (53.4%)	293 (50.6%)
Current smoking	23 (8.4%)	52 (9.0%)
Ex-smoking	130 (47.4%)	295 (50.9%)
Familial history cardiovascular disease	248 (90.5%)	511 (88.3%)
Alcohol use:		
never	109 (38.9%)	210 (36.3%)
1-3 units/ week	94 (34.3%)	167 (28.8%)
1-3 units/day	65 (23.7%)	185 (32.0%)
>3 units/day	2 (0.7 %)	7 (1.2%)
Sedentary lifestyle	98 (35.8%)	230 (39.7%)
Socio-economic status (SES)		
low	53 (19.3%)	113 (19.5%)
moderate	150 (54.7%)	329 (56.8%)
high	71 (25.9%)	134 (23.1%)
Systolic blood pressure (mmHg)	148.3 (22.4)	142.6 (22.6) *
Diastolic blood pressure (mmHg)	88.9 (10.7)	85.9 (10.2) *
BMI (kg/m^2)	26.6 (4.6)	25.7 (4.3) *
Waist circumference (cm)	87 (12)	85 (12) *
Total cholesterol (mmol/l)	5.6 (1.1)	5.6 (1.1)
HDL cholesterol (mmol/l)	1.7 (0.5)	1.7 (0.5)
LDL cholesterol (mmol/l)	3.3 (1.0)	3.3 (1.0)
Ratio HDL/Total cholesterol	3.6 (1.2)	3.6 (1.2)
Triglycerides (mmol/l)	1.5 (1.0)	1.4 (1.1)
Glucose (mmol/l)	5.5 (1.2)	5.3 (0.8) *
Hypertension	211 (77.0%)	341 (58.9%) *
Use anti-hypertensiva	86 (31.4%)	128 (22.1%)
Hypercholesterolemia	93 (33.9%)	193 (33.3%)
Statin use	27 (9.9%)	62 (10.7%)
Diabetes mellitus	15 (5.5%)	27 (4.7%)
Cardiovascular disease	15 (5.5%)	28 (4.8%)
Parity (n)	2.6 (1.1)	1.9 (1.3)
Miscarriages and stillbirths	88 (32.1%)	163 (28.2%)
Gestational diabetes mellitus	15 (5.5%)	13 (2.2%) *
Pre-/perimenopausal	46 (16.8%)	170 (29.3%) *
Use of oral contraceptives or hormone therapy in history	236 (86.1%)	466 (80.4%) *

*$p<0.05$.

Data analysis

Baseline characteristics were described as mean (SD) for continuous data and as frequency (%) for categorical data. Differences between women with HPD and women without HPD were analyzed with independent-sample Student's *t*-test for continuous data and with X^2 or Fisher exact test for categorical data, when appropriate.

Logistic regression analysis was used to analyse the associations between the presence of HPD and the risk of VMS. We present odds ratios (OR) with 95% confidence intervals (CI) as crude OR and after stepwise adjustment according to three models. Model 1 only adjusts for age; model 2 for age, SES, sedentary lifestyle, smoking, hormone use (ever) and menopausal status; and model 3 for age, SES, sedentary lifestyle, smoking, hormone use (ever), menopausal status, BMI and hypertension.

Data analyses were performed with SPSS software (version 16.0). All p values were two-sided; statistical significance was assumed when two-tailed probability value was less than 0.05.

Table 2: VMS by presence of hypertensive pregnancy disease (n = 853)

Variable	With hypertensive pregnancy disease n = 274 n (%)	Without hypertensive pregnancy disease n = 579 n (%)
VMS	226 (82.5%)	433 (74.8%) *
Only night sweats	35 (12.8%)	73 (12.6%)
Only flushes	19 (6.9%)	39 (6.7%)
Both	165 (60.2%)	314 (54.2%)
Age at first VMS (year)	48.2 (5.0)	47.8 (5.3)
Duration VMS >1 year	196 (71.5%)	346 (59.8%) *
Severe VMS	166 (60.6%)	307 (53.0%) *
Frequency VMS		
low	120 (43.8%)	265 (45.8%)
moderate	41 (15.0%)	59 (10.2%) *
high	53 (19.3%)	85 (14.7%)
Intensity VMS		
low	116 (42.3%)	245 (42.3%)
moderate	34 (12.4%)	64 (11.1%)
high	63 (23.0%)	99 (17.1%) *

*p<0.05. VMS, vasomotor menopausal symptoms.

RESULTS

The mean (SD) age of 853 women was 55.5 (7.9) years. In total, 274 women (32.1%) had a history of HPD. Compared with women who had no history of HPD, those who had a history of HPD had a higher BMI, waist circumference, glucose level and blood pressure, and were more likely to have a history of gestational diabetes, to be postmenopausal and to have hypertension (Table 1).
Women with previous HPD significantly more often had VMS (82.5%) during the menopausal transition than women without HPD (74.8%), as demonstrated in Table 2. Most symptomatic women reported both night sweats and hot flushes (73% in both groups). Age at first symptoms was equal between both groups, with a mean age of 48 years. Other VMS parameters are described in Table 2. Table 3 shows the associations between HPD and VMS characteristics. The crude OR (95%CI) for the presence of VMS in women with a history of HPD was 1.73 (1.15; 2.59) compared with women without history of HPD. After stepwise correction for potential confounders in different models, as described above, the presence of VMS was still significantly higher in women with history of HPD compared with women with normotensive pregnancies (OR 1.62, 95%CI 1.00; 2.63). Women with previous HPD more often had symptoms with a duration longer than 1 year compared with women without HPD (OR 2.05, 95%CI 1.08; 3.89). In addition, their symptoms were more often severe, with a crude OR (95%CI) of 1.36 (1.02; 1.82). After correction for potential confounders, however, this association attenuated to non-significance, with an OR (95%CI) of 1.28 (0.92; 1.80). The frequency and intensity of VMS did not differ for women with and without a history of HPD.

DISCUSSION

In this study, we found that VMS during menopause occur more often in middle-aged women with a history of hypertensive disease in pregnancy (at our 'Kampen women cardiology clinic') than in women with a history of normotensive pregnancies. VMS in women with a history of HPD were also more severe and more frequently more frequently lasted longer than 1 year compared with women with a history of normotensive pregnancies. However, the magnitude of the association between HPD and VMS is modest.

Table 3: Associations between history of HPD and risk of VMS (n = 853)

HPD (n = 274)	Crude OR (95%CI)	Model 1 OR (95%CI)	Model 2 OR (95%CI)	Model 3 OR (95%CI)
Presence VMS	1.73 (1.15; 2.59)	1.58 (1.05; 2.39)	1.60 (1.00; 2.56)	1.62 (1.00; 2.63)
Duration VMS > 1 year	2.23 (1.25; 3.97)	2.03 (1.13; 3.64)	2.05 (1.08; 3.89)	2.05 (1.08; 3.89)
Severe VMS	1.36 (1.02; 1.82)	1.34 (1.00; 1.80)	1.28 (0.93;1.78)	1.28 (0.92; 1.80)
Frequency VMS				
Low	0.92 (0.69; 1.23)	0.91 (0.68; 1.22)	1.96 (0.70; 1.32)	1.01 (0.73; 1.39)
Moderate	1.55 (1.01; 2.38)	1.53 (1.00; 2.35)	1.28 (0.80; 2.05)	1.20 (0.75; 1.94)
High	1.39 (0.96; 2.03)	1.33 (0.91; 1.95)	1.27 (0.84; 1.92)	1.22 (0.80; 1.86)
Intensity VMS				
Low	1.0 (0.75; 1.34)	0.99 (0.73; 1.32)	1.01 (0.74; 1.40)	1.06 (0.77; 1.46)
Moderate	1.14 (0.73; 1.78)	1.15 (0.74; 1.80)	1.01 (0.62; 1.64)	0.99 (0.60; 1.61)
High	1.45 (1.02; 20.7)	1.38 (0.96; 1.97)	1.31 (0.88; 1.94)	1.25 (0.84; 1.86)

Mode1 1: adjusted age.
Model 2: adjusted age, SES, sedentary lifestyle, smoking, hormone use ever, menopausal status.
Model 3: age, SES, sedentary lifestyle, smoking, hormone use ever, menopausal status, BMI, hypertension.
HPD, hypertensive pregnancy disease; VMS, vasomotor menopausal symptoms.

This is the first study to investigate the presence of VMS in women with a history of HPD. We found an interesting clustering of these female-specific cardiovascular risk factors. The development of both HPD and VMS is associated with a number of common risk factors, especially higher BMI and abdominal adiposity.[8,12-15] However, correction for one of the most important confounders (BMI) did not materially change the established association between HPD and VMS, suggesting that other underlying mechanisms may be involved.

Persistent endothelial dysfunction after hypertensive disease in pregnancy, mainly described in women post preeclampsia,[16,17] may contribute to the development of VMS later in life.[11] Another possible mechanism is increased sympathic nervous system (SNS) activity, which has been suggested to be present in women with VMS. Early VMS, occurring at the onset of menopause but not thereafter,[10] are presumably associated with the change in estrogen levels around menopause. Hormonal changes are involved in the activation of the sympathetic nervous system, which triggers a lowering of the thermoneutral zone in the brain. Within this re-setting of the thermoneutral zone, small increases in core body temperature may induce sweating and shivering as core body temperature decreases.[18,19] The relation between hypertension and increased sympathetic nervous activity and increased plasma catecholamines has also been generally acknowledged.[20] It is hypothesized that women with a history of HPD – especially if they remain hypertensive after pregnancy – experience increased SNS activity, which may explain the association between HPD and VMS, as described by Collén et al.[21] More data on SNS activity in women with history of HPD are needed to examine this hypothesis.

Strengths of our study include the number of women and the high response rate (79%) on the VMS questionnaire. The questionnaire on VMS was extensive and included duration, severity, frequency and intensity of VMS. The design of our study, which included women with different reasons for referral, may have induced inclusion bias, however. Half of the women who visited the outpatient cardiovascular women clinic in Kampen were referred to the cardiologist because they had cardiac symptoms (comparable in women with and without history of HPD). This means that our data cannot be generalized to all middle-aged women. Furthermore, one in three women had a history of HPD, which is not representative of the general female Dutch population (10% prevalence of HPD, including gestational hypertension and preeclampsia).[22] Moreover, 30% of the women in this cohort reported a history of miscarriages and stillbirths, which is higher than the 15-20% expected. We speculate that, through self-selection, we have a population at increased cardiovascular risk. That pregnancy loss is associated with a doubling of the cardiovascular risk[23], may explain the enrichment of

women with pregnancy losses in this study population. When we additionally adjusted the relation between HPD and VMS for the presence of a history of miscarriage and stillbirth, the association did was not attenuated (OR 1.72 95%CI 1.04; 2.82).

Another limitation is the self-reported history of both HPD and VMS. The specificity of self-reported HPD is rather high (95-100%), however, sensitivity is lower (ranging from 23% to 85% for different HPD).[24,25] As self-report of HPD is probably not related to reporting of VMS, we assume that the recall bias of HPD most probably have led to an underestimation of the association between HPD and VMS. Furthermore, we do not have any data available on the severity of the reported HPD, birth weight, and gestational age at delivery. This information is important for future research because these parameters influence long-term health outcomes in affected women.[6] The use of self-reported VMS data may have induced recall-bias and fails to discriminate between the occurrence of early VMS and the occurrence of late VMS, which may also affect future cardiovascular risk.[10] Finally, menopausal status was categorized according to bleeding patterns and is therefore likely to reflect women's experiences. This differs slightly from the recent proposed Stages of Reproductive Aging Workshop definition that also takes hormone levels into account.[26]

We recommend additional observational research in the general female population to test the consistency and magnitude of our found associations in a more general female population and to reveal more of the underlying pathophysiological mechanisms between HPD and VMS. The next step would be to investigate the cardiovascular risk in women with both history of HPD and history of VMS later in life, as both HPD and VMS have been founded to increase CVD risk. Preventive measures among women with history of HPD are currently under debate, but expert opinion tends to advise monitoring of cardiovascular risk factors in women after HPD.[2,26]

CONCLUSION

In our 'Kampen women cardiology clinic' cohort, women with a history of HPD report significantly more VMS compared to women without a history of HPD. As the adjusted differences between both groups are only borderline significant, more research is needed to evaluate these associations in a general female population.

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CHAPTER 9

General discussion

Cardiovascular disease (CVD) is the leading cause of death in Europe, with a percentage of 46% of all deaths, and causes a substantial burden to health care systems.[1] Mortality from CVD in women is even higher than in men, 51% versus 42%.[1] Traditional CVD risk factors for both sexes are well defined, but emerging data in the last decades have shown that female-specific factors, related to hormonal and reproductive status are importantly involved in the development of atherosclerosis in women.[2] Pregnancy is increasingly considered as a maternal "stress test" for future CVD risk. Certain disorders of pregnancy, such as hypertension and diabetes, can unmask a woman's vulnerability for CVD (Figure 1).[3,4]

Of the various hypertensive pregnancy diseases (HPD), preeclampsia (PE) seems to have the most detrimental effects on future cardiovascular health.[5,6] In the present thesis we focused on the development of CVD risk factors at intermediate term in women post HPD, and mainly PE, to identify possible targets for timely intervention.

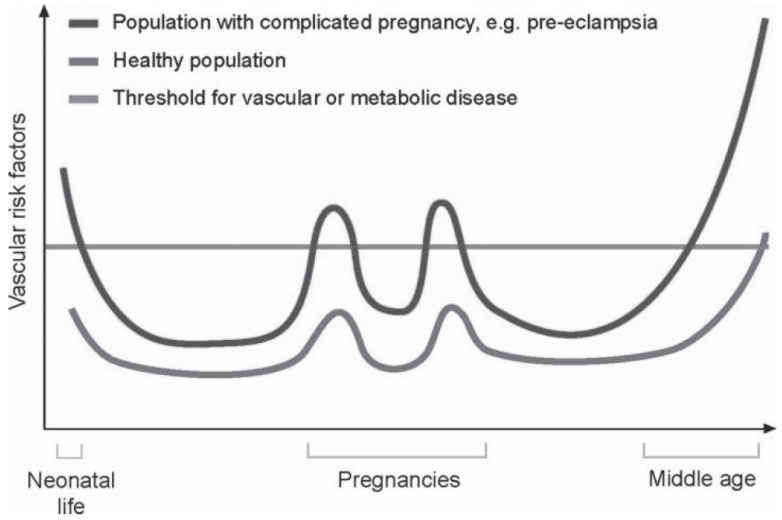

Figure 1: Pregnancy as stress test for future health, from Powe 2011.[4]

CARDIOVASCULAR RISK FACTORS POST PE

The higher risk of CVD later in life in women post PE has been found in several large studies and meta-analyses.[5,7,8] With a mean follow-up of 15 years postpartum Bellamy et al. ascertained a relative risk (RR) of 3.7 for hypertension; 2.2 for ischemic heart disease; and 1.5 for overall mortality.[5] Over 30 years of follow-up Wilson et al. found an odds ratio (OR) of 4.0 for hypertension and 3.4 for stroke in women after PE.[9] However, before CVD events occur the first signs of impaired cardiac function are already apparent.[10] Prevention should therefore start many years earlier. Before we can establish the ideal timing for preventive measures, we first need to understand the development of CVD risk in women post PE. For this purpose we performed the PREVFEM study (Preeclampsia Risk EValuation in FEMales) and determined the prevalence of traditional CVD risk factors in women at 10 years post PE, and compared these in women with uncomplicated pregnancies. In this study we demonstrated that at 10 years post index pregnancy hypertension and the metabolic syndrome (MetS), predominantly based on high blood pressure and waist circumference, are significantly more prevalent in women post PE compared to the reference group (CHAPTER 4). Prevalences of hypercholesterolemia and diabetes mellitus were not different. We conclude that women post PE already are more often hypertensive within 10 years post index pregnancy, which imposes an increased CVD risk on the longer term. Despite the increased prevalence of hypertension, we did not find any differences between women with and without history of PE in hypertension associated electrocardiographic deviations (CHAPTER 5). Probably it takes longer than 10 years post PE to develop identifiable hypertension induced ECG changes. However, we do know that the sensitivity of ECG criteria for left ventricular hypertrophy (LVH) is low in detecting the detrimental effects of hypertension. Although its specificity is high, echocardiography has a higher sensitivity of demonstrating diastolic dysfunction and LVH.[11] Echocardiography in women at 9 months post PE demonstrates an increased left ventricular mass preceding chronic hypertension.[12]

For women with milder forms of hypertensive pregnancy disorders (HPD) in the Doetinchem cohort, we also found increased levels of blood pressure (systolic and diastolic) and BMI during follow-up. Another apparent finding in our analysis in the Doetinchem Cohort was the comparable annual changes of various CVD risk factors in women with and without previous HPD. The established baseline differences in blood pressure and BMI between both groups does not further diverge with age (CHAPTER 3). Based on these data we hypothesize that HPD initiates a change in the metabolic

constitution of affected women postpartum, which does not deteriorate with age. Literature shows that pre-pregnancy CVD risk factors importantly (in 50-65%) contribute to the postpartum elevated risk after HPD.[13] This may indicate a life-time different metabolic constitution for women who develop HPD.
In both our cohorts we found no differences in lipid levels between women with and without HPD complications. The literature on lipid levels in women post HPD is not consistent. Some studies found unfavorable lipid profiles after HPD shortly postpartum[14], but also on the long term until 16 years postpartum.[13,15] However, the reported differences long after HPD were demonstrated in large cohort studies, but were very small (approximately 4%) and maybe even not clinical relevant.[13,15] Others described comparable lipid levels in women with and without HPD.[16,17] Participating females within both the PREVFEM and the Doetinchem cohort study were still mainly premenopausal and their estrogen status may override the harmful effect of PE on lipid levels.[18,19] It may be relevant to evaluate lipid levels consecutively over time and to determine whether disturbed lipids shortly postpartum persist over time. It is unknown yet whether menopause-related lipid changes are more adverse in women after HPD than in women after normotensive pregnancies.

PROGRESSION OF VASCULAR AGEING POST HYPERTENSIVE PREGNANCY DISORDERS

Given the increased CVD risk in young women post PE, it is still uncertain which mechanisms are involved in this increased risk. To better understand these causative factors we first need to understand the pathophysiologic mechanisms leading to a preeclamptic pregnancy. The currently most accepted hypothesis is that the primary cause of PE is a disturbed placental function, provoked by impaired throphoblast invasion and poor spiral artery invasion throughout the placenta, developing between week 8-18 of gestation.[4,20] As a consequence of this disturbed placental function, oxidative stress arises with the release of several anti-angiogenic proteins and cytokines. These have a synergistic role and lead to an exaggerated endothelial activation with a generalized maternal systemic inflammatory response.[20-22] This results in the clinical features of PE, hypertension and proteinuria, which may arise from the 20th week of gestation.[4,20,21]
The extent of this maternal systemic response is dependent on several maternal constitutional factors like genetics and environmental factors.[23] Pre-existing medical

conditions such as hypertension and DM, but also renal diseases and the antiphospholipid syndrome are risk factors for development of PE.[24] Genetics are also importantly involved in the pathophysiology of PE.[23] This is demonstrated by the increased risk of developing PE in women with a positive family history of CVD and by the increased risk of PE after a partner change (paternal antigen exposure).[23,24] Until now single gene studies have not given clear answers,[23] while a recent meta-analysis identified two prothrombotic gene variants but with moderate epidemiological reliability because of moderate amount of evidence for one, and inability to rule out protection from bias for both.[25] Most studies on genetics in PE are relatively small and focus on candidate genes, while PE is a complex disease. In the ongoing Genome Wide Association Studies (GWAS) more information will be ascertained on the role of genetic determinants and environmental exposure in the development of PE.[25]

It is assumed that persistent endothelial dysfunction post PE is an important factor for the increased future CVD risk later in life.[26] However, studies on cardiovascular biomarkers in these women are very heterogeneous and inconsistent.[17,27-30] Insulin resistance post PE has been recurrently described as the possible link between PE and future CVD.[29-31] Pre-pregnancy insulin resistance has been shown to be a risk factor for the development of PE and is also related with chronic hypertension and a higher BMI.[32] This supports a variety of metabolic constitutions in women at risk. In CHAPTER 6 we described levels of biomarkers associated with different stages of CVD development in women post PE. SE-selectin and pregnancy-associated plasma protein A (PAPPA) were significantly increased in women post early-onset PE, independent of traditional CVD risk factors. Especially the increased level of PAPPA is interesting, as this factor is associated with vulnerable atherosclerotic plaques.[33] This may lead to the hypothesis that women post PE may develop plaques that are involved in premature atherosclerotic disease. The potentially higher vulnerability of these plaques may contribute to earlier manifestation of CVD events.

Besides the differences in levels of biochemical markers, which may reflect endothelial dysfunction, impaired endothelial function can be measured. Two studies have demonstrated impaired endothelial function in women post PE compared to women after uncomplicated pregnancies in the early postpartum period (respectively after 3 and 16 months).[27,34] However, intermediate and long term follow-up data on vascular endothelial function are very scarce. This information is needed to test the hypothesis that persistent endothelial dysfunction postpartum is responsible for the increased CVD risk later in life.

EARLY AND LATE PE

Preeclampsia, defined as hypertension and proteinuria in the second half of pregnancy, can be subclassified in a mild-moderate and a severe condition. The American College of Obstetricians and Gynecologists (ACOG) defines PE as severe if blood pressure is ≥160 mmHg systolic and/or ≥110 mmHg diastolic or if proteinuria is ≥5 g/24 h.[35] Other criteria for severe PE are signs of systemic involvement like oliguria, cerebral disturbances, pulmonary edema, liver dysfunction, thrombocytopenia or fetal growth restriction.[35] Next to classification of the severity, PE can also be defined as early-onset (EOP) or late-onset (LOP). The most common used definition of early-onset PE in recent literature is the occurrence before 34 weeks of gestation.[36] Maternal and fetal outcome post PE improve with a later manifestation of PE during pregnancy.[21]
Future CVD risk is also different for women post early- and late-onset PE.[37] It has been hypothesized that both conditions may have a different etiology, in which EOP reflects a primary placental problem and LOP a predominant maternal constitutional syndrome.[21,23] This is supported by abnormal placenta in EOP and a normal villous morphology of the placenta in LOP.[38] Mukharjee et al. investigated the metabolic profiles of women with EOP and LOP with a Fourier transform infrared (FTIR) spectroscopy.[39] They found a significantly higher atherosclerotic index for women with PE early in pregnancy.
These findings are important for the interpretation of our data of the PREVFEM cohort, as described in CHAPTERS 4 to 6. The PREVFEM cohort consists of women with a history of very early PE, with a first onset before 32 weeks of gestation, therefore our findings cannot be generalized to all women with PE. In a sub-analysis of the PREVFEM study, serum levels of Anti-Müllerian hormone (AMH) were found to be significantly lower in women post PE compared to normotensive women.[40] Therefore, signs of a reduced ovarian reserve, as measured by reduced AMH levels, may not only express signs of early biological aging, but also impairment of vascular function.[40]

PREVENTION

Despite the abundant evidence of the increased CVD risk in women post PE, recommendations for the prevention of CVD in these high-risk subset of women are yet unclear. Several national and international guidelines advise to incorporate the obstetric history in the female cardiovascular risk assessment.[41-43] The recently published stroke guidelines for women, from the American Heart Association and the

American Stroke Association, provide a number of follow up measures.[44] Stroke is one of the major cardiovascular event entities,[45] and risk of stroke post PE is increased with odds ratios up to 3.59.[9,44] These new guidelines recommend to evaluate all women starting at 6 months to 1 year postpartum after a history of a HPD for the presence of CVD risk factors like hypertension, obesity and dyslipidemia and to start treatment if needed (level of evidence class IIa).[44] The authors do not make further recommendations on the frequency of postpartum follow-up and the executive clinician (general practitioner, obstetrician or cardiologist).

Postpartum counseling and follow-up after a divers spectrum of pregnancy complications (almost 30% PE) seems to be effective in the first year postpartum to identify women at risk for future CVD and is the first step to create awareness and initiate long-term prevention.[46] Spaan et al. advise an individualized CVD risk management program which starts already at 6 weeks postpartum with CVD risk counseling and tailored lifestyle advise, followed by yearly CVD risk management by the general practitioner. [47]

However, literature on the (cost)effectiveness of long-term CVD screening and lifestyle interventions in women post PE is scarce. Berks et al. demonstrated an reduction of CVD risk in women post PE with adequate lifestyle interventions, with the important limitation that effect data of interventions in the general female population were used in their analysis.[48] Postpartum weight interventions are effective in achieving weight loss, but again data in a specific population of women after HPD are lacking.[49] In our Markov model analysis (CHAPTER 7) we demonstrated the cost-effectiveness of a yearly blood pressure measurement, including treatment of established hypertension, in women post early onset preeclampsia. In a time-horizon of 20 years regularly blood pressure screening and early treatment gives an increment of 12 days in perfect health, but a saving of €1,203 per person in 20 years. Future research should focus on the most appropriate timing and frequency of CVD prevention programs in women post HPD. Our Markov analysis is one of the first cost-effectiveness studies on CVD prevention post PE, but shows that it might be effective to measure and treat blood pressure in young premenopausal women. This in disagreement with the Dutch CVD prevention guideline[42], that advices risk evaluation in women post HPD after menopause.

FUTURE PERSPECTIVES

The increased lifetime CVD risk for women post HPD, especially post early-onset PE, needs more follow-up at intermediate and long term. The PREVFEM cohort has

focused at 10 years postpartum, when hypertension and abdominal obesity are the predominant risk factors. More data are needed on the development of lipid disorders, endothelial dysfunction and other pathophysiological parameters that may predict premature CVD events.

Despite many unanswered questions, we can make some recommendations. Firstly, affected women need to be informed more thoroughly about the increased risk of future disease post HPD and the importance of a healthy lifestyle needs to be underscored. Secondary, awareness under healthcare workers, especially general practitioners and cardiologists, of HPD as a gender-specific risk factor needs to be established. The next step will be that all health care workers involved in CVD prevention should incorporate the obstetric history in their assessment procedure. As evidence on cost-effectiveness of counsel programs for women post PE is limited, we can now only recommend a yearly blood pressure check-up. As health care costs are rising steeply and young women want to participate actively in health prevention, other modalities of care are needed. The development of E-health programs with self-monitoring will facilitate patients and professionals (GPs and clinicians).[50]

CONCLUSION

Women with a history of HPD have increased CVD risk at intermediate term, which is mainly caused by increased blood pressure and obesity. Early life-style intervention and risk factor identification is needed to prevent premature manifestations of CVD events in this high risk subset of female patients.

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CHAPTER 10

Summary

Samenvatting

Dankwoord

Curriculum vitae

Summary

Cardiovascular disease (CVD) is one of the most important causes of death in Western world. The traditional risk factors, such as hypertension, dyslipidemia and diabetes, are well known. Recently the role of gender-specific risk factors has gained more attention. Hypertensive and metabolic pregnancy disorders are increasingly acknowledged as female specific risk factors for future cardiovascular disease. However until now data on CVD risk factor development at intermediate term are relatively scarce. Therefore, it is uncertain when preventive measures are needed and how they should be executed.
In this thesis we examined the occurrence of traditional CVD risk factors in women with a history of a hypertensive pregnancy disorder (HPD), with a special focus on women post preeclampsia (PE). Furthermore we sought for potential markers of early cardiovascular disease and evaluated the cost-effectiveness of early hypertension screening in women after preeclampsia. We also investigated the association between a history of HPD and the presence, frequency, severity and intensity of vasomotor symptoms during menopause transition.

CHAPTER 2 reviews the risk of future hypertension in women with a history of gestational hypertension (GH) and preeclampsia. GH is defined as hypertension (blood pressure above 140/90 mmHg) in the second half of pregnancy, PE is defined as hypertension in combination with proteinuria (>0.3 g/24 h) after 20 weeks of gestation. GH is generally considered the most benign condition of both; however, the reported relative risks (RR) of hypertension vary from 1.7 until 7.2 up to 16 years of follow-up. Risk of developing hypertension post PE is strongly related to the severity and timing of the PE during gestation. The RR is almost twice as high in women with a history of severe PE versus women with a history of mild PE (RR 6.0 vs 3.6, reference 1.0 women with a normotensive pregnancy). As hypertension is a major CVD risk factor, early detection and treatment of hypertension might be an important element of prevention.

In CHAPTER 3 we describe CVD risk factors in women with a history of hypertensive pregnancy disorders. For this study we included women, mean age 40 years, of the Doetinchem Cohort Study (1987-1991), a population-based study in de city of Doetinchem. History of HPD was assessed by questionnaires and included all

manifestations. Women with a history of HPD (n=689) had significantly higher systolic blood pressure (2.8 mmHg, 95%CI 1.7; 3.9), diastolic blood pressure (2.3 mmHg, 95%CI 1.6; 3.0) and BMI (0.7 kg/m^2, 95%CI 0.4; 1.1) than women with a normotensive pregnancy. We also evaluated the annual change for these parameters with ageing, which was comparable in both groups. Based on these data we do not advise long-term monitoring of CVD risk factors from pregnancy onwards in women after HPD. Future research should focus on the evaluation of individuals at higher risk and the lifetime development of CVD risk factors.

CHAPTER 4 describes the presence of traditional CVD risk factors in the PReclampsia Risk Evaluation in FEMales (PREVFEM) cohort, a specific population of 339 women with a history of early preeclampsia (EOP) and 332 women with a normotensive pregnancy in history. This study was performed 10 years post index pregnancy to gain more insight into the intermediate CVD risk in women post PE. In this cohort we found an increased risk of hypertension (adjusted OR 3.6, 2.5; 5.2) and a higher risk of the metabolic syndrome (adjusted OR 2.2, 1.3; 3.5) for women post EOP in comparison with women after previous normotensive pregnancies. Body mass index (BMI) and waist circumference were significantly higher in women with a history of EOP compared to the reference women, however the prevalence of other traditional CVD risk factors like hypercholesterolemia and diabetes mellitus (DM) was not different between both groups.

In CHAPTER 5, we describe ECG changes related to increased blood pressure and the effect of EOP on these changes. Non-specific ECG changes are useful in evaluating future CVD morbidity and mortality in hypertensive populations. We evaluated major and minor repolarization abnormalities, signs of left ventricular hypertrophy (LVH) and abnormalities in frontal T and QRS-T angles. In our cohort, both systolic blood pressure (SBP) and diastolic blood pressure (DBP) as well as stage 2 hypertension (defined as SBP $\geq$160 mmHg or DBP $\geq$100 mmHg) were significantly associated with LVH. There were no associations with the other evaluated ECG parameters. Although hypertension is significantly more prevalent in women with a history of EOP compared to reference women, 43% versus 17%, history of EOP was not associated with higher prevalences of ECG abnormalities. Based on these data we cannot recommend routine ECG screening for women with a history of EOP at ten years after index pregnancy.

In CHAPTER 6, we evaluated CVD biomarker profiles in the PREVFEM cohort. Different predictive CVD biomarkers have been identified in recent years, in this

chapter we searched for various biomarkers in women with a history of preeclampsia. A subset of eight different biomarkers was investigated, reflecting inflammatory, metabolic, thrombotic and endothelial function markers.
Associations between PE and these novel biomarkers were adjusted for traditional CVD risk factors. Women post PE had significantly higher levels of SE-selectin (adjusted difference 4.55, 99%CI 0.37; 8.74) and PAPPA (adjusted difference 19.08; 99%CI 13.18; 24.99), whereas ApoB (adjusted difference -0.23, 99%CI -0.32; -0.14) was inversely associated with PE, Adiponectin, leptin, sICAM-1, sVCAM-1 and PAI-1 were not different between affected women and the reference group. These results show that despite adjustment for traditional CVD risk factors, biomarker profiles for vascular dysfunction are different in women post PE compared to women with a normotensive pregnancy. More research is needed to clarify the prognostic impact and utility of these cardiovascular biomarkers in women post PE.

In CHAPTER 7 we assessed the cost-effectiveness of screening and early treatment for hypertension in women after PE with a decision-analytic Markov model. Screening consisted of a postpartum annual blood pressure measurement during a timeframe of 20 years by the general practitioner, whereas the non-intervention group did not receive any planned cardiovascular risk check-ups. Our hypothesis was that timely identification and adequate treatment of hypertension in women with a history of PE could decrease the risk on future CVD events and mortality with a reduction in associated health costs. Outcomes were measured in absolute costs, events, life-years and quality-adjusted life-years (QALYs). Over a 20 year time horizon events occurred in 0.072% of the population after screening, and in 0.085% of the population without screening. QALYs increased with an increment of 0.03 QALY (95%CI 0.01; 0.05), which means 12 days in perfect health. Total expected costs were €7,834 in the screening strategy, and €9,038 in the no screening strategy, an expected saving of €1,203 (95%CI -3223; -247) per person. The presented Markov model demonstrates that annual hypertension screening and treatment in primary care in women after PE might be cost-effective in preventing future CVD. However, the modest clinical effects and described assumptions should be taken into account before any recommendations according to screening programs post PE can be made.

Endothelial dysfunction is known to play a role in the aetiology of HPD. Interestingly, endothelial dysfunction is also suggested to play a role in another female-specific cardiovascular risk factor, i.e. vasomotor menopausal symptoms (VMS), specifically night sweats and hot flushes. In CHAPTER 8 we evaluated whether there is an

association between HPD and VMS. For this purpose, we used data of the Kampen cohort, a database which consecutively included 853 women (mean age 55.5 years) who visited the outpatient cardiovascular clinic for women in Kampen between 2003 and 2010. We found that, adjusted for potential confounders, VMS were more often present (OR 1.62, 95%CI 1.00; 2.63) and persisted more frequently longer that 1 year (OR 2.05, 95% CI 1.08; 3.89) among women with a history of HPD than among women with normotensive pregnancies. Other qualitative parameters, like severity, frequency and intensity of VMS, were not significantly different between both groups. This study was the first to show an association between previous HPD and VMS, a finding that needs confirmation in other populations.

In CHAPTER 9 we discuss the clinical significance of our studies and the future perspectives of CVD prevention in women with a history of the different entities of HPD. At intermediate term the increased CVD is mainly caused by elevated blood pressure and obesity. For the long term, more prospective data are needed to investigate the development of lipid disorders, endothelial dysfunction and other pathophysiological parameters that may predict premature CVD events. Based on the data described in this thesis we recommend that both women with a history of HPD (and mainly post PE) and health care workers need to be more aware on the predictive role of HPD on future CVD risk and the importance of a healthy lifestyle with early CVD risk factor identification in these high risk subset of women.

Samenvatting

Hart- en vaatziekten (HVZ) behoren tot de meest belangrijke oorzaken van sterfte in de Westerse wereld. De impact van de traditionele risicofactoren, zoals hypertensie, diabetes mellitus, hyperlipidemie en roken, is bekend. De laatste jaren wordt ook de rol van vrouwspecifieke risicofactoren steeds duidelijker. Hoge bloeddruk in de zwangerschap en andere metabole zwangerschapsaandoeningen worden gezien als belangrijke risicofactoren voor toekomstig hart- en vaatziekten. Op dit moment is het nog niet bekend hoe en op welke termijn na de zwangerschap deze factoren kunnen leiden tot een verhoogd risico. Om die reden is het dan ook onduidelijk of er preventieve maatregelen genomen moeten worden.
In deze thesis onderzoeken wij de ontwikkeling van de traditionele risicofactoren voor HVZ bij vrouwen die een hypertensieve zwangerschapscomplicatie hebben doorgemaakt. Hierbij focussen wij vooral op vrouwen met een doorgemaakte preeclampsie (PE). Naast een onderzoek naar de ontwikkeling van cardiale risicofactoren bij vrouwen met PE in vergelijking met vrouwen zonder hypertensie in de zwangerschap, beoordelen wij of het kosteneffectief is om vrouwen na een doorgemaakte PE jaarlijks in de eerste lijn te screenen op hypertensie. Verder hebben wij de onderlinge relatie onderzocht tussen hypertensieve zwangerschapsaandoeningen en vasomotore symptomen in de menopauze (opvliegers en nachtzweten).

In HOOFDSTUK 2 evalueren wij de bestaande literatuur ten aanzien van het toekomstige risico op hypertensie bij vrouwen met een doorgemaakte zwangerschapshypertensie en PE. Hypertensie in de zwangerschap (GH) is gedefinieerd als een bloeddruk boven de 140/90 mmHg in het tweede semester van de zwangerschap, in geval van PE gaat deze hypertensie ook gepaard met proteïnurie (0,3 g/24 h). Zwangerschapshypertensie wordt over het algemeen gezien als een relatief milde complicatie, waarbij er in de literatuur toch een relatief risico (RR) op toekomstige hypertensie gevonden wordt van 1,7 tot 7,2 maal het risico ten opzichte van normotensieve zwangerschappen bij een follow-up tot 16 jaar. Voor vrouwen met een doorgemaakte PE is dit toekomstige risico op hypertensie afhankelijk van de ernst en het tijdstip van ontstaan van de PE in de zwangerschap. Ernstige PE geeft een bijna tweemaal zo hoog risico op hypertensie als een milde PE, RR 6,0 vs 3,6, ten opzichte van vrouwen die een normotensieve zwangerschap hebben doorgemaakt (RR 1,0).

In HOOFDSTUK 3 evalueren wij de aanwezigheid van risicofactoren voor HVZ bij vrouwen met een voorgeschiedenis van hypertensieve zwangerschapsaandoeningen (zowel GH als PE). Deze studie voerden wij uit onder alle vrouwen uit de Doetinchem Cohort Study (1987-1991), een populatie studie in de stad Doetinchem. De gemiddelde leeftijd van deze vrouwen was 40 jaar. Een voorgeschiedenis van hypertensieve zwangerschapscomplicaties werd vastgesteld aan de hand van een vragenlijst. In dit cohort vonden wij dat vrouwen met hypertensieve zwangerschapscomplicaties (n=689) vergeleken met vrouwen met een normotensieve zwangerschap in het verleden (n=2.703) een significant hogere systolische bloeddruk (2,8 mmHg, 95%BI 1,7; 3,9); diastolische bloeddruk (2,3 mmHg, 95%BI 1,6;3,0) en BMI (0,7 kg/m^2, 95%BI 0,4; 1,1) hadden. De lipiden waarden (totaal en HDL cholesterol) waren gelijk in beide groepen. De jaarlijkse veranderingen in alle parameters met het toenemen van de leeftijd waren gelijk in beide groepen. Op basis van deze data is geen lange termijn advies te geven voor het monitoren van cardiale risicofactoren na een hypertensieve zwangerschap.

In HOOFDSTUK 4 beschrijven wij het voorkomen van de traditionele risicofactoren voor HVZ in het PREVFEM (PReclampsia Risk EValuation in FEMales) cohort, een populatie bestaande uit 339 vrouwen die een vroege PE hebben doorgemaakt en een groep van 332 vrouwen die een normotensieve zwangerschap hebben doorgemaakt. Deelnemers aan dit onderzoek werden gemiddeld 10 jaar na de index zwangerschap opgeroepen voor een poliklinisch cardiaal screeningsonderzoek bestaande uit een vragenlijst, lichamelijk onderzoek, ECG registratie en laboratoriumonderzoek. Bij vrouwen na een doorgemaakte PE vonden wij een verhoogd risico op hypertensie (OR 3,6, BI 2,5; 5,2) en het metabole syndroom (OR 2,2, BI 1,3; 3,5) in vergelijking met vrouwen die een ongecompliceerde zwangerschap hadden doorgemaakt. Wij vonden geen verschil in het voorkomen van diabetes mellitus en hypercholesterolemie tussen beide groepen.

Vervolgens hebben wij in HOOFDSTUK 5 onderzocht of de gemaakte ECG registraties verschilden tussen vrouwen met en zonder doorgemaakte PE in het PREVFEM cohort. Wij onderzochten de aanwezigheid van (aspecifieke) repolarisatie stoornissen, aanwijzingen voor linkerventrikelhypertrofie (LVH) en afwijkingen in de frontale T en QRS-T assen. In het PREVFEM cohort waren zowel de systolische bloeddruk (SBP), diastolische bloeddruk (DBP) en stadium 2 hypertensie (gedefinieerd als SBP $\geq$160 mmHg of DBP $\geq$100 mmHg) significant geassocieerd met de aanwezigheid van LVH. Er waren geen associaties met andere ECG parameters. Hoewel hypertensie significant

meer voorkwam bij vrouwen met een voorgeschiedenis van PE vergeleken met de referentie groep, 43% versus 17% (zie HOOFDSTUK 3), was vroege PE niet geassocieerd met meer ECG afwijkingen. Op basis van deze gegevens adviseren wij om niet routinematig een ECG te maken bij vrouwen in deze levensfase na een doorgemaakte PE.

In HOOFDSTUK 6 hebben wij een aantal cardiovasculaire biomarkers onderzocht in het PREVFEM cohort. In de laatste jaren zijn er verschillende biomarkers geïdentificeerd die het risico op HVZ kunnen voorspellen. Wij hebben acht verschillende biomarkers onderzocht, die betrekking hebben op zowel de inflammatoire, metabole, trombotische als de endotheelfunctie. Associaties tussen PE en deze biomarkers werden gecorrigeerd voor de aanwezigheid van traditionele cardiovasculaire risico factoren. Vrouwen na een doorgemaakte PE hadden een significant hoger niveau van SE-selectin (gecorrigeerd verschil 4,55, 99%BI 0,37; 8,74) en PAPPA (gecorrigeerd verschil 19,08; 99%BI 13,18; 24,99), terwijl ApoB (gecorrigeerd verschil -0,23 99%BI -0,32; -0,14) significant lager was bij vrouwen na PE, vergeleken met de referentiegroep. Adiponectin, leptin, sICAM-1, sVCAM-1 en PAI-1 waren niet verschillend tussen beide groepen. Deze resultaten laten zien dat de vasculaire functie anders is bij vrouwen na een doorgemaakte PE ten opzichte van vrouwen na een normotensieve zwangerschap, en niet volledig verklaard kan worden door de verschillende in traditionele risicofactoren voor HVZ. Meer onderzoek is nodig om de rol en de prognostische impact van de diverse cardiovasculaire biomarkers bij vrouwen na een doorgemaakte PE te bepalen.

In HOOFDSTUK 7 analyseren wij de kosteneffectiviteit van screening en vroege behandeling van hypertensie bij vrouwen met een voorgeschiedenis van PE door middel van een Markov model. Wij onderzochten of een jaarlijkse bloeddrukcontrole bij de huisarts vanaf het eerste jaar postpartum gedurende een tijdsbestek van 20 jaar kosteneffectief is. Onze hypothese daarbij was dat vroeg identificatie en behandeling van hypertensie bij vrouwen na een doorgemaakte PE het risico op toekomstig HVZ kan reduceren met een vermindering in zorgkosten. Uitkomsten werden gemeten in absolute kosten, het voorkomen van events, het aantal levensjaren en de voor kwaliteit-van-leven gecorrigeerde levensjaren (quality-adjusted life-years, QALYs). Gedurende een periode van 20 jaren zullen er 0,072% events voorkomen in de gescreende groep en 0,085% in de niet gescreende groep. De QALYs nemen toe met 0,03 (95% BI 0,01; 0,05), dit betekent 12 extra dagen in goede gezondheid. De totale verwachte kosten per vrouw (inclusief screening, behandeling hypertensie en cardiovasculaire zorgkosten)

zullen €7.834 zijn in de screening strategie, ten opzichte van €9.038 in de niet-screening strategie. Dat is een besparing van €1.204 (95% BI -3223; -247) per persoon. Uit de resultaten van dit Markov model concluderen wij dat een jaarlijkse screening en vroege behandeling van hypertensie bij vrouwen na een PE kosten kan besparen. De klinische effectiviteit is echter beperkt en afhankelijk van een aantal aannames zoals beschreven in hoofdstuk 7.

Endotheel dysfunctie speelt een belangrijke rol in de etiologie van hypertensieve zwangerschapscomplicaties, met name PE. Dit mechanisme speelt mogelijk ook een rol bij andere vrouwspecifieke risicofactoren voor HVZ. In HOOFDSTUK 8 onderzoeken wij de relatie tussen hypertensieve zwangerschapscomplicaties en het voorkomen van vasomotore symptomen in de menopauze (VMS), zoals opvliegers en nachtzweten. Hiervoor hebben wij gebruikt gemaakt van data uit het Kampen cohort. Hierin zijn de gegevens verzameld van 853 vrouwen (gemiddelde leeftijd 55,5 jaar) die tussen 2003 en 2010 de cardiologische polikliniek voor vrouwen in Kampen bezocht hebben. Wij vonden dat VMS vaker aanwezig waren bij vrouwen met een doorgemaakte hypertensieve zwangerschap in het verleden ten opzichte van vrouwen zonder een dergelijke zwangerschap (OR 1,62, 95% BI 1,00;2,63). Ook hadden vrouwen na een zwangerschapshypertensie vaker langer dan 1 jaar VMS (OR 2,05, 95% BI 1,08;3,89) dan de vrouwen in de referentiegroep. Andere kwalitatieve parameters zoals de ernst, frequentie en intensiteit van de VMS waren niet verschillende tussen beide groepen. Aangezien deze studie de eerste is die een associatie tussen hypertensieve zwangerschapscomplicaties en VMS heeft aangetoond, is meer onderzoek in andere populaties nodig om deze associatie te bevestigen.

In HOOFDSTUK 9 bediscussiëren wij de klinische betekenis van de beschreven studies en de aanbevelingen voor preventie bij vrouwen na hypertensieve zwangerschaps-complicaties. Op de middellange termijn na de indexzwangerschap wordt het verhoogde risico op HVZ vooral veroorzaakt door een verhoogde bloeddruk en (abdominale) obesitas. Voor de langere termijn is meer informatie nodig over de ontwikkeling van lipidenafwijkingen, insulineresistentie en andere metabole parameters die de pathofysiologie van premature HVZ kunnen voorspellen in deze vrouwen. Gebaseerd op onze onderzoeksgegeven adviseren wij om vrouwen na een hypertensieve zwangerschap, en vooral na een doorgemaakte PE, in eerste instantie te monitoren voor een gezonde leefstijl en alert te zijn op de voege ontwikkeling van hypertensie.

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José Drost

Curriculum vitae

The author of this thesis was born in Zwolle, The Netherlands, on 18 July 1985. In 2003 she graduated cum laude from secondary school, the Lambert Franckens College in Elburg. The same year she started to attend medical school at the University of Groningen. During her final scientific internship at the Department of Cardiology of the Isala klinieken in Zwolle, she started to set up the PREVFEM cohort and analysed the prevalence of traditional cardiovascular risk factors in women post preeclampsia. In October 2009, she obtained her Master of Science in medicine.

In 2009 she started working at the Cardiology Department at the Isala klinieken in Zwolle and proceeded working on this thesis.

In January 2011 she started her cardiology residency under supervision of dr. A.R. Ramdat Misier and in 2012 continued this residency for 2 years at the Department of Internal Medicine of the Isala klinieken in Zwolle, under supervision of dr. P.H.P. Groeneveld.

In January 2014 she returned to the Cardiology Department for the final 3 years of her Cardiology residency.