# Cardiovascular Assessment after Hypertensive Pregnancy Disorders

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ISBN/EAN: 9789461086426
Cover Illustration: “Pregnancy and the Nurturing of Baby within” by Xiaohong Zhang
Printed by: Gildeprint, Enschede

The research described in this thesis was performed within the Dutch Consortium of studies in Women’s health and reproductivity.
The research described in this thesis was supported by a non-commercial grant from the Medical Center Haaglanden and the Landsteiner Institute, The Hague, the Netherlands (Stipendium Wetenschapsfonds Medisch Centrum Haaglanden) and the Nuts Ohra Foundation, the Netherlands.

Financial support for the publication of this thesis was kindly provided by:
Raad van Bestuur Medisch Centrum Haaglanden
Stichting HELLP-syndroom

Financial support by the Dutch Heart Foundation for the publication of this thesis is gratefully acknowledged.

VRIJE UNIVERSITEIT

# Cardiovascular Assessment after Hypertensive Pregnancy Disorders

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad Doctor aan
de Vrije Universiteit Amsterdam,
op gezag van de rector magnificus
prof.dr. F.A. van der Duyn Schouten,
in het openbaar te verdedigen
ten overstaan van de promotiecommissie
van de Faculteit der Geneeskunde
op woensdag 28 mei 2014 om 15.45 uur
in de aula van de universiteit,
De Boelelaan 1105

door

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geboren te Hoorn

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|---|---|
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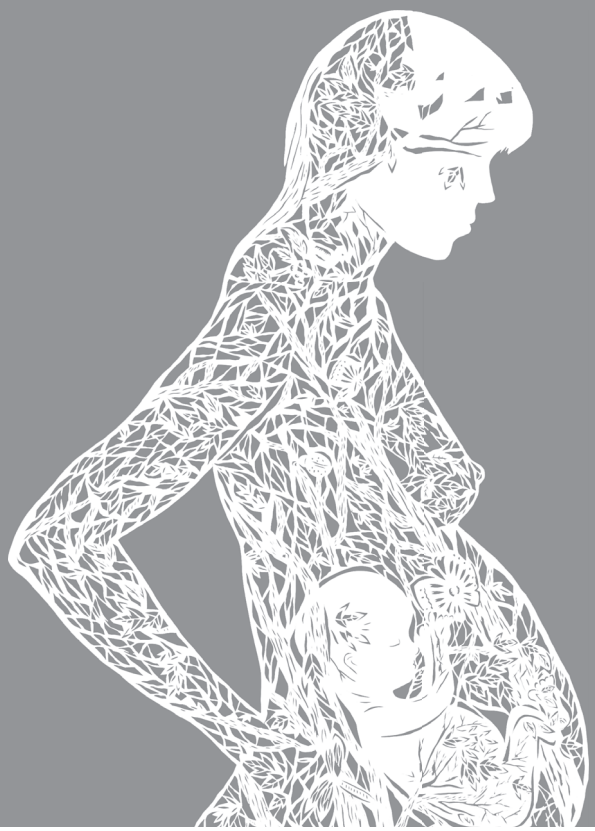
# Part One

# Introduction

# *Chapter 1*

## General introduction



Hypertensive pregnancy disorders largely contribute to maternal and neonatal morbidity and mortality worldwide[1]. In the Netherlands, hypertensive pregnancy disorders are the most frequent direct cause of maternal mortality with a Maternal Mortality Ratio of 1.4 in the period 2006 – 2010[2]. Although extensive efforts have been made to unravel its pathogenesis, the exact underlying etiology remains unclear and still there are no preventive or therapeutic interventions available beside delivery of the foetus and placenta.
Several epidemiological studies have described the association between hypertensive pregnancy disorders and cardiovascular disease in later life[3-8]. In the Netherlands, cardiovascular disease is currently the leading cause of death, namely 30% of all women who died in 2011[9]. Thus, the most frequent cause of maternal mortality and morbidity during pregnancy may act as "a natural stress test" for the most frequent cause of death in women[7]. Women who develop hypertensive disorders during pregancy fail the stress test and may be considered at high risk women for developing cardiovascular disease in later life. On the other hand, women who have only uncomplicated normotensive pregnancies passed the stress test and may be considered at low risk women for developing cardiovascular disease in later life. Moreover, beside vaccination programs, pregnancy is the first life event to visit a doctor or midwife for a medical examination for most women and at that moment the blood pressure is measured for the first time.
The exact mechanism of the underlying pathological link between hypertensive pregnancy disorders and cardiovascular disease in later life has not been clarified yet. It is unknown whether hypertension during pregnancy and cardiovascular disease share common antecedents or that vascular damage from hypertensive disorders during pregnancy leads to cardiovascular disease development in later life. Another possibility is a combination of the two above described hypotheses: Hypertension during pregnancy and cardiovascular disease have a common cause but the development of hypertension will deteriorate cardiovascular dysfunction.

It has been hypothesized that early onset preeclampsia with an onset before 34 weeks of gestation, has a (partly) different pathophysiology compared to late onset preeclampsia[10;11] and epidemiological studies describe that early onset preeclampsia has the strongest association with cardiovascular disease later[12]. However, hypertensive pregnancy disorders after 36 weeks' of gestation are far more common than early onset preeclampsia and affected 19% of all singleton pregnancies in the Netherlands in 2012 according to the Dutch LVR insight database. Therefore, women with term hypertensive pregnancy disorders may represent an ideal target population for a high risk primary prevention strategy. However, studies of risk factors discriminating between individuals who will develop cardiovascular disease and who will not are lacking. Furthermore, due

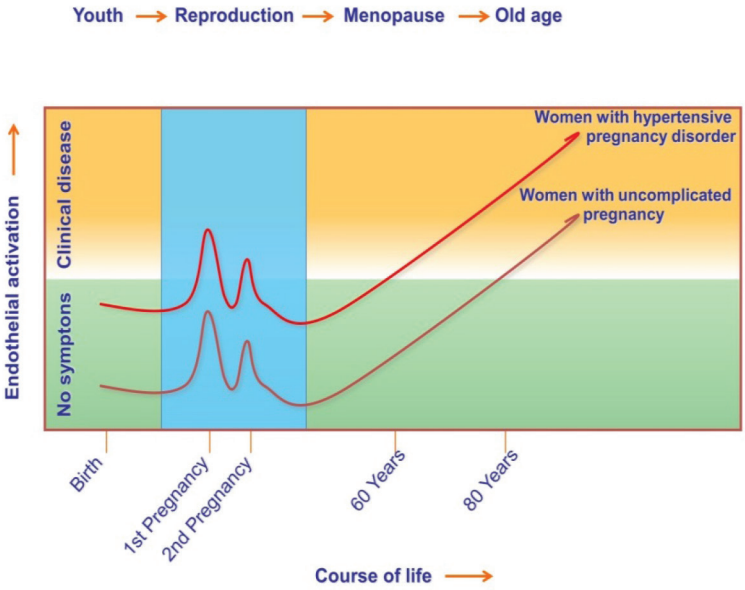



**Figure 1.** Endothelial activation during women's life course.

to the lack of evidence, it is unknown at what time interval after the complicated pregnancy (subclinical) cardiovascular disorders may manifest. In current practice physicians are only focused on the outcome of mother and child during pregnancy and puerperium but not on the future cardiovascular health of the mother. This seems a missed oppurtunity.

In this thesis we focus on cardiovascular risk after term hypertensive pregnancy disorders. We first review the literature on the link between preeclampsia and cardiovascular disease. Hereafter we describe different cardiovascular risk factors, including glucose, insulin, HbA1c, lipids and HsCRP and estimated cardiovascular event risks after hypertensive pregnancy disorders by the Framingham, SCORE and Reynolds risk scores. Finally, we describe the cost-effectiveness of screening and prevention of cardiovascular disease in women with a history of term hypertensive pregnancy disorders. We conclude with a general discussion and suggestions for further research.

## Aims and outline of the thesis

**Part One:**
**Chapter 2** To describe different facets of the association between preeclampsia and cardiovascular disease.

**Part Two:**
**Chapter 3** To assess traditional biochemical cardiovascular risk factors in women with previous hypertensive pregnancy disorders and women with previous normotensive pregnancies.
**Chapter 4** To assess non-classic biochemical cardiovascular biomarkers in women with previous hypertensive pregnancy disorders and women with previous normotensive pregnancies.

**Part Three:**
**Chapter 5 and Chapter 6** To assess cardiovascular risk factors in women with a history of term hypertensive pregnancy disorders.
**Chapter 7** To estimate individual cardiovascular event risks in women with a history of term hypertensive pregnancy disorders.
**Chapter 8** To compare estimated individual cardiovascular event risks between women with a history of very early onset preeclampsia and women with a history of term hypertensive pregnancy disorders.
**Chapter 9** To evaluate whether cardiovascular risk factors postpartum differ between women who had induction of labour and women who had expectant monitoring for term hypertensive pregnancy disorders.
**Chapter 10** To describe the cost-effectiveness of cardiovascular risk factor screening in women with a history of term hypertensive pregnancy disorders.

**Part Four:**
**Chapter 11** General discussion of the thesis.
English summary and Dutch summary.

## Reference List


(1) http://www.who.int/mediacentre/factsheets/fs310/en/index.html. 11-2-2013.

(2) Schutte JM, van den Akker Th, Engel NMAA, de Groot CJ, Kuppens SMI, Schuitemaker NW et al. Moedersterfte in Nederland op de 'goede' weg? Nederlands Tijdschrift voor Obstetrie & Gynaecologie 2013; 126:288-292.

(3) Haukkamaa L, Salminen M, Laivuori H, Leinonen H, Hiilesmaa V, Kaaja R. Risk for subsequent coronary artery disease after preeclampsia. Am J Cardiol 2004; 93(6):805-808.

(4) Irgens HU, Reisaeter L, Irgens LM, Lie RT. Long term mortality of mothers and fathers after pre-eclampsia: population based cohort study. BMJ 2001; 323(7323):1213-1217.

(5) Jonsdottir LS, Arngrimsson R, Geirsson RT, Sigvaldason H, Sigfusson N. Death rates from ischemic heart disease in women with a history of hypertension in pregnancy. Acta Obstet Gynecol Scand 1995; 74(10):772-776.

(6) Ramsay JE, Stewart F, Greer IA, Sattar N. Microvascular dysfunction: a link between pre-eclampsia and maternal coronary heart disease. BJOG 2003; 110(11):1029-1031.

(7) Sattar N, Greer IA. Pregnancy complications and maternal cardiovascular risk: opportunities for intervention and screening? BMJ 2002; 325(7356):157-160.

(8) Wilson BJ, Watson MS, Prescott GJ, Sunderland S, Campbell DM, Hannaford P et al. Hypertensive diseases of pregnancy and risk of hypertension and stroke in later life: results from cohort study. BMJ 2003; 326(7394):845.

(9) http://www.hartstichting.nl/9800/13333/13374/hvz_in_nederland_2011. 11-2-2013. 11-2-2013.

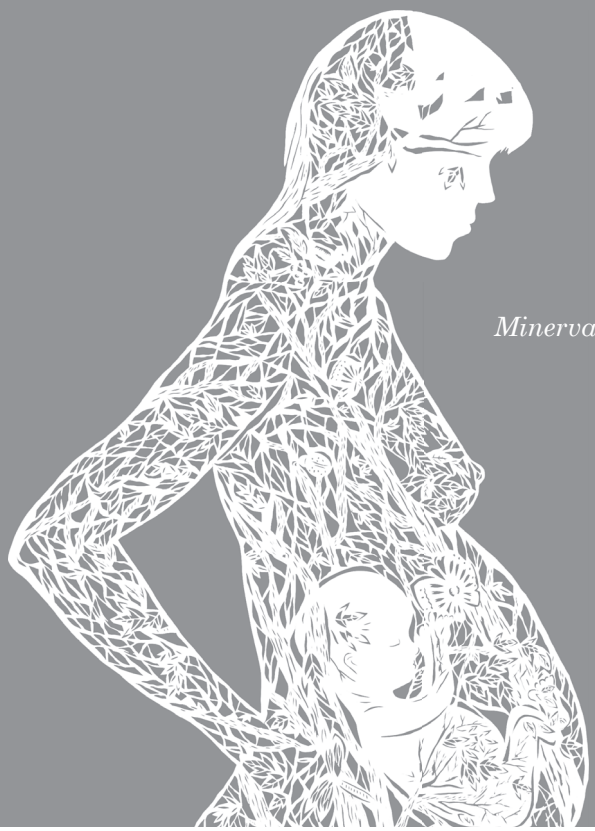
(10) Huppertz B. Placental origins of preeclampsia: challenging the current hypothesis. Hypertension 2008; 51(4):970-975.

(11) von DP, Magee LA, Roberts JM. Subclassification of preeclampsia. Hypertens Pregnancy 2003; 22(2):143-148.

(12) Bellamy L, Casas JP, Hingorani AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. BMJ 2007; 335(7627):974.

# *Chapter 2*

## Preeclampsia and cardiovascular risk



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*Minerva Ginecol. 2012 Aug; 64 (4):281-92*

## Abstract

The association between preeclampsia and cardiovascular disease has been an increasing area of interest over the last years. Cardiovascular disease is the number one cause of death in women in the western world and more women than men die of heart disease each year. The most common pregnancy disorder is preeclampsia. Preeclampsia is defined by hypertension and de novo proteinuria and remains responsible for high maternal and fetal morbidity and mortality worldwide. Pregnancy has been described as a "stress test" for future cardiovascular disease, to identify women young enough to benefit from screening. Women with a history of early onset (severe) preeclampsia have the highest risk of cardiovascular disease later. However, the exact underlying link between the two disorders is still unknown.

In this review we describe different facets of the association between preeclampsia and cardiovascular disease and we give an overview of the recent literature.

## Introduction

Preeclampsia is a common pregnancy specific disorder, which occurs in 2-8% of pregnancies and is characterized by *de novo* hypertension in combination with proteinuria after 20 weeks of gestation[1;2]. Preeclampsia remains a leading cause of maternal and perinatal morbidity and mortality worldwide[2]. In current practice, preeclampsia is a disorder confined to pregnancy and its treatment includes delivery of the neonate and the placenta. Up to now there is no systematic care or attention for women with pregnancy related hypertension *after* delivery. However, last decade, several epidemiological studies have described the association between preeclampsia and cardiovascular disease in later life[3-9]. This might an important finding for women's future health, as cardiovascular disease is the main cause of death in women in the western world[10;11]. Although cardiovascular disease is often considered as a health problem for predominantly men, more women than men die of heart disease each year[12]. Heart disease symptoms in women are often different from symptoms in men and diagnostic tools are less sensitive and specific.

Despite intensive research, the underlying link between hypertensive pregnancy disorders and future risk of cardiovascular disease remains unknown. Both preeclampsia and cardiovascular disease share the same risk factors e.g. hyperlipidemia, hyperglycemia, genetic predisposition, insulin resistance, obesity, and hypertension. Therefore, it is likely that both preeclampsia and cardiovascular disease share a common pathogenesis. Furthermore, the existing subclinical vascular (endothelium) damage in both diseases leads to vascular changes; clinically manifest as metabolic syndrome and arteriosclerosis.

Epidemiological studies have resulted in the novel concept that pregnancy is a vascular 'stress test' for women, in whom the development of preeclampsia is a positive test result and the result has to be interpreted as an individual elevated cardiovascular risk later. In contrast, women who pass the stress test, i.e. women who have normotensive uncomplicated pregnancies, could be considered as "low risk" for developing cardiovascular disease. In daily obstetric practice, however, women with previous preeclampsia and health care providers are not aware of this association and as a consequence women attend generally not in a follow up program after delivery. This might imply "a missed opportunity" for follow up and preventive care of these women. With current knowledge, the clinician has a screening opportunity to detect women at risk for future cardiovascular disease using pregnancy complicated by preeclampsia. In addition, the clinician might have a preventive tool by changing lifestyle and medication, if necessary, that may help to avoid cardiovascular consequences on the long term. However, until

now the above mentioned hypothesis is mainly based on epidemiologic studies; data concerning the mechanisms and/or interventions are lacking.

## Definitions

Several definitions of preeclampsia and pregnancy induced hypertension are used in literature, resulting in a lack of uniformity of criteria used to classify hypertensive disorders of pregnancy. Especially older studies (before 2001) are less exact about the diagnosis of preeclampsia, leading to misclassification (women with pregnancy induced hypertension are often incorrectly classified as preeclampsia)[13].

Nowadays, it is generally agreed to use the definitions according to the ISSHP criteria[14]. ISSHP defines preeclampsia as the onset of a blood pressure exceeding 140/90 mmHg with proteinuria greater than 0.3 g/24 h after 20 weeks gestation. Severe preeclampsia is defined as a blood pressure exceeding 160/110 mmHg or proteinuria greater than 5 g/24 h, or both. Superimposed preeclampsia is defined as new onset proteinuria (0.3 g/ 24 h) after 20 weeks of gestation in women with chronic hypertension. Another hypertensive disorder in pregnancy is pregnancy induced hypertension, defined by diastolic blood pressure equal to or above 90 mmHg measured at two occasions at least six hours apart in a woman who was normotensive at the start of pregnancy until week 20 of gestational age[14].

## Preeclampsia

Preeclampsia is a pregnancy specific disorder. The onset, clinical presentation and course of preeclampsia are variable and unpredictable. It is a multi-systemic and complex syndrome, which can affect multiple maternal organ systems including heart, lungs, kidneys, liver, brain and placenta.

Despite decades of intensive research, the exact etiology of preeclampsia still remains unknown. However, it is generally accepted that the etiology of preeclampsia is associated with abnormal placental development in early pregnancy; deficient trophoblastic invasion, leading to generalized endothelial dysfunction and an exaggerated inflammatory response[15-17]. From this hypothesis it is evident that preeclampsia is not explained by only a distinct cause, but consistent with a syndrome. Preeclampsia is likely to originate from complex interactions among maternal constitutional factors, including preexisting metabolic abnormalities, placenta-derived products, and the exaggerated adaptive mechanisms that normally occur during pregnancy[18]. The syndrome can be categorized into one whose genesis is the result of primarily reduced placental perfusion, which is termed “placental” in literature, and another in which the

clinical syndrome is primarily due to preexisting maternal disorder, which is termed "maternal"[19].

Preeclampsia has been described as a two stage disorder[20-22] and in 2009 this model has been modified[17]. The pathophysiological process in preeclampsia can be described in two stages, preclinical and clinical. The first trimester is the important contributor to stage 1; poor development of the early placenta. This subsequently results in reduced placental perfusion, due to failed remodeling of the maternal vessels supplying the intervillous space. Only stage 1 is not sufficient to cause preeclampsia, but requires co-interaction with many factors, i.e. genetic, behavioral, or environmental[23]. Stage 2, in the second half of pregnancy, is associated with placental oxidative stress, exaggerated endothelial activation and inflammation. Oxidative stress, due to placental hypoxia, results in the release of components from the intervillous space into the systemic maternal circulation, including sFlt-1, VEGF, endoglin, inhibin-A, and other mediators[16;22]. The maternal systemic inflammatory stress results in endothelial dysfunction and increased vascular reactivity, preceding the onset of "the clinical syndrome" preeclampsia.

Different presentations of the syndrome, combining maternal and placental contributions are common. This supports the current concept of the heterogeneous causes of the syndrome preeclampsia[19], probably different linkage mechanisms between stage 1 and 2[22]. The modified two stage model[17] describes the new concept, that interactions between genetic, behavioral and environmental factors, not only contribute to stage 2, but also have influence on stage 1. This implies that preeclampsia is not only an endothelial disease, but systemic inflammatory response plays an important role[16].

## Preeclampsia and Cardiovascular Risk: Epidemiology

Evidence from large epidemiological studies has consistently shown that a history of preeclampsia exerts an independent risk for future cardiovascular disease. These study results are summarized in comprehensive systematic reviews by McDonald et al[24] and Bellamy et al.[13] Bellamy et al. included 25 prospective and retrospective cohort studies (nested case-controls studies and case cohort studies were also included). Studies were included assessing women of any parity or age or any severity of preeclampsia and different lengths of time in follow up. The relative risk (95% confidence interval) of ischemic heart disease was increased in women with previous preeclampsia 2.16 (1.86 to 2.52) after 11.7 years (n=2346997). A relative risk of fatal ischemic heart disease in women with previous preeclampsia was found of 2.60 (1.94 to 3.49). Furthermore, all-cause mortality was increased with a relative risk of 1.49 (1.05 to 2.14) after 14.5 years (n=794462). Relative risks for

stroke were 1.81 (1.45 to 2.27) after 10.4 years (n=1671578) and for hypertension 3.70 (2.70 to 5.05) after 14.1 years after pregnancy complicated by preeclampsia (n=21030). Women with preeclampsia in one of their pregnancies (5.96 (3.42 to 10.38)) had a higher risk of future hypertension compared to preeclampsia in primiparous women (3.23 (2.32 to 4.52))[13]. Bellamy et al. stated that the major contribution to all- cause mortality seemed to be cardiovascular disease, as there was no difference in the relative risk of death from breast cancer (1.04 (0.78 to 1.39)) or any other cancers (0.96 (0.73 to 1.27)).

In addition, two other large cohort studies were recently published, concerning preeclampsia and subsequent cardiovascular morbidity or mortality[25;26]. The study results were in line with the results published by Bellamy et al.. Mongraw- Chaffin et al.[26] found in a large prospective cohort study (N= 14403) with a median follow up time of 37 years, that a history of preeclampsia was independently associated with cardiovascular death, with an adjusted hazard ratio (95% confidence interval) of 2.14 (1.29- 3.57). Women with a history of preeclampsia before 34 weeks of gestation had a hazard ratio (95% confidence interval) of 9.54 (4.50 to 20.26). Lykke et al.[25] investigated in a registry based retrospective cohort study in Denmark, the risk of developing cardiovascular disease after preeclampsia in 782287 primiparous women (median follow up 14.6 years) and 536419 multiparous women (median follow up 12.9 years). They made a distinction between mild and severe preeclampsia and recurrent preeclampsia or preeclampsia in a single pregnancy. A 3.6- fold (range 3.43 to 3.80) higher risk was described for hypertension in women with a history of mild preeclampsia and a 6.0- fold higher risk (range 5.45 to 6.77) in women with severe preeclampsia. Furthermore, women with preeclampsia in only the first pregnancy had a 2.70- fold (range 2.51 to 2.90) higher risk, women with preeclampsia in only the second pregnancy a 4.34- fold (range 3.98 to 4.74) higher risk and women with preeclampsia in two pregnancies had a 6- fold higher risk (range 5.40 to 6.67) of hypertension compared with women with two normotensive pregnancies in history. Relative risks of recurrent preeclampsia and cardiovascular morbidity and mortality described by three different studies are summarized in table 1.[25;27;28] Overall, women who had early onset preeclampsia and women who had preeclampsia in two pregnancies are at greatest risk for hypertension later.

**Table 1.** Recurrent preeclampsia and cardiovascular morbidity and mortality

| Author, year, country, study design | Number included | Follow up in years | Outcome | RR, (95%) CI |
|---|---|---|---|---|
| Funai 2005, Israel, retrospective cohort | PE*, N= 1070<br>NT*, N= 35991 | 24 to 36 | Cardiovascular mortality | 2.18 (1.81 to 2.62) †<br>3.49 (2.22 to 5.49) ‡<br>6.18 (2.95 to 13.0) § |
| Lykke, 2009, Denmark, retrospective cohort | PE*, N= 28838<br>NT*, N= 507581 | 12.9 | Cardiovascular disease | 1.30 (1.13 to 1.49) ††<br>2.01 (1.70 to 2.38) ‡‡<br>2.79 (2.27 to 3.43) §§ |
| Wikström, 2005, Sweden, retrospective cohort | PE**, N= 207054<br>NT*, N= 194572 | 15 | Cardiovascular disease or Cardiovascular mortality | 1.9 (1.5 to 2.4) ††<br>2.4 (1.8 to 3.2) ‡‡<br>2.8 (2.0 to 3.9) §§ |

* PE= preeclampsia, NT = normotensive pregnancy

† Preeclampsia in the first pregnancy compared with pregnancy without preeclampsia

‡ Preeclampsia in the first and second pregnancy compared with pregnancy without preeclampsia

§ Preeclampsia in the first, second and third pregnancy compared with pregnancy without preeclampsia

†† Preeclampsia in the first pregnancy and a normotensive second pregnancy compared to women with two normotensive pregnancies

‡‡ Normotensive in the first pregnancy and preeclampsia in the second pregnancy compared to women with two normotensive pregnancies

§§ Preeclampsia in first and second pregnancy compared to women with two normotensive pregnancies

** Both preeclampsia and gestational hypertension were included

The studies mentioned above have demonstrated an association between preeclampsia and adverse long term cardiovascular outcomes. Other studies have examined cohorts of women with cardiovascular events and compared their pregnancy histories with those of age-matched control women without cardiovascular events. Mann et al. and Croft et al. have demonstrated relative risks (95% confidence interval) of 3.0[29] and 2.8 (1.7 to 4.8)[30] respectively for a history of preeclampsia after myocardial infarction and two other case control studies described odds ratios of 1.94 (1.26 to 2.97)[31] and 1.63 (1.02 to 2.62)[32] for a history of preeclampsia after a cerebrovascular accident.

The pathogenesis of the association between preeclampsia and cardiovascular disease in later life is not fully explained. It is well established, that endothelial dysfunction plays a central role in both preeclampsia and cardiovascular disease[15]. Several hypotheses about the association have been described; (1) elevated risk of cardiovascular morbidity and mortality after preeclampsia suggests a common (preexisting) cause of these two disorders, or (2) preeclampsia activates the maternal vascular system, leading to cardiovascular disease in the future. A third hypothesis is a combination of both theories; both theories are responsible for later cardiovascular morbidity and mortality[33].

The first hypothesis, preeclampsia and cardiovascular disease have a common cause, is supported by a population based prospective cohort study from 1995 to 2005 by Magnussen et al., which was published in 2007. Magnussen et al.[34] studied cardiovascular risk factors in women before pregnancy and those who subsequently developed preeclampsia. It was a linkage study between a Norwegian population based study (HUNT 2) and the Norway's medical birth registry. 3494 Women were included before pregnancy with an on average time interval of four years from cardiovascular risk measurement until delivery. In this study, a strong linear positive association was found between pre-pregnancy systolic and diastolic blood pressure and preeclampsia; the adjusted odds ratio and 95% confidence interval with a pre-pregnancy systolic blood pressure > 130 mmHg was 7.3 (3.1 to 17.2) compared to women with a pre-pregnancy systolic blood pressure less than 111 mmHg. The adjusted odds ratio for women with a pre-pregnancy diastolic blood pressure greater than 78 mmHg was 6.3 (2.9 to 14.6) compared to women with a pre-pregnancy diastolic blood pressure less than 64 mmHg. Other positive associations were found between pre-pregnancy body mass index, waist circumference and development of preeclampsia[34]. In pre-pregnancy biochemical risk factor measurement positive associations were found with serum levels of triglycerides, total cholesterol, LDL and the risk of preeclampsia. The risk of preeclampsia increased with increasing levels of biochemical risk factors. A less robust association was found with HDL cholesterol and glucose, however, there was an association with preeclampsia and unfavorable levels of these two biochemical risk factors. These data suggest that unfavorable cardiovascular and metabolic factors, present before pregnancy, might predispose for both preeclampsia and cardiovascular disease (hypothesis 1). However, the possibility that preeclampsia itself contributes to cardiovascular disease is not ruled out (hypothesis 2). Thus, long term (difficult) cohort studies combining pre-pregnancy, pregnancy and postpartum data would help to determine whether preeclampsia has a common cause as cardiovascular disease (hypothesis 1), unmasking cardiovascular disease or accelerate cardiovascular dysfunction (hypothesis 2), or a combination of the above mentioned hypotheses (hypothesis 3).

## Early Onset (Severe) and Late Onset (Mild) Preeclampsia

Distinction has been made in several studies between early (severe) – and late – onset (mild) preeclampsia[35-38]. Early onset preeclampsia is often associated with maternal and neonatal morbidity and mortality, as the risk of progression to severe maternal disease is inversely related with gestational age at onset. Furthermore, early onset preeclampsia is typically associated with impaired placental function, reduction in placental volume, small for gestational age, abnormal uterine and

umbilical artery Doppler evaluation. On the other hand, late onset preeclampsia is more or less a maternal disorder, a maternal constitutional disorder. Mostly, a normal placenta, normal placental volume, normal birth weight, normal Doppler artery evaluation and more favorable maternal and neonatal outcomes are seen in late onset preeclampsia[35].

Early- onset preeclampsia is associated with a greater risk of cardiovascular disease compared to late- onset preeclampsia. Smith et al. and Irgens at al. found an nearly 8-fold increased risk of ischemic heart disease in women with preeclampsia before 37 weeks compared to women with normotensive term pregnancy (ies) in history (7.71, 95% confidence interval 4.40 to 13.52)[4;8;13]. Furthermore, Smith et al. found additive associations between birth weight for gestational age, preterm birth and preeclampsia in the first pregnancy and the mothers risk of fatal and non-fatal ischemic heart disease; for the combination of lowest birth weight quintile and preterm birth the adjusted hazard ratio and 95% confidence interval for death due to ischemic heart disease was 8.7 (2.0 to 22.9), for preterm birth and preeclampsia 6.4 (1.9 to 21.3), for lowest birth weight quintile and preeclampsia 3.9 (1.3 to 11.6) and for lowest birth weight quintile, preeclampsia and preterm birth 16.1 (3.6 to 72.6).

Another elevated risk, however less strong, is found in the severity of preeclampsia, as women with severe pre-eclampsia, defined as blood pressure >160/110 mm Hg plus proteinuria >0.3 g/24 or diastolic blood pressure >110 mm Hg plus proteinuria >5 g/24) have a greater risk of later ischemic heart disease (2.86, 95% confidence interval 2.25 to 3.65) compared to women with mild pre-eclampsia (1.92, 95% confidence interval 1.65 to 2.24)[9;13;39]. These findings are confirmed by recent studies[25;26]. Mongraw- Chaffin et al. described that a history of preeclampsia before 34 weeks of gestation had a hazard ratio of 9.54 (95% confidence interval 4.50 to 20.26) for cardiovascular mortality. Furthermore, at 30 years of follow up and a median age of 56 years, a cumulative cardiovascular disease death survival for women with early preeclampsia was 85.9% compared with 98.3% for women with late preeclampsia and 99.3% for women with a history without preeclampsia[26].

In summary, both early (severe) preeclampsia and recurrent preeclampsia are associated with a greater risk of cardiovascular disease compared to late (mild) and single episode preeclampsia, the severity of preeclampsia seems to show a “dose response” effect with cardiovascular disease. This leads to the hypothesis that women with more severe disease have an underlying pathological phenotype that puts them at risk for hypertension, cardiovascular disease and preeclampsia[7;34;40].

## Cardiovascular Risk Factors after Preeclampsia

Cardiovascular disease and preeclampsia share common risk factors, including non- modifiable risk factors (age, family history, and ethnicity), and modifiable risk factors ((pre-existing) hypertension, diabetes mellitus, renal disease, obesity, dyslipidemia, metabolic syndrome, microalbuminuria, thrombophilia, and hyperhomocystinaemia)[41]. The unsolved exception is smoking[34]. For developing preeclampsia, smoking is a 'protecting' factor, while in cardiovascular disease; smoking is a consistent risk factor (table 2). According to a recent systematic review by Huxley et al., women who smoke have a 25% greater relative risk of coronary heart disease than male smokers compared with non- smokers, independent of other cardiovascular risk factors[42]. Other cardiovascular risk factors and their relative risks for cardiovascular disease risk are described in table 2. The risk score and contribution of preeclampsia *per se* for cardiovascular disease is still unknown.

**Table 2.** Risk factors in women and relative risks for cardiovascular disease

| Risk factor | Relative risks * |
|---|---|
| Hypertension | 2.0 to 3.0† |
| Smoking | 2.2† |
| Diabetes Mellitus | 3.7† |
| Obesity | 2.1† |
| Metabolic syndrome | 2.3 (95% CI 1.3 to 3.9)[43] |

Cardiovascular disease includes coronary events or stroke, or both.

* Modified from Padwal et al.[44]; relative risks for women are reported in this table.

Padwal at al., originally reported ranges of relative risks between men and women without confidence intervals, extracted from highest quality studies.

† 95% confidence interval not reported

As preeclampsia and cardiovascular disease share common cardiovascular risk factors, several studies described different biochemical risk factors after a pregnancy complicated by preeclampsia or gestational hypertension to identify the high risk patient. Most common risk factors described are; glucose, insulin, lipid concentrations, CRP, insulin resistance, and prevalence of metabolic syndrome[40;45-60;60;61]. Most studies have either limited sample sizes, have measured single cardiovascular risk biomarkers, or have measured these risk factors shortly after pregnancy, with few exceptions. These heterogeneous studies could be the reason why these studies are contra dictionary. In some studies significantly higher levels were found for glucose[46;48;51;54;60], insulin[48;51;55;57;59;60;62], lipid levels[45;48;49;53;59] and CRP[50;63] after a hypertensive pregnancy compared to women with a normotensive pregnancy in history. However, these results were not

confirmed by others (glucose[40;47;50;55;57;59;62;64], insulin[50;58], lipid levels[46;47;50-52;54;55;57;58] and CRP[62]). Recently, Fraser et al. published an article in which a follow up after pregnancy was performed in a large prospective cohort of 4,376 women with a mean follow up time of 18 years (range:16-20 years). In this cohort, both gestational hypertension and preeclampsia were associated with a greater number of cardiovascular risk factors: body mass index, waist circumference, systolic and diastolic blood pressure, insulin, pro-insulin, triglycerides, and HDL cholesterol. Furthermore, overall future risk of cardiovascular disease was described based on the 10 year Framingham score. In this cohort the overall future risk of cardiovascular disease was low (as would be expected given that the mean age of participants is 48 years), with a median predicted risk of 3.0% (inter-quartile range 2.2-4.2%). However, the calculated risk of a cardiovascular event over 10 years was elevated in women with hypertensive disorders in pregnancy compared to those without; mean score (SE) of 5.09 (0.41), odds ratio (adjusted for age) 1.42 (95% confidence interval 1.19 to 1.69)[61].

Until now, a systematic review or meta-analysis with pooled data of these biochemical risk factors for cardiovascular disease after pregnancies complicated by hypertensive disorders is lacking. Such a meta- analysis would be necessary to gain insight into which cardiovascular risk factor is elevated after a hypertensive pregnancy compared to normotensive pregnancy and which risk factor can be useful for screening to identify "the high risk patient for later manifested cardiovascular disease". Most studies have focused on early onset (severe) preeclampsia, which is a relative rare disorder, with a prevalence of 0.5%.[65] It is essential that further research is not only focused on early severe preeclampsia, but also pays attention to the association between late (mild) onset preeclampsia and elevated cardiovascular risk factors, persistent hypertension after pregnancy and metabolic syndrome, as late (mild) onset preeclampsia is a more common disorder.

Early onset preeclampsia and late onset preeclampsia may have two distinct pathogeneses. Abnormal placental development is believed to be more strongly associated with early-onset preeclampsia. Late- onset preeclampsia is believed to occur secondary to maternal vascular diseases including hypertension, metabolic syndrome and maternal genetic disposition. For the association with cardiovascular disease, these two disorders may also have a distinct pathogenesis.

## Metabolic Syndrome and Preeclampsia

Normal pregnancy is described as a state of temporarily metabolic syndrome with relative insulin resistance and up-regulation of inflammatory markers (IL-6 and coagulation factors)[66;67]. It is thought that in women with more abnormal

pre-pregnancy carbohydrate, lipid or vascular function, the metabolic stress of pregnancy may push them past a clinical threshold for manifestation of vascular or metabolic disease, i.e. preeclampsia or gestational diabetes[7].

Metabolic syndrome is a spectrum of metabolic abnormalities associated with insulin resistance. Criteria for metabolic syndrome include waist circumference ≥ 80 cm. plus any two of raised triglycerides (> 150 mg/dL), reduced HDL cholesterol (< 50 mg/dL), raised blood pressure (systolic ≥ 130 mmHg and diastolic ≥ 85 mmHg), treatment of previously diagnosed hypertension, raised fasting plasma glucose (≥ 100 mg/dL) or previously diagnosed type 2 diabetes[68]. According to the Framingham Heart Study, women with metabolic syndrome have a relative risk of developing any cardiovascular disease of 2.25 (95% CI 1.3 to 3.9)[43].

Insulin resistance manifests as hyperglycemia, hyperlipidemia, and disturbance of coagulation[69]. Insulin resistance leads to vascular endothelial dysfunction, an abnormal lipid profile, hypertension, and vascular inflammation, all of which promote the development of cardiovascular disease[70]. Normal pregnancy is associated with increased insulin levels; however, fasting insulin is higher in preeclampsia, even prior to the onset of clinical disease[40;71].

The metabolic syndrome is more common in women with a history of preeclampsia[45;48;57]. It is likely that the cause of preeclampsia is multifactorial and many factors are involved. However, the metabolic syndrome has been suggested to play an important role in the pathophysiology of preeclampsia and pregnancy induced hypertension and may be the underlying mechanism linking hypertensive disease in pregnancy and cardiovascular disease in later life[63].

Several studies described the association between new onset hypertension in pregnancy, metabolic syndrome, insulin resistance and cardiovascular risk in later life[40;48;58;59]. In a large Canadian population-based retrospective cohort study by Ray et al.[39], an elevated cardiovascular risk was described in women with a history of preeclampsia, or gestational hypertension, placental abruption, or placental infarction, in combination with features of the metabolic syndrome. For example, women with a history of preeclampsia and who had one or two features of the metabolic syndrome, the adjusted hazard ratio for future cardiovascular disease was 4.5 (95% CI 3.7 to 5.4), and for women who had three to four features the adjusted hazard ratio was 11.7 (95% CI 4.9 to 28.3), compared with women who had neither[39].

Overweight and obesity are important factors in metabolic syndrome and a risk factor for both preeclampsia and cardiovascular disease. Nowadays obesity is a growing problem, especially in developed countries, of which we can expect that the prevalence of preeclampsia, metabolic syndrome and cardiovascular disease will increase in the next years.

## Follow up after Preeclampsia and Further Research

Until now, from epidemiologic data, it is justified to accomplish a randomized controlled trail to compare lifestyle modification for women with a history of preeclampsia, including smoking cessation, weight reduction in case of overweight or obesity, and an overall healthy lifestyle advice (healthy diet, physical activity) versus care as usual. This randomized controlled trial will gain insight in the question if screening and treating women after a pregnancy complicated by preeclampsia is effective in reduction of individual cardiovascular risk, and if blood pressure, lipid levels, smoking and bodyweight will be positively influenced. Until now, it is unclear how the increased long-term cardiovascular risk should exactly be handled in women with a history of pre-eclampsia, as evidence concerning screening, treatment and cost-benefit is lacking.

Still, there is no systematic care for women with preeclampsia after delivery, as current obstetric practice is only focused on the outcome of pregnancy and not on the future health of the mother. However, recently, progression on this topic has been made. Since the rising evidence of the association of preeclampsia and cardiovascular disease, and that authors of recent studies have recommended that women with a history of preeclampsia should be counseled regarding their increased risk for cardiovascular disease and be followed closely for modifiable cardiovascular risk factors[60], guidelines are changed. The 2011 guidelines from the American Heart Association include a recommendation to obtain a pregnancy history and also consider preeclampsia as a risk factor for later life maternal cardiovascular disease[72]. However, evidence for reduction of the individual's risk after pregnancy is lacking.

Another point, the awareness of women and (general) physicians of the elevated cardiovascular risk after preeclampsia, still remains challenging[73]. Young et al.[74] performed a web-based survey in Boston USA in May 2009 assessing the physician's knowledge of the association between preeclampsia and future cardiovascular disease risk. 56% of the internists (N = 118) and 22% of the gynecologists (N = 53) were not aware that preeclampsia is associated with cardiovascular disease. Only 9% of internists and 38% of obstetricians were providing cardiovascular risk reduction counseling to women with a history of preeclampsia[74]. Recently we studied the awareness of gynecologists in the Netherlands for the prevention of cardiovascular disease after early onset preeclampsia (< 34 weeks of gestation). We found that 44% of the gynecologists advise women to have frequent observations of their blood pressure after pregnancy complicated by preeclampsia. Furthermore only 28% of the gynecologists stated that they advise to increase the physical activity after pregnancy complicated by early preeclampsia and 64% of the gynecologists advise weight reduction postpartum. These preliminary data

reveal that the awareness of gynecologists for the prevention of cardiovascular disease after preeclampsia is limited. As a consequence an opportunity may be missed for secondary preventive activities for cardiovascular disease in these relatively young women, and prevention may be the key factor for solving this great health problem in women. Therefore, it is a first important step to study the effect of lifestyle changes and medication for women with hypertension and/or metabolic syndrome after pregnancy complicated by preeclampsia or pregnancy induced hypertension. After identifying rational tools for these women to reduce their cardiovascular risk, implementation should follow in the national guidelines. The American Heart Association guidelines have included preeclampsia as a risk factor for cardiovascular disease and recommend referral after preeclampsia by the obstetrician to a primary care physician or cardiologist for risk factor screening. However, further recommendations are lacking in these guidelines, concerning how women with a history of preeclampsia and normal values of cardiovascular risk factors should be managed.

In daily practice, risk stratification is performed by internists, cardiologists and GP's. They use validated cardiovascular risk scores to raise population awareness of individual cardiovascular risk. These cardiovascular risk prediction models are used as a tool for assessing individual risks, which are subsequently used to motivate adherence to recommended lifestyle changes or therapy. Common factors used in these models are; sex, age, blood pressure, cholesterol levels and smoking. The Framingham risk score[75], the European Systematic COronary Risk Evaluation (SCORE) algorithm[76], QRISK[77], the Prospective Cardiovascular Munster (PROCAM) model[78], Reynold's Risk Score[79] and many others are in use. In none of these risk prediction models, pregnancy history is added as a component, while, for example, early severe preeclampsia seems to be a stronger risk factor than smoking and blood pressure[44]. A question rises; is preeclampsia only the stress test to identify young women at risk, or is preeclampsia an independent risk factor, which has to be included in women's cardiovascular risk prediction models, to make these tools more sensitive and specific for women? The answer is currently under investigation.

Another problem of cardiovascular risk calculators is that they are focused on short-term risk in the next 10 years. Because of the young age of women after pregnancy, these risks are likely to be low. As a consequence, women may be falsely reassured and not pursue any lifestyle changes if necessary. Pencina et al.[75] published a method for estimating long-term 30-year risks for cardiovascular disease that also accounts for competing risks. This long term risk equation may be a powerful tool as an alternative for the current 10-year risk assessment scores.

We have to achieve information by further research to adjust and create adequate guidelines for screening and prevention of cardiovascular disease in women. This should be a healthcare priority.



## Conclusion

Preeclampsia is a common pregnancy disorder and clearly associated with an elevated cardiovascular morbidity and mortality risk. Therefore, pregnancy can be used as a stress test for future cardiovascular disease in relative young women, who can benefit from screening. Women with a history of early (severe) preeclampsia or recurrent preeclampsia have the highest cardiovascular risks. Until now, the exact underlying link between preeclampsia and cardiovascular disease remains unclear. Large prospective cohort studies, assessing women before, during and after pregnancy, are necessary to out the cause between the two related disorders. Furthermore, evidence for postpartum risk factor screening, prevention and treatment is still lacking.

## Reference List

(1) Duley L. The global impact of pre-eclampsia and eclampsia. Semin Perinatol 2009;33:130-137.
(2) Khan KS, Wojdyla D, Say L, Gulmezoglu AM, Van Look PF. WHO analysis of causes of maternal death: a systematic review. Lancet 2006;367:1066-1074.
(3) Haukkamaa L, Salminen M, Laivuori H, Leinonen H, Hiilesmaa V, Kaaja R. Risk for subsequent coronary artery disease after preeclampsia. Am J Cardiol 2004;93:805-808.
(4) Irgens HU, Reisaeter L, Irgens LM, Lie RT. Long term mortality of mothers and fathers after pre-eclampsia: population based cohort study. BMJ 2001;323:1213-1217.
(5) Jonsdottir LS, Arngrimsson R, Geirsson RT, Sigvaldason H, Sigfusson N. Death rates from ischemic heart disease in women with a history of hypertension in pregnancy. Acta Obstet Gynecol Scand 1995;74:772-776.
(6) Ramsay JE, Stewart F, Greer IA, Sattar N. Microvascular dysfunction: a link between pre-eclampsia and maternal coronary heart disease. BJOG 2003;110:1029-1031.
(7) Sattar N, Greer IA. Pregnancy complications and maternal cardiovascular risk: opportunities for intervention and screening? BMJ 2002;325:157-160.
(8) Smith GC, Pell JP, Walsh D. Pregnancy complications and maternal risk of ischaemic heart disease: a retrospective cohort study of 129,290 births. Lancet 2001;357:2002-2006.
(9) Wilson BJ, Watson MS, Prescott GJ et al. Hypertensive diseases of pregnancy and risk of hypertension and stroke in later life: results from cohort study. BMJ 2003;326:845.
(10) http://statline.cbs.nl/StatWeb/publication/?DM=SLNL&PA=7233&D1=0,300,639-716,1064,1070,1083,1086&D2=0,2&D3=0&D4=a&VW=T. 31-1-2011. Online Source
(11) Burell G, Granlund B. Women's hearts need special treatment. Int J Behav Med 2002;9:228-242.
(12) Pina IL. Cardiovascular disease in women: challenge of the middle years. Cardiol Rev 2011;19:71-75.
(13) Bellamy L, Casas JP, Hingorani AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. BMJ 2007;335:974.
(14) Brown MA, Lindheimer MD, De SM, Van AA, Moutquin JM. The classification and diagnosis of the hypertensive disorders of pregnancy: statement from the International Society for the Study of Hypertension in Pregnancy (ISSHP). Hypertens Pregnancy 2001;20:IX-XIV.
(15) Steegers EA, von DP, Duvekot JJ, Pijnenborg R. Pre-eclampsia. Lancet 2010;376:631-644.
(16) Redman CW, Sargent IL. Placental stress and pre-eclampsia: a revised view. Placenta 2009;30 Suppl A:S38-S42.
(17) Roberts JM, Hubel CA. The two stage model of preeclampsia: variations on the theme. Placenta 2009;30 Suppl A:S32-S37.
(18) Craici I, Wagner S, Garovic VD. Preeclampsia and future cardiovascular risk: formal risk factor or failed stress test? Ther Adv Cardiovasc Dis 2008;2:249-259.
(19) Ness RB, Roberts JM. Heterogeneous causes constituting the single syndrome of preeclampsia: a hypothesis and its implications. Am J Obstet Gynecol 1996;175:1365-1370.

(20) Redman CW, Sargent IL. Latest advances in understanding preeclampsia. Science 2005;308:1592-1594.
(21) Roberts JM, Hubel CA. Is oxidative stress the link in the two-stage model of pre-eclampsia? Lancet 1999;354:788-789.
(22) Steegers EA, von DP, Duvekot JJ, Pijnenborg R. Pre-eclampsia. Lancet 2010;376:631-644.
(23) Roberts JM, Hubel CA. The two stage model of preeclampsia: variations on the theme. Placenta 2009;30 Suppl A:S32-S37.
(24) McDonald SD, Malinowski A, Zhou Q, Yusuf S, Devereaux PJ. Cardiovascular sequelae of preeclampsia/eclampsia: a systematic review and meta-analyses. Am Heart J 2008;156:918-930.
(25) Lykke JA, Langhoff-Roos J, Sibai BM, Funai EF, Triche EW, Paidas MJ. Hypertensive pregnancy disorders and subsequent cardiovascular morbidity and type 2 diabetes mellitus in the mother. Hypertension 2009;53:944-951.
(26) Mongraw-Chaffin ML, Cirillo PM, Cohn BA. Preeclampsia and cardiovascular disease death: prospective evidence from the child health and development studies cohort. Hypertension 2010;56:166-171.
(27) Wikstrom AK, Haglund B, Olovsson M, Lindeberg SN. The risk of maternal ischaemic heart disease after gestational hypertensive disease. BJOG 2005;112:1486-1491.
(28) Funai EF, Paltiel OB, Malaspina D, Friedlander Y, Deutsch L, Harlap S. Risk factors for pre-eclampsia in nulliparous and parous women: the Jerusalem perinatal study. Paediatr Perinat Epidemiol 2005;19:59-68.
(29) Mann JI, Doll R, Thorogood M, Vessey MP, Waters WE. Risk factors for myocardial infarction in young women. Br J Prev Soc Med 1976;30:94-100.
(30) Croft P, Hannaford PC. Risk factors for acute myocardial infarction in women: evidence from the Royal College of General Practitioners' oral contraception study. BMJ 1989;298:165-168.
(31) Haemorrhagic stroke, overall stroke risk, and combined oral contraceptives: results of an international, multicentre, case-control study. WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Lancet 1996;348:505-510.
(32) Brown DW, Dueker N, Jamieson DJ et al. Preeclampsia and the risk of ischemic stroke among young women: results from the Stroke Prevention in Young Women Study. Stroke 2006;37:1055-1059.
(33) Roberts JM, Gammill H. Pre-eclampsia and cardiovascular disease in later life. Lancet 2005;366:961-962.
(34) Magnussen EB, Vatten LJ, Lund-Nilsen TI, Salvesen KA, Davey SG, Romundstad PR. Prepregnancy cardiovascular risk factors as predictors of pre-eclampsia: population based cohort study. BMJ 2007;335:978.
(35) Raymond D, Peterson E. A critical review of early-onset and late-onset preeclampsia. Obstet Gynecol Surv 2011;66:497-506.
(36) Clausen T, Djurovic S, Henriksen T. Dyslipidemia in early second trimester is mainly a feature of women with early onset pre-eclampsia. BJOG 2001;108:1081-1087.
(37) Sibai B, Dekker G, Kupferminc M. Pre-eclampsia. Lancet 2005;365:785-799.
(38) Vatten LJ, Skjaerven R. Is pre-eclampsia more than one disease? BJOG 2004;111:298-302.
(39) Ray JG, Vermeulen MJ, Schull MJ, Redelmeier DA. Cardiovascular health after maternal placental syndromes (CHAMPS): population-based retrospective cohort study. Lancet 2005;366:1797-1803.

(40) Wolf M, Hubel CA, Lam C et al. Preeclampsia and future cardiovascular disease: potential role of altered angiogenesis and insulin resistance. J Clin Endocrinol Metab 2004;89:6239-6243.
(41) Bilhartz TD, Bilhartz PA, Bilhartz TN, Bilhartz RD. Making use of a natural stress test: pregnancy and cardiovascular risk. J Womens Health (Larchmt ) 2011;20:695-701.
(42) Huxley RR, Woodward M. Cigarette smoking as a risk factor for coronary heart disease in women compared with men: a systematic review and meta-analysis of prospective cohort studies. Lancet 2011;378:1297-1305.
(43) Wilson PW, D'Agostino RB, Parise H, Sullivan L, Meigs JB. Metabolic syndrome as a precursor of cardiovascular disease and type 2 diabetes mellitus. Circulation 2005;112:3066-3072.
(44) Padwal R, Straus SE, McAlister FA. Evidence based management of hypertension. Cardiovascular risk factors and their effects on the decision to treat hypertension: evidence based review. BMJ 2001;322:977-980.
(45) Barden AE, Beilin LJ, Ritchie J, Walters BN, Michael C. Does a predisposition to the metabolic syndrome sensitize women to develop pre-eclampsia? J Hypertens 1999;17:1307-1315.
(46) Berends AL, de Groot CJ, Sijbrands EJ et al. Shared constitutional risks for maternal vascular-related pregnancy complications and future cardiovascular disease. Hypertension 2008;51:1034-1041.
(47) Chambers JC, Fusi L, Malik IS, Haskard DO, De SM, Kooner JS. Association of maternal endothelial dysfunction with preeclampsia. JAMA 2001;285:1607-1612.
(48) Forest JC, Girouard J, Masse J et al. Early occurrence of metabolic syndrome after hypertension in pregnancy. Obstet Gynecol 2005;105:1373-1380.
(49) He S, Silveira A, Hamsten A, Blomback M, Bremme K. Haemostatic, endothelial and lipoprotein parameters and blood pressure levels in women with a history of preeclampsia. Thromb Haemost 1999;81:538-542.
(50) Hubel CA, Snaedal S, Ness RB et al. Dyslipoproteinaemia in postmenopausal women with a history of eclampsia. BJOG 2000;107:776-784.
(51) Innes KE, Weitzel L, Laudenslager M. Altered metabolic profiles among older mothers with a history of preeclampsia. Gynecol Obstet Invest 2005;59:192-201.
(52) Laivuori H, Tikkanen MJ, Ylikorkala O. Hyperinsulinemia 17 years after preeclamptic first pregnancy. J Clin Endocrinol Metab 1996;81:2908-2911.
(53) Manten GT, Sikkema MJ, Voorbij HA, Visser GH, Bruinse HW, Franx A. Risk factors for cardiovascular disease in women with a history of pregnancy complicated by preeclampsia or intrauterine growth restriction. Hypertens Pregnancy 2007;26:39-50.
(54) Nisell H, Erikssen C, Persson B, Carlstrom K. Is carbohydrate metabolism altered among women who have undergone a preeclamptic pregnancy? Gynecol Obstet Invest 1999;48:241-246.
(55) Paradisi G, Biaggi A, Savone R et al. Cardiovascular risk factors in healthy women with previous gestational hypertension. J Clin Endocrinol Metab 2006;91:1233-1238.
(56) Portelinha A, Belo L, Cerdeira AS et al. Lipid levels including oxidized LDL in women with history of preeclampsia. Hypertens Pregnancy 2010;29:93-100.
(57) Pouta A, Hartikainen AL, Sovio U et al. Manifestations of metabolic syndrome after hypertensive pregnancy. Hypertension 2004;43:825-831.
(58) Sattar N, Ramsay J, Crawford L, Cheyne H, Greer IA. Classic and novel risk factor parameters in women with a history of preeclampsia. Hypertension 2003;42:39-42.

(59) Smith GN, Walker MC, Liu A et al. A history of preeclampsia identifies women who have underlying cardiovascular risk factors. Am J Obstet Gynecol 2009;200:58.
(60) Magnussen EB, Vatten LJ, Smith GD, Romundstad PR. Hypertensive disorders in pregnancy and subsequently measured cardiovascular risk factors. Obstet Gynecol 2009;114:961-970.
(61) Fraser A, Nelson SM, Macdonald-Wallis C et al. Associations of pregnancy complications with calculated cardiovascular disease risk and cardiovascular risk factors in middle age: the avon longitudinal study of parents and children. Circulation 2012;125:1367-1380.
(62) Spaan JJ, Houben AJHM, Musella A, Ekhart T, Spaanderman MEA, Peeters LLH. Insulin resistance relates to microvascular reactivity 23years after preeclampsia. Microvasc Res 2010;80:417-421.
(63) Girouard J, Giguere Y, Moutquin JM, Forest JC. Previous hypertensive disease of pregnancy is associated with alterations of markers of insulin resistance. Hypertension 2007;49:1056-1062.
(64) Barden A. Pre-eclampsia: contribution of maternal constitutional factors and the consequences for cardiovascular health. Clin Exp Pharmacol Physiol 2006;33:826-830.
(65) Zhang WH, Alexander S, Bouvier-Colle MH, Macfarlane A. Incidence of severe pre-eclampsia, postpartum haemorrhage and sepsis as a surrogate marker for severe maternal morbidity in a European population-based study: the MOMS-B survey. BJOG 2005;112:89-96.
(66) Rodie VA, Freeman DJ, Sattar N, Greer IA. Pre-eclampsia and cardiovascular disease: metabolic syndrome of pregnancy? Atherosclerosis 2004;175:189-202.
(67) Sattar N. Do pregnancy complications and CVD share common antecedents? Atheroscler Suppl 2004;5:3-7.
(68) Alberti KG, Zimmet P, Shaw J. The metabolic syndrome--a new worldwide definition. Lancet 2005;366:1059-1062.
(69) Solomon CG, Seely EW. Brief review: hypertension in pregnancy: a manifestation of the insulin resistance syndrome? Hypertension 2001;37:232-239.
(70) Defronzo RA, Ferrannini E. Insulin resistance. A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. Diabetes Care 1991;14:173-194.
(71) Innes KE, Wimsatt JH. Pregnancy-induced hypertension and insulin resistance: evidence for a connection. Acta Obstet Gynecol Scand 1999;78:263-284.
(72) Mosca L, Benjamin EJ, Berra K et al. Effectiveness-based guidelines for the prevention of cardiovascular disease in women--2011 update: a guideline from the American Heart Association. J Am Coll Cardiol 2011;57:1404-1423.
(73) Nijdam ME, Timmerman MR, Franx A et al. Cardiovascular risk factor assessment after pre-eclampsia in primary care. BMC Fam Pract 2009;10:77.
(74) Young B, Hacker MR, Rana S. Physicians' knowledge of future vascular disease in women with preeclampsia. Hypertens Pregnancy 2012;31:50-58.
(75) Pencina MJ, D'Agostino RB, Sr., Larson MG, Massaro JM, Vasan RS. Predicting the 30-year risk of cardiovascular disease: the framingham heart study. Circulation 2009;119:3078-3084.
(76) Conroy RM, Pyorala K, Fitzgerald AP et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J 2003;24:987-1003.

(77) Hippisley-Cox J, Coupland C, Robson J, Brindle P. Derivation, validation, and evaluation of a new QRISK model to estimate lifetime risk of cardiovascular disease: cohort study using QResearch database. BMJ 2010;341:c6624.
(78) Assmann G, Cullen P, Schulte H. Simple scoring scheme for calculating the risk of acute coronary events based on the 10-year follow-up of the prospective cardiovascular Munster (PROCAM) study. Circulation 2002;105:310-315.
(79) Ridker PM, Buring JE, Rifai N, Cook NR. Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: the Reynolds Risk Score. JAMA 2007;297:611-619.

# Part Two

# Biochemical Cardiovascular Risk Factors after Hypertensive Pregnancy Disorders

# *Chapter 3*

## Biochemical cardiovascular risk factors after hypertensive pregnancy disorders: A systematic review and meta-analysis

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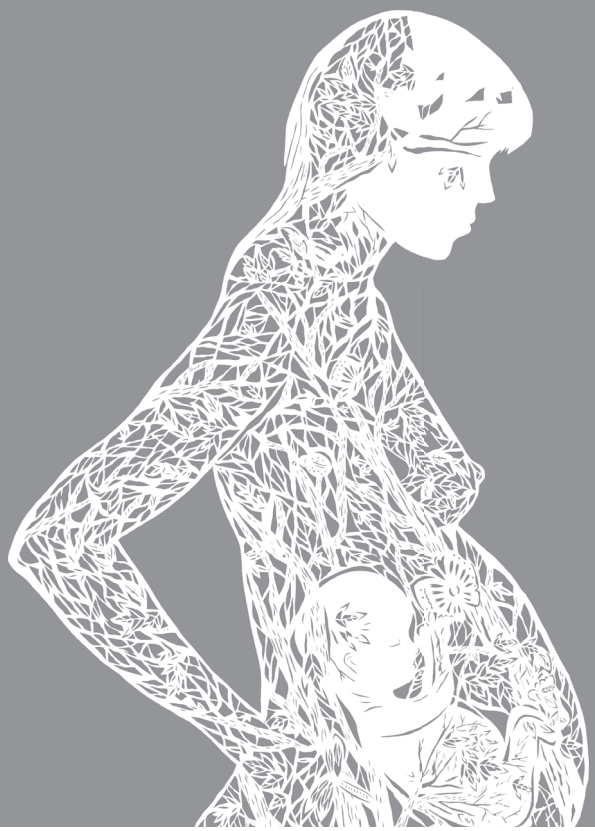

## Abstract

The objective of this study was to perform a systematic review and meta-analysis of studies assessing biochemical cardiovascular risk factors in women with previous hypertensive pregnancy disorders and women with previous normotensive pregnancies. Data were collected from PubMed and EMBASE (from inception to February 28, 2011) supplemented by manual searches of bibliographies.

Included were cohort studies and case-control studies assessing biochemical cardiovascular risk factors in women with previous hypertensive pregnancy disorders compared with women with previous normotensive pregnancies. Of 2573 studies reviewed for eligibility, quality, and data extraction, 22 were included in the review, of which 15 could be meta-analyzed. The pooled mean differences for the outcomes of interest were 0.17 mmol/L (95% confidence interval [CI], 0.08 to 0.25 mmol/L) for glucose (10 studies), 3.46 mU/mL (95% CI, 2.34 to 4.58 mU/mL) for insulin (5 studies), 0.13 mmol/L (95% CI, 0.05 to 0.21) for triglycerides (10 studies), 0.22 mmol/L (95% CI, 0.11 to 0.33 mmol/L) for total cholesterol (11 studies), 0.11 mmol/L (95% CI, 0.18 to 0.04 mmol/L) for high-density lipoprotein cholesterol (10 studies), and 0.21 mmol/L (95% CI, 0.10 to 0.32) for low-density lipoprotein cholesterol (9 studies), all in the disadvantage in women with previous hypertensive pregnancy disorders. Analyses for preeclampsia alone showed similar results.

Conclusions: Women with previous hypertensive pregnancy disorders have higher glucose, insulin, triglycerides, total cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol levels measured after pregnancy compared with women with previous normotensive pregnancies. These biochemical cardiovascular risk factors may identify women who will benefit from primary prevention of cardiovascular disease.

## Introduction

Hypertensive disorders are the most common complications in pregnancy with a prevalence of approximately 6% to 8%.[1,2] Hypertensive disorders include a spectrum of conditions including gestational hypertension, preeclampsia, eclampsia, and superimposed preeclampsia. Preeclampsia is a pregnancy-specific syndrome, defined by the onset of hypertension and proteinuria. In the developed world, preeclampsia affects 2% to 4% of pregnancies and is still largely responsible for high maternal and fetal mortality rates.[3] It has been suggested that pregnancy acts as a natural stress test that can predict women's health in later life.[4] Pregnancy can unmask subclinical diseases including hypertensive disorders that express in later life by the effects of aging clinically diagnosed as cardiovascular disease. Cardiovascular disease is the leading cause of death in women in the Western world.[5] Both hypertensive disorders in pregnancy and cardiovascular disease share features of subclinical vascular (endothelium) damage clinically manifesting as metabolic syndrome and arteriosclerosis. From this point of view, pregnancies complicated by hypertensive disorders might be used as indicator for screening for cardiovascular risk factors and primary prevention programs. Several studies assessed biochemical cardiovascular risk factors after pregnancy in women with a history of hypertensive disorders in pregnancy. These studies used different inclusion criteria, that is, early severe or mild term preeclampsia or gestational hypertension or combination of both disorders. Moreover, these studies reported on a large spectrum of cardiovascular risk factors. Measurement of biochemical cardiovascular risk factors after pregnancy might be a tool to identify women at risk for cardiovascular disease later in life. However, it is still not clear which biochemical cardiovascular risk factor is elevated after pregnancies complicated by hypertensive disorders. The objective of this study was to conduct a comprehensive systematic review and meta-analysis assessing biochemical cardiovascular risk factors in women with a history of hypertensive disorders in pregnancy compared with women with a history of normotensive pregnancies. Our aim was to identify which biochemical cardiovascular risk factor women exhibit after their hypertensive pregnancies and may be used for screening for primary prevention of cardiovascular disease in women. We focus on the most common biochemical cardiovascular risk factors, that is, glucose, insulin, triglycerides, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, (micro) albuminuria, high-sensitivity C-reactive protein (HsCRP), and hemoglobin A1c (HbA1c). The results might support the epidemiological data of the association of a history of hypertensive disorders in pregnancy and increased risk of cardiovascular disease in women in later life.[3,6-11] This is the first prerequisite step for further, prospective

research to investigate whether screening for biochemical cardiovascular risk factors is rational in women with a history of hypertensive disorders in pregnancy.

## Materials and methods

This systematic review and meta-analysis were performed according to the MOOSE (Meta-analysis of Observational Studies in Epidemiology) guidelines.

### Definitions

Gestational hypertension was defined according to the International Society for the Study of Hypertension in Pregnancy criteria as either a systolic blood pressure equal to or greater than 140mmHg or a diastolic blood pressure equal to or greater than 90 mm Hg measured at 2 occasions at least 6 hours apart in a woman who was normotensive at the start of pregnancy until week 20 of gestational age (patients).[12] Preeclampsia was defined according to the International Society for the Study of Hypertension in Pregnancy criteria: equal to or greater than 140 mm Hg or a diastolic blood pressure equal to or greater than 90 mm Hg with proteinuria greater than 0.3 g/24 h after 20 weeks' gestation.[12] Severe preeclampsia was defined as a blood pressure exceeding 160/110 mm Hg or proteinuria greater than 5 g/24 h, or both.[12] Eclampsia was defined as the presence of seizures.[12,13] Superimposed preeclampsia was defined as preexisting hypertensionwith new-onsetproteinuria greater than 0.3 g/24 h after 20 weeks' gestation.

### Sources

We used a priori eligibility criteria for studies.PubMed and EMBASE were searched from inception to February 28, 2011 (by J.C.F.K. and W.H.). For this literature search, the following terms were used (with synonyms and closely related words) as thesaurus terms and free-text words: pregnancy induced hypertension or preeclampsia or eclampsia and lipids or cholesterol or triglycerides or lipoproteins and systematic reviews or meta-analyses or cohort studies or case control studies. The full search strategies for both databases can be requested from the corresponding author. Additional eligible studies were sought by hand searching the reference lists from primary articles and by the titles with your search terms (a function in PubMed).

### Study Selection

Two reviewers (W.H. and C.J.M.G.) independently screened the title, abstract, and keywords of each reference (Fig. 1). If a reference was potentially eligible, a full-text article was scored using a scoring list conducted by the reviewers (W.H.,

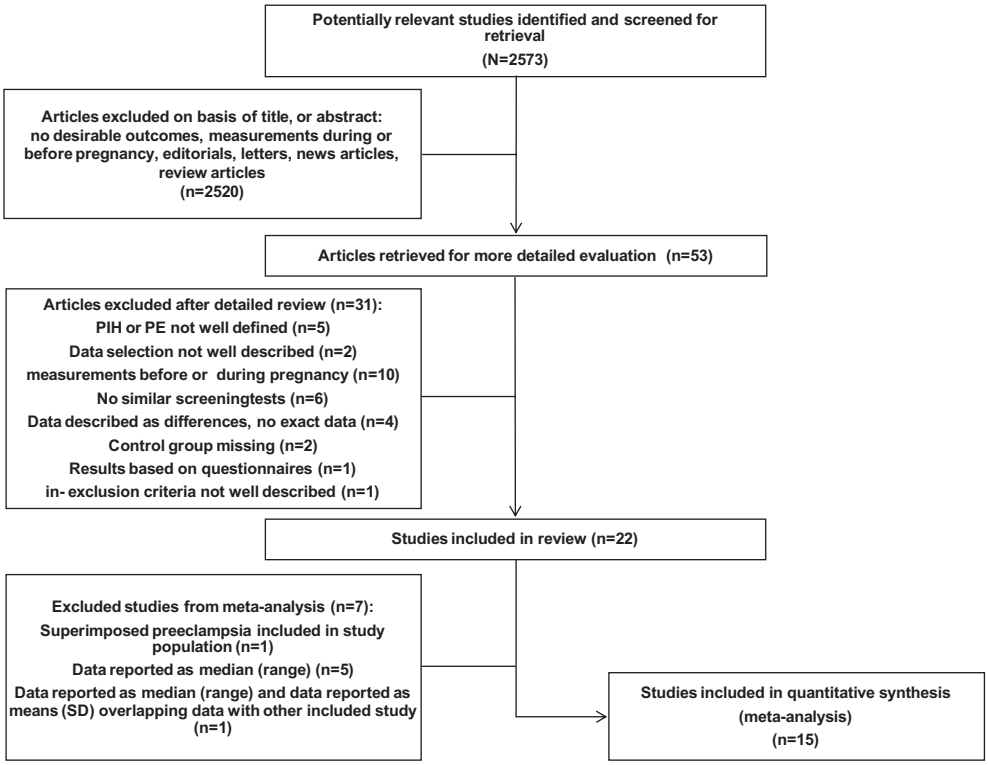


**Figure 1.** Study Selection Process

PIH = gestational hypertension, PE= preeclampsia

H.H., E.H., S.L., C.J.M.G., and B.W.M.) to assess the article's quality (ie, clear definition of gestational hypertension and (pre)eclampsia, study design, evaluated risk factors, information about blood collection and blood analysis, patient's characteristics; inclusion and exclusion criteria, information on bias, and number of inclusions in the study). During the comparison of these scoring lists by the reviewers (W.H. and C.J.M.G.), any inconsistencies were resolved by discussion with a third reviewer (B.W.M.). If 2 or more studies reported similar data of the same cohort, we included the most extensive, detailed report with regard to our study question. We included cohort and case-control studies, assessing women with a history of gestational hypertension or (pre)eclampsia of any parity or age or any severity of hypertensive disorder (patients) compared with women with a history of uncomplicated normotensive pregnancies (control subjects). We excluded studies without the previously mentioned definitions of gestational hypertension or (pre)- eclampsia or without accurate description of the study population. Studies that included superimposed preeclampsia were excluded from the meta-

analysis. Control subjects had to be women who completed pregnancies without developing gestational hypertension or (pre)eclampsia. Outcomes evaluated were 9 biochemical cardiovascular risk factors determined only after pregnancy, including glucose, insulin, triglycerides, total cholesterol, HDL cholesterol, LDL cholesterol, (micro)- albuminuria, HsCRP, and HbA1c.

**Outcomes of Interest**

Our primary outcomes were differences in biochemical cardiovascular risk factors between women with a history of hypertensive disorders in pregnancy and women with a history of normotensive pregnancies. Where possible, we divided hypertensive disorders in 2 subgroups: gestational hypertension and preeclampsia. Biochemical cardiovascular risk factors; glucose, insulin, triglycerides, total cholesterol, HDL cholesterol, LDL cholesterol, (micro) - albuminuria, HsCRP, and HbA1cVwere extracted from the eligible studies and pooled in the metaanalysis. Only studies reporting outcome values as means ± SEM or SD were included in the meta-analysis, because it is impossible to pool and analyze data reported as medians (range/interquartile range [IQR]). Studies reporting outcome values as medians (range/IQR) were described separately. Values of the outcome measures were reported in different units in the studies. According to the International System of Units (SI), standard units were converted before analyzing into mmol/L for glucose, triglycerides, total plasma cholesterol, HDL cholesterol, and LDL cholesterol; mU/mL for insulin; mg/24 h for (micro)- albumin; mg/L for HsCRP; and % for HbA1c. If values were reported as means T SEM, SEM was converted into SD before pooling.

**Data Synthesis**

We used Review Manager 5.1 (Cochrane Collaboration) for statistical analyses. Outcomes were reported as continuous data and analyzed using a mean difference. Raw numbers were used from each study, as adjustments for confounding effects varied among the different studies. Weighting of studies in the meta-analyses was calculated on the basis of the inverse variance of the study. The random-effects model was chosen, as a clinical and statistical heterogeneity was expected among the studies. We used forest plots to visualize data and assessed heterogeneity using the $I^2$ test.14 For all effect estimates, $P < 0.05$ indicated statistical significance.

## Results

### Literature Identification and Study Quality

The search detected 2573 articles. After screening the titles and abstracts, 52 articles were retrieved for detailed evaluation, of which 22 were included in this review.[15-36] Finally, 15 articles were included in the meta-analys is,[15,16,18-20,23,25-27,29-31,34-36] and 7 articles were described separately,[17,21,22,24,28,32,33] as these articles described median values. Fig. 1 shows the number of identified and included studies and in detail the reason for exclusion. The studies included in the meta-analysis were published from 1996 to 2011 and included 736 women (patients) with a history of hypertensive disease in pregnancy and 701 women (control subjects) with a history of a normotensive pregnancy. Laivuori et al[26] included 2 women with eclampsia in the preeclampsia group without distinguishing preeclampsia from eclampsia in their analysis. Therefore, we excluded this study from subgroup analysis in the meta-analysis for triglycerides, total cholesterol, HDL cholesterol, and LDL cholesterol.

### Study Characteristics

The characteristics of the included studies are shown in Table 1A. Data collection of studies in the meta-analysis was prospective design in 3 studies (20%).[19,34,35] Eleven studies (73%) were designed as cohort studies,[15,16,19,20,23,25,27,29,30,34,35] and 4 (27%) were case-control studies.[18,26,31,36] In 1 study, only women with a history of gestational hypertension were included[30]; 1 study included eclampsia,[23] and 11 studies (73%) included preeclampsia.[15,16,18,20,25,27,29,31,34-36] One study reported on preeclampsia and eclampsia,26 and 1 study reported on gestational hypertension and preeclampsia.19 In 6 studies (40%), women at index pregnancy were primigravid.[19,20,25,26,35,36] The other 9 studies (60%) reported both primigravid and multigravid women at index pregnancy.[15,16,18,23,27,29-31,34] In 5 studies (30%), the mean gestational age of the index pregnancy was not reported,[15,18,23,25,36] and in 5 studies (30%) it was not reported whether term or preterm pregnancies were analyzed.[18,23,25] Eight studies (53%) reported on both term and preterm hypertensive disorders in pregnancy,[15,16,19,20,26,31,34,35] 2 studies included only term pregnancies (13%),[29,30] and 1 study (7%) included only preterm pregnancies.[27] The follow-up periods of the included studies are described in Table 1A. Overall mean weighted followup was not calculated, because the follow-up periods in the different studies were reported as means (TSD) or medians (ranges/IQR). All women in the included studies were sober fasten at the time of biochemical cardiovascular risk factor assessment. The characteristics of the excluded studies from meta-analysis are separately described in Table 1B.

**Table 1 A.** Characteristics of Included Studies in Review and Meta-analysis

| Study, country | Study design | Exposure | Parity index pregnancy | Mean gestational age (weeks) index pregnancy | Preterm and/ or term pregnancy | Cases no. | Controls no. | Follow up period (years) | Biochemical cardiovascular risk factor(s) determined |
|---|---|---|---|---|---|---|---|---|---|
| 1. Bar 1999, *Israel*[15] | Retr. Cohort | PE | NP+ MP | Not reported | P+T | 48 | 48 | Range: 3-5 | MA |
| 2. Barden 1999, *Australia*[16] | Retr. Cohort | PE | NP+MP | Cases: 32.1 Controls: 39.9 | Cases: P+T Controls:T | 62 | 84 | Mean: 0.5 | Gluc, Trigl, TChol, HDLc, LDLc |
| 3. Chambers 2001, *UK*[18] | Retr.Case-control | PE | NP+ MP | Not reported | Not reported | 78 | 48 | Median: 3 | Gluc, Trigl, TChol, HDLc |
| 4. Forest 2005, *Canada*[19] | Prosp. Cohort | PIH+PE | NP | Cases: 38.8 Controls: 39.4 | P+T | 168 | 168 | Mean: 7.8 | Gluc, Ins, Trigl, TChol, HDLc, LDLc |
| 5. Freeman 2004, *Scotland*[20] | Retr. Cohort | PE | NP | Cases: 35.3 Controls: 39.1 | Cases: P+T Controls:T | 40 | 40 | Mean: 19.9 | HsCRP |
| 6. Hubel 2000, *Iceland*[23] | Retr. Cohort | E | NP+MP | Not reported | Not reported | 30 | 30 | Mean: 32.6 | Gluc, Ins, Trigl, TChol, HDLc, LDLc |
| 7. Innes 2005, *USA*[25] | Retr. Cohort | PE | NP | Not reported | Not reported | 13 | 13 | Mean: 3.69 | Gluc, Ins, Trigl, TChol, HDLc |
| 8. Laivuori 1996, *Finland*[26] | Retr.Case-control | PE+E | NP | Cases: 36.2 Controls: 40.1 | Cases: P+T Controls:T | 22 | 22 | Mean: 17 | Trigl, TChol, HDLc, LDLc |
| 9. Lampinen 2008, *Finland*[27] | Retr. Cohort | PE | NP+MP | Cases: 33 Controls: 40 | Cases: P Controls:T | 28 | 20 | Median: case: 5 control:6 | HbA1c |
| 10. Nisell 1999, *Sweden*[29] | Retr. Cohort | PE | NP+ MP | Cases: 37.1 Controls: 40.1 | T | 21 | 22 | Median: case: 1.54 control: 0.98 | Gluc, Trigl, TChol, HDLc, LDLc |
| 11. Paradisi 2006, *Italy*[30] | Retr. Cohort | PIH | NP+ MP | Cases: 37.9 Controls: 39.2 | T | 15 | 15 | Mean: 1.7 | Gluc, Ins, Trigl, TChol, HDLc, LDLc |
| 12. Portelinha 2010, *Portugal*[31] | Retr. Case-control | PE | NP+ MP | Cases: 35 Controls: 39 | Cases: P+T Controls: T | 90 | 60 | Mean:6 | TChol, LDLc |
| 13. Smith 2009, *Canada*[34] | Prosp. Cohort | PE | NP+ MP | Cases: 35.6 Controls: 39.2 | Cases: P+T Controls: T | 70 | 70 | Mean:1 | Gluc, Ins, Trigl, TChol, HDLc, LDLc, HsCRP |

**Table 1 A.** (Continued) Characteristics of Included Studies in Review and Meta-analysis

| Study, country | Study design | Exposure | Parity index pregnancy | Mean gestational age (weeks) index pregnancy | Preterm and/ or term pregnancy | Cases no. | Controls no. | Follow up period (years) | Biochemical cardiovascular risk factor(s) determined |
|---|---|---|---|---|---|---|---|---|---|
| 14. Spaan 2010, *The Netherlands*[36] | Retr. Case-control | PE | NP | Not reported | Not reported | 22 | 29 | Median: 23 | Gluc, Ins, Trigl, TChol, HDLc, LDLc, HsCRP |
| 15. Wolf 2004, *USA*[35] | Prosp. Cohort | PE | NP | Cases: not reported Controls: 38 | Cases: P+T Controls: T | 29 | 32 | Mean: 1.5 | Gluc, Ins |

Retr. = retrospective, Prosp.= prospective

PIH = gestational hypertension, PE= preeclampsia, E= eclampsia

P= preterm pregnancy, T= term pregnancy

NP= nulliparous, MP= multiparous

MA= microalbumin, Gluc= glucose, Ins= insuline, Trigl= triglycerides, Tchol= total cholesterol, HDLc= HDL cholesterol, LDLc= LDL cholesterol.

Wolf 2004: Lactating women were not excluded from the study

Chambers 2001 reported on first episode preeclampsia and recurrent preeclampsia. In this meta-analysis values of first episode preeclampsia were used.

Only Hubel 2000, Wolf 2004 and Nisell 1999 reported on interassay variation of blood samples, while all other studies did not.

Forest 2005: Majority delivered at term.

Hubel 2000 included only postmenopausal women. In Laivuori 1996 postmenopausal women were not excluded.

Spaan 2010: Insulin and HsCRP were reported as medians (IQR). The results of insulin and HsCRPare excluded from meta-analyses and are described in Table 2.

**Table 1 B.** Characteristics of Included Studies in Review and Excluded from Meta-analysis

| **Study,** *country* | **Study design** | **Exposure** | **Parity index pregnancy** | **Mean/ Median gestational age (weeks) index pregnancy** | **Preterm and/or term pregnancy** | **Cases no.** | **Controls no.** | **Follow up period (years)** | **Biochemical cardiovascular risk factor(s) determined** |
|---|---|---|---|---|---|---|---|---|---|
| 1.Berends 2008, *The Netherlands*[17] | Retr. Cohort | PE | NP + MP | Case: 37 (3.4) Controls: 39.9 (1.4) | Cases: P+T Controls: T | 50* | 106 | Mean: Case: 7 Control: 13.1 | Gluc, Trigl, TChol, HDLc, LDLc |
| 2. Girouard 2007, *Australia*[21] | Prosp. Cohort | PIH + PE | NP | Cases: 38.8 Controls: 39.4 | Cases: P+T Controls: Not reported | 168 | 168 | Median: 7.8 | HsCRP |
| 3. He, 1999, *Sweden*[38] | Retr.Case-control | PE | NP + MP | Not reported | Not reported | 25 | 24 | Mean: 4.5 | Trigl, TChol, HDLc, LDLc |
| 4. Hubel 2008, *Iceland*[24] | Retr. Cohort | E | NP + MP | Not reported | Not reported | 25 | 28 | Mean: Case: 32.6 Control: 32.2 | HsCRP |
| 5. Manten 2007, *The Netherlands*[28] | Retr. Cohort | PE | NP + MP | Cases: 31 Controls: 40,4 | Cases: P Controls: T | 256† | 53 | Mean: Case: 0.48 Control: 0.82 | Trigl, TChol, HDLc |
| 6. Pouta 2004, *Finland*[32] | Retr. Cohort | PIH + PE | NP | Not reported | P + T | 49 | 1369 | Mean: 6 | Gluc, Ins, Trigl, TChol, HDLc, LDLc |
| 7. Sattar 2003, *Scotland*[33] | Retr. Cohort | PE | NP | Cases: 36 (33.2-38) Controls: 40 (38-41) | Cases: P+T Controls: T | 40 | 40 | Median: 20 | Ins, Trigl, TChol, HDLc, LDLc, HbA1c |

Retr. = retrospective, Prosp.= prospective

PIH = gestational hypertension, PE= preeclampsia

P=preterm pregnancy, T= term pregnancy

NP= nulliparous, MP= multiparous

MA= microalbumin, Gluc= glucose, Ins= insuline, Trigl= triglycerides, Tchol= total cholesterol, HDLc= HDL cholesterol, LDLc= LDL cholesterol.

* 3 of 50 (6%) included women had superimposed preeclampsia.

† 56 of 256 (22%) of the included women had superimposed preeclampsia.

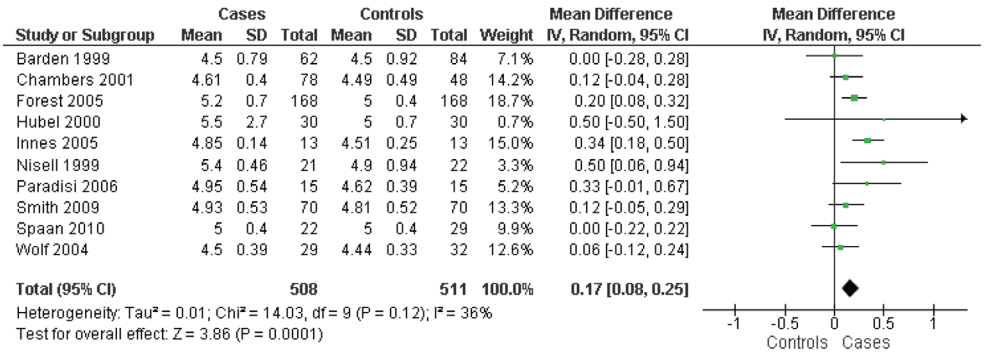


**Figure 2. Glucose**.
Cases (history of preeclampsia, eclampsia, or gestational hypertension) versus Controls (history of normotensive pregnancies).

## Biochemical Cardiovascular Risk Factors After Hypertensive Disorders in Pregnancy

*Glucose*

Ten studies fulfilled the criteria for glucose measurement after pregnancy, of which 508 patients and 511 control subjects were included.[16,18,19,23,25,29,30,34-36] Glucose levels were higher in women with a history of hypertensive disorders in pregnancy compared with women with a history of normotensive pregnancies; mean difference was 0.17 mmol/L (95% confidence interval [CI], 0.08 to 0.25; P = 0.0001) (Fig. 2). The heterogeneity observed was not significant (P = 0.12; $I^2$ = 36%). Subgroup analyses of preeclampsia (8 studies) and gestational hypertension (2 studies) resulted in similar overall results in both subgroups; however, the heterogeneity in the preeclampsia studies was moderate (P = 0.08, $I^2$ = 44% compared with the gestational hypertension group; P = 0.50, $I^2$ = 0%) (Figs. 2A, B). Two studies, Berends et al[17] and Pouta et al[32] reported on glucose in medians (IQR) after pregnancy. Berends et al[17] found a significant difference between patients (7 years after pregnancy) and control subjects (13 years after pregnancy): cases median, 4.8 mmol/L (4.4 to 5.2 mmol/L); control subjects median, 4.2 mmol/L (3.8 to 4.5 mmol/L), 7 and 13 years. This study included superimposed preeclampsia (3/50 women, 6%) (Table 2). Pouta et al[32] found no significant difference between patients and control subjects 6 years after pregnancy: cases median, 5.00 mmol/L (4.70 to 5.10 mmol/L); control subjects median, 4.90mmol/L (4.60 to 5.10mmol/L) (P = 0.25).

*Insulin*

Five studies fulfilled the criteria for insulin measurement after pregnancy.[19,23,25,30,34] Two hundred ninety-six women in both groups were analyzed, and the insulin levels were significantly higher in women who had hypertensive disorders

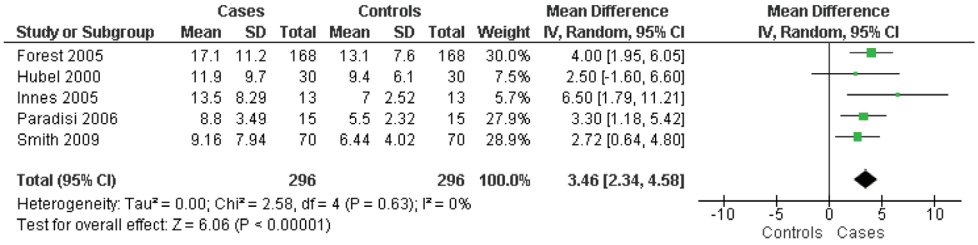


**Figure 3. Insulin**.
Cases (history of preeclampsia, eclampsia, or gestational hypertension) versus Controls (history of normotensive pregnancies).

in pregnancy compared with control subjects: mean difference, 3.46mU/mL(95%CI,2.34 to 4.85mU/mL)(PG0.00001), with a test heterogeneity of P = 0.63, $I^2$ = 0% (Fig. 3). For subanalysis according to preeclampsia, 3 studies[19,25,34] and gestational hypertension, 2 studies[19,30] resulted in similar effect estimates. In both groups, patients had higher insulin levels after pregnancy compared with control subjects (Figs. 3A, B). Three studies, Pouta et al,[32] Spaan et al,[36] and Sattar et al[33] reported on insulin in medians (IQR) after pregnancy. Pouta et al32 and Spaan et al[36] found both a significantly higher insulin levels in patients compared with control subjects at 6 and 23 years after pregnancy, respectively. Sattar et al[33] found no significant difference at 20 years after pregnancy, although there was a trend to higher insulin levels in patients compared with control subjects (results shown in Table 2).

**Table 2.** Biochemical Cardiovascular Risk Factors Determined in Excluded Studies from Meta-Analysis

| **Study,** *country* | **Glucose** | **Insulin** | **Triglycerides** | **Total Cholesterol** | **HDL Cholesterol** | **LDL Cholesterol** | **Micro al-bumin-uria** | **HsCRP** | **HbA1c** |
|---|---|---|---|---|---|---|---|---|---|
| 1.Berends 2008, *The Netherlands*[17] | **Case: 4.8† (4.4-5.2) Contr:4.2 (3.8-4.5)** | NM | Case: 1.0 (0.7-1.6) Contr: 1.0 (0.7-1.3) | Case: 4.8 (4.4-5.8) Contr: 5.4 (4.6-6.2) | Case:1.3 (1.1-1.6) Contr:1.3 (1.1-1.6) | Case: 3.0 (2.6-3.8) Contr: 3.6 (2.9-4.1) | NM | NM | NM |
| 2. Girouard 2007, *Canada*[21] | ‡ | NM | ‡ | ‡ | ‡ | ‡ | NM | **Case: 1.8† (0.7-4.9) Contr: 1.2 (0.5-3.5)** | NM |
| 3. He, 1999, *Sweden*[38] | NM | NM | CaseF: 0.91 (0.55-1.61) ContrF: 0.86 (0.41-1.67) **CaseL: 0.85˜ (0.50-1.98) ContrL: 0.64 (0.50-1.98)** | CaseF:4.63 (3.47-6.34) ContrF:4.40 (2.98-5.75) **CaseL:4.97˜ (3.20-6.09) ContrL:4.22 (2.79-6.08)** | CaseF:1.21 (0.86-0.67) ContrF:1.26 (0.75-1.73) CaseL:1.30 (0.80-.53) ContrL:1.39 (0.79-0.90) | CaseF:3.11 (2.12-4.36) ContrF:2.62 (1.82-3.94) CaseL:3.27 (2.18-4.60) ContrL:2.66 (2.01-4.97) | NM | NM | NM |
| 4. Hubel 2008, Iceland[24] | ‡ | ‡ | ‡ | ‡ | ‡ | ‡ | NM | **Case:9.0 ˜ (0.9-13.2) Contr: 2.0 (0.2-5.1)** | NM |
| 5. Manten 2007, *The Netherlands*[28] | NM | NM | **Case: 1.21˜ (0.45-8.12) Contr: 1.04 (0.44-6.78)** | **Case: 5.2 ˜ (0.9) Contr: 4.7 (0.8)** | Case: 1.37 (0.32) Contr: 1.37 (0.34) | NM | NM | NM | NM |
| 6. Pouta 2004, *Finland*[32] | Case: 5.00 (4.70-5.10) Contr: 4.90 (4.60-5.10) | **Case:7.80 ˜ (6.60-9.60) Contr: 7.30 (5.90-8.90)** | Case: 0.92 (0.73-1.20) Contr: 0.84 (0.65-1.18) | Case: 4.81 (4.36-5.27) Contr: 4.72 (4.21-5.35) | Case: 1.63 (1.36-1.89) Contr: 1.61 (1.38-1.84) | Case: 2.80 (2.40-3.20) Contr: 2.70 (2.30-3.20) | NM | NM | NM |

**Table 2.** (Continued) Biochemical Cardiovascular Risk Factors Determined in Excluded Studies from Meta-Analysis

| **Study,** *country* | **Glucose** | **Insulin** | **Triglycerides** | **Total Cholesterol** | **HDL Cholesterol** | **LDL Cholesterol** | **Micro al-bumin-uria** | **HsCRP** | **HbA1c** |
|---|---|---|---|---|---|---|---|---|---|
| 7. Sattar 2003, *Scotland*[33] | NM | Case: 8.35 (5.3-12.8) Contr: 6.4 (4.5-9.3) | Case: 1.0 (0.7-1.3) Contr: 0.9 (0.7-1.2) | Case: 5.2 (4.4-5.6) Contr: 4.7 (4.0-5.6) | Case: 1.55 (1.3-1.8) Contr: 1.45 (1.2-1.8) | Case: 2.85 (2.5-3.6) Contr: 2.81 (2.1-3.6) | NM | NM | **Case:4.7 ˜ (4.4-5.2) Contr:4.5 (4.4-4.6)** |
| 8. Spaan 2010, *The Netherlands*[36] | I | **Case: 8.3 ˜ (6.8-14.0) Contr: 6.4 (4.3-9.8)** | I | I | I | I | NM | Case: 1.5 (1.0-2.3) Contr: 1.5 (1.0-2.5) | NM |

Data are expressed as medians (range) or (IQR) or as means (SD)

NM= Not Measured

I = included in meta-analysis

* 3 of 50 included women had superimposed preeclampsia.

† Significant <.001

‡ Data reported in Forest 2005 or Hubel 2000 and included in meta-analysis.

° Determined in follicular phase (F) and Luteal phase (L) in menstrual cycle.

˜ Significant <.05

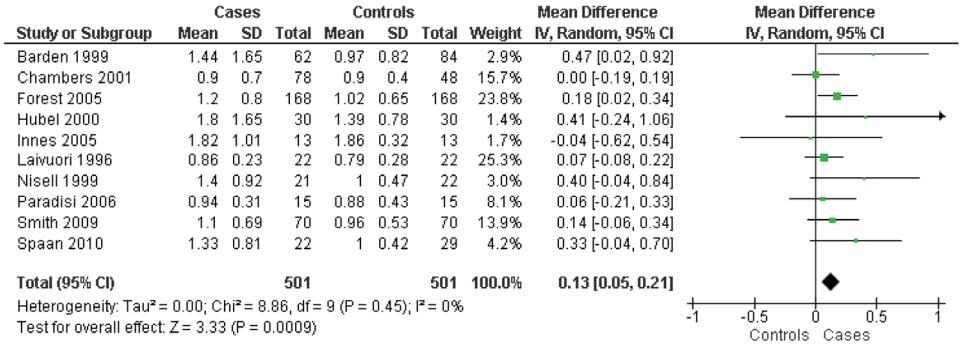


**Figure 4. Triglycerides**.
Cases (history of preeclampsia, eclampsia, or gestational hypertension) versus Controls (history of normotensive pregnancies).

*Triglycerides*

Ten studies fulfilled the criteria for triglyceride measurement after pregnancy, of which 501 patients and 501 control subjects were included.[16,18,19,23,25,26,29,30,34,36] Women with a history of hypertensive disorders in pregnancy had significantly higher triglycerides levels after pregnancy compared with the control subjects. We found a mean difference of 0.13 mmol/L (95% CI, 0.05 to 0.21 mmol/L) (Fig. 4). In the preeclampsia subgroup, we found a significant mean difference of 0.15 mmol/L (95% CI, 0.04 to 0.27 mmol/L). In the gestational hypertension subgroup, we found no significant mean difference: 0.15 mmol/L (95% CI, 0.01 to 0.30 mmol/L). In both subgroup analyses, heterogeneity was not significant (Figs. 4A, B). Five studies reported on triglycerides after pregnancy in medians (ranges or IQR) (Table 2).[17,22,28,32,33] He et al[22] (in the luteal phase of the menstrual cycle) and Manten et al[28] found significantly higher triglycerides levels in patients compared with control subjects at 4.5 years[22] and 0.48 years (for patients) and 0.82 years (for control subjects)[28] after pregnancy. On the contrary, Berends et al,[17] Pouta et al,[32] and Sattar et al[33] found no significant differences in triglycerides levels after pregnancy between patients and control subjects (results shown in Table 2).

*Total Cholesterol*

Eleven studies fulfilled the criteria for total cholesterol measurement after pregnancy, of which 591 patients and 561 control subjects were included.[16,18,19,23,25,26,29Y31,34,36] A significant elevating effect on the level of total cholesterol was found in the case group: mean difference, 0.22 mmol/L (95% CI, 0.11 to 0.33 mmol/L) ($P < 0.0001$), with a test heterogeneity of $P = 0.57$, $I^2 = 0\%$ (Fig. 5). After subanalysis, only women with a history of preeclampsia had higher total cholesterol compared with control subjects:mean difference, 0.26 mmol/L

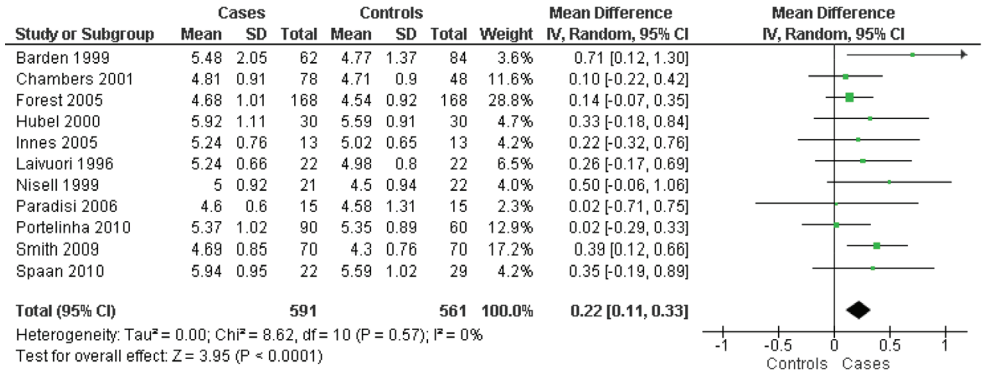


**Figure 5. Total Cholesterol**.
Cases (history of preeclampsia, eclampsia, or gestational hypertension) versus Controls (history of normotensive pregnancies).

(95% CI, 0.12 to 0.39 mmol/L).Women with a history of gestational hypertension had no significantly different levels: mean difference, 0.08 mmol/L (95% CI, 0.14 to 0.31). There was no statistical heterogeneity in both subgroups when results were pooled across the different studies (Figs. 5A, B). Five studies reported on total cholesterol after pregnancy in medians (ranges or IQR) (Table 2). 17,22,28,32,33 Two studies found significantly higher levels of total cholesterol in patients compared with control subjects, 4.5 years[22] and 0.48 years (for patients) and 0.82 years (for control subjects) after pregnancy.[28]

*HDL Cholesterol*

Ten studies fulfilled the criteria for HDL cholesterol measurement after pregnancy, of which 501 patients and 501 control subjects were included.[16,18,19,23,25,26,29,30,34,36] A significantly reduced mean difference was found in patients compared with control subjects: 0.12 mmol/L (95% CI, 0.18 to 0.04). However, a significant heterogeneity was found across the 9 studies: P = 0.03, $I^2$ = 51% (Fig. 6). In both preeclampsia and gestational hypertension subgroup analysis, we found a significantly reduced mean difference in the patients compared with control subjects: 0.08 (95% CI 0.14 to 0.02; P = 0.008) for preeclampsia subgroup and 0.23 (95% CI, 0.43 to 0.02; P = 0.03) for gestational hypertension subgroup. No statistical heterogeneity was found in the preeclampsia subgroup analysis (Fig. 6A). However, the heterogeneity was significant in the gestational hypertension subgroup analysis: P = 0.03, $I^2$ = 77% (Fig. 6B). Five studies reported on HDL cholesterol after pregnancy in medians (ranges or IQR).[17,22,28,32,33] These 5 studies did not find significant differences between patients and control subjects (Table 2).

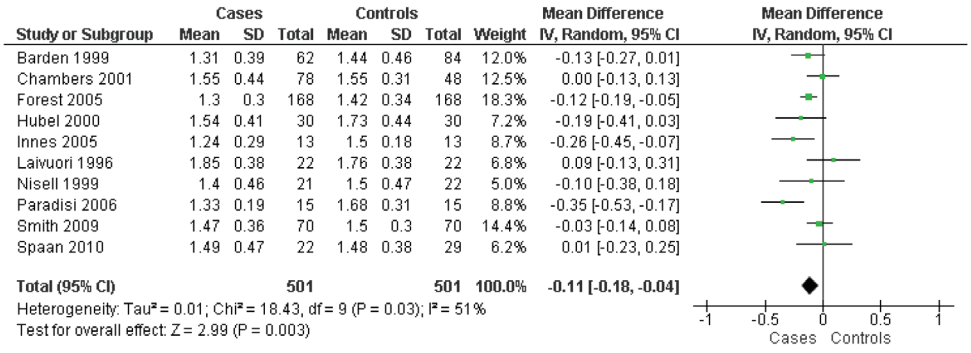


**Figure 6. HDL Cholesterol.**
Cases (history of preeclampsia, eclampsia, or gestational hypertension) versus Controls (history of normotensive pregnancies).

*LDL Cholesterol*

Nine studies fulfilled the criteria for LDL cholesterol measurement after pregnancy, of which 500 patients and 500 control subjects were included.[16,19,23,26,29-31,34,36] Patients had a significantly higher level of LDL cholesterol compared with control subjects: mean difference, 0.21 mmol/L (95% CI, 0.10Y0.32 mmol/L) (Fig. 7). In the subanalysis of preeclampsia, we found a significantly higher LDL cholesterol level: mean difference, 0.25 mmol/L (95% CI, 0.12 to 0.39; P = 0.0002), whereas in the gestational hypertension subgroup, we found no significant difference: mean difference, 0.12 mmol/L (95% CI, 0.06 to 0.30; P = 0.20). No significant heterogeneity was found in the subanalyses for LDL cholesterol (Figs. 7A, B). Four studies reported on LDL cholesterol after pregnancy in medians (ranges or IQR).[17,22,32,33] These 4 studies did not find a significant difference between patients and control subjects (Table 2).

*Microalbuminuria*

Only 1 study in which 48 patients and 44 control subjects were included reported on microalbuminuria after a pregnancy complicated by preeclampsia.[15] In this study, preeclampsia was associated with elevated urinary albumin excretion rate 2 to 4 months after delivery and 3 to 5 years after delivery. Bar et al[15] found albumin excretion in 24 hours after 3 to 5 years a significantly higher value in patients: mean,[23.5] (SD, 26.8) mg/24 h compared with control subjects: mean, 6.7 (SD 2.8) mg/24 h. No studies were found assessing albumin secretion after a history of gestational hypertension.

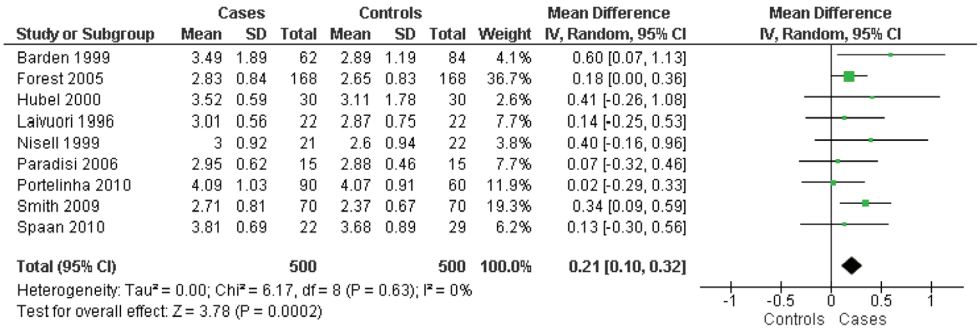


**Figure 7. LDL Cholesterol.**
Cases (history of preeclampsia, eclampsia, or gestational hypertension) versus Controls (history of normotensive pregnancies).

*High-Sensitivity C-Reactive Protein*

Two studies fulfilled the criteria for HsCRP measurement after pregnancy, of which 110 patients and
110 control subjects were included.[20,34] Both studies included women with a history of preeclampsia. Freeman et al[20] included only primigravid women with a mean follow-up of 19.9 years, whereas Smith et al included both primigravid and multigravid women at the time of index pregnancy with a mean follow-up of 1 year. No significant difference was found between patients and control subjects. The test heterogeneity for HsCRP was not significant (P = 0.28, $I^2$ = 15%). Three studies reported on HsCRP after pregnancy in medians (range or IQR).[21,24,36] Two studies found significantly higher HsCRP levels after pregnancy in patients compared with control subjects, whereas Spaan et al[36] did not confirm these findings. The results are summarized in Table 2.

*Hemoglobin A1c*

Lampinen et al[27] reported on HbA1c levels 5 to 6 years after preterm pregnancies complicated by preeclampsia in mean (SD) compared with term normotensive pregnancies. No significant differences were found between patients and control subjects: mean difference, 0.10% (95% CI, 0.07 to 0.27). However, Sattar et al[33] reported on HbA1c levels in medians (IQR) 20 years after pregnancy and found a significant difference between women with a history of preeclampsia and women with a history of a normotensive pregnancy (Tables 1B and 2).

## Discussion

### Main Findings

We found that 7 of the 9 biochemical cardiovascular risk factors were higher in women with a history of hypertensive disorders in pregnancy compared with women with a history of normotensive pregnancies. These biochemical cardiovascular risk factors are glucose, insulin, triglycerides, total cholesterol, HDL and LDL cholesterol, and microalbumin. We found a similar association of these risk factors in subgroup analyses of women with a history of preeclampsia. Women with a history of gestational hypertension had higher glucose and insulin levels and lower HDL cholesterol levels after their pregnancy compared with women with a history of normotensive pregnancies.

### Biochemical Cardiovascular Risk Factors

Increased glucose levels, even within the reference range, are predictive for an increased risk of type 2 diabetes and cardiovascular disease.[37] Women with a history of preeclampsia are at increased risk of developing type 2 diabetes; diabetes is a major independent risk factor for cardiovascular disease.[38] We found higher fasting glucose levels in women with a history of gestational hypertension and preeclampsia in this meta-analysis compared with women with a history of normotensive pregnancies. We did not study the interaction between bodymass index and glucose levels, as adjustments for confounding effects varied among the different studies. However, the increase in cardiovascular risk attributed to hyperglycemia is independent of overweight/obesity and dyslipidemia.[38] Hemoglobin A1c, glycated hemoglobin, correlates with mean blood glucose over the previous 8 to 12 weeks. Only 2 studies were included in this review, evaluating HbA1c levels after previous preeclampsia. Sattar et al[33] found a significant difference between patients and control subjects 20 years after pregnancy, whereas Lampinen et al[27] did not at 5 to 6 years after pregnancy. Increased levels of insulin are an indirect marker of insulin resistance.[39] Insulin resistance is closely associated with metabolic syndrome and leads to vascular endothelial dysfunction, an abnormal lipid profile, hypertension, and vascular inflammation, all of which promote the development of cardiovascular disease.[40] In literature, metabolic syndrome has been suggested to play an important role in the pathophysiology of gestational hypertension and preeclampsia and may be the underlying mechanism linking hypertensive disease in pregnancy and cardiovascular disease in later life.[21] In this meta-analysis, we found higher fasting insulin levels in women with a history of gestational hypertension and preeclampsia compared with women with uncomplicated pregnancies. Suboptimal levels of lipids represent a major risk factor for cardiovascular disease. A positive relationship exists between serum

cholesterol levels and the development of first or subsequent coronary heart disease; the higher the level, the greater the risk.[41] Furthermore, 3 prospective studies with long-term follow-up described the detection of elevated serum cholesterol in early adulthood and the subsequent effect of an increased incidence of coronary heart disease inmiddle age. This is of importance for the higher lipid levels (and lower HDL cholesterol levels) found in this review in mainly young women with previous gestational hypertension or preeclampsia. Bar et al[15] reported on microalbuminuria after pregnancies complicated by preeclampsia. Preeclampsia was associated with elevated urinary albumin excretion 2 to 4 months after delivery and 3 to 5 years after delivery. Microalbuminuria is a risk factor for organ damage, such as left ventricular hypertrophy, myocardial infarction, stroke, peripheral vascular disease, and retinopathy, independent of blood pressure.[42-44] The risk of an adverse cardiovascular event increases progressively with increasing absolute levels of microalbuminuria.[45] Low-grade albuminuria carries a 3-fold increased risk of cardiovascular disease (in women with the sex-specific median of 7.5 g/mg),[46] and even albuminuria increasing from 5 to 10 mg/L was associated with a 29% increased risk of cardiovascular death during a 3-year follow-up (hazard ratio, 1.29 [95% CI, 1.18 to 1.10]).[47] Elevated serum CRP, measured by high-sensitivity assay (HsCRP), provides a sensitive biomarker of chronic systemic inflammation.[48] C-reactive protein is an independent predictor of future cardiovascular events,[49,52] and evidence also implicates CRP, and thus inflammation, as a useful clinical measure for identifying risk of developing the insulin resistance syndrome, particularly in women.[50,51] In our meta-analysis, we found no significant difference between patients and control subjects after a median follow-up of 19.9 years in both patients and control subjects; however, only 1 study was included in the meta-analysis. The 2 other studies included in this review, reporting on median values of HsCRP,[21,24] found a significant difference between patients and control subjects after 32.6 and 7.8 years, respectively.

**Strengths and Limitations**

This is the first report that systematically reviewed and meta-analyzed various biochemical cardiovascular risk factors for cardiovascular disease after pregnancies complicated by hypertensive disorders. The study selection was carried out without language restrictions, and attention was paid to quality assessment by using scoring lists and evaluation by multiple investigators, preventing selection and publication bias. The clinical consequences of the results of this review, however, are still under development. We found 7 cardiovascular risk factors to appear higher in women with a history of hypertensive disorders in pregnancy compared with normotensive women.

This systematic review has a few limitations. First, a differentiation between gestational hypertension and preeclampsia was limited by the lack of studies, concerning the long-term follow-up of gestational hypertension and risk factor screening for cardiovascular disease. Until now, most investigators paid attention to the long-term effects of preeclampsia, especially for severe preterm preeclampsia, rather than for mild term preeclampsia or gestational hypertension. Severe preterm preeclampsia may have another underlying pathophysiology and different longterm effects compared with hypertensive disorders at term. Therefore, it is important to know whether cardiovascular risk factors are increased only after (severe) preterm preeclampsia or even after (mild) term preeclampsia. Subanalysis of these groups would have been optimal, especially because mild term preeclampsia is much more prevalent than severe preterm preeclampsia. Unfortunately, as the included studies did not distinguish between severe preterm preeclampsia and mild term hypertensive disorders, it was impossible to perform a separate analysis. In 4 retrospective studies, the gestational age of included women was not described.[15,18,23,25]

Second, population variability in the included studies exists. Most women were premenopausal at the time of inclusion, except for the studies of Hubel et al[23], Spaan et al,[36] Freeman et al,[20] and Laivuori et al.[26] The follow-up period after index pregnancy in the study of Laivuori et al was at least 16.9 years and was 23 years in Spaan et al, and Hubel et al included only postmenopausalwomen after eclampsia. It is well known that postmenopausal women have a higher risk of cardiovascular disease and probably higher biochemical cardiovascular risk factors compared with premenopausal women, causing a confounding effect on risk factor screening. However, excluding these 3 studies from the combined group analysis had no consequences for the significant outcome of glucose, insulin, total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides (results not reported). A third limitation is the inadequate reporting in the various studies on the test techniques and intervals between blood sampling and blood analysis. Laboratories use different intra-assay and interassay variations on their test results; only 3 studies[23,29,35] described their intra-assay and interassay variations, and overall medication use, that is, lipid-lowering therapy, was not well described. Furthermore, 3 studies[25,30,36] chose a certain time point in the menstrual cycles of included women to determine the risk factors, as previous studies have shown that endothelial function may vary according to the phase of menstrual cycle. As a consequence, interpretations after combining data from different studies must be carried out carefully.

The impact of adjustment for possible confounding factors on cardiovascular disease such as body mass index, smoking status, and family history could not be

investigated because the present review was based on unadjusted data reported in the published literature rather than on individual participant data.
Finally, limitations of the meta-analyses merit careful consideration. The comparability of the 9 biochemical cardiovascular risk factor distributions between the different studies could not be accurately assessed, as a few studies did not report appropriate measures of distribution, that is, medians (ranges or IQR). These studies reporting medians (ranges/IQR) were discussed separately and excluded from the metaanalysis, causing bias. However, the results of these excluded studies mainly supported the findings in the meta-analysis.

**Hypertensive Pregnancy Disorders and the Association With Cardiovascular Disease, Implications and Future Research**

Women with preeclampsia have a 2-fold higher risk of death from cardiovascular disease later in life and even a higher risk in combination with certain circumstances, that is, preterm delivery, intrauterine growth restriction, or recurrent preeclampsia.[7,52,53] It still remains unclear whether preeclampsia and cardiovascular disease share the same etiology, or cardiovascular disease is a result of preeclampsia, or preexistent subclinical cardiovascular disease is unmasked in pregnancy by developing preeclampsia. However, in all cases mentioned, pregnancy can be seen as a stress test for cardiovascular disease in women. The main question rises: who, when, and how frequently after pregnancy should doctors screen for biochemical cardiovascular risk factors in apparently healthy postpartum women with a history of hypertensive pregnancy disorders to prevent cardiovascular disease? Nowadays, these questions are actively debated, and still the answers are not clear.
In 2011, the American Heart Association guidelines included preeclampsia, as first, as a risk factor for cardiovascular disease and recommended referral after preeclampsia by the obstetrician to a primary care physician or cardiologist for cardiovascular risk factor screening.[54] Unfortunately, further detailed recommendations were lacking in these guidelines, for example, how women with a history of preeclampsia and normal values of cardiovascular risk factors should bemanaged. Evidence concerning screening, treatment, and cost-benefit after hypertensive pregnancy disorders is still lacking in literature. According to the American Heart Association guidelines, individual risk factor screening and subsequent 10-year cardiovascular risk prediction may be used to determine whether women need blood pressure medication, lipid-lowering therapy, omega-3-fatty acids, or aspirin treatment to prevent cardiovascular disease.[54] However, age is an important variable in the Framingham Risk prediction algorithm,[55] and as a consequence, 10-year individual cardiovascular disease risk is likely to be low in the relatively young women immediately after pregnancy. This may

result in undertreatment in this specific group of women, and it may be a missed opportunity.

Unfortunately, our findings in this meta-analysis do not answer the questions, concerning who, when, and how frequently doctors should screen for cardiovascular risk factors, as the absolute levels of the assessed risk factors are not above a threshold above which the international guidelines recommend pharmacological intervention or diet and lifestyle modification. Furthermore, individual cardiovascular risk depends not only on unfavorable biochemical cardiovascular risk factors, but mostly on a combination of several nonmodifiable (ie, age, family history, and ethnicity) and modifiable (ie, [preexisting] hypertension, diabetes mellitus, renal disease, obesity, dyslipidemia, metabolic syndrome, microalbuminuria) risk factors, which were not all analyzed in this meta-analysis. However, results of our meta-analysis will provide awareness of women and (general) physicians of the elevated cardiovascular risk after hypertensive pregnancy disorders, and together with the existing epidemiological evidence, it justifies to accomplish a randomized controlled trial to compare lifestyle modification for women with a history of hypertensive pregnancy disorders, including smoking cessation, weight reduction in case of overweight or obesity, and an overall healthy lifestyle advice (healthy diet, physical activity) versus care as usual. This randomized controlled trial is needed and will gain insight in the question if screening and treating women after a pregnancy complicated by hypertensive disorders are effective in reduction of biochemical cardiovascular risk factor levels, individual cardiovascular risk, and if blood pressure, smoking, and body weight will be positively influenced. Only after identifying rational tools for women to reduce their cardiovascular risk, implementation will follow in the national guidelines and adequate treatment and prevention might occur. After completing this educational activity, physicians should be better able to evaluate and interpret the evidence regarding biochemical cardiovascular risk factor assessment after pregnancy and counsel women with a history of hypertensive pregnancy disorders regarding the effectiveness of cardiovascular risk factor assessment in the primary prevention of cardiovascular disease.

## Conclusions

Women with a history of hypertensive disorders in pregnancy have higher levels of glucose, insulin, triglycerides, total cholesterol, LDL cholesterol, and microalbumin and lower levels of HDL cholesterol compared with women with a history of a normotensive pregnancy. These biochemical cardiovascular risk factors are potential predictors for cardiovascular disease later in life and may identify high-risk women early enough to benefit from intervention.

## Reference List

(1) ACOG Technical Bulletin. Hypertension in pregnancy. Number 219 - January 1996 (replaces no. 91, February 1986). Committee on Technical Bulletins of the American College of Obstetricians and Gynecologists. Int J Gynaecol Obstet. 1996;53: 175-183.
(2) Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. Am J Obstet Gynecol. 2000;183:S1-S22.
(3) Sattar N, Greer IA. Pregnancy complications and maternal cardiovascular risk: opportunities for intervention and screening? BMJ. 2002;325:157-160.
(4) McDonald SD, Malinowski A, Zhou Q, et al. Cardiovascular sequelae of preeclampsia/eclampsia: a systematic review and meta-analyses. Am Heart J. 2008;156:918-930.
(5) Burell G, Granlund B. Women's hearts need special treatment. Int J Behav Med. 2002;9:228-242.
(6) Haukkamaa L, Salminen M, Laivuori H, et al. Risk for subsequent coronary artery disease after preeclampsia. Am J Cardiol. 2004;93:805-808.
(7) Irgens HU, Reisaeter L, Irgens LM, et al. Long term mortality of mothers and fathers after pre-eclampsia: population based cohort study. BMJ. 2001;323:1213-1217.
(8) Jonsdottir LS, Arngrimsson R, Geirsson RT, et al. Death rates from ischemic heart disease in women with a history of hypertension in pregnancy. Acta Obstet Gynecol Scand. 1995;74:772-776.
(9) Ramsay JE, StewartF, Greer IA, et al.Microvasculardysfunction: a link between pre-eclampsia and maternal coronary heart disease. BJOG. 2003;110:1029-1031.
(10) Smith GC, Pell JP, Walsh D. Pregnancy complications and maternal risk of ischaemic heart disease: a retrospective cohort study of 129,290 births. Lancet. 2001;357:2002-2006.
(11) Wilson BJ, Watson MS, Prescott GJ, et al. Hypertensive diseases of pregnancy and risk of hypertension and stroke in later life: results from cohort study. BMJ. 2003;326:845.
(12) Brown MA, Lindheimer MD, De SM, et al. The classification and diagnosis of the hypertensive disorders of pregnancy: statement from the International Society for the Study of Hypertension in Pregnancy (ISSHP). Hypertens Pregnancy. 2001;20: IXYXIV.
(13) Sibai BM. Diagnosis, prevention, and management of eclampsia. Obstet Gynecol. 2005;105:402-410.
(14) Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ. 2003;327:557-560.
(15) Bar J, Kaplan B, Wittenberg C, et al. Microalbuminuria after pregnancy complicated by pre-eclampsia. Nephrol Dial Transplant. 1999;14:1129-1132.
(16) Barden AE, Beilin LJ, Ritchie J, et al. Does a predisposition to the metabolic syndrome sensitize women to develop preeclampsia? J Hypertens. 1999;17:1307-1315.
(17) Berends AL, de Groot CJ, Sijbrands EJ, et al. Shared constitutional risks for maternal vascular-related pregnancy complications and future cardiovascular disease. Hypertension. 2008;51:1034-1041.
(18) Chambers JC, Fusi L, Malik IS, et al. Association of maternal endothelial dysfunction with preeclampsia. JAMA. 2001;285: 1607-1612.

(19) Forest JC, Girouard J, Masse J, et al. Early occurrence of metabolic syndrome after hypertension in pregnancy. Obstet Gynecol. 2005;105:1373-1380.
(20) Freeman DJ, McManus F, Brown EA, et al. Short- and longterm changes in plasma inflammatory markers associated with preeclampsia. Hypertension. 2004;44:708-714.
(21) Girouard J, Giguere Y, Moutquin JM, et al. Previous hypertensive disease of pregnancy is associated with alterations of markers of insulin resistance. Hypertension. 2007;49:1056-1062.
(22) He S, Silveira A, Hamsten A, et al. Haemostatic, endothelial and lipoprotein parameters and blood pressure levels in women with a history of preeclampsia. Thromb Haemost. 1999;81:538-542.
(23) Hubel CA, Snaedal S, Ness RB, et al. Dyslipoproteinaemia in postmenopausal women with a history of eclampsia. BJOG. 2000;107:776-784.
(24) Hubel CA, Powers RW, Snaedal S, et al. C-reactive protein is elevated 30 years after eclamptic pregnancy. Hypertension. 2008;51:1499-1505.
(25) Innes KE, Weitzel L, Laudenslager M. Altered metabolic profiles among older mothers with a history of preeclampsia. Gynecol Obstet Invest. 2005;59:192-201.
(26) Laivuori H, Tikkanen MJ, Ylikorkala O. Hyperinsulinemia 17 years after preeclamptic first pregnancy. J Clin Endocrinol Metab. 1996;81:2908-2911.
(27) Lampinen KH, Ronnback M, Groop PH, et al. A relationship between insulin sensitivity and vasodilation in women with a history of preeclamptic pregnancy. Hypertension. 2008;52:394-401.
(28) Manten GT, Sikkema MJ, Voorbij HA, et al. Risk factors for cardiovascular disease in women with a history of pregnancy complicated by preeclampsia or intrauterine growth restriction. Hypertens Pregnancy. 2007;26:39-50.
(29) Nisell H, Erikssen C, Persson B, et al. Is carbohydrate metabolism altered among women who have undergone a preeclamptic pregnancy? Gynecol Obstet Invest. 1999;48:241-246.
(30) Paradisi G, Biaggi A, Savone R, et al. Cardiovascular risk factors in healthy women with previous gestational hypertension. J Clin Endocrinol Metab. 2006;91:1233-1238.
(31) Portelinha A, Belo L, Cerdeira AS, et al. Lipid levels including oxidized LDL in women with history of preeclampsia. Hypertens Pregnancy. 2010;29:93-100.
(32) Pouta A, Hartikainen AL, Sovio U, et al. Manifestations of metabolic syndrome after hypertensive pregnancy. Hypertension. 2004;43:825-831.
(33) Sattar N, Ramsay J, Crawford L, et al. Classic and novel risk factor parameters in women with a history of preeclampsia. Hypertension. 2003;42:39-42.
(34) Smith GN, Walker MC, Liu A, et al. A history of preeclampsia identifies women who have underlying cardiovascular risk factors. Am J Obstet Gynecol. 2009;200:58.
(35) Wolf M, Hubel CA, Lam C, et al. Preeclampsia and future cardiovascular disease: potential role of altered angiogenesis and insulin resistance. J Clin Endocrinol Metab. 2004;89: 6239-6243.
(36) Spaan JJ, Houben AJHM, Musella A, et al. Insulin resistance relates to microvascular reactivity 23 years after preeclampsia. Microvasc Res. 2010;80:417-421.
(37) Libby G, Murphy DJ, McEwan NF, et al. Pre-eclampsia and the later development of type 2 diabetes in mothers and their children: an intergenerational study from the Walker cohort.Diabetologia. 2007;50:523-530.

(38) Third Report of the National Cholesterol Education Program (NCEP) expert panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation. 2002;106:3143-3421.
(39) Sarwar N, Sattar N, Gudnason V, et al. Circulating concentrations of insulin markers and coronary heart disease: a quantitative review of 19 Western prospective studies. Eur Heart J. 2007;28:2491-2497.
(40) Defronzo RA, Ferrannini E. Insulin resistance. A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. Diabetes Care. 1991;14:173-194.
(41) Stamler J, Wentworth D, Neaton JD. Is relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? Findings in 356,222 primary screenees of the Multiple Risk Factor Intervention Trial (MRFIT). JAMA. 1986;256:2823-2828.
(42) Cerasola G, Cottone S, Mule G, et al. Microalbuminuria, renal dysfunction and cardiovascular complication in essential hypertension. J Hypertens. 1996;14:915-920.
(43) Parving HH. Microalbuminuria in essential hypertension and diabetes mellitus. J Hypertens Suppl. 1996;14:S89-S93.
(44) Pontremoli R. Microalbuminuria in essential hypertensionVits relation to cardiovascular risk factors. Nephrol Dial Transplant. 1996;11:2113-2115.
(45) Gerstein HC, Mann JF, Yi Q, et al. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. JAMA. 2001;286:421-426.
(46) Arnlov J, Evans JC, Meigs JB, et al. Low-grade albuminuria and incidence of cardiovascular disease events in nonhypertensive and nondiabetic individuals: the Framingham Heart Study. Circulation. 2005;112:969-975.
(47) Hillege HL, Fidler V, Diercks GF, et al. Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in general population. Circulation. 2002;106:1777-1782.
(48) Ridker PM, Hennekens CH, Buring JE, et al. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. N Engl J Med. 2000;342: 836-843.
(49) Ridker PM. C-reactive protein and the prediction of cardiovascular events among those at intermediate risk: moving an inflammatory hypothesis toward consensus. J Am Coll Cardiol. 2007;49:2129-2138.
(50) Meng YX, Ford ES, Li C, et al. Association of C-reactive protein with surrogate measures of insulin resistance among nondiabetic US from National Health and Nutrition Examination Survey 1999-2002. Clin Chem. 2007;53:2152-2159.
(51) Yeh ET. High-sensitivity C-reactive protein as a risk assessment tool for cardiovascular disease. Clin Cardiol. 2005; 28:408-412.
(52) Chesley SC, Annitto JE, Cosgrove RA. The remote prognosis of eclamptic women. Sixth periodic report. Am J Obstet Gynecol. 1976;124:446-459.
(53) Funai EF, Paltiel OB, Malaspina D, et al. Risk factors for preeclampsia in nulliparous and parous women: the Jerusalem perinatal study. Paediatr Perinat Epidemiol. 2005;19:59-68.
(54) Mosca L, Benjamin EJ, Berra K, et al. Effectiveness-based guidelines for the prevention of cardiovascular disease in womenV2011 update: a guideline from the American Heart Association. J Am Coll Cardiol. 2011;57:1404-1423.
(55) D'Agostino RB Sr, Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation. 2008;117:743-753.

## Addendum: Subgroup Analyses

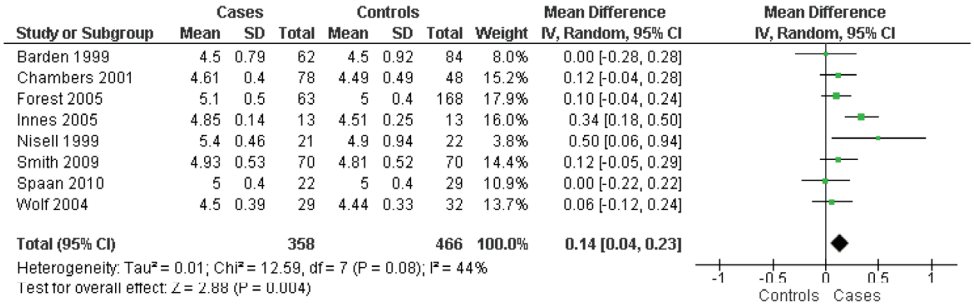


**Figure 2A.** Glucose Preeclampsia Subgroup.

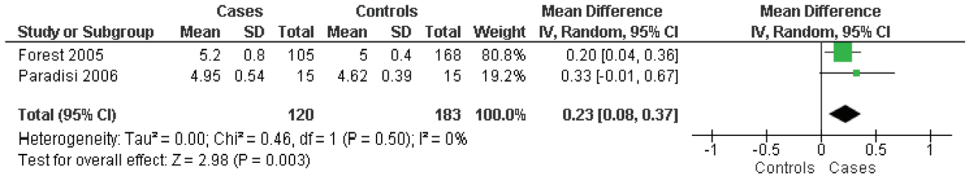


**Figure 2B.** Glucose Gestational Hypertension Subgroup.

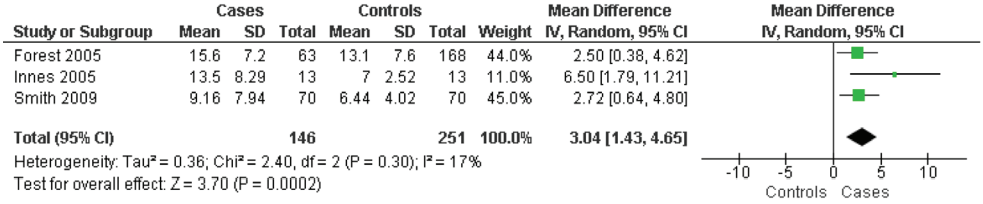


**Figure 3A.** Insulin Preeclampsia Subgroup.

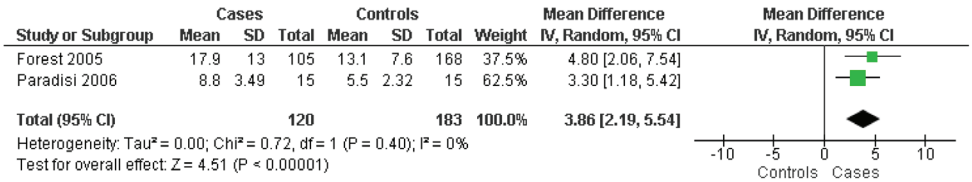


**Figure 3B.** Insulin Gestational Hypertension Subgroup.

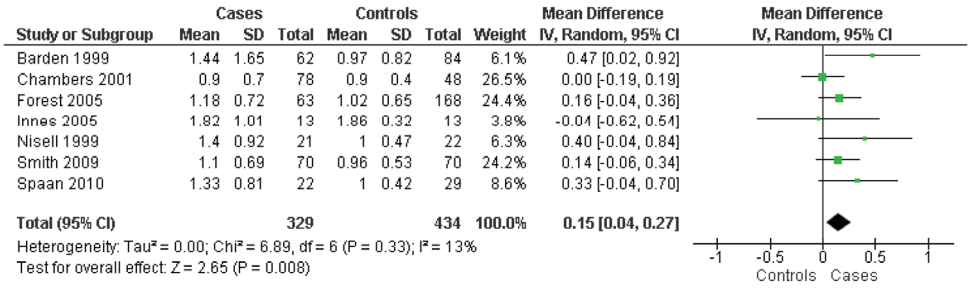


**Figure 4A.** Triglycerides Preeclampsia Subgroup.

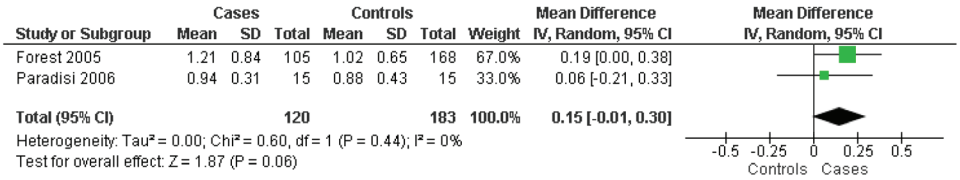


**Figure 4B.** Triglycerides Gestational Hypertension Subgroup

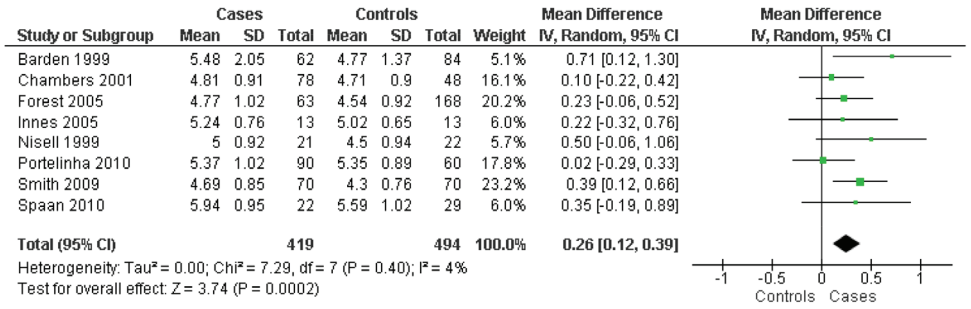


**Figure 5A.** Total Cholesterol Preeclampsia Subgroup

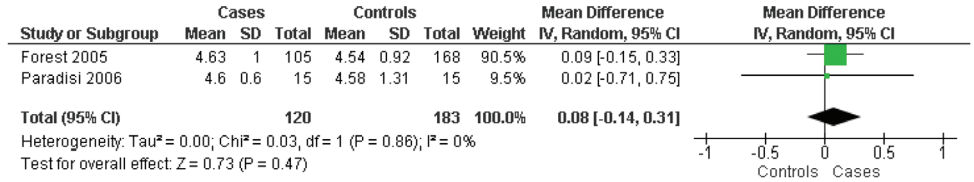


**Figure 5B.** Total Cholesterol Gestational Hypertension Subgroup

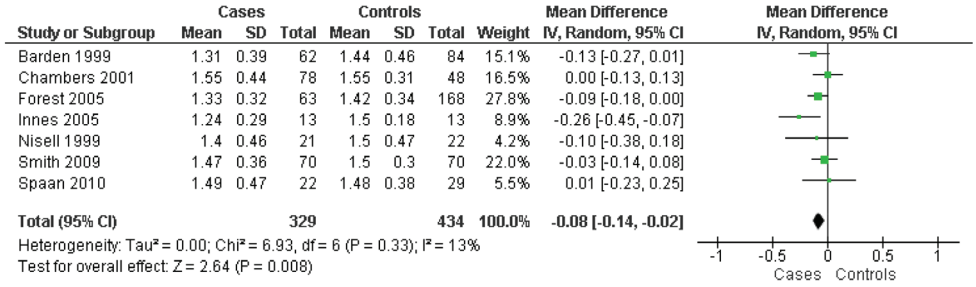


**Figure 6A.** HDL Cholesterol Preeclampsia Subgroup

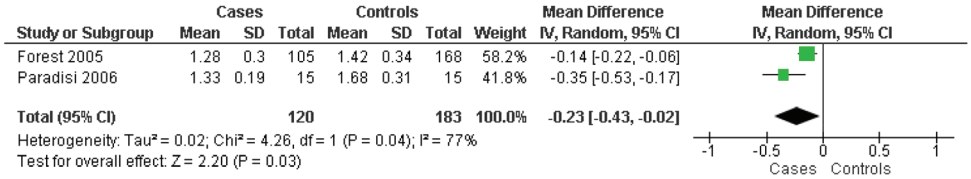


**Figure 6B.** HDL Cholesterol Gestational Hypertension Subgroup

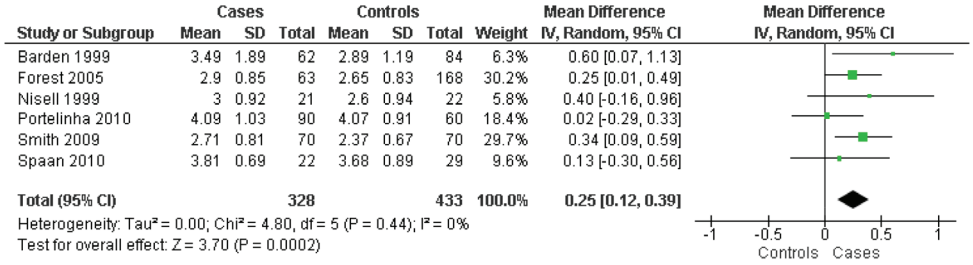


**Figure 7A.** LDL Cholesterol Preeclampsia Subgroup

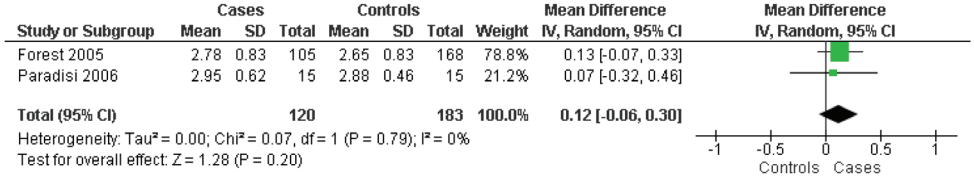


**Figure 7B.** LDL Cholesterol Gestational Hypertension Subgroup

# *Chapter 4*

## Systematic review and meta-analysis on non-classic cardiovascular biomarkers after hypertensive pregnancy disorders

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*Am J Obstet Gynecol 2014 Mar 14*

## Abstract

**Objective:** The aim of this study is to investigate which non-classic cardiovascular biomarkers are associated with persistent endothelial dysfunction after pregnancy in women with a history of hypertensive pregnancy disorders compared to women with uncomplicated pregnancies.

**Design:** Systematic review and meta-analysis of observational studies.

**Data Sources:** A search was performed in PubMed, Embase, Cochrane and Cinahl including articles from inception to 27 February 2013.

**Inclusion Criteria:** Included were cohort studies and case-control studies. Cases were women with a history of hypertension in pregnancy, control subjects were women with a history of uncomplicated pregnancies.

**Studies Reviewed:** Of the 3136 found, 21 studies on 16 non-classic cardiovascular biomarkers are described in this review; 12 studies on 5 biomarkers were included in the meta-analysis.

**Results:** Women with a history of hypertensive pregnancy disorders had a higher homocysteine level compared to women with a history of uncomplicated pregnancies (5 studies; pooled mean difference 0.77ng/ml; 95% confidence interval 0.27 to 1.26; p <0.01). For the other non-classic cardiovascular biomarkers including markers in areas of inflammation, thrombosis and angiogenesis, we found trends towards higher levels in women with a history of hypertensive pregnancy disorders.

**Conclusion:** This review and meta-analysis showed that women with a history of hypertensive pregnancy disorders have higher homocysteine levels compared to women with a history of uncomplicated pregnancies. Biomarkers in areas of inflammation, thrombosis and angiogenesis were increased in women with a history of hypertensive pregnancy disorders, albeit non-significant. These data suggest persistent endothelial alteration after pregnancies complicated by hypertensive disorders.

## Introduction

Cardiovascular disease is the leading cause of death in women in the western world[1]. Cardiovascular disease manifests itself differently between men and women; diagnostic tools in women are less sensitive and specific. Therefore, it is of additional value to identify specific risk factors for cardiovascular disease in women[2-5]. For women, preeclampsia has been suggested as a specific risk factor for cardiovascular disease later in life[6].



Increasing evidence suggests the association of hypertensive pregnancy disorders and increased risk of cardiovascular disease later in life[7]. Therefore hypertensive disorders in pregnancy are hypothesized to act as a "stress test" for cardiovascular disease later in life[9]; women who fail this 'stress test' by developing hypertensive pregnancy disorders have an increased cardiovascular risk which will become apparent during pregnancy. Both disorders, hypertensive pregnancy disorders and cardiovascular disease later in life, share a common pathophysiologic pathway[8] of endothelial dysfunction.

A review on classic cardiovascular biomarkers showed higher levels of glucose, insulin, triglycerides, total cholesterol, LDL cholesterol and micro albumin and lower levels of HDL cholesterol in women with a history of hypertensive pregnancy disorders compared to women with a history of uncomplicated pregnancies[10]. These biochemical cardiovascular risk markers are predictors for cardiovascular disease later in life and might identify high risk young women early enough to benefit from screening and intervention.

In addition to classic cardiovascular biomarkers, biomarkers used nowadays in cardiovascular risk assessment, there is a wide variety of non-classic cardiovascular biomarkers associated with endothelial dysfunction which might even more strongly associated with future risk of cardiovascular disease and which might give options for preventive interventions[11-13].

In this systematic review and meta-analysis we focus on 16 non-classic cardiovascular biomarkers associated with persistent endothelial dysfunction, including inflammation, (intercellular adhesion molecule (ICAM), vascular cell adhesion molecule (VCAM), interleukin-6 (IL-6), interleukin-10 (IL-10) and E-selectin), thrombosis (homocysteine, Von Willebrand Factor (VWF), fibrinogen, fibronectin, endothelin, D-dimer, plasminogen activator inhibitor-1(PAI-1), tissue plasminogen activator (tPA),) and angiogenesis (Vascular endothelial growth factor (VEGF), soluble Fms-like tyrosine kinase-1 (sFLT-1) and tumor necrosis factor alpha (TNF-α)). Previous research suggests that these cardiovascular biomarkers could be useful in prediction, identification and assessment of hypertensive pregnancy disorders, especially preeclampsia[14,15].

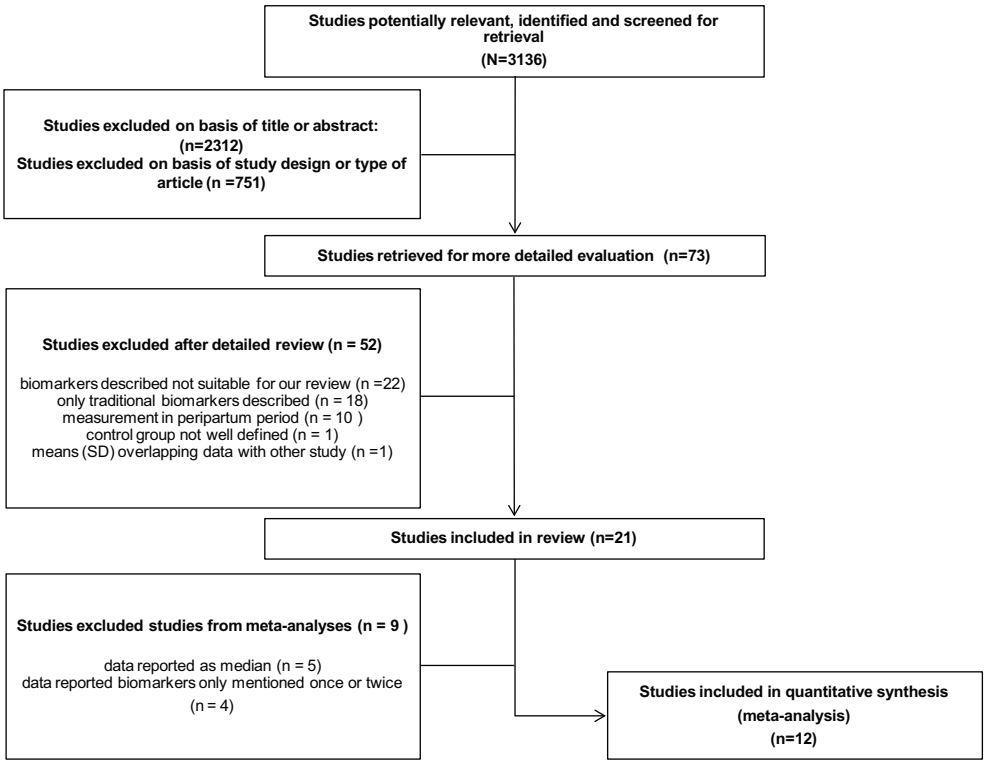


**Figure 1.** Study selection process

The aim of this study is to investigate whether non-classic cardiovascular biomarkers are associated with persistent endothelial dysfunction after pregnancy in women with a history of hypertensive pregnancy disorders compared to women who have had uncomplicated pregnancies.

## Methods

### Definitions

Hypertensive pregnancy disorders include gestational hypertension, preeclampsia, superimposed preeclampsia and eclampsia. Gestational hypertension was defined according to the ISSHP criteria as diastolic blood pressure equal to or above 90 mmHg measured at two occasions at least six hours apart in a woman who was normotensive at the start of pregnancy until week 20 of gestational age[16]. Preeclampsia was defined according to the ISSHP criteria: onset of a blood pressure exceeding 140/90 mmHg with proteinuria greater than 0.3 gram/24 hours after 20 weeks gestation[16]. Severe preeclampsia was defined as a blood pressure exceeding 160/110 mmHg or proteinuria greater than 5 gram/24 hours,

or both[16]. Eclampsia was defined as the presence of seizures[16,17]. Superimposed preeclampsia was defined as preexisting hypertension with new onset proteinuria greater than 0.3 gram/24 hours after 20 weeks gestation.

**Sources**

We searched PubMed, Embase.com, Cochrane Library (via Wiley) and Cinahl (via EBSCO) (JCFK, RHJO and SV) from inception to February 27, 2013. The following search terms with synonyms were used: gestational hypertension, preeclampsia and eclampsia.

The search on non-classic cardiovascular biomarkers in the area of inflammation included the following terms with synonyms: intercellular adhesion molecule (ICAM), vascular cell adhesion molecule (VCAM), interleukin-6 (IL-6), interleukin-10 (IL-10) and E-selectin. The search on non-classic cardiovascular biomarkers in the area of thrombosis included the following terms with synonyms: homocysteine, Von Willebrand Factor (VWF), fibrinogen, fibronectin, endothelin, D-dimer, plasminogen activator inhibitor-1(PAI-1) and tissue plasminogen activator (tPA). The search on non-classic cardiovascular biomarkers in the area of angiogenesis included the following terms with synonyms: vascular endothelial growth factor (VEGF), soluble Fms-like tyrosine kinase-1 (sFLT-1) and tumor necrosis factor alpha (TNF-α). The search for study type included the following terms with synonyms: systematic reviews, meta-analyses, cohort studies and case-control studies. The choice of biochemical markers was based on the knowledge of their role in hypertensive disorders in pregnancy and suspected endothelial activation.

**Study Selection**

Two reviewers screened the title, abstract and keywords (SV, WH) figure 1. If a reference was potentially eligible, a full text article was scored using a scoring list conducted by the reviewers (SV, WH, CJMdG) to assess the article's quality (i.e. clear definition of gestational hypertension and (pre)eclampsia, study design, evaluated risk factors, information about blood collection and blood analysis, patient's characteristics; inclusion and exclusion criteria, information on bias, and number of inclusions in the study). During the comparison of these scoring lists by the reviewers (SV, WH) any inconsistencies were resolved by discussion with a third reviewer (CJMdG).

We included case-control studies and cohort studies. Cases were women with a history of hypertensive pregnancy disorder. Control subjects were women with a history of uncomplicated pregnancies.

We excluded studies without the previous mentioned definitions of gestational hypertension or (pre)eclampsia or without accurate description of the study

**Table 1.** Characteristics of Included Studies in Review and Meta-analysis

| Study, country | Study design | Expo-sure | Parity index pregnancy NP: nullipara, MP: mutipara | Mean gestational age (weeks) index pregnancy | Preterm and/or term pregnancy | Cases no. | Controls no. | Follow up period (years) | Non-classic Cardiovascular Marker described |
|---|---|---|---|---|---|---|---|---|---|
| 1. Deng 1994*, *Sweden*[19] | Prospective Cohort | PE | NP+MP | Not reported | T | 63 | 29 | 1 (5-15months) | VWF, fibronectin (means) |
| 2. Bremme 1996*, *Sweden*[20] | Retrospective CaseControl | PE | NP+MP | Severe PE 33 Mild PE 35 | PT+T | 42 | 26 | 1 (6-15months) | Fibronectin, Fibrinogen, PAI-1, Ddimer (means) |
| 3. Laivuori 1997, *Finnland*[21] | Retrospective CaseControl | PE | Not reported | Not reported | Not reported | 22 | 22 | Cases 16.9 Controls 17.0 | Endothelin (means) |
| 4. Barden 1999, *Australia*[22] | Retrospective CaseControl | PE | NP+ MP | Not reported | Not reported | 62 | 84 | 0.5 (6months) | Endothelin (means) |
| 5. He 1999, *Sweden*[23] | Retrospective CaseControl | PE | NP+MP | Not reported | Not reported | 24 | 23 | Range:2-5 | Fibrinogen, VWF, PAI-1, tPA (medians) |
| 6. Chambers 2001*, *England*[24] | Prospective CaseControl | PE | NP+MP | Not reported | Not reported | 78 | 48 | Mean:3 | Homocysteine, E-selectin, ICAM (means) |
| 7. Sattar 2003, *Scotland*[25] | Retrospective Cohort | PE | NP | Cases 36 Controls 40 | PT+T | 40 | 40 | Range:18-28 | ICAM, VCAM, E-selectin (medians) |
| 8. Vickers 2003*, *Scotland*[26] | Prospective Cohort | PE+PIH | NP | Not reported | Not reported | 392+297 | 163 | Range:33-52 | Fibrinogen, VWF (means) |
| 9. Freeman 2004*, *Scotland*[27] | Retrospective CaseControl | PE | NP | Not reported | Not reported | 40 | 40 | Mean: 19.8 (cases), 19.9 (controls) | ICAM, VCAM, IL-6, IL-10, TNF-α (means) |
| 10. Raijmakers 2004*, *Netherlands*[28] | Retrospective CaseControl | PE | NP+MP | Not reported | Not reported | 113 | 94 | 2 (28months) | Homocysteine (means) |
| 11. Wolff 2004, *USA*[29] | Retrospective CaseControl | PE | NP | Not reported | Not reported | 29 | 32 | 2 (18±7.9 months) | sFlt-1 (means), VEGF (medians) |
| 12. Paradisi 2006*, *Italy*[30] | Prospective Cohort | PIH | NP+MP | Cases 37.9 Controls 39.2 | T | 15 | 15 | >1 (20months) | Homocysteine (means) |

**Table 1.** (Continued) Characteristics of Included Studies in Review and Meta-analysis

| Study, country | Study design | Expo-sure | Parity index pregnancy NP: nullipara, MP: mutipara | Mean gestational age (weeks) index pregnancy | Preterm and/or term pregnancy | Cases no. | Controls no. | Follow up period (years) | Non-classic Cardiovascular Marker described |
|---|---|---|---|---|---|---|---|---|---|
| 13. Girouard 2007*, *Canada*[31] | Prospective Cohort | PE+PIH | NP+MP | Cases 38.8 Controls 39.4 | T | 168 63 +105 | 168 | Mean: 7.8 | Homocysteine (means) IL-6, PAI-1, TNF-α (medians) |
| 14. Hamad 2007*, *Sweden*[32] | Retrospective CaseControl | PE | NP | Not reported | Not reported | 18 | 17 | 1 (15months) | Fibrinogen, VWF, tPA ICAM, VCAM, E-selectin (means) PAI-1(medians) |
| 15. v Rijn 2007*, *Netherlands*[33] | Retrospective CaseControl | PE | NP | Cases 29.9 Controls 40.0 | PT+T | 340 | 113 | 0.5 (>6months) | Fibrinogen, IL-6, ICAM, VWF (means) |
| 16. Lampinen 2008, *Finland*[34] | Retrospective CaseControl | PE | NP+MP | Cases 33 Controls 40 | PT+T | 28 | 20 | Range:5-6 | IL-6, VWF (medians) |
| 17. Portelinha 2008, *Portugal*[35] | Retrospective CaseControl | PE | Not reported | Cases 35 Controls 39 | PT + T | 65 | 54 | Mean: 6 | PAI-1 (means) Ddimer, Fibrinogen, tPA (medians) |
| 18. Porthelina 2008*, Portugal[36] | Retrospective CaseControl | PE | NP | Cases 34 Controls 39 | PT+T | 58 | 49 | Mean: 6 | VCAM, ICAM (means) |
| 19. Coffeng 2011*, *Netherlands*[37] | Retrospective CaseControl | PE | NP+MP | Not reported | Not reported | 16 | 17 | Median: 4 | Homocysteine (means) |
| 20. Stepan 2011, *Germany*[38] | Prospective Cohort | PE | Not reported | Not reported | Not reported | 37 | 37 | 0.5 (6months) | TNFα (medians) |
| 21. Gaugler 2012, *Netherlands*[39] | Retrospective CaseControl | PE | NP+MP | Cases 22.8 Controls 40.2 | PT+T | 16 | 18 | Median:9.4 (cases) 9.7 (controls) | sFlt , VEGF, E-selectin(medians) |

* **Studies included in meta-analyses**

population. Studies that included superimposed preeclampsia were excluded from this review.
Outcomes evaluated were non-classic cardiovascular biomarkers determined after hypertensive pregnancy disorders.

**Outcomes of Interest**
Outcomes were differences in non-classic cardiovascular biomarkers, measured after pregnancy, between women with a history of hypertensive pregnancy disorders and women with a history of uncomplicated pregnancies. Non-classic cardiovascular biomarkers found in case control and cohort studies were numerous **[table 1]**. In this review we describe a specific selection of non-classic cardiovascular biomarkers (n = 16), intercellular adhesion molecule (ICAM), vascular cell adhesion molecule (VCAM), interleukin-6 (IL-6), interleukin-10 (IL-10), E-selectin, homocysteine, Von Willebrand Factor (VWF), fibrinogen, fibronectin, endothelin, D-dimer, plasminogen activator inhibitor-1(PAI-1), tissue plasminogen activator (tPA), vascular endothelial growth factor (VEGF), soluble Fms-like tyrosine kinase-1 (sFLT-1) and tumor necrosis factor alpha (TNF-α). Only if three or more studies reported on a non-classic biomarker and reported outcome values as means ± SEM or SD, we performed meta-analysis including the non-classic biomarker. If studies reported values as medians (range/interquartile range (IQR)) or if less than three studies reported on the non-classic biomarker, we described the non-classic biomarker separately.

**Data Synthesis**
We used Review Manager 5.0 (Cochrane Collaboration, Oxford, UK) for statistical analyses. Outcomes were reported as continuous data and analyzed using a mean difference. Raw numbers were used from each study, as adjustments for confounding effects varied among the different studies. Weighting of studies in the meta-analyses was calculated on the basis of the inverse variance of the study. The random effects model was chosen, as a clinical and statistical heterogeneity was expected among the studies. We used forest plots to visualize data and assessed heterogeneity using the $I^2$ test[18]. For all effect estimates, a p-value < 0.05 indicated statistical significance.

## Results

**Literature Identification and Study Quality**
The initial search produced 4995 articles; Pubmed 1775 articles, Embase 2757 articles, Cinahl 260 articles, Cochrane 119 articles. After removing duplicates of references that were selected from more than one database,

3136 papers remained. After screening the titles and abstracts we retrieved 73 articles for detailed evaluation of the full text. As described in figure 1, we included 21 articles of these 73 in this review. For the meta-analyses we included 12 articles which reported on 5 different non-classic cardiovascular biomarkers. The other non-classic cardiovascular biomarkers will be described separately.

## Study Characteristics



The studies included in this review were published from 1994 to 2012. Study characteristics are shown in **table 1**. Data collection of studies in this review was prospective design in fifteen (71%) studies[20,21,22,23,25,27,28,29,32,33,34,35,36,37,39]. Six studies (29%) were designed as cohort studies[19,25,26,30,31,38] and 15 (71%) were case control studies[20,21,22,23,24,27,28,29,32,33,34,35,36,37,39].
In one study (5%) only women with a history of pregnancy induced hypertension were included[30]; two studies (9%) included women with a history of pregnancy induced hypertension and preeclampsia[25,31] and 18 studies (86%) included women with a history of preeclampsia[19,20,21,22,23,24,27,28,29,30,32,33,34,35,36,37,38,39].
In 11 studies (52%) both nulliparous and multiparous women were included[19,20,22,23,24,28,30,31,34,37,39], in seven other studies (32%) only nulliparous women were included[25,26,27,29,32,33,36]. We included three studies (14%) in which parity wasn't described[21,35,38]. In three studies (14%) only women were included after a term pregnancy[19,30,31], in seven studies (33%) both women who delivered at term and at preterm were included[20,25,33,34,35,36,39]. In the other 11 studies (52%) it was not reported if women delivered at term or preterm[21,22,23,24,26,27,28,29,32,37,38].
The follow up period of the included studies varied from 5 months to 52 years. An overall mean weighted follow up was not calculated, since the follow up periods in the different studies were reported as means (+/- SD) or medians (ranges/IQR).

## Biomarkers for inflammation

**ICAM and VCAM[24,25,27,32,33,36].**
Five studies with a total of 534 cases and 264 controls were able to be included in meta-analyses on ICAM[24,27,32,33,36] which showed no significant difference in mean ICAM levels in women with a history of hypertensive pregnancy disorders compared to women with a history of uncomplicated pregnancy, mean difference 11.04ng/ml (95% confidence interval -12.10 - 34.18, p = 0.35). The test heterogeneity observed was significant, p= 0.04, $I^2$= 61% **(figure A).** One study described a higher median ICAM level[25] in women with a history of hypertensive pregnancy disorders compared to women with uncomplicated pregnancy.

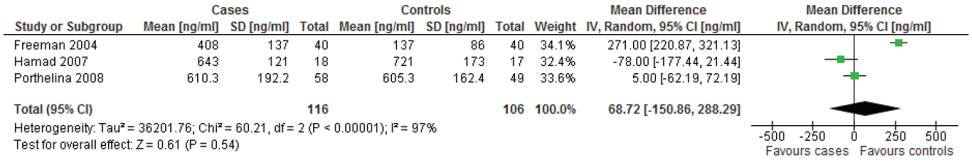


**Figure A.** ICAM

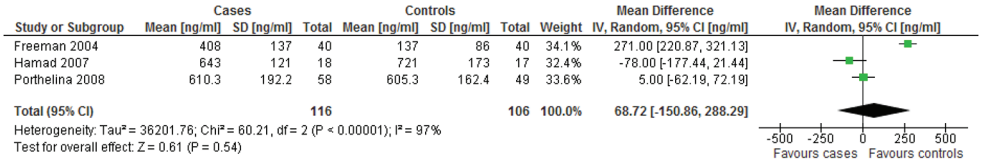


**Figure B.** VCAM

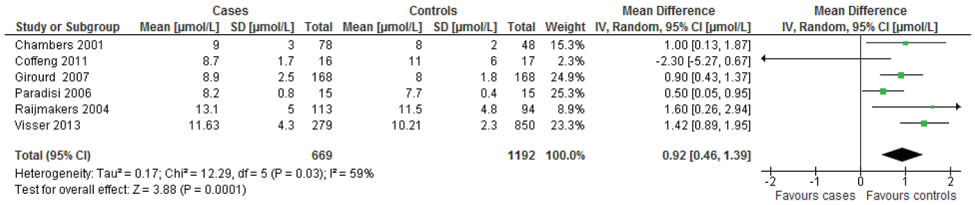


**Figure C**. Homocysteine

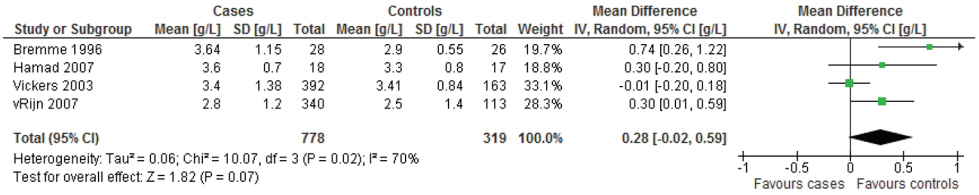


**Figure D**. Fibrinogen

Three studies with a total of 116 cases and 106 controls were able to be included in meta-analyses on VCAM which showed no significant difference in mean VCAM levels in women with a history of hypertensive pregnancy disorders compared to women with a history of uncomplicated pregnancy, mean difference 68.72 ng/ml (95% confidence interval -150.86 - -288.29) The test heterogeneity observed was significant, $p < 0.00$, $I^2 = 97\%$ **(figure B).** One study described a higher median VCAM level[25] in women with a history of hypertensive pregnancy disorders compared to women with uncomplicated pregnancy.

Other non-classic cardiovascular biomarkers in the area of inflammation; IL-6, IL-10 and E-selectin, showed a trend of elevated levels in women with a history

of hypertensive pregnancy disorders compared to women with a history of uncomplicated pregnancy.
Two studies described higher mean IL-6 levels[27,33] and one study described a higher median IL-6 level[31] in women with a history of hypertensive pregnancy disorders compared to women with uncomplicated pregnancy. One study described a lower median IL-6 level[34] in women with a history of hypertensive pregnancy disorders compared to women with a history of uncomplicated pregnancy. Overall, IL-6 levels were described higher after pregnancy in women with a history of hypertensive pregnancy disorders compared to women with a history of uncomplicated pregnancy.
One study described a higher mean IL-10 level[27] in women with a history of hypertensive pregnancy disorders compared to women with uncomplicated pregnancy.
One study described a higher mean E-selectin level[24] in women with a history of hypertensive pregnancy disorders compared to women with uncomplicated pregnancy. One study described the same mean E-selectin level[32] in women with a history of hypertensive pregnancy disorders and women with uncomplicated pregnancy. Two studies described higher median E-selectin levels[25,39] in women with a history of hypertensive pregnancy disorders compared to women with uncomplicated pregnancy. Overall, E-selectin levels were described higher after pregnancy in women with a history of hypertensive pregnancy disorders compared to women with a history of uncomplicated pregnancy.



## Biomarkers for thrombosis

### Homocysteine, Von Willebrand Factor (VWF) and fibrinogen[19,20,23,24,26,28,30,31,32,33,34,35,37].

Five studies with a total of 390 cases and 342 controls could be included in meta-analyses on homocysteine[24,28,30,31,37] which showed higher mean homocysteine levels in women with a history of hypertensive pregnancy disorders compared to women with a history of uncomplicated pregnancy, mean difference 0.77ng/ml (95% confidence interval 0.27 to 1.26; p <0.00). The test heterogeneity observed was not significant, p= 0.11, $I^2$= 48% **(figure C).**
Three studies with a total of 473 cases and 209 controls could be included in meta-analyses on VWF[19,26,32] which showed no significant difference in mean VWF levels in women with a history of hypertensive pregnancy disorders compared to women with a history of uncomplicated pregnancy, mean difference 0.06 ng/ml (95% confidence interval -0.05 - 0.17; p = 0.28). The test heterogeneity observed was not significant, p = 0.47, $I^2$= 0% **(figure C).** Two studies described higher

VWF median levels[23,34] in women with a history of hypertensive pregnancy disorders compared to women with uncomplicated pregnancy.
Four studies with a total of 778 cases and 319 controls could be included in meta-analyses on fibrinogen[20,26,32,33] which showed no significant difference in mean fibrinogen levels in women with a history of hypertensive pregnancy disorders compared to women with a history of uncomplicated pregnancy, mean difference 0.28 g/L (95% confidence interval -0.02 - 0.59; p = 0.07). The test heterogeneity observed was significant, P = 0.02, $I^2$= 70% **(figure D).** Two studies described higher median fibrinogen levels[23,35] in women with a history of hypertensive pregnancy disorders compared to women with uncomplicated pregnancy.

Other non-classic cardiovascular biomarkers in the area of thrombosis, including fibronectin, endothelin, D-dimer, PAI-1 and tPA, showed a trend of elevated levels in women with a history of hypertensive pregnancy disorders compared to women with a history of uncomplicated pregnancy.
Two studies described higher mean cellular fibronectin levels[19,20] in women with a history of hypertensive pregnancy disorders compared to women with uncomplicated pregnancy.
One study described a higher mean endothelin levels[21] in women with a history of hypertensive pregnancy disorders compared to women with uncomplicated pregnancy. One study described the same mean endothelin level[22] in women with a history of hypertensive pregnancy disorders and women with uncomplicated pregnancy.
One study described a higher mean D-dimer level[20] and one study described a higher median D-dimer level[35] in women with a history of hypertensive pregnancy disorders compared to women with uncomplicated pregnancy.
One study described a higher mean PAI-1 level[20] and three studies described higher median PAI-1 levels[23,31,32] in women with a history of hypertensive pregnancy disorders compared to women with uncomplicated pregnancy. One study described a lower mean PAI-1 level[35] in women with a history of hypertensive pregnancy disorders compared to women with uncomplicated pregnancy.
One study described a higher mean tPA level[32] and two studies described higher median tPA levels[23,35] in women with a history of hypertensive pregnancy disorders compared to women with uncomplicated pregnancy.

## Biomarkers for angiogenesis

### Vascular Growth Factors (VEGF), Soluble Fms-like Tyrosine Kinase-1 (sFLT-1) and TNF-α.

These non-classic markers in the area of angiogenesis show a trend of elevated levels in women with a history of hypertensive pregnancy disorders compared to women with a history of uncomplicated pregnancy.

Two studies described higher median VEGF levels[29,39] in women with a history of hypertensive pregnancy disorders compared to women with uncomplicated pregnancy. One study described a higher mean sFlt level[29] and one study describes higher median sFlt level[39] in women with a history of hypertensive pregnancy disorders compared to women with uncomplicated pregnancy.

One study described a higher mean TNF-α level[27] and one study described a higher median TNF-α level[38] in women with a history of hypertensive pregnancy disorders compared to women with uncomplicated pregnancy. One study described a lower median TNF-α level[31] in women with a history of hypertensive pregnancy disorders compared to women with uncomplicated pregnancy.



## Discussion

### Main Finding

In this review and meta-analysis we found that most non-classic cardiovascular biomarkers, including homocysteine, were higher in women with a history of hypertensive pregnancy disorders compared to women with a history of uncomplicated pregnancies in the areas of inflammation (ICAM, VCAM, IL-6, IL-10, E-selectin), thrombosis (homocysteine, VWF, fibrinogen, fibronectin, endothelin, D-dimer, PAI-1, tPA) and angiogenesis (VEGF, sFLT-1, TNF-α).

### Strengths and Limitations

This is the first review and meta-analyses that focuses on non-classic cardiovascular biomarkers in women with a history of hypertensive pregnancy disorders. We used a wide spectrum of search terms to evaluate the most important non-classic cardiovascular biomarkers. The study selection was carried out without language restrictions, and attention was paid to quality assessment by using scoring lists and evaluation by multiple investigators, preventing selection bias and publication bias.

This review and meta-analyses shows higher levels of non-classic cardiovascular biomarkers in women with a history of hypertensive pregnancy disorders. These elevated biomarkers suggest endothelial activation in hypertensive pregnancy

disorders and cardiovascular disease, inclining towards a shared pathofysiology. Our meta-analyses suggest an additional value of one specific biomarker, homocysteine, in cardiovascular risk assessment. Guidelines advise treatment in women with elevated cardiovascular risk scores and unfavorable classic cardiovascular risk factors, such as hypercholesterolemia or diabetes to prevent cardiovascular disease later in life[52,53]. However, until now, no evidence exists that treatment of non-classic cardiovascular risk factors is effective in prevention of cardiovascular disease in women[53]. An example is the lack of evidence that, in case of elevated homocysteine, folic acid supplementation can result in reduction of cardiovascular events[44].

This review has some limitations. First, due to the small number of studies we were not able to separately analyze women with a history of gestational hypertension and women with a history of preeclampsia, which may have different pathophysiologies[54]. Second, studies did not distinguish between severe and between preterm and term hypertensive pregnancy disorders, which may also differ pathophysiologically[55]. Third, follow up time after pregnancy differed between studies. Fourth, both premenopausal and postmenopausal subjects were included in the studies reviewed. Postmenopausal women have a higher cardiovascular disease risk compared to premenopausal women. Thus, post menopause may have confounded our results, although studies that describe only premenopausal women seem to show comparable elevated levels of non-classical biomarkers in women with a history of hypertensive pregnancy disorders compared to women with a history of uncomplicated pregnancy remained.

## Non-classic Cardiovascular Biomarkers

*Homocysteine*

For thrombotic biomarker homocysteine we found a significantly higher level in our meta-analyses for women with a history of hypertensive pregnancy disorders compared to women with a history of uncomplicated pregnancies. Homocysteine is a biomarker that is linked to the development of atherosclerosis, inflammation, and endothelium injury[40,41]. A large review conducted in 2002[42] concluded that an increase in fasting plasma homocysteine is associated with an increase in the incidence of ischemic heart disease and an increase in the incidence of stroke.
Homocysteine is not only a marker for cardiovascular disease, but also for hypertensive pregnancy disorders[45]. A recent study included homocysteine in an early prediction model for preeclampsia[46]. This study concluded that higher levels of homocysteine, in combination with elevation of other biomarkers, in the first

trimester of pregnancy could predict the onset of the hypertensive pregnancy disorders later in pregnancy.
In our review, we included homocysteine levels after hypertensive pregnancy disorders. In two studies on homocysteine, it is not completely clear if results included fasting homocysteine levels[28,31]. Since homocysteine levels can be influenced by oral intake this could disturb the results of this meta-analyses. The higher levels of homocysteine after a pregnancy complicated by hypertension can result from already present endothelial alteration or persistent endothelial alteration after complicated pregnancy. However, the impact of this finding and clinical consequences are unknown.
The effectiveness of lowering of homocysteine levels, by folate acid or vitamine suppletion, to prevent cardiovascular disease has been investigated in several studies[43]. A Cochrane Review published in 2013[44] however failed to evidence to sustain this.



**Biomarkers for inflammation**
For inflammatory biomarkers ICAM and VCAM we found non-significant higher levels in our meta-analyses in women with a history of hypertensive pregnancy disorders compared to women with a history of uncomplicated pregnancies. For all other inflammatory biomarkers we found a trend towards higher levels in women with a history of hypertensive pregnancy disorders compared to women with a history of uncomplicated pregnancies.
An increase in systemic inflammation can be interpreted as either a cause or a result of atherogenesis in cardiovascular disease or both. Systemic inflammation induces a heightened state of cardiovascular activity, endothelium dysfunction, and induction of adhesion molecules on endothelial cells to which recruited inflammatory cells adhere and translocate to the arterial wall. This inflammatory process results in macrophage activation with the production of cytokines and other inflammatory biomarkers. These inflammatory biomarkers include ICAM, VCAM, interleukin-6 and -10. We expected higher levels of inflammatory biomarkers in women with a history of hypertensive pregnancy disorders compared to women with a history of uncomplicated pregnancies, as the inflammatory process is an important part of the pathofysiology of both hypertensive pregnancy disorders as of cardiovascular disease[48,47]. However, we only found a nonsignificant trend towards higher inflammatory biomarkers in women with a history of hypertensive pregnancy disorders. Limited sample size might account for this.

### Biomarkers for thrombosis

For fibrinogen and all other thrombotic biomarkers we found a non-significant higher level in our meta-analyses in women with a history of hypertensive pregnancy disorders compared to women with a history of uncomplicated pregnancies. For all other thrombotic biomarkers we found a trend towards higher levels in women with a history of hypertensive pregnancy disorders compared to women with a history of uncomplicated pregnancies.

Biomarkers for thrombosis indicate overactivation of thrombotic reactions without any blood vessel injury and may result in reduced blood flow, reduced perfusion and finally cardiovascular disease. In this review we described established biomarkers for thrombosis in women with a history of hypertensive pregnancy disorders. Most of these biomarkers are known to be elevated in women with preeclampsia and are even used in early prediction of preeclampsia[48,49]. It has been suggested that thrombosis might be a shared pathophysiologic pathway, partly explaining the link between hypertensive pregnancy disorders and cardiovascular disease later life. However we did not find strong evidence for this in our present review.

### Biomarkers for angiogenesis

For angiogenic biomarkers we found a trend towards higher levels in women with a history of hypertensive pregnancy disorders compared to women with a history of uncomplicated pregnancies.

Biomarkers of angiogenesis are suggested to be sensitive markers for cardiovascular disease[50]. Moreover, sFlt-1 is suggested to be a strong predictor of the outcome of pregnancies complicated by hypertensive disorders. In this review, however we found no strong evidence for altered angiogenesis as the pathophysiologic link between hypertensive pregnancy disorders and cardiovascular disease later in life.

## Conclusion

Women with a history of hypertensive pregnancy disorders show significantly higher levels of homocysteine compared to women with a history of uncomplicated pregnancy. For biomarkers of inflammation, thrombosis and angiogenesis, we found non-significant increases. These findings suggest impaired endothelial function that persists after or is even already present before hypertensive pregnancy disorders.

## Reference List


(1) Burell G, Granlund B. Women's hearts need special treatment. Int J Behav Med 2002;9(3):228-42.

(2) Stramba-Badiale M, Fox KM, Priori SG, Collins P, Daly C, Graham I et al. Cardiovascular diseases in women: a statement from the policy conference of the European Society of Cardiology. Eur Heart J 2006; 27(8):994-1005.

(3) Douglas PS, Ginsburg GS. The evaluation of chest pain in women. N Engl J Med 1996; 334(20):1311-1315.

(4) Vaccarino V, Badimon L, Corti R, de WC, Dorobantu M, Hall A et al. Ischaemic heart disease in women: are there sex differences in pathophysiology and risk factors? Position paper from the working group on coronary pathophysiology and microcirculation of the European Society of Cardiology. Cardiovasc Res 2011; 90(1):9-17.

(5) Sullivan AK, Holdright DR, Wright CA, Sparrow JL, Cunningham D, Fox KM. Chest pain in women: clinical, investigative, and prognostic features. BMJ 1994; 308(6933):883-886.

(6) Arslanian-Engoren C. Women's risk factors and screening for coronary heart disease. J Obstet3 Gynecol Neonatal Nurs. 2011 May;40(3):337-46; quiz 346-7.

(7) Berks D, Hoedjes M, Raat H, Duvekot J, Steegers E, Habbema J. Risk of cardiovascular disease after pre-eclampsia and the effect of lifestyle interventions: a literature-based study. BJOG. 2013 Mar 26. doi: 10.1111/1471-0528.12191. [Epub ahead of print]

(8) Buurma AJ, Turner RJ, Driessen JH, Mooyaart AL, Schooned JW, Bruijn JA, Bloemenkamp KW, Dekkers OM, Baelde HJ. Genetic variants in pre-eclampsia: a meta-analysis. Hum Reprod Update. 2013 May-June;19(3):289-303. doi:10.1093/humupd/cims060.Epud 2013 Jan 8. Pubmed.

(9) Sattar N, Greer A. Pregnancy complications and maternal cardiovascular risk: opportunities for intervention and screening?. BMJ 2002; 325:157-60

(10) Hermes W, Ket JC, van Pampus MG, Franx A, Veenendaal MV, de Groot CJ et al. Biochemical cardiovascular risk factors after hypertensive pregnancy disorders: a systematic review and meta-analysis. Obstet Gynecol Surv. 2012 Dec;67(12):793-809. doi: 10.1097/OGX.0b013e31827682fc.

(11) Ge Y, Wang TJ. Identifying novel biomarkers for cardiovascular disease risk prediction. J Intern Med. 2012 Sep 5. doi: 10.1111/j.1365-2796.2012.02589.x. [Epub ahead of print]

(12) Gilstrap LG, Wang TJ. Biomarkers and cardiovascular risk assessment for primary prevention: an update. Clin Chem. 2012 Jan;58(1):72-82. Epub 2011 Nov 28.

(13) Dotsenko O, Chackathayil J, Patel JV, Gill PS, Lip GY. Candidate circulating biomarkers for the cardiovascular disease continuum. Curr Pharm Des. 2008;14(24):2445-61.

(14) Masoura S, Kalogiannidis IA, Gitas G, Goutsioulis A, Koiou E, Athanasiadis A et al. Biomarkers in pre-eclampsia: a novel approach to early detection of the disease. J Obstet Gynaecol. 2012 Oct;32(7):609-16. doi: 10.3109/01443615.2012.709290.

(15) Baumann MU, Bersinger NA, Surbek DV. Serum markers for predicting pre-eclampsia. Mol Aspects Med. 2007 Apr;28(2):227-44. Epub 2007 Apr 27.

(16) Ge Y, Wang TJ. Identifying novel biomarkers for cardiovascular disease risk prediction. J Intern Med. 2012 Sep 5. doi: 10.1111/j.1365-2796.2012.02589.x. [Epub ahead of print]

(17) Gilstrap LG, Wang TJ. Biomarkers and cardiovascular risk assessment for primary prevention: an update. Clin Chem. 2012 Jan;58(1):72-82. Epub 2011 Nov 28.
(18) Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003 Sep 6;327(7414):557-60.
(19) Deng L, Bremme K, Hansson LO, Blombäck M. Plasma levels of von Willebrand factor and fibronectin as markers of persisting endothelial damage in preeclampsia. Obstet Gynecol. 1994 Dec;84(6):941-5.
(20) Bremme K, Blombäck M. Hemostatic abnormalities may predict chronic hypertension after preeclampsia. Gynecol Obstet Invest. 1996;41(1):20-6.
(21) Laivuori H, Kaaja R, Rutanen EM, Viinikka L, Ylikorkala O. Evidence of high circulating testosterone in women with prior preeclampsia. J Clin Endocrinol Metab. 1998 Feb;83(2):344-7.
(22) Barden AE, Beilin LJ, Ritchie J, Walters BN, Michael C. Does a predisposition to the metabolic syndrome sensitize women to develop pre-eclampsia? J Hypertens. 1999 Sep;17(9):1307-15.
(23) He S, Silveira A, Hamsten A, Blombäck M, Bremme K. Haemostatic, endothelial and lipoprotein parameters and blood pressure levels in women with a history of preeclampsia. Thromb Haemost. 1999 Apr;81(4):538-42.
(24) Chambers JC, Fusi L, Malik IS, Haskard DO, De Swiet M, Kooner JS. Association of maternal endothelial dysfunction with preeclampsia. JAMA. 2001 Mar 28;285(12):1607-12.
(25) Sattar N, Ramsay J, Crawford L, Cheyne H, Greer IA. Classic and novel risk factor parameters in women with a history of preeclampsia. Hypertension. 2003 Jul;42(1):39-42. Epub 2003 May 12.
(26) Vickers M, Ford I, Morrison R, Prescott G, Watson S, Hannaford P et al. Markers of endothelial activation and atherothrombosis in women with history of preeclampsia or gestational hypertension. Thromb Haemost. 2003 Dec;90(6):1192-7.
(27) Freeman DJ, McManus F, Brown EA, Cherry L, Norrie J, Ramsay JE et al. Short- and long-term changes in plasma inflammatory markers associated with preeclampsia. Hypertension. 2004 Nov;44(5):708-14. Epub 2004 Sep 27.
(28) Raijmakers MT, Roes EM, Zusterzeel PL, Steegers EA, Peters WH. Thiol status and antioxidant capacity in women with a history of severe pre-eclampsia. BJOG. 2004 Mar;111(3):207-12.
(29) Wolf M, Hubel CA, Lam C, Sampson M, Ecker JL, Ness RB et al. Preeclampsia and future cardiovascular disease: potential role of altered angiogenesis and insulin resistance. J Clin Endocrinol Metab. 2004 Dec;89(12):6239-43.
(30) Paradisi G, Biaggi A, Savone R, Ianniello F, Tomei C, Caforio L et al. Cardiovascular risk factors in healthy women with previous gestational hypertension. J Clin Endocrinol Metab. 2006 Apr;91(4):1233-8. Epub 2006 Jan 24.
(31) Girouard J, Giguère Y, Moutquin JM, Forest JC. Previous hypertensive disease of pregnancy is associated with alterations of markers of insulin resistance. Hypertension. 2007 May;49(5):1056-62. Epub 2007 Mar 26.
(32) Hamad RR, Eriksson MJ, Silveira A, Hamsten A, Bremme K. Decreased flow-mediated dilation is present 1 year after a pre-eclamptic pregnancy. J Hypertens. 2007 Nov;25(11):2301-7.
(33) van Rijn BB, Franx A, Steegers EA, de Groot CJ, Bertina RM, Pasterkamp G et al. Maternal TLR4 and NOD2 gene variants, pro-inflammatory phenotype and susceptibility to early-onset preeclampsia and HELLP syndrome. PLoS One. 2008 Apr 2;3(4):e1865. doi: 10.1371/journal.pone.0001865.

(34) Lampinen KH, Rönnback M, Groop PH, Kaaja RJ. A relationship between insulin sensitivity and vasodilation in women with a history of preeclamptic pregnancy. Hypertension. 2008 Aug;52(2):394-401. Epub 2008 Jun 23.
(35) Portelinha A, Cerdeira AS, Belo L, Braga J, Tejera E, Pinto A et al. Haemostatic factors in women with history of preeclampsia. Thromb Res. 2009 May;124(1):52-6. Epub 2008 Dec 2.
(36) Portelinha A, Belo L, Tejera E, Rebelo I. Adhesion molecules (VCAM-1 and ICAM-1) and C-reactive protein in women with history of preeclampsia. Acta Obstet Gynecol Scand. 2008;87(9):969-71.
(37) Coffeng SM, Blaauw J, Souwer ET, Rakhorst G, Smit AJ, Graaff R et al. Skin autofluorescence as marker of tissue advanced glycation end-products accumulation in formerly preeclamptic women. Hypertens Pregnancy. 2011;30(2):231-42. Epub 2010 Aug 11.
(38) Stepan H, Philipp A, Roth I, Kralisch S, Jank A, Schaarschmidt W et al.Serum levels of the adipokine chemerin are increased in preeclampsia during and 6 months after pregnancy. Regul Pept. 2011 Jun 7;168(1-3):69-72. doi: 10.1016/j.regpep.2011.03.005. Epub 2011 Apr 12.
(39) Gaugler-Senden IP, Tamsma JT, van der Bent C, Kusters R, Steegers EA, de Groot CJ. Angiogenic factors in women ten years after severe very early onset preeclampsia. PLoS One. 2012;7(8):e43637. doi: 10.1371/journal.pone.0043637. Epub 2012 Aug 31.
(40) Bogdanski P, Miller-Kasprzak E, Pupek-Musialik D, Jablecka A, Lacinski M, Jagodzinski PP et al. Plasma total homocysteine is a determinant of carotid intima-media thickness and circulating endothelial progenitor cells in patients with newly diagnosed hypertension. Clin Chem Lab Med. 2012 Jan 14;50(6):1107-13. doi: 10.1515/cclm-2011-0856.
(41) Ruijter W, Westendorp RG, Assendelft WJ, Elzen WP, Craen AJ, Cessie S et al. Use of framingham risk score and new biomarkers to predict cardiovascular mortality in older people: population based observational cohort study. BMJ. 2009;338:a3083. doi: 10.1136/bmj.a3083.
(42) Homocysteine Studies Collaboration, Homocysteine and risk of ischemic heart disease and stroke: a meta-analysis. JAMA 288:2015–2022.
(43) Smulders YM, Blom HJ. The homocysteine controversy. J Inherit Metab Dis. 2011 Feb;34(1):93-9. doi: 10.1007/s10545-010-9151-1. Epub 2010 Jun 22.
(44) Martí-Carvajal AJ, Solà I, Lathyris D, Karakitsiou DE, Simancas-Racines D. Homocysteine-lowering interventions for preventing cardiovascular events. Cochrane Database Syst Rev. 2013 Jan 31;1:CD006612. doi: 10.1002/14651858.CD006612.pub3.
(45) Demir B, Demir S, Pasa S, Guven S, Atamer Y, Atamer A, Kocyigit Y. The role of homocysteine, asymmetric dimethylarginine and nitric oxide in pre-eclampsia. J Obstet Gynaecol 2012 Aug;32(6):525-8. doi: 10.3109/01443615.2012.693985.
(46) Masoura S, Kalogiannidis IA, Gitas G, Goutsioulis A, Koiou E, Athanasiadis A, Vavatsi N. Biomarkers in pre-eclampsia: a novel approach to early detection of the disease. J Obstet Gynaecol. 2012 Oct;32(7):609-16. doi: 0.3109/01443615.2012.709290.
(47) Fontes JD, Yamamoto JF, Larson MG, Wang N, Dallmeier D, Rienstra M et al. Clinical correlates of change in inflammatory biomarkers: The Framingham Heart Study. Atherosclerosis. 2013 Feb 4. pii: S0021-9150(13)00054-3. doi: 10.1016/j.atherosclerosis.2013.01.019. [Epub ahead of print]

(48) Forest JC, Charland M, Massé J, Bujold E, Rousseau F, Lafond J, Giguère Y. Candidate biochemical markers for screening of pre-eclampsia in early pregnancy. Clin Chem Lab Med. 2012 Jun;50(6):973-84. doi: 10.1515/cclm.2011.820.
(49) Aref S, Goda H. Increased VWF antigen levels and decreased ADAMTS13 activity in preeclampsia. Hematology. 2013 Feb 20. [Epub ahead of print]
(50) Ky B, French B, Ruparel K, Sweitzer NK, Fang JC, Levy WC, Sawyer DB, Cappola TP. The vascular marker soluble fms-like tyrosine kinase 1 is associated with disease severity and adverse outcomes in chronic heart failure. J Am Coll Cardiol. 2011 Jul 19;58(4):386-94. doi: 10.1016/j.jacc.2011.03.032.
(51) Poprawski G, Wender-Ozegowska E, Zawiejska A, Brazert J. Modern methods of early screening for preeclampsia and pregnancy-induced hypertension--a review. Ginekol Pol. 2012 Sep;83(9):688-93.
(52) Mosca L. Guidelines for prevention of cardiovascular disease in women: a summary of recommendations. Prev Cardiol. 2007 Fall;10 Suppl 4:19-25.
(53) Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren WM et al; European Association for Cardiovascular Prevention & Rehabilitation (EACPR). European guidelines on cardiovascular disease prevention in clinical practice (version 2012): the fifth joint task force of the European society of cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of nine societies and by invited experts). Int J Behav Med. 2012 Dec;19(4):403-88. doi: 10.1007/s12529-012-9242-5.
(54) Ros HS, Cnattingius S, Lipworth L.Comparison of risk factors for preeclampsia and gestational hypertension in a population-based cohort study. Am J Epidemiol. 1998 Jun 1;147(11):1062-70.
(55) Raymond D, Peterson E. A critical review of early-onset and late-onsetpreeclampsia. Obstet Gynecol Surv. 2011 Aug;66(8):497-506. doi: 10.1097/OGX.0b013e3182331028.

# Part Three

# Clinical Aspects: Cardiovascular Risk after Hypertensive Pregnancy Disorders

# *Chapter 5*

## 10-Year cardiovascular event risks for women who experienced hypertensive disorders in late pregnancy: the HyRAS study

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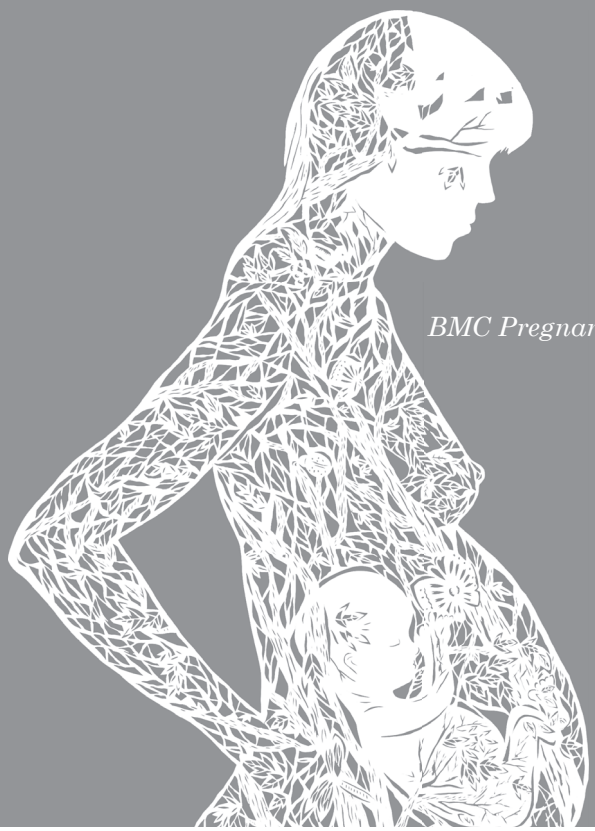

## Abstract

**Background:** Cardiovascular disease is the cause of death in 32% of women in the Netherlands. Prediction of an individual's risk for cardiovascular disease is difficult, in particular in younger women due to low sensitive and specific tests for these women. 10% to 15% of all pregnancies are complicated by hypertensive disorders, the vast majority of which develop only after 36 weeks of gestation. Preeclampsia and cardiovascular disease in later life show both features of "the metabolic syndrome" and atherosclerosis. Hypertensive disorders in pregnancy and cardiovascular disease may develop by common pathophysiologic pathways initiated by similar vascular risk factors. Vascular damage occurring during preeclampsia or gestational hypertension may contribute to the development of future cardiovascular disease, or is already present before pregnancy. At present clinicians do not systematically aim at the possible cardiovascular consequences in later life after a hypertensive pregnancy disorder at term. However, screening for risk factors after preeclampsia or gestational hypertension at term may give insight into an individual's cardiovascular risk profile.

**Methods/Design:** Women with a history of preeclampsia or gestational hypertension will be invited to participate in a cohort study 2.5 years after delivery. Participants will be screened for established modifiable cardiovascular risk indicators. The primary outcome is the 10-year cardiovascular event risk. Secondary outcomes include differences in cardiovascular parameters, SNP's in glucose metabolism, and neonatal outcome.

**Discussion:** This study will provide evidence on the potential health gains of a modifiable cardiovascular risk factor screening program for women whose pregnancy was complicated by hypertension or preeclampsia. The calculation of individual 10-year cardiovascular event risks will allow identification of those women who will benefit from primary prevention by tailored interventions, at a relatively young age. Trial registration: The HYPITAT trial is registered in the clinical trial register as ISRCTN08132825.

## Background

Cardiovascular disease is the cause of death of 32% of women in the Netherlands[1]. Not all women are at the same risk of cardiovascular disease. Prediction of risk in younger women is particularly difficult due to low sensitive and specific tests for these women. Identification of individual women at higher risk is a challenge. This proposal takes an innovative angle to gain insight in cardiovascular morbidity and mortality later in life in women using pregnancy related hypertensive complications. Approximately 10% to 15% of all pregnancies are complicated by hypertension and largely contribute to maternal and neonatal morbidity and mortality worldwide. In the Netherlands it is the largest single cause of maternal mortality[2]. The vast majority of hypertensive disorders present themselves after 36 weeks of gestation[3]. Therefore, we focus in this study on those women with pregnancy related hypertensive complications (near) at term (> 36 weeks gestation).



The etiology of hypertensive disorders of pregnancy is not fully understood, but the causal treatment is delivery of the baby and the placenta. Recently it was shown that in women at term with gestational hypertension or preeclampsia induction of labor is advisable to avoid progression to more severe disease[4]. However, the health status of these women after pregnancy has been given little of any attention in routine clinical practice up to now. Obstetricians and midwifes are traditionally completely focused on pregnancy outcome and do not seem to bother about the significance of complications of pregnancy for the future health of the mother, this is also true for general practitioners.

Recently, data from epidemiologic studies incited the novel concept of pregnancy as cardiovascular challenge test; women who have had a pregnancy complicated by hypertensive disorders are prone to develop cardiovascular disease in later life[5-10]. In line with this concept is that pregnancy acts as a metabolic and cardiovascular stress test for the mother. During pregnancy a failure to meet the physiological demands will unmask impaired organ function, e.g. hypertension will arise and most often subside after delivery. However, these failures will remanifest in later life when the cumulative effects of ageing diminish the reserves of an already vulnerable (organ) system[5]. Jonsdottir et al. examined causes of death in 374 women with a history of hypertensive complications in pregnancy and noted that their death rate from complications of coronary heart disease was significantly higher than expected from analysis of population data[11].

This concept is further supported by case-control studies by others and ourselves, demonstrating that women with a history of early preeclampsia have higher circulating concentrations of fasting insulin, lipid and coagulations factors

post partum than controls matched for body mass index[12-13]. These changes in vascular risk markers in women with a history of preeclampsia are part of the spectrum of the metabolic syndrome. The metabolic syndrome is hypothesised to be a key factor underlying cardiovascular disease and in particular coronary heart disease.

The mechanism of the link between preeclampsia and cardiovascular disease has not been clarified. Hypertensive disorders in pregnancy and cardiovascular disease may develop by common pathophysiologic pathways initiated by similar risk factors. Permanent vascular damage may occur during preeclampsia or gestational hypertension and subsequently contributes to the development of cardiovascular disease in later life, or cardiovascular disease is already present before pregnancy. However, determinants or risk indicators to be measured after pregnancy which would predict cardiovascular disease are lacking. Such risk indicators may identify women at risk at an early stage for them to benefit from intervention.

The concept described above is based on studies focusing on early, severe preeclampsia, which is a relatively rare disorder[14], while preeclampsia at (near) term is mostly mild and more common (75% of cases)[15]. Therefore, prospective evaluation of those women is required to identify cardiovascular risk indicators after hypertensive pregnancy complications at term, with the eventual aim to offer these women the opportunity for primary prevention at a relatively young age[16].

We propose a cohort study to establish whether women with gestational hypertension or preeclampsia at term are at increased risk for cardiovascular disease in later life, and if these women are likely to benefit from tailored preventative interventions directed at modifiable cardiovascular risk indicators at a relative young age.

## Methods/Design

### Aims

The aim of this study is to identify modifiable risk indicators for future cardiovascular disease 2½ years postpartum in women with (near) term preeclampsia or gestational hypertension. The proposed research concerns a multi-centre cohort study in women who had a pregnancy complicated by mild preeclampsia or gestational hypertension (near) at term which is recently published[4]. This study will provide insight on the health costs and benefits of a

screening program for all women with hypertensive complications at term. This study is embedded in a Dutch Obstetric Consortium in the Netherlands. Almost all obstetric centres nationwide participate in this structure, including academic hospitals, non-academic teaching hospitals and non-teaching hospitals.

**Participants: Exposed**

In this study women who had preeclampsia or gestational hypertension at term, who participated in the HYPITAT study, will be eligible for the follow up study 2½ years after their delivery. The HYPITAT study was a national randomised clinical trial in which women 18 years of age or older with gestational hypertension or mild preeclampsia at (near) term were included. Eligible were women with a singleton pregnancy in cephalic presentation and a gestational age between $36^{+0}$ and $41^{+0}$ weeks, whose pregnancy was complicated by gestational hypertension or mild preeclampsia. Gestational hypertension was defined as diastolic blood pressure equal to or above 95 mmHg measured at two occasions at least six hours apart in a woman who was normotensive at the start of pregnancy until week 20 of gestational age. Mild preeclampsia was defined as diastolic blood pressure equal to or above 90 mmHg measured at two occasions at least six hours apart combined with proteinuria. Proteinuria was defined as ≥ 2+ protein on dipstick, > 300 mg total protein in a 24 hour urine collection and/ or protein/ creatinine ratio > 30 mg/mmol. Exclusion criteria were severe gestational hypertension or severe preeclampsia, defined as diastolic blood pressure ≥ 110 mmHg, systolic blood pressure ≥ 170 mmHg and/ or proteinuria ≥ 5 gram in 24 hours, pre-existing hypertension treated with antihypertensive drugs, diabetes mellitus, diabetes gravidarum requiring insulin therapy, renal disease, heart disease, previous caesarean section, HELLP syndrome, oliguria < 500 milliliter in 24 hours, pulmonary edema or cyanosis, HIV seropositivity, use of intravenous anti-hypertensive medication, fetal anomalies, intra-uterine growth restriction and abnormalities at the fetal heart rate (FHR) –monitoring. Participants were randomly allocated to induction of labour or expectant monitoring (n=1162)[4].
Women at study entry (randomisation) were inquired for a follow up 2 years after delivery, the hypertension risk assessment study (HyRAS).

**Participants: Non-exposed**

All exposed women will be asked to invite a friend as control. These women are required to have a history of one (or multiple) uncomplicated pregnancy (ies). This method will be used because of expected similar age and similar potential environmental exposures (i.e. socio-economic status). The non-exposed undergo the same procedure as the exposed at the local centre. Relatives of the exposed or of her partner will not be accepted in the non exposed group.

If the recruitment of non-exposed subjects in the method described above is not sufficient, the non-exposed group will be extended by approaching women with a history of at least one uncomplicated pregnancy in midwifery practices from three different locations in the Netherlands (Groningen, Leiden and The Hague).

**Ethical approval**

The Hyras and HYPITAT studies were approved both primarily for all participating hospitals in The Netherlands by the medical ethics committee of Leiden University Medical Centre (HYPITAT: P04·210) and locally by the hospital board of the participating hospitals. The clinical trial registration number of the HYPITAT trial is: ISRCTN08132825.

**Procedures, recruitment and collection of baseline data**

Women who participated in the HYPITAT study will be contacted by the research nurses 2½ years after delivery (study entry date) and they will be invited to participate in the HyRAS study in their local centre. Before entry into the study the research nurse or midwife counsels the patients, asks informed consent and emphasizes that participation is voluntarily. Patients who decide not to participate in this study for complete follow up will be asked to fill out the questionnaire to be analyzed separately. This questionnaire includes medical history, psychological status, social status, use of medication, contraceptive methods, obstetric history, and family history including thrombosis, diabetes and cardiovascular disease. Furthermore, pregnancy and lactation are exclusion criteria's for risk factor screening and those women will be asked to only fill out the questionnaire and participate for risk factor screening (blood samples, urine collection and blood pressure, length, weight and anthropometrics measurement) 3 months after the delivery or lactation, with an extension to 12 months after the original study entry date.

After enrollment exposed and non-exposed subjects will be asked to fill out a questionnaire and will be invited for risk indicator screening (blood samples, urine collection and blood pressure, length, weight and anthropometrics measurement). Venous blood samples will be taken after an overnight fast for analysis of lipids and lipoproteins, insulin, glucose and high sensitive CRP. Urine will be collected immediately after waking up for microalbuminuria. After centrifuging the blood samples for 9 minutes at 3000 bpm at the local centre, all samples will be sent to the same laboratory (Medical Centre Haaglanden, the Hague, the Netherlands) and analyzed within 24 hours. Plasma will be prepared and stored at -70 °C in 1.5 mL volumes until used. DNA will be isolated from leukocytes and stored at -20 °C. Blood pressure will be measured manually in sitting position at the

right upper arm. Body height (cm) and –weight (kg) will be measured with the participant dressed in light underclothes wearing shoes (except high heels) and waist circumference (cm) will be measured on uncovered skin using an inelastic tape measure with the participant in upright position, halfway between the rib cage and the pelvic bone. Hip circumference will also be measured.

Data- collection will be centralized and processed with adequate precautions to ensure patient confidentially. With the participant's informed consent, the study results will be sent to the general practitioner. Participants will also be informed on the results by mail, and in case of abnormal results it will be recommended to contact the general practitioner for evaluation or treatment.



**Outcome measures**

*Primary outcome measure*

The primary outcome measure will be the 10- year cardiovascular event risk. An absolute 10-year cardiovascular risk (fatal and non-fatal) of > = 10% as estimated with the SCORE risk function, will be considered as elevated risk. In addition, risk will be calculated using the Adult Treatment Panel III risk score, Reynolds Risk Score and QRISK.

*Secondary outcome measure*

Secondary outcomes will be differences between exposed and non-exposed subjects in cardiovascular parameters, differences in SNP's in glucose metabolism, and neonatal outcome 2 ½ years after pregnancy complicated by preeclampsia and gestational hypertension. Neonatal outcome includes neurological development and development of motor skills at the age of 2½ years. We will use a parental questionnaire (the Child Behaviour Checklist (CBCL) and ages and stages questionnaire (ASQ)). The health costs and benefits of a screening program for women with hypertensive complications at term will be analyzed.

**Statistical issues**

*Sample size*

Due to the young age of our participants, the estimated absolute 10-year cardiovascular risk is likely to be low. Therefore, the approach taken for each woman is to estimate the risk as if the woman was 60 years of age. This approach has been recommended in the cardiovascular risk factor management guidelines for young women with elevated risk factor levels. We plan to include women in 3:1 ratio, i.e. three women who had hypertension in pregnancy as compared to 1 control. A sample size of 414 women (310 exposed, 104 non exposed) is sufficient to demonstrate a risk increase from 5% to at least 15% (sided alpha.05. power

80%). This estimate is in line with our earlier studies showing a risk estimate > = 10% in over 30% of the *early* preeclampsia women[17].

*Data analysis*
All data are primarily analyzed to investigate the costs and potential health benefits of a screening program in order to assess if this screening programme is justified for all women with hypertensive pregnancy complications at term. In order to investigate the association between hypertensive disorders in pregnancy and maternal cardiovascular status Mann Whitney U tests or where indicated Chi-square will be used for comparisons between groups (exposed vs. non-exposed). Analysis in subgroups (i.e. gestational hypertension and preeclampsia) will be performed. Logistic regression analyses will be done with the maternal scores as dependent variables and the metabolic status, obstetric history, cardiovascular risk factors, diabetes risk factors and as independent variables.

## Discussion

Cardiovascular disease is the main cause of death of women in the Netherlands. In this study we will identify women that may be at higher risk for cardiovascular disease by their pregnancy complication: hypertensive pregnancy disorders at (near) term. Gestational hypertension and preeclampsia at (near) term are very common complications in pregnancy. Data concerning long term effects of pregnancies complicated by a hypertensive disorder at (near) term on cardiovascular disease are lacking for these women. Most studies concerning the effect of hypertensive disorders in pregnancy and cardiovascular disease in later life studied women who had severe *early-onset* preeclampsia, which is a rare disorder. Therefore, we conduct present study, which will provide evidence for the necessity of screening women on cardiovascular risk factors 2½ years after a pregnancy complicated by *term* gestational hypertension or preeclampsia.

## Reference List


(1) RIVM 2007 [http://www.rivm.nl/vtv/object_document/o2305n18837.html]

(2) Schuitemaker NEW, van Roosmalen J, Dekker GA, van Dongen P, van Geijn H, Bennebroek Gravenhorst J: Confidential enquiry into maternal deaths in the Netherlands 1983-1992. *Eur J Obstet Gynecol Reprod Biol* 1998, 79: 57-62

(3) Baha M, Sibai BM: Diagnosis and management of gestational hypertension and preeclampsia. *Obstet Gynecol* 2003, 102:181–192.

(4) Koopmans CM, Bijlenga D, Groen H, Vijgen SM, Aarnoudse JG, Bekedam DJ, van den Berg PP, de Boer K, Burggraaff JM, Bloemenkamp KW, Drogtrop AP, Franx A, de Groot CJM, Huisjes AJ, Kwee A, van Loon AJ, Lub A, Papatsonis DN, van der Post JA, Roumen FJ, Scheepers HC, Willekes C, Mol BW, van Pampus MG; for the HYPITAT study group: *Induction of labour versus expectant monitoring for gestational hypertension or mild pre-eclampsia after 36 weeks' gestation (HYPITAT): a multicentre, open-label randomised controlled trial. Lancet* 2009, 374: 979-88

(5) Sattar N, Greer IA, Pregnancy complications and maternal cardiovascular risk: opportunities for intervention and screening?. *BMJ* 2002, 325: 157-160

(6) Ramsay JE, Stewart F, Green IA and Sattar N: Microvascular dysfunction: a link between pre-eclampsia and maternal coronary heart disease. *BJOG* 2003, 110: 1029–1031

(7) Wilson BJ, Watson MS, Prescott GJ, Sunderland S, Campbell DM, Hannaford P, Smith WC: Hypertensive diseases of pregnancy and risk of hypertension and stroke in later life: results from cohort study. *BMJ* 2003, 326: 1–7.

(8) Haukkamaa L, Salminen, M Laivuori H, *Leinonen H*, *Hiilesmaa V*, *Kaaja R*.: Risk for subsequent coronary artery disease after preeclampsia. *Am J Cardiol* 2004, 93: 805–808.

(9) Smith GCS, Pell JP, Walsh D: Pregnancy complications and maternal risk of ischaemic heart disease: a retrospective cohort study of 129 290 births. *Lancet* 2001, 357: 2002-2006

(10) Irgens HU, Reisaeter L, Irgens LM, Lie RT: *Long term mortality of mothers and fathers after pre-eclampsia: population based cohort study. BMJ* 2001, 323(7323): 1213-7

(11) Jonsdottir LS, Arngrimsson R, Geirsson RT, Sigvaldason H, Sigfússon N: Death rates from ischemic heart disease in women with a history of hypertension in pregnancy. *Acta Obstet Gynecol Scand* 1995, 74: 772-6

(12) Manten GTR, Sikkema JM, Voorbij HAM, Visser GHA, Bruinse HW, Franx A: Risk factors for cardiovascular disease in women with a history of pregnancy complicated by preeclampsia or intrauterine growth restriction. Pregnancy as a challenge test for future cardiovascular disease. *Hypertens Pregnancy* 2007, 26: 39-50.

(13) Sattar N, Ramsay J, Crawford L, Cheyne H, Greer IA: Classic and novel risk factor parameters in women with a history of preeclampsia. *Hypertension* 2003, 42(1): 39-42

(14) van Rijn BB, Hoeks LB, Bots ML, Franx A, Bruinse HW: Outcomes of subsequent pregnancy after first pregnancy with early-onset preeclampsia. *Am J Obstet Gynecol* 2006, 195(3): 723-728

(15) Sibai B, Dekker G, Kupferminc M: Pre-eclampsia. *Lancet* 2005, 365: 785-799

(16) Wood DA, Kotseva K, Connolly S, Jennings C, Mead A, Jones J, Holden A, De Bacquer D, Collier T, De Backer G, Faergeman O; EUROACTION Study Group. Nurse-coordinated multidisciplinary, family-based cardiovascular disease prevention programme (EUROACTION) for patients with coronary heart disease and asymptomatic individuals at high risk of cardiovascular disease: a paired, cluster-randomised controlled trial. *Lancet* 2008, 371(9629):1999-201

(17) van Rijn BB: Early-onset preeclampsia: Constitutional factors and consequences for future pregnancy outcome and cardiovascular health. *PhD thesis*. Utrecht University; 2008

# *Chapter 6*

## Cardiovascular risk factors in women who had hypertensive disorders late in pregnancy: a cohort study

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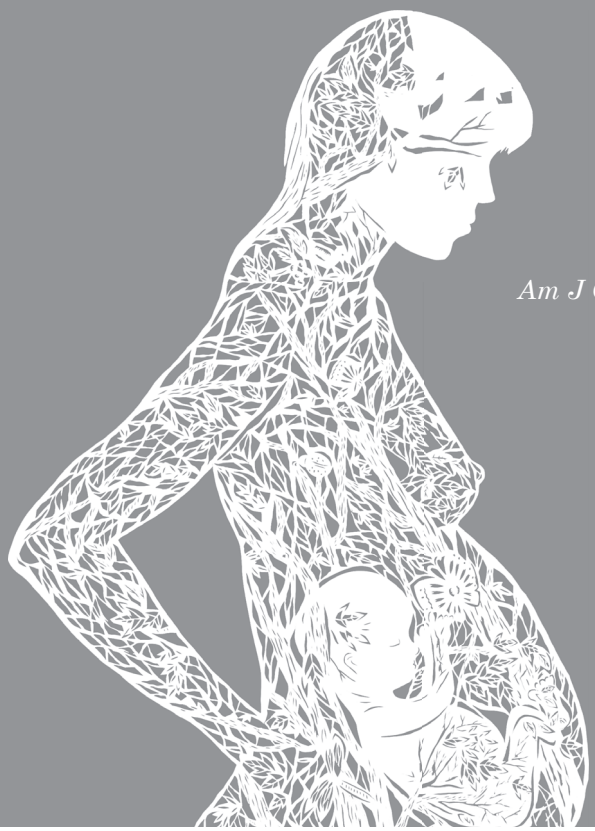
*Am J Obstet Gynecol 2013;208:474.e1-8*



## Abstract

**Objective:** The purpose of this study was to determine cardiovascular risk factors in women with a history of hypertensive pregnancy disorders at term, 2.5 years after pregnancy.

**Study Design:** In a multicenter cohort study in the Netherlands between June 2008 and November 2010, cardiovascular risk factors were compared between women with a history of hypertensive pregnancy disorders at term (HTP cohort, n=306) and women with a history of normotensive pregnancies at term (NTP cohort, n=99). HTP women had participated in a randomized, longitudinal trial assessing the effectiveness of induction of labor in women with hypertensive pregnancy disorders at term. All women were assessed 2.5 years after pregnancy for blood pressure, anthropometrics, glucose, HbA1C, insulin, HOMA score, total cholesterol, HDL cholesterol, triglycerides, high sensitive CRP and micro-albumin and metabolic syndrome.

**Results:** After a mean follow-up period of 2.5 years, hypertension (HTP, 34%; NTP, 1%; P<.001) and metabolic syndrome (HTP, 25%; NTP, 5%; P<.001) were more prevalent in HTP women compared with NTP women. HTP women had significantly higher systolic and diastolic blood pressure, higher BMI and waist circumference. Glucose, HbA1C, insulin, HOMA score, total cholesterol, triglycerides and high sensitive CRP-levels were significantly higher and HDL cholesterol was significantly lower in HTP women.

**Conclusions:** In women with a history of hypertensive pregnancy disorders at term hypertension and metabolic syndrome are more common, and they have higher levels of biochemical cardiovascular risk factors 2.5 years after pregnancy.

## Introduction

Cardiovascular disease (CVD) is the leading cause of death in women in the Western world.[1] Heart disease symptoms in women are different from symptoms in men and diagnostic tools in women seem to be less sensitive and specific than for men.[2]

Hypertensive disorders are common complications of pregnancy.[3] Observational studies have shown a relation between hypertensive disorders in pregnancy and CVD morbidity and mortality later in life.[4-10] This suggests that hypertensive disorders in pregnancy share common risk factors and pathophysiological pathways.[11;12] The exact underlying link between hypertensive pregnancy disorders and future CVD remains unclear. It has been suggested that pregnancy can potentially be looked upon as a "stress test", unmasking underlying defects, thus identifying women at a young age at increased risk for cardiovascular events.[13] Determining cardiovascular risk factors in women who respond to this "stress test" with transient hypertension could be an opportunity for identifying high-risk women for early prevention of modifiable cardiovascular risk factors.[14;15] Until now, most studies have focused on severe preterm preeclampsia, which is a rare disease. Most hypertensive disorders develop after 36 weeks of gestation. Therefore, we conducted a follow-up study of a randomized controlled trial in The Netherlands to assess cardiovascular risk factors in women with a history of hypertensive pregnancy disorders at term 2.5 years after their complicated pregnancy.



## Materials and Methods

### Ethics Statement

The follow-up study, was approved by the Institutional Review Board of the University of Leiden and locally approved by the hospital board of the participating hospitals. The study protocol has previously been published.[16] The current study is a follow-up study of the HYpertension and Preeclampsia Intervention Trial At Term, the HYPITAT study (trial registration: ISRCTN08132825).[17]

## Participants

### Hypertension in pregnancy cohort (HTP cohort)

Between October 2005 and March 2008 the HYPITAT study,[17] a multicenter, parallel, open-label randomized controlled trial of induction of labor versus expectant management, included women with gestational hypertension or preeclampsia at term (N=1153). At baseline (randomization), these women

consented to be contacted 2.5 years after their delivery to participate in the follow-up study.

**The HYPITAT study**

The HYPITAT study evaluated whether induction of labour improved maternal outcome in women with gestational hypertension or preeclampsia at term and included women with a singleton pregnancy at a gestational age between $36^{+0}$ and $41^{+0}$ weeks. The diastolic blood pressure thresholds for inlcusion in the HYPITAT study differed between gestational hypertension and preeclampsia as diastolic blood pressure of 90 mmHg without proteinuria was discussed and considered too mild and trivial for inclusion in the HYPITAT trial. Therefore, gestational hypertension was defined as a diastolic blood pressure of 95 mmHg or higher measured on two occasions at least six hours apart without proteinuria. Preeclampsia was defined as diastolic blood pressure of 90 mmHg or higher measured on two occasions at least six hours apart, combined with proteinuria (two or more occurrences of protein on a dipstick, > 300 mg total protein within a 24 hours urine collection, or ratio of protein to creatinine > 30 mg/mmol).

Other exclusion criteria included: antihypertensive medication use for chronic hypertension, diabetes mellitus, gestational diabetes treated with insulin, renal disease, heart disease, previous caesarean section, hemolysis elevated liver enzymes and low platelets syndrome (HELLP), oliguria of less than 500 mL per 24 hours, pulmonary edema or cyanosis, human immunodeficiency virus (HIV), use of intravenous antihypertensive medication, fetal anomalies, intrauterine growth restriction (IUGR), and abnormal fetal- heart rate monitoring.
In the HYPITAT study, which was analysed according intention to treat, women allocated to expectant monitoring were induced if they developed severe preeclampsia. Patients who refused randomization were analyzed separately after informed consent as non-randomized patients.

**The follow-up study**

From June 2008 until November 2010, women who had participated in the HYPITAT study were invited to participate in a longitudinal, follow-up study assessing cardiovascular risk factors 2.5 years after pregnancy. We used a follow-up period of 2.5 years as this time interval allows using pregnancy as a stress test to identify young women who are at high risk for cardiovascular disease in later life. Furthermore, 2.5 years is long enough to ensure that pregnancy and lactation have no influence on biochemical cardiovascular risk factor levels. Three academic hospitals and 17 non-academic hospitals across four geographical regions in the Netherlands (Leiden, Groningen, Amsterdam, Brabant) participated.

**Normotensive pregnancy cohort (NTP cohort)**

The NTP women were either friends of the HTP women or women from midwifery practices. NTP women were required to have had only uncomplicated normotensive pregnancies. Exclusion criteria for the NTP cohort included HELLP, gestational hypertension, preeclampsia, pre-existing hypertension, (gestational) diabetes, premature delivery, delivery of a neonate with intra uterine growth restriction (below the 5$^{th}$ percentile), renal disease, heart disease, and HIV. Initially, we asked HTP women if they had a friend who had given birth in the same period as the HTP woman and who could function as NTP woman. We assumed that friends would be similar in terms of age, demographic region, and ethnic origin. If an HTP woman did not have a friend who could function as NTP woman, we searched for a NTP woman in a midwifery practice of the same demographic region and matched for elapsed time since delivery. It is common practice in The Netherlands for women with no medical history or obstetrical history to have their antenatal care provided by a midwife. Data were collected from their medical records in midwifery practices. We collected and reviewed the NTP women's blood pressure measurements, maternal and fetal outcomes of index and previous pregnancies and deliveries in thorough detail. Relatives of the HTP women were excluded from the NTP cohort. Furthermore, women who were pregnant or lactating within the last three months were excluded from our study (n=101).



**Follow-up Study Procedure and Cardiovascular Risk Factor Assessment**

The study protocol has been previously published.[16] We refer to the supplement for a detailed description of the risk factor assessment methods and the laboratory methods.

In short, local research nurses counseled the participants, obtained written informed consent, monitored the study protocol in each center and collected the data. After enrollment all participants were invited for cardiovascular risk factor assessment, including blood pressure measurement, weight, height, and hip and waist circumference. Furthermore, all participants were asked to complete a questionnaire. This questionnaire included: medical history, current use of medication, obstetric history, subsequent pregnancy after index pregnancy and family history, including CVD.

Venous blood samples were collected after an overnight fast and assayed for: glucose, HbA1c, insulin, total cholesterol, HDL cholesterol, triglycerides and HsCRP. Insulin resistance was assessed by the homeostasis model assessment (HOMA): insulin concentration/ (22.5 $e^{-ln}$ glucose concentration).[18] Urine was collected immediately after waking up for assessment of micro-albuminuria.

After immediately centrifuging, the blood and urine samples were sent to a central laboratory in the Netherlands (Medical Center Haaglanden, The Hague, The Netherlands) and were analyzed within 36 hours after blood drawing.

## Definitions

Hypertension 2.5 years postpartum was defined as systolic blood pressure ≥ 140 mmHg, or a diastolic blood pressure ≥ 90 mmHg or current use of antihypertensive medication. Major independent risk factors were defined according to the American Heart Association, including blood pressure ≥ 140/90 mmHg, HDL cholesterol < 40 mg/dL, current smoking (%) and a family history of early cardiovascular disease (%)[19]. Metabolic syndrome was defined as waist circumference ≥ 80 cm. plus any two of raised triglycerides (> 150 mg/dL), reduced HDL cholesterol (< 50 mg/dL), raised blood pressure (systolic ≥ 130 mmHg and diastolic ≥ 85 mmHg), treatment of previously diagnosed hypertension, raised fasting plasma glucose (≥ 100 mg/dL) or previously diagnosed type 2 diabetes.[20]

## Sample size considerations

Our power analysis was based on individual risk estimation based on the Framingham Heart Study,[21] rather than on cardiovascular risk factors alone.[22] Due to the young age of our participants, the estimated absolute 10-year cardiovascular risk was likely to be low. Therefore, our approach was to estimate the risk for each woman as if the woman was 60 years old. This approach has been recommended in the cardiovascular risk factor management guidelines for young women with elevated risk factor levels.[23]

For detecting an estimated absolute 10-year cardiovascular risk difference between the HTP and NTP cohorts of 10% increase after extrapolation, we needed a sample size of 456 women for 80% power and a 5% type 1 error probability (two sided), for inclusion in 3:1 ratio (3 HTP: 1 NTP). This method was used according to an earlier study performed in severe early PE.[22] According to earlier studies[24-26] we expected a homogeneous effect with low prevalence of unfavorable cardiovascular risk factors in NTP women. Therefore, we have used a 3:1 inclusion ratio instead of 1:1 as we assumed that including more NTP women in 1:1 ratio would have no additional value in this study as a result of homogeneous outcome of cardiovascular risks.

## Statistical Analysis

Data were analyzed using SPSS software (version 18.0). Baseline continuous data are expressed as means and standard deviations (SD) or as medians with $25^{th}$ – $75^{th}$ percentile (IQR) for the not normally distributed values; dichotomous data are presented as numbers and percentages. Differences between groups were tested with the Student's t test and categorical data with the Chi-squared test ($X^2$ test). Comparisons of continuous data with a skewed distribution were performed using the non-parametric Mann-Whitney U test. We used logistic regression analyses and results were reported as odds ratios with corresponding 95% confidence intervals. We made adjustments for potential confounders, where appropriate, i.e. parity, BMI, smoking and age at follow-up and BMI at booking, systolic and diastolic blood pressure at booking and parity at booking. Furthermore, we performed a multi-center analysis which resulted in an intra-class correlation coefficient (ICC) of 2-4%. Therefore, we did not use a multi-level model for our analyses. For all tests, a p-value <0.05 indicated statistical significance.



## Results

Between June 2008 and November 2010, 306 women with a history of gestational hypertension or preeclampsia at term and 99 women with a history of uncomplicated normotensive pregnancies at term were included in the follow-up study.
Of the 751 eligible HTP women for the 2.5 year follow-up study, 168 women refused participation, 175 women were lost to follow-up and 101 pregnant or lactating women were excluded. One woman died in a car accident. The NTP cohort consisted of 40 women who were friends of the HTP women and 59 women who were identified from midwifery practices.

Baseline characteristics of the subjects are shown in Table 1. At index pregnancy, HTP women were more often nulliparous, had higher BMI at booking, higher systolic and diastolic blood pressures at booking, lower gestational age at delivery and lower birth weight compared with NTP women.

**Table 1.** Baseline characteristics at index pregnancy.

| Characteristic | NTP cohort[a] (n=99) | HTP cohort[b] (n=306) | P value |
|---|---|---|---|
| Maternal age, years | 31 (4.5) | 31 (5.1) | .70 |
| Ethnic origin: Caucasian | 94 (95%) | 273 (89%) | .15 |
| Other | 5 (5%) | 30 (10%) | |
| Unknown | 0 (0%) | 3 (1%) | |
| Nulliparous | 30 (30%) | 211 (69%) | <.001 |
| Systolic blood pressure at booking, mmHg | 113 (11) | 120 (12) | <.001 |
| Diastolic blood pressure at booking, mmHg | 66 (7.6) | 73 (9.0) | <.001 |
| Body mass index at booking, kg/m$^2$ | 24 (4.2) | 26 (4.9) | <.001 |
| Gestational age at delivery, weeks | 39.9 (1.2) | 39.4 (1.3) | <.001 |
| Birth weight, grams | 3630 (465) | 3395 (519) | <.001 |

Table shows mean (SD) or number (%). Differences between groups were tested with the Student's *t* test and categorical data with the Chi-squared test ($X^2$ test).

[a] NTP= normotensive term pregnancy

[b] HTP= hypertensive disorder in term pregnancy

At the 2.5 year follow-up study, HTP women were found to use more antihypertensive medication, had higher BMI, higher systolic and diastolic blood pressures and higher waist circumferences compared with NTP women. There were no significant differences in maternal age, elapsed time since delivery or smoking rates (Table 2).

**Table 2.** Outcome characteristics at 2.5 years follow-up.

| Characteristic | NTP cohort[a] (n=99) | HTP cohort[b] (n=306) | P value |
|---|---|---|---|
| Maternal age at follow up, years | 34 (4.7) | 34 (5.2) | .67 |
| Time elapsed since delivery, days | 965 (387) | 921 (161) | .11 |
| Primiparous | 30 (30%) | 123 (40%) | .04 |
| Antihypertensive medication use | 0 (0%) | 29 (9%) | <.001 |
| Systolic blood pressure at follow up, mmHg | 110 (9.3) | 124 (13) | <.001 |
| Diastolic blood pressure at follow up, mmHg | 72 (8.8) | 82 (9.6) | <.001 |
| Body mass index at follow up, kg/m$^2$ | 24 (4.6) | 28 (5.5) | <.001 |
| Waist circumference, cm. | 81 (12) | 90 (13) | <.001 |
| Hip circumference, cm. | 104 (11) | 109 (12) | <.001 |
| Smoking | 19 (19%) | 60 (20%) | .89 |

Table shows mean (SD) or number (%). Differences between groups were tested with the Student's *t* test and categorical data with the Chi-squared test ($X^2$ test).

[a] NTP= normotensive term pregnancy

[b] HTP= hypertensive disorder in term pregnancy

Table 3 shows biochemical cardiovascular risk factors 2.5 years after index pregnancy in HTP and NTP women. Fasting blood glucose, HbA1c, insulin, HOMA scores, total cholesterol, triglycerides and HsCRP were all significantly higher in HTP compared with NTP women. HDL cholesterol was significantly

lower in HTP women. We found higher micro-albumin levels in urine in HTP women, however this difference was not significant (P= 0.06).

**Table 3.** Biochemical cardiovascular risk factors 2.5 years after pregnancy.

| Biochemical cardiovascular risk factor | NTP cohort[a] (n=99) | HTP cohort[b] (n=306) | P value |
|---|---|---|---|
| Microalbumin urine[c], mmol/L | 4.0 (3.0-8.0) | 5.0 (3.0-10.0) | .06 |
| Fasting blood glucose[d], mg/dL | 85 (79-88) | 85 (81-92) | .01 |
| HbA1c[e], % | 5.3 (5.1-5.5) | 5.3 (5.1-5.6) | .04 |
| Insulin[f], mU/L | 2.9 (2.0-5.0) | 4.4 (2.0-7.6) | .003 |
| HOMA score[g] | 0.6 (0.4-1.0) | 1.0 (0.4-1.6) | .001 |
| HsCRP[h], mg/L | 0.9 (0.4-2.2) | 2.2 (1.0-5.0) | <.001 |
| Total cholesterol[i], mg/dL | 178 (151-197) | 182 (162-207) | .02 |
| HDL cholesterol[j], mg/dL | 56 (50-63) | 54 (46-62) | .03 |
| Triglycerides[j], mg/dL | 63 (48-91) | 81 (58-110) | <.001 |

Table shows median (interquartile range 25$^{th}$ to 75$^{th}$ percentile). Differences were tested with the non-parametric Mann-Whitney U test.

[a]NTP= normotensive term pregnancy, [b]HTP= hypertensive disorder in term pregnancy, [c]missing data of 6 NTP women and 9 HTP women, [d]missing data of 11 NTP women and 15 HTP women, [e]missing data of 6 NTP women and 14 HTP women, [f]missing data of 9 NTP women and 24 HTP women,[g]missing data of 11 NTP women and 25 HTP women, [h]missing data of 7 NTP women and 10 HTP women, [i]missing data of 5 NTP women and 5 HTP women, [j]missing data of 5 NTP women and 4 HTP women. The majority of missing data was caused by the fact that urine and blood samples were only processed within 36 hours after sampling. Samples which arrived after this period were cancelled for analysis.

The prevalence of four major cardiovascular risk factors and the prevalence of multiple major cardiovascular risk factors and metabolic syndrome in HTP and NTP women are summarized in Table 4. The adjusted odds ratio of HTP women for hypertension 2.5 years postpartum was 48. On the contrary, there were no significant differences between HTP and NTP women in the other three major independent risk factors: HDL cholesterol, currently smoking or family history of early cardiovascular disease. Multiple risk factors were present in 18% of the HTP women compared with 7% of NTP women (P= 0.01), including 4% of HTP women with three or more independent risk factors compared to 0% in NTP women. Metabolic syndrome was found in 25% of HTP and in 5% of NTP women; OR 6.0 (95% CI 2.3 to 15.3) even after adjustment for maternal age and after adjustment for baseline differences.

Surprisingly, we found a prevalence of chronic hypertension of 34% in the HTP cohort 2.5 years postpartum, of which 29 women (28%) had started antihypertensive medication at 2.5 years after pregnancy. This unexpected high prevalence might partially be explained by inclusion in the HYPITAT study of some women with chronic hypertension, which was initially masked by the

physiological fall of blood pressure in early pregnancy. Therefore, we performed sub-analyses and divided the HTP cohort in 'MAP at booking and blood pressure at booking' subgroups. As can be seen from table 5, even when we studied the subgroup of women who had a blood pressure of <120/70 mmHg at booking, the probability of hypertension after 2.5 years was still as high as 27%. 94 HTP women (31%) had developed severe hypertensive disease during their index pregnancy.

**Table 4.** Major independent cardiovascular risk factors, multiple risk factors and metabolic syndrome.

| Independent CVD Risk Factor and Metabolic Syndrome | NTP cohort[a] (n=99) | HTP cohort[b] (n=306) | Unadjusted OR (95% CI) | Adjusted OR[1] (95% CI) | Adjusted OR[2] (95% CI) | P value |
|---|---|---|---|---|---|---|
| Blood pressure[c], ≥ 140/90 mmHg | 1 (1%) | 105 (34%) | 51.5 (7.1 to 374) | 47.5[d] (6.5 to 350) | 36.4 (4.8 to 276) | <.001 |
| HDL cholesterol[e], < 40 mg/dL | 10 (11%) | 37 (12%) | 1.2 (0.6 to 2.5) | 0.8[d] (0.3 to 1.8) | 1.1 (0.4 to 2.8) | 0.53 |
| Current smoking[f], % | 19 (19%) | 60 (21%) | 1.1 (0.6 to 1.9) | 1.01[g] (0.6 to 1.1) | 1.1 (0.5 to 2.1) | 0.98 |
| Family history, early CVD[h], % | 11 (11%) | 48 (16%) | 1.6 (0.8 to 3.1) | 1.7[g] (0.8 to 3.5) | 2.0 (0.9 to 4.2) | 0.15 |
| ≥ 1 independent risk factor [i] | 32 (34%) | 184 (61%) | 3.0 (1.9 to 4.9) | 3.2[j] (1.9 to 5.3) | 2.7 (1.5 to 4.9) | <.001 |
| ≥ 2 independent risk factors [i] | 7 (7%) | 54 (18%) | 2.7 (1.2 to 6.2) | 3.1[j] (1.3 to 7.5) | 3.0 (1.0 to 9.0) | 0.01 |
| Metabolic syndrome[k] | 5 (5%) | 73 (25%) | 6.0 (2.3 to 15) | 5.9 [l] (2.3 to 15) | 3.3 (1.2 to 9.1) | <.001 |

Table shows number (%) and odds ratio (OR) with corresponding 95% confidence intervals (95% CI).

We used logistic regression analyses; we made adjustments for potential confounders 2.5 years after pregnancy (= adjusted OR[1]) inlcuding parity, BMI (continuous variable), smoking and age at follow-up and we made adjustment for differences at baseline (= adjusted OR[2]) including BMI at booking, systolic and diastolic blood pressure at booking and parity at booking.

[a]NTP= normotensive term pregnancy, [b]HTP= hypertensive disorder in term pregnancy. [c]Missing data of 1 HTP woman, [d] adjusted for age, BMI, parity and smoking, [e]Missing data of 5 NTP women and 4 HTP women,[f]Missing data of 1 NTP women and 13 HTP women, [g]Adjusted for age, [h]missing data of 1 NTP women and 14 HTP women, [i]missing data of 5 NTP women and 4 HTP women, [j]adjusted for age and parity, [k]missing data of 4 NTP women and 14 HTP women, [l]adjusted for age, parity and smoking. The majority of missing data was caused by the fact that urine and blood samples were only processed within 36 hours after sampling. Samples which arrived after this period were cancelled for analysis.

**Table 5.** Prevalence of hypertension per blood pressure subgroup 2.5 years' postpartum

| **Cutoff value for subgroup based on blood pressure at booking in index pregnancy** | | | |
|---|---|---|---|
| MAP[a] at booking ≥ 100 mmHg | Criterion | Yes | No |
| | No of women (%) | 35 (11%) | 271 (89%) |
| | Prevalence of hypertension 2.5 years postpartum | 57% | 32% |
| MAP[a] at booking ≥ 90 mmHg | Criterion | Yes | No |
| | No of women (%) | 147 (48%) | 159 (52%) |
| | Prevalence of hypertension 2.5 years postpartum | 44% | 25% |
| Blood pressure at booking ≥ 130/75 mmHg | Criterion | Yes | No |
| | No of women (%) | 167 (55%) | 139 (45%) |
| | Prevalence of hypertension 2.5 years postpartum | 44% | 23% |
| Blood pressure at booking ≥ 120/70 mmHg | Criterion | Yes | No |
| | No of women (%) | 251 (82%) | 55 (18%) |
| | Prevalence of hypertension 2.5 years postpartum | 36% | 27% |

Table shows number (%).

[a] MAP = Mean Arterial Pressure.



## Comment

The main finding of the follow-up study is that women with a history of gestational hypertension or preeclampsia at term have a high risk of hypertension 2.5 years after their pregnancy. Additionally, women with a history of gestational hypertension or preeclampsia at term exhibit more cardiovascular risk factors 2.5 years after their pregnancy compared with women with a history of uncomplicated normotensive pregnancies. They have higher waist circumferences, higher BMI, higher systolic and diastolic blood pressures, a higher prevalence of metabolic syndrome and higher levels of biochemical risk factors, including glucose, HbA1c, insulin, insulin resistance (HOMA), total cholesterol, triglycerides and HsCRP and lower levels of HDL cholesterol 2.5 years postpartum compared with women with a history of normotensive pregnancies.

Our results after hypertensive pregnancy disorders at term are in line with results from previous studies. These studies reported higher blood pressure, higher BMI, higher concentrations of lipids and insulin resistance in women with previous hypertensive pregnancy disorders.[7;24;27-46] However, previous studies included only women with severe preterm preeclampsia[29;36;37] gestational age was not reported,[27;28;38;39;41;42;45] nor was distinction made between preterm preeclampsia and term preeclampsia.[24;32-34;38;40;43;44;46] This makes it difficult to draw a conclusion about the association of hypertensive disorders in term

pregnancy and the presence of cardiovascular risk factors after pregnancy. In literature, two other studies have determined cardiovascular risk factors after "mainly" term hypertensive pregnancy disorders.[34;43] These studies showed similar results to our study, despite the fact that both studies are small (N= 43 and N= 30, respectively). Differences between our study and previous studies can be explained by differences in follow-up periods, study population, e.g. nulliparous and multiparous women, or chronic hypertension. While other studies, which mostly included women with severe preterm preeclampsia, found significantly higher microalbumin levels postpartum compared to control subjects (mean difference 8.55, 95% CI 2.11-14.98)[47], we showed a trend towards higher micro albumin levels in HTP women compared to NTP women (p=.06). Due to the sample size, our finding did not reach statistical significance.

We found an unexpected high prevalence of hypertension 2.5 years postpartum in the HTP cohort, namely 34% compared with 1% in the NTP cohort. The high prevalence was unexpected; especially because women with preexisting hypertension with antihypertensive medication use (before index pregnancy) were excluded from our study. Due to physiological blood pressure reduction in the first trimester, inclusion of women with (sub) clinical chronic hypertension without the use of antihypertensive medication might explain, at least partly, the high prevalence of hypertension 2.5 years postpartum in our study. However, the prevalence of chronic hypertension 2.5 years postpartum in the lowest blood pressure at booking subcategory ≤ 130/75 mmHg was still as high as 23% and thus of clinical interest. We assumed that women with a blood pressure at booking below 130/75 mmHg do not suffer chronic hypertension.Another consideration is that we performed the follow-up of only 306 HTP women (27% of the HYPITAT cohort (N=1153)), which might have resulted in selection bias. The selection bias might result in an overestimation of the prevalence of chronic hypertension in HTP women. However, the fact that women who were not included in the follow-up study had higher diastolic blood pressures at booking compared to included women argues against overestimation of chronic hypertension in HTP women. Women who were included in the follow-up study were significantly older at baseline compared to women who were not included. All other baseline characteristics were comparable between included and non-included women (data not shown). If the resulting 847 women, who were not included in the follow-up study, would all have been normotensive 2.5 years postpartum, we would have introduced the most extreme selection bias. Even then, the minimum detection rate for chronic hypertension for HTP women is 9%. To put these percentages in perspective: The prevalence of chronic hypertension in The Netherlands, among women in a comparable age group between 30 and 40 years in 2010, was 5.5%. Thus, a detection rate between a minimum of 9% and a maximum of 34% in

women with a history of gestational hypertension or preeclampsia at term is of great interest for health care providers.

The major strength of our study is twofold: First, we focused on women with a history of hypertensive pregnancy disorders at term, which are common disorders in pregnancy and of daily obstetric care. Second, we longitudinal followed HTP women who were included in a randomized controlled trial and we had a pre-specified hypothesis and objective at baseline, providing a large and strong HTP cohort.
The finding, that the common pregnancy disorders gestational hypertension and preeclampsia at term are associated with a high risk of hypertension and more cardiovascular risk factors, makes this study original and of interest for not only obstetricians, but also for internists, cardiologists and general physicians.



Our study has a few limitations. First, the study design of the HYPITAT trial was to compare two different strategies at term in women with one pregnancy complication, namely gestational hypertension or preeclampsia, without comparison to a control group. To compare cardiovascular risk factors after 2.5 years we secondarily added a control group. For that purpose, baseline data of the index pregnancy of NTP women were collected from review of medical records at the time of inclusion in the follow-up study. The information on the variables addressed in this manuscript was nearly all complete in the medical charts. HTP and NTP women were comparable according to age, race, and demographic region. From etiological perspective, it would have been ideally to have matched HTP and NTP women for BMI at booking, blood pressure at booking and parity. Instead, we preferred a pragmatic approach as we aimed to study whether hypertensive pregnancy disorders in term pregnancy can be used as a stress test for cardiovascular risk factor screening to identify women who are at risk for cardiovascular disease later. We performed a multivariate analysis taking all the differences at baseline into account (table 4). The results of that approach showed that even after adjustment for baseline factors HTP women had a significantly higher prevalence of hypertension and metabolic syndrome 2.5 years after pregnancy. A problem with a multivariate model like that is that the differences were based on definitions of the cohort. However, it does not invalidate our findings showing that women with a history of hypertensive pregnancy disorders at term still have unfavourable risk factors 2.5 years after pregnancy.
A second limitation concerns the voluntary contribution of NTP women, which may have introduced selection bias. NTP women with a family history of CVD are probably more likely to participate in a study on risk of CVD than women

with a "healthy" family history. However, family history of first degrees with a cardiovascular event < 60 years was not significantly different between both groups. Moreover, this potential bias underestimates the differences between HTP and NTP women.
Finally, as a consequence of the relative young age of the study participants, this study evaluated surrogate endpoints; cardiovascular risk factors rather than cardiovascular clinical outcomes.

Our study results strongly suggest that women with a history of gestational hypertension or preeclampsia at term may be offered screening and counseling for cardiovascular risk factors after their pregnancy. Before wide implementation in practice however, strategies of cardiovascular risk factor screening and subsequent tailored preventive interventions need to be evaluated for feasibility and clinical and cost effectiveness.

## Reference List


(1) Jacobs AK, Eckel RH. Evaluating and managing cardiovascular disease in women: understanding a woman's heart. Circulation 2005; 111(4):383-384.

(2) Rich-Edwards JW, Manson JE, Hennekens CH, Buring JE. The primary prevention of coronary heart disease in women. N Engl J Med 1995; 332(26):1758-1766.

(3) Sibai BM. Diagnosis and management of gestational hypertension and preeclampsia. Obstet Gynecol 2003; 102(1):181-192.

(4) Haukkamaa L, Salminen M, Laivuori H, Leinonen H, Hiilesmaa V, Kaaja R. Risk for subsequent coronary artery disease after preeclampsia. Am J Cardiol 2004; 93(6):805-808.

(5) Irgens HU, Reisaeter L, Irgens LM, Lie RT. Long term mortality of mothers and fathers after pre-eclampsia: population based cohort study. BMJ 2001; 323(7323):1213-1217.

(6) Jonsdottir LS, Arngrimsson R, Geirsson RT, Sigvaldason H, Sigfusson N. Death rates from ischemic heart disease in women with a history of hypertension in pregnancy. Acta Obstet Gynecol Scand 1995; 74(10):772-776.

(7) Ramsay JE, Stewart F, Greer IA, Sattar N. Microvascular dysfunction: a link between pre-eclampsia and maternal coronary heart disease. BJOG 2003; 110(11):1029-1031.

(8) Sattar N, Greer IA. Pregnancy complications and maternal cardiovascular risk: opportunities for intervention and screening? BMJ 2002; 325(7356):157-160.

(9) Smith GC, Pell JP, Walsh D. Pregnancy complications and maternal risk of ischaemic heart disease: a retrospective cohort study of 129,290 births. Lancet 2001; 357(9273):2002-2006.

(10) Wilson BJ, Watson MS, Prescott GJ, Sunderland S, Campbell DM, Hannaford P et al. Hypertensive diseases of pregnancy and risk of hypertension and stroke in later life: results from cohort study. BMJ 2003; 326(7394):845.

(11) Rodie VA, Freeman DJ, Sattar N, Greer IA. Pre-eclampsia and cardiovascular disease: metabolic syndrome of pregnancy? Atherosclerosis 2004; 175(2):189-202.

(12) Sattar N, Bendomir A, Berry C, Shepherd J, Greer IA, Packard CJ. Lipoprotein subfraction concentrations in preeclampsia: pathogenic parallels to atherosclerosis. Obstet Gynecol 1997; 89(3):403-408.

(13) McDonald SD, Malinowski A, Zhou Q, Yusuf S, Devereaux PJ. Cardiovascular sequelae of preeclampsia/eclampsia: a systematic review and meta-analyses. Am Heart J 2008; 156(5):918-930.

(14) Stampfer MJ, Hu FB, Manson JE, Rimm EB, Willett WC. Primary prevention of coronary heart disease in women through diet and lifestyle. N Engl J Med 2000; 343(1):16-22.

(15) Pearson TA, Blair SN, Daniels SR, Eckel RH, Fair JM, Fortmann SP et al. AHA Guidelines for Primary Prevention of Cardiovascular Disease and Stroke: 2002 Update: Consensus Panel Guide to Comprehensive Risk Reduction for Adult Patients Without Coronary or Other Atherosclerotic Vascular Diseases. American Heart Association Science Advisory and Coordinating Committee. Circulation 2002; 106(3):388-391.

(16) Hermes W, Franx A, van Pampus MG, Bloemenkamp KW, van der Post JA, Porath M et al. 10-Year cardiovascular event risks for women who experienced hypertensive disorders in late pregnancy: the HyRAS study. BMC Pregnancy Childbirth 2010; 10:28.

(17) Koopmans CM, Bijlenga D, Groen H, Vijgen SM, Aarnoudse JG, Bekedam DJ et al. Induction of labour versus expectant monitoring for gestational hypertension or mild pre-eclampsia after 36 weeks' gestation (HYPITAT): a multicentre, open-label randomised controlled trial. Lancet 2009; 374(9694):979-988.
(18) Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985; 28(7):412-419.
(19) Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002; 106(25):3143-3421.
(20) Alberti KG, Zimmet P, Shaw J. The metabolic syndrome--a new worldwide definition. Lancet 2005; 366(9491):1059-1062.
(21) Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. Circulation 1998; 97(18):1837-1847.
(22) van Rijn BB. Early onset preeclampsia: Constitutional factors and consequences for future pregnancy outcome and cardiovascular health [ 2008.
(23) De BG, Ambrosioni E, Borch-Johnsen K, Brotons C, Cifkova R, Dallongeville J et al. European guidelines on cardiovascular disease prevention in clinical practice. Third Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice. Eur Heart J 2003; 24(17):1601-1610.
(24) Smith GN, Walker MC, Liu A, Wen SW, Swansburg M, Ramshaw H et al. A history of preeclampsia identifies women who have underlying cardiovascular risk factors. Am J Obstet Gynecol 2009; 200(1):58.
(25) Spaan JJ, Houben AJHM, Musella A, Ekhart T, Spaanderman MEA, Peeters LLH. Insulin resistance relates to microvascular reactivity 23years after preeclampsia. Microvasc Res 2010; 80(3):417-421.
(26) Nijdam ME, Timmerman MR, Franx A, Bruinse HW, Numans ME, Grobbee DE et al. Cardiovascular risk factor assessment after pre-eclampsia in primary care. BMC Fam Pract 2009; 10:77.
(27) He S, Silveira A, Hamsten A, Blomback M, Bremme K. Haemostatic, endothelial and lipoprotein parameters and blood pressure levels in women with a history of preeclampsia. Thromb Haemost 1999; 81(4):538-542.
(28) Hubel CA, Snaedal S, Ness RB, Weissfeld LA, Geirsson RT, Roberts JM et al. Dyslipoproteinaemia in postmenopausal women with a history of eclampsia. BJOG 2000; 107(6):776-784.
(29) Manten GT, Sikkema MJ, Voorbij HA, Visser GH, Bruinse HW, Franx A. Risk factors for cardiovascular disease in women with a history of pregnancy complicated by preeclampsia or intrauterine growth restriction. Hypertens Pregnancy 2007; 26(1):39-50.
(30) Barden AE, Beilin LJ, Ritchie J, Walters BN, Michael C. Does a predisposition to the metabolic syndrome sensitize women to develop pre-eclampsia? J Hypertens 1999; 17(9):1307-1315.
(31) Berends AL, de Groot CJ, Sijbrands EJ, Sie MP, Benneheij SH, Pal R et al. Shared constitutional risks for maternal vascular-related pregnancy complications and future cardiovascular disease. Hypertension 2008; 51(4):1034-1041.
(32) Forest JC, Girouard J, Masse J, Moutquin JM, Kharfi A, Ness RB et al. Early occurrence of metabolic syndrome after hypertension in pregnancy. Obstet Gynecol 2005; 105(6):1373-1380.

(33) Laivuori H, Tikkanen MJ, Ylikorkala O. Hyperinsulinemia 17 years after preeclamptic first pregnancy. J Clin Endocrinol Metab 1996; 81(8):2908-2911.
(34) Nisell H, Erikssen C, Persson B, Carlstrom K. Is carbohydrate metabolism altered among women who have undergone a preeclamptic pregnancy? Gynecol Obstet Invest 1999; 48(4):241-246.
(35) Sattar N, Ramsay J, Crawford L, Cheyne H, Greer IA. Classic and novel risk factor parameters in women with a history of preeclampsia. Hypertension 2003; 42(1):39-42.
(36) Lampinen KH, Ronnback M, Groop PH, Kaaja RJ. A relationship between insulin sensitivity and vasodilation in women with a history of preeclamptic pregnancy. Hypertension 2008; 52(2):394-401.
(37) Norden LS, Hanson U. Hypertension and factors associated with metabolic syndrome at follow-up at 15 years in women with hypertensive disease during first pregnancy. Hypertens Pregnancy 2000; 19(2):191-198.
(38) Bar J, Kaplan B, Wittenberg C, Erman A, Boner G, Ben-Rafael Z et al. Microalbuminuria after pregnancy complicated by pre-eclampsia. Nephrol Dial Transplant 1999; 14(5):1129-1132.
(39) Chambers JC, Fusi L, Malik IS, Haskard DO, De SM, Kooner JS. Association of maternal endothelial dysfunction with preeclampsia. JAMA 2001; 285(12):1607-1612.
(40) Freeman DJ, McManus F, Brown EA, Cherry L, Norrie J, Ramsay JE et al. Short- and long-term changes in plasma inflammatory markers associated with preeclampsia. Hypertension 2004; 44(5):708-714.
(41) Hubel CA, Powers RW, Snaedal S, Gammill HS, Ness RB, Roberts JM et al. C-reactive protein is elevated 30 years after eclamptic pregnancy. Hypertension 2008; 51(6):1499-1505.
(42) Innes KE, Weitzel L, Laudenslager M. Altered metabolic profiles among older mothers with a history of preeclampsia. Gynecol Obstet Invest 2005; 59(4):192-201.
(43) Paradisi G, Biaggi A, Savone R, Ianniello F, Tomei C, Caforio L et al. Cardiovascular risk factors in healthy women with previous gestational hypertension. J Clin Endocrinol Metab 2006; 91(4):1233-1238.
(44) Portelinha A, Belo L, Cerdeira AS, Braga J, Tejera E, Pinto F et al. Lipid levels including oxidized LDL in women with history of preeclampsia. Hypertens Pregnancy 2010; 29(1):93-100.
(45) Pouta A, Hartikainen AL, Sovio U, Gissler M, Laitinen J, McCarthy MI et al. Manifestations of metabolic syndrome after hypertensive pregnancy. Hypertension 2004; 43(4):825-831.
(46) Wolf M, Hubel CA, Lam C, Sampson M, Ecker JL, Ness RB et al. Preeclampsia and future cardiovascular disease: potential role of altered angiogenesis and insulin resistance. J Clin Endocrinol Metab 2004; 89(12):6239-6243.
(47) McDonald SD, Han Z, Walsh MW, Gerstein HC, Devereaux PJ. Kidney disease after preeclampsia: a systematic review and meta-analysis. Am J Kidney Dis 2010; 55(6):1026-1039.

# *Chapter 7*

## Cardiovascular risk estimation in women with a history of hypertensive pregnancy disorders at term: A longitudinal follow-up study

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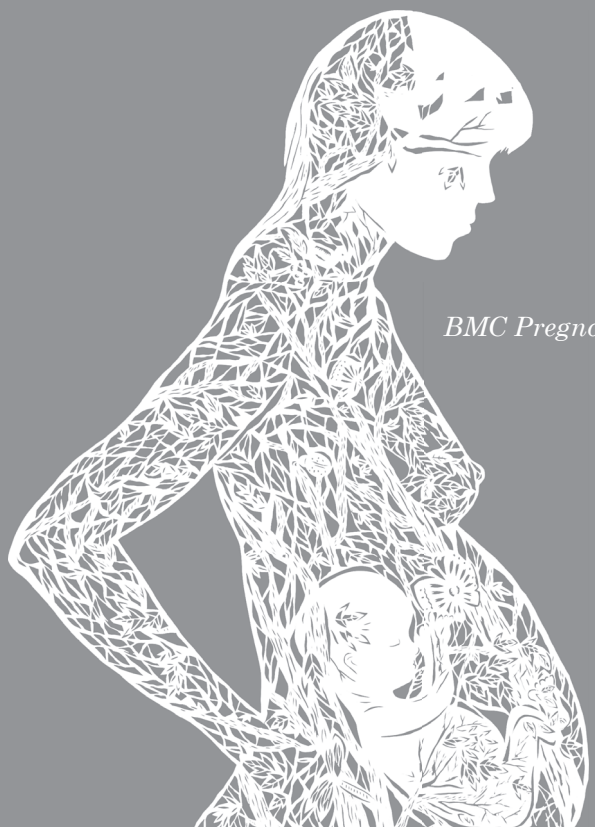


## Abstract

**Background:** Cardiovascular disease is associated with major morbidity and mortality in women in the Western world. Prediction of an individual cardiovascular disease risk in young women is difficult. It is known that women with hypertensive pregnancy complications have an increased risk for developing cardiovascular disease in later life and pregnancy might be used as a cardiovascular stress test to identify women who are at high risk for cardiovascular disease. In this study we assess the possibility of long term cardiovascular risk prediction in women with a history of hypertensive pregnancy disorders at term.

**Methods:** In a longitudinal follow-up study, between June 2008 and November 2010, 300 women with a history of hypertensive pregnancy disorders at term (HTP cohort) and 94 women with a history of normotensive pregnancies at term (NTP cohort) were included. From the cardiovascular risk status that was known two years after index pregnancy we calculated individual (extrapolated) 10-and 30-year cardiovascular event risks using four different risk prediction models including the Framingham risk score, the SCORE score and the Reynolds risk score. Continuous data were analyzed using the Student's T test and Mann-Whitney U test and categorical data by the Chi-squared test. A poisson regression analysis was performed to calculate the incidence risk ratios and corresponding 95% confidence intervals for the different cardiovascular risk estimation categories.

**Results:** After a mean follow-up of 2.5 years, HTP women had significantly higher mean (SD) extrapolated 10-year cardiovascular event risks (HTP 7.2% (3.7); NTP 4.4% (1.9) ($p<.001$, IRR 5.8, 95% CI 1.9 to 19)) and 30-year cardiovascular event risks (HTP 11% (7.6); NTP 7.3% (3.5) ($p<.001$, IRR 2.7, 95% CI 1.6 to 4.5)) as compared to NTP women calculated by the Framingham risk scores. The SCORE score and the Reynolds risk score showed similar significant results.

**Conclusions:** Women with a history of gestational hypertension or preeclampsia at term have higher predicted (extrapolated) 10-year and 30-year cardiovascular event risks as compared to women with a history of uncomplicated pregnancies. Further large prospective studies have to evaluate whether hypertensive pregnancy disorders have to be included as an independent variable in cardiovascular risk prediction models for women.

## Background

Cardiovascular disease is associated with major morbidity and mortality in women in the Western world[1]. Women are less likely to receive appropriate cardiovascular preventive care compared to men and heart disease in women is not always recognized as a major health care concern[2]. Several epidemiological studies have demonstrated the association between hypertensive pregnancy disorders and cardiovascular morbidity and mortality in later lifes[3-9]. Subsequently, it has been suggested that pregnancy may act as an early natural *"stress test"* unmasking underlying defects and thereby identifying women at high risk for cardiovascular disease in later life[10].

Worldwide, different risk prediction models have been developed for individual risk prediction of cardiovascular disease in both apparently healthy men and women[11-17]. Currently, the Framingham risk score is the most compared score in literature and widely used in North American countries[18], while the systematic coronary risk evaluation (SCORE) score has been advised by the European guidelines[19]. In spite of the existence and use of several risk prediction models, it remains a great challenge to determine which *specific* woman is at high risk for cardiovascular disease, especially in *young* women.



Obstetric history, e.g. hypertensive pregnancy disorders, is not included as a variable in cardiovascular risk prediction models. However, obstetric history may help to identify women, who are at high risk for cardiovascular disease in later life; they may benefit from early cardiovascular risk screening after their complicated pregnancy together with subsequent individual cardiovascular risk prediction and primary prevention programs[20, 21]. Mosca et al. showed that women, who perceive themselves at risk for cardiovascular disease and know the goals for prevention, are motivated to take action toward a heart healthy life style[2, 22].

In the present study, we assess cardiovascular event risks in women with a history of gestational hypertension or preeclampsia at term using four previous described validated cardiovascular risk prediction models, including the 10-year Framingham risk score, the 30-year Framingham risk score, the 10-year estimation by the SCORE score, and the 10-year estimation by the Reynolds risk score. According to the European cardiovascular risk factor management guidelines for young women with elevated risk factor levels[23], we extrapolate the 10-year cardiovascular disease risks as if the woman is 60 years old. The aim of this study is to compare these estimated (extrapolated) 10-year and 30-year cardiovascular disease risks between women with a history of term gestational

hypertension or term preeclampsia and women with a history of term normotensive pregnancies, in order to improve assessment of reliable cardiovascular risk estimation for the long term cardiovascular disease outcome in relatively young women.

## Methods

### Participants

We studied 300 women who had delivered in the Netherlands between 2005 and 2008, with the diagnosis term gestational hypertension or term preeclampsia after 36 weeks' gestation and 94 healthy control women after uncomplicated term pregnancies. The women were invited for participation in the current follow-up study on cardiovascular event risk estimation.

We enrolled women with a history of term gestational hypertension or term preeclampsia from the Hypertension and Pre-eclampsia Intervention Trial At Term (the HYPITAT study)[24]. Control women were friends of the patients or women from midwifery practices from three different locations in the Netherlands (Groningen, Leiden and The Hague) and they were required to have only previous uncomplicated normotensive pregnancies. A detailed description of all inclusion and exclusion criteria was previously published elsewhere[25,26]. Exclusion criteria for participation in the HYPITAT trial and the follow-up study included: antihypertensive medication use for chronic hypertension, diabetes mellitus, gestational diabetes treated with insulin, renal disease, heart disease, previous caesarean section, hemolysis elevated liver enzymes and low platelets syndrome (HELLP), oliguria of less than 500 mL per 24 hours, pulmonary edema or cyanosis, human immunodeficiency virus (HIV), use of intravenous antihypertensive medication, fetal anomalies, intrauterine growth restriction (IUGR), and abnormal fetal- heart rate monitoring. Exclusion criteria for the NTP cohort included HELLP, gestational hypertension, preeclampsia, pre-existing hypertension, (gestational) diabetes, premature delivery, delivery of a neonate with intra uterine growth restriction (below the 5$^{th}$ percentile), renal disease, heart disease, and HIV.

Pregnant and lactating women (within the last three months) were excluded from the follow-up study.

The study was approved by the Institutional Review Board of the University of Leiden (HYPITAT: P04.210) and locally approved by the hospital board of the participating hospitals.

**Definitions**

Gestational hypertension was defined as diastolic blood pressure of 95 mmHg or higher measured on two occasions at least six hours apart. Preeclampsia was defined as diastolic blood pressure of 90 mmHg or higher measured on two occasions at least six hours apart, combined with proteinuria (two or more occurrences of protein on a dipstick, > 300 mg total protein within a 24 hours urine collection, or ratio of protein to creatinine > 30 mg/mmol). Severe gestational hypertension or severe preeclampsia were defined as either systolic blood pressure of 170 mmHg or higher, diastolic blood pressure of 110 mmHg or higher, or proteinuria of 5 gram or higher per 24 hours.

Hypertension at follow-up was defined as systolic blood pressure ≥ 140 mmHg, or a diastolic blood pressure ≥ 90 mmHg or current use of antihypertensive medication.

**Classic cardiovascular risk factor assessment**

A detailed description of the cardiovascular risk factor assessment and laboratory procedures has been published elsewhere[25]. In short, after enrolment all participants were invited for cardiovascular risk factor assessment. After written informed consent they were asked to complete a questionnaire including questions about their medical history, current medication use, obstetric history, subsequent pregnancy after index pregnancy and family history, including cardiovascular disease. Cardiovascular risk factor assessment included: blood pressure measurement, height and weight (with calculated body mass index (BMI)), and fasting venous blood sample drawing, assayed for: glucose, HDL cholesterol, triglycerides and (high sensitive) C-reactive protein.

**Individual cardiovascular risk prediction**

For the prediction of the 10-year general cardiovascular disease risk by the Framingham risk score, cardiovascular risk factors were used according to the methodology reported by D'Agostino et al.[27], i.e. age, total cholesterol, HDL cholesterol, systolic blood pressure, treatment for hypertension, and smoking. 10-Year general cardiovascular disease was defined as coronary death, myocardial infarction, coronary insufficiency, angina, ischemic stroke, hemorrhagic stroke, transient ischemic attack, peripheral artery disease, and heart failure.

30-Year full cardiovascular disease estimation by the Framingham risk score was calculated using the algorithm reported by Pencina et al.[15] 30-Year full cardiovascular disease was defined as coronary death, myocardial infarction, fatal and non-fatal stroke, coronary insufficiency, angina pectoris, transient ischemic attack, intermittent claudication and congestive heart failure.

For prediction of 10-year risk of fatal cardiovascular disease by the SCORE score estimation, risk factors were used according to the algorithm reported by Conroy et al.[11], including age, total cholesterol, systolic blood pressure and smoking. Fatal cardiovascular disease was defined as ICD-9 codes 798.1, 798.2, 401 through 414 and 426 through 443, with the exception of the ICD-9 codes: 426.7, 429.0, 430.0, 432.1, 437.3, 437.4 and 437.5.

For prediction of global cardiovascular disease risk by the Reynolds risk score we used cardiovascular risk factors according to the algorithm reported by Ridker et al., including systolic blood pressure, smoking, total cholesterol, HDL cholesterol, hsCRP and a family history of myocardial infarction < 60 years in first- degree relative[16]. They defined global cardiovascular disease as incident myocardial infarction, stroke, coronary revascularization, or cardiovascular death.

**Sample size and statistical analysis**

Our power analysis was based on cardiovascular risk estimation based on the Framingham Heart Study[17]. Due to the young age of our participants, the estimated absolute 10-year cardiovascular risk was likely to be low. Therefore, our approach was to estimate the risk for each woman as if the woman was 60 years old. This approach has been recommended in the cardiovascular risk factor management guidelines for young women with elevated risk factor levels[23]. For detecting an estimated absolute 10-year cardiovascular risk difference between women with a history of term gestational hypertension or term preeclampsia (HTP) and women with a history of normotensive pregnancies (NTP) of 10% increase after extrapolating to the age of 60, we needed a sample size of 456 women for 80% power and a 5% type 1 error probability (two sided), for inclusion in 3:1 ratio (3 HTP: 1 NTP). According to earlier studies[28-30] we expected a homogeneous effect with low prevalence of unfavorable cardiovascular risk factors in normotensive term pregnancy women. Therefore, we have used a 3:1 (HTP:NTP) inclusion ratio instead of 1:1 as we assumed that including more normotensive pregnancy women in 1:1 ratio would have no additional value in this study as a result of homogeneous outcome of cardiovascular risks.

Data were analyzed using SPSS software (version 20.0). Baseline continuous data were expressed as means and standard deviations or as medians and interquartile ranges for not normally distributed values; dichotomous data were presented as numbers and percentages. Comparison of continuous data with a skewed distribution was performed using the non- parametric Mann-Whitney U test and categorical data by the Chi-squared test. A poisson regression analysis was performed to calculate the incidence risk ratios and corresponding 95% confidence intervals for the different cardiovascular risk estimation categories. We made adjustments for potential confounders, where appropriate, including

parity (continuous variable) and current BMI (continuous variable). For all tests, a p-value < 0.05 indicated statistical significance.

## Results

Between June 2008 and November 2010, a total of 300 women with a history of term gestational hypertension or term preeclampsia and 94 women with a history of normotensive term pregnancies were included in this follow-up study. Of the eligible 751 women with a history of term gestational hypertension or term preeclampsia, 168 women declined participation in the follow-up study, 6 women refused blood drawing, 175 women were lost to follow-up, 101 women were pregnant or lactating and 1 woman had died in a car accident.

At index pregnancy, women with term gestational hypertension or term preeclampsia were more often nulliparous, had higher body mass index at the first antenatal visit, higher systolic and diastolic blood pressures at the first antenatal visit, lower gestational age at delivery and lower birth weight compared with women with a history of normotensive term pregnancies (table 1).



**Table 1.** Baseline characteristics at index pregnancy*

| Characteristics | HTP cohort (n=300) | NTP cohort (n=94) | p value |
|---|---|---|---|
| Maternal age at delivery (years) | 31 (28-35) | 31 (28-34) | .82 |
| Ethnic origin: Caucasian | 273 (89%) | 94 (95%) | .14 |
| Other | 30 (10%) | 5 (5%) | |
| Unknown | 3 (1%) | 0 (0%) | |
| Nulliparous | 211 (69%) | 30 (30%) | <.001 |
| Systolic blood pressure at first antenatal visit (mmHg)‡ | 120 (110-130) | 110 (109-120) | <.001 |
| Diastolic blood pressure at first antenatal visit (mmHg)‡ | 75 (68-80) | 65 (60-70) | <.001 |
| BMI at first antenatal visit (kg/m$^2$) | 25.2 (22.5-29.1) | 22.7 (21.2-24.3) | <.001 |
| Gestational age at delivery (weeks) | 39.5 (38.4-40.2) | 39.9 (39.3-40.7) | .001 |
| Birth weight (gram) | 3398 (3030-3710) | 3693 (3216-3942) | <.001 |

* Continuous data are expressed as median (IQR), dichotomous data as number of patients (%).

HTP = women with a history of term gestational hypertension or term preeclampsia

NTP= women with a history of normotensive term pregnancies

‡ 38 HTP women (12%) had a systolic blood pressure of ≥ 140 mmHg or a diastolic blood pressure of ≥ 90 mmHg at the first antenatal visit (without use of antihypertensive medication).

At 2.5 year follow-up women with a history of term gestational hypertension or term preeclampsia were more often primiparous, used more antihypertensive medication, and had higher body mass index, higher systolic and diastolic blood pressures and higher waist circumferences compared with women with a history

of normotensive term pregnancy. There were no significant differences in age, elapsed time since delivery and smoking rates (table 2).

**Table 2.** Outcome characteristics of the follow-up study, 2.5 years postpartum*

| Characteristics | HTP cohort (n=300) | NTP cohort (n=94) | p value |
|---|---|---|---|
| Age at follow up (years) | 34 (30-37) | 34 (31-37) | .80 |
| Time elapsed since delivery (years) | 2.4 (2.2-2.7) | 2.5 (2.2-2.9) | .54 |
| Primiparous | 134 (44%) | 21 (22%) | <.001 |
| Smoking | 60 (20%) | 19 (19%) | .82 |
| BMI at follow up (kg/m$^2$) | 26.6 (23.8-30.5) | 23.2 (21.8-25.5) | <.001 |
| Antihypertensive medication use | 29 (10%) | 0 (0%) | .001 |
| Hypertension | 104 (35%) | 1 (1%) | <.001 |
| Systolic blood pressure (mmHg) | 124 (115-130) | 110 (105-118) | <.001 |
| Diastolic blood pressure (mmHg) | 80 (78-90) | 74 (66-80) | <.001 |
| Family history of MI** < 60 years in first-degree relative | 48 (16%) | 11 (11%) | .21 |

* Continuous data are expressed as median (IQR), dichotomous data as number of patients (%).

** MI= Myocardial infarction

HTP = women with a history of term gestational hypertension or term preeclampsia

NTP= women with a history of normotensive term pregnancies

Biochemical cardiovascular risk factors 2.5 years postpartum, including glucose, HsCRP, total cholesterol, HDL cholesterol and triglycerides, were all significantly higher in women with a history of term gestational hypertension or term preeclampsia compared with women with a history of normotensive term pregnancies (table 3).

**Table 3.** Cardiovascular biomarkers in HTP women and NTP women 2.5 years postpartum*

| Cardiovascular biomarker | HTP cohort (n=300) | NTP cohort (n=94) | p value |
|---|---|---|---|
| Glucose, mg/dl | 84.7 (81.1-91.9) | 84.7 (79.3-88.3) | .01 |
| HsCRP, mg/l | 2.2 (1.0-5.0) | 0.9 (0.4-2.2) | <.001 |
| Total cholesterol, mg/dl | 181.8 (162.4-206.9) | 177.9 (150.8-197.2) | .02 |
| HDL-cholesterol, mg/dl | 54.1 (46.4-61.9) | 58.0 (50.3-65.8) | .03 |
| Triglycerides, mg/dl | 80.6 (58.5-110.1) | 62.9 (47.6-91.2) | <.001 |

* Data are expressed as median (IQR).

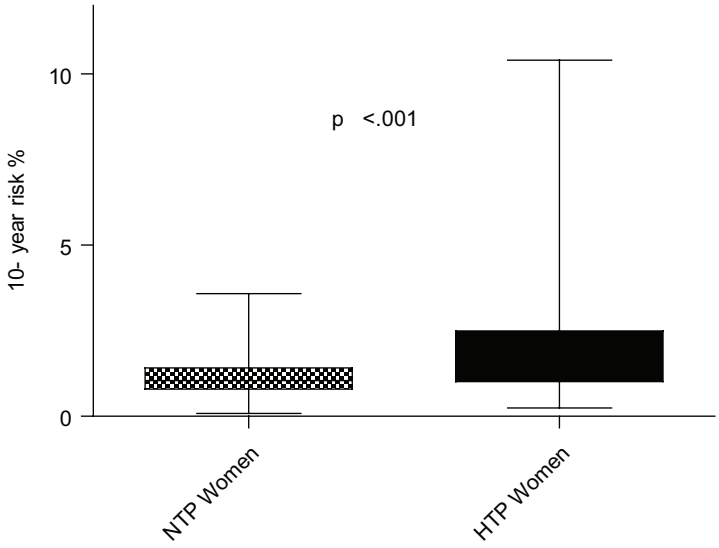



**Figure 1.** 10-year Framingham risk score at current age

10-Year Framingham risk scores (%) of women with a history of gestational hypertension or preeclampsia at term (HTTP women, closed bars) and women with a history of uncomplicated normotensive pregnancies (NTP women, dotted bars).The top and bottom of each box correspond to the 75th percentile and 25th percentile, respectively. The whiskers (t bars) on the top and bottom denote the 90th percentile and 10th percentile, respectively.



## Cardiovascular disease risk prediction

*1. 10-year general cardiovascular disease risk prediction by the Framingham risk score*

Figure 1 illustrates the risk percentages of developing general cardiovascular disease within 10 years in women with a history of term gestational hypertension or term preeclampsia and women with a history of normotensive term pregnancies *at current age*, calculated with the Framingham risk score. At current age, 16 women (5%) with a history of term gestational hypertension or term preeclampsia had a 10-year general cardiovascular disease risk of > 5%, compared with no women (0%) with a history of normotensive pregnancies, p=.02. Figures 2 A and 2B show the risk percentages of developing general cardiovascular disease within 10 years (figure 2A) and the different risk categories of the 10-year prediction of developing general cardiovascular disease calculated with the Framingham risk score (figure 2B) of hypertensive term pregnancy women and normotensive term pregnancy women after extrapolation of their age to 60 years.

Poisson regression showed that women with a history of term gestational hypertension or term preeclampsia, compared with women with a history of normotensive term pregnancies, had a 2.5-fold higher extrapolated risk of >5% (p<.001, IRR 2.5 95% CI (1.6 – 3.7)) and even an almost 6-fold higher extrapolated risk of >10% (p=.001, IRR 5.8 95% CI (1.8 - 19)) to suffer from cardiovascular disease within 10-years. After adjustment for parity and current BMI, women with a history of term gestational hypertension or term preeclampsia had still higher extrapolated cardiovascular event risks of >5% (p<.001, IRR 2.3 95% CI (1.5 - 3.5)) and > 10% (p=.01, IRR 5.0 95% CI (1.6 - 16)) compared with women with a history of normotensive term pregnancies.

*2. 30-year full cardiovascular disease risk prediction by the Framingham risk score*

Figure 3A illustrates the risk percentages of developing overall cardiovascular disease within 30 years in women with a history of term gestational hypertension or term preeclampsia and women with a history of normotensive term pregnancies at current age, calculated with the Framingham risk score. Figure 3B illustrates different risk categories of the 30-year prediction of developing general cardiovascular disease calculated with the Framingham risk score at current age. Poisson regression analysis showed that women with a history of term gestational hypertension or term preeclampsia, compared with women with a history of normotensive term pregnancies had an almost 3-fold higher of >10% (p<.001, IRR 2.7 95% CI (1.6 – 4.5)) to suffer from cardiovascular disease within 30 years, even after adjustment for parity and current BMI (p=.002, IRR 2.4 95% CI (1.4 – 4.1)).

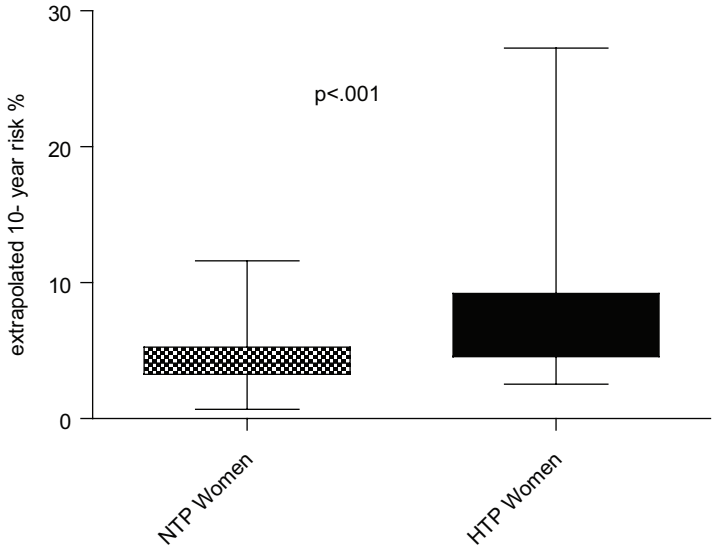



**Figure 2A.** 10-year Framingham risk score extrapolated to the age of 60 years

10-Year Framingham risk scores (%) extrapolated to the age of 60 years of women with a history of gestational hypertension or preeclampsia at term (HTTP women, closed bars) and women with a history of uncomplicated normotensive pregnancies (NTP women, dotted bars). The top and bottom of each box correspond to the 75th percentile and 25th percentile, respectively. The whiskers (t bars) on the top and bottom denote the 90th percentile and 10th percentile, respectively.

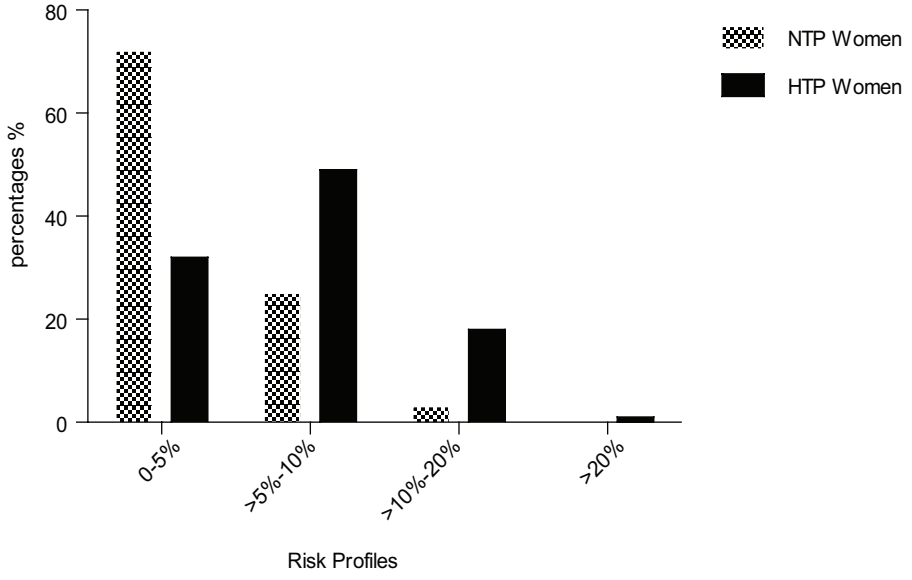



**Figure 2B.** 10-year Framingham risk score extrapolated to the age of 60 years

Division into 4 different risk categories (0-5%, >5%-10%, >10%-20% and > 20%). 10- Year risk estimation of overall cardiovascular disease risk according to the Framingham Heart Study algorithm, based on the following risk factors, i.e. age, smoking, systolic blood pressure, HDL cholesterol, total cholesterol.

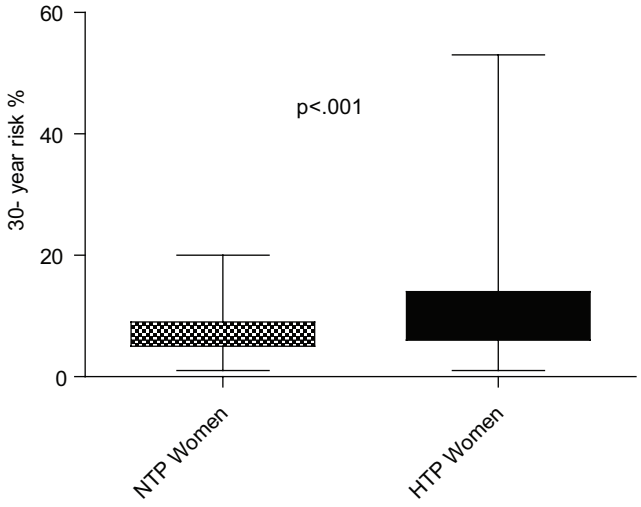



**Figure 3A.** 30-year Framingham risk score at current age

30-Year Framingham risk scores (%) at current age of women with a history of gestational hypertension or preeclampsia at term (HTP women, closed bars) and women with a history of uncomplicated normotensive pregnancies (NTP women, dotted bars). The top and bottom of each box correspond to the 75th percentile and 25th percentile, respectively. The whiskers (t bars) on the top and bottom denote the 90th percentile and 10th percentile, respectively.

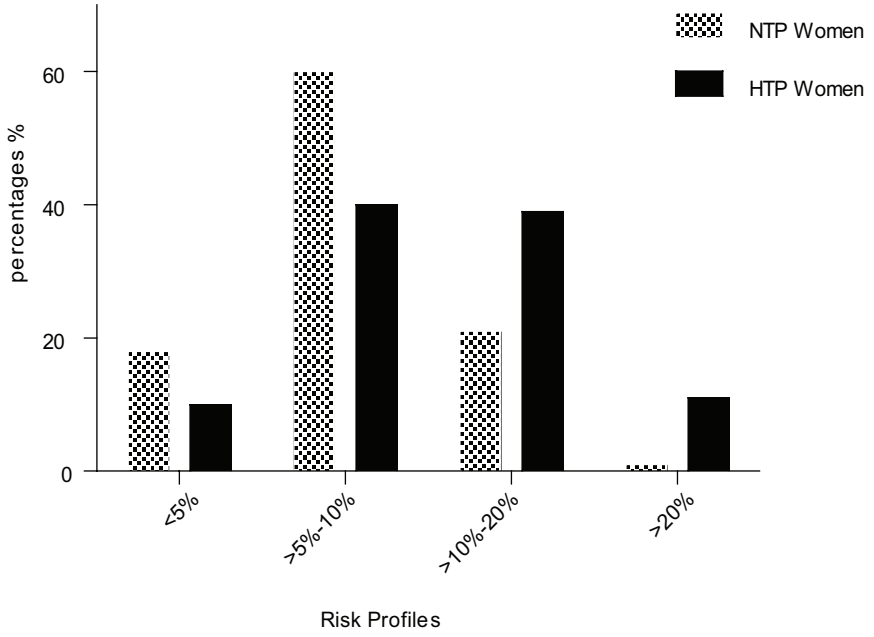



**Figure 3B.** 30-year Framingham risk score at current age

Division into 4 different categories (0-5%, >5%-10%, >10%-20% and > 20%) for 30-year risk estimation of full cardiovascular disease by the Framingham Heart Study algorithm based on the following risk factors i.e. age, smoking, systolic blood pressure, HDL cholesterol, total cholesterol, treatment for hypertension and presence of diabetes.

*3. 10-Year fatal cardiovascular disease risk prediction by the SCORE score and 10-Year global cardiovascular disease risk prediction by the Reynolds risk score*

Mean (SD) 10-year cardiovascular disease risk predictions and different risk categories calculated by the SCORE score and the Reynolds risk score are shown in table 4. Women with a history of term gestational hypertension or term preeclampsia had significant higher mean risks calculated by the SCORE score and the Reynolds risk score compared with women with a history of normotensive term pregnancies. Furthermore, women with a history of term gestational hypertension or term preeclampsia were more often represented in higher risk categories.

**Table 4.** Cardiovascular event risk prediction by the SCORE score and Reynolds risk score

| Risk Prediction | HTP Cohort (N=300) | NTP Cohort (N=94) | p value | IRR (95% CI) |
|---|---|---|---|---|
| *10-year fatal CVD risk prediction by the SCORE score (extrapolation to 60 years)* | | | | |
| Mean (SD), % | 1.2 (0.5) | 1.1 (0.3) | .02 | |
| Risk category 1% | 242 (81%) | 85 (90%) | | |
| Risk category 2% | 48 (16%) | 9 (10%) | | |
| Risk category 3% | 9 (3%) | 0 (0%) | | |
| Risk category 4% | 1 (0.3%) | 0 (0%) | | |
| 10-year SCORE score risk >1% | 58 (19%) | 9 (10%) | | 2.0 (1.0 - 4.1) |
| *10-year global CVD risk prediction by Reynolds risk score (extrapolation to 60 years)* | | | | |
| Mean (SD), % | 2.8 (2.1) | 1.6 (1.1) | .001 | |
| Risk category 1% | 87 (29%) | 60 (64%) | | |
| Risk category >1-5% | 168 (56%) | 30 (32%) | | |
| Risk category >5-10% | 39 (13%) | 4 (4%) | | |
| Risk category >10% | 6 (2%) | 0 (0%) | | |
| 10-year Reynolds risk score risk > 5% | 45 (15%) | 4 (4%) | | 4.0 (1.0 - 17) |

HTP = women with a history of term gestational hypertension or term preeclampsia

NTP= women with a history of normotensive term pregnancies

**Sub-analyses of the hypertensive term pregnancy cohort**

We divided the hypertensive term pregnancy cohort (n=300) in a primiparous subgroup (n=134, 44%) and a multiparous subgroup (n=166, 56%) 2.5 years postpartum. Furthermore, we subanalysed women with a history of gestational hypertension at term (n=225, 75%) and women with a history of preeclampsia at term (n=75, 25%) and women with (n=93, 31%) or without (n=207, 69%) severe gestational hypertension or severe preeclampsia during their index pregnancy.

No significant differences were found between the subgroups in the prevalence of hypertension 2.5 years postpartum, biochemical cardiovascular risk factors 2.5 years postpartum and in the estimated 10- and 30 year Framingham cardiovascular event risks.

## Discussion

In this longitudinal follow-up study, we found that women with a history of term gestational hypertension or term preeclampsia have an increased 10-year cardiovascular disease risk at current age and after extrapolating the age to 60 years at least two years postpartum. Furthermore, an increased 30-year cardiovascular risk at current age was found in women with a history of term gestational hypertension or term preeclampsia.

### Risk Prediction Models

Screening and treatment of cardiovascular disease should target women at high risk rather than at women with a single elevated risk factor[31]. Many risk prediction models have been developed the last three decades to estimate individual cardiovascular risk. The Framingham Risk Score was the most influential multivariate risk predictor of developing cardiovascular disease in the future and this algorithm has been most often compared by other studies[15, 17, 27, 32]. The Reynolds Risk Score was developed in women adding CRP and parental history of early myocardial infarction before the age of 60 years as independent risk variables in a female cohort[16] and reclassified 40%-50% of women who were predicted by the Framingham risk score[17] to be at intermediate risk into higher- or lower risk categories. The SCORE equation has been validated for the European population and has been recommended by the Third Joint European Task Force on cardiovascular prevention in Europe[11]. This risk score focuses at fatal total cardiovascular risk rather than at fatal coronary heart disease. Other prediction models were mostly designed and developed for men and therefore not considered for this study. The QRISK score was developed using a population-based clinical research database in the UK incorporating ethnicity, deprivation and other clinical conditions in the algorithm[13, 14], resulting in more accurate quantification of risks in south Asian women compared to the Framingham risk score. However, participants in our study were predominantly Caucasian women and adding ethnicity to the risk estimate was considered to have no additional value for risk estimates. Therefore, we did not use the QRISK score for our study. In 2012, Siontis et al. undertook a meta-analysis to compare established risk prediction models for cardiovascular disease[32]. They did not reach robust conclusions about the best risk prediction model or the ranking of performance of

different models. An important question rises: which algorithm or model is best suited for women with a history of hypertensive pregnancy disorders at term to accurately estimate their future cardiovascular risk? Unfortunately, we can not answer this question with our present study results.

All four algorithms showed a significantly higher risk in hypertensive term pregnancy women. This is understandable, because the four scores are mostly based on equivalent cardiovascular parameters and these parameters were significantly higher in the hypertensive term pregnancy cohort compared with the normotensive term pregnancy cohort. However, the definitions and cardiovascular endpoints between the four risk prediction models differ. Only the Framingham Heart Study provides a 30-year risk prediction model. This might be the most useful prediction model for our relatively young study cohort, as age remains the most important parameter in cardiovascular risk prediction models and extrapolation is not necessary in this model for our relatively young cohort. Furthermore, the Framingham 30-year risk score focuses at cardiovascular morbidity and mortality rather than at cardiovascular mortality alone (SCORE score), which seems important in young women. Morbidity caused by non fatal cardiovascular events is not only disabling for young women, but it is also the major economic burden for the health care system and society. Young women might benefit from early screening and prevention and it might be cost-effective. However, we have to keep in mind that the longer the prediction period, the less accurate the prediction will be for an individual, as the nature of the design does not account for individual changes in risk factor levels that could have taken place during the course of follow-up[15].



**Comparison with other studies**

Three other studies[29, 33, 34] previously assessed cardiovascular risk scores in women with a history of hypertensive pregnancy disorders. Fraser et al.[33] reported significant higher mean Framingham 10-year cardiovascular risks of 4.6% (0.15) in women with a history of gestational hypertension, 5.1% (0.41) in women with a history of preeclampsia compared with 3.6% (0.06) in women with a history without hypertensive pregnancy disorders. These risks were higher compared with the 10-year cardiovascular risks (at current age) in our study in women with a history of hypertensive pregnancy disorders. This might be explained by two differences.

First, Fraser et al. included not only women with a history of hypertensive pregnancy disorders at term but also women with a history of preterm hypertensive pregnancy disorders, which are known for their higher risk of cardiovascular disease later. Second, the follow-up period of 18 years by Fraser et al. was longer compared with our follow-up period of 2.5 years, which resulted in a significant

age difference between the two studies and, per definition, in lower estimation of cardiovascular risk in our study. Smith et al.[29, 34] reported comparable 10-year cardiovascular event risks as our study. However, they included women with a history of both preterm and term preeclampsia and they had a shorter follow-up period of 1 year.

Mongraw-Chaffin et al.[35] prospectively investigated the contribution of hypertensive pregnancy complications on the risk of cardiovascular disease death. They found that women with a history of preeclampsia with onset after 34 weeks' gestation, after a follow-up period of 30 years and with a median age of 56 years, had a cumulative cardiovascular disease death survival of 98.3% and women without a history of preeclampsia had a cardiovascular death survival of 99.3%. We calculated a mean 10-year fatal cardiovascular disease risk of 1.2% (0.5) in our hypertensive term pregnancy cohort after extrapolating the age of each participant to 60 years. This is a slightly lower risk compared with the 1.7% cardiovascular death risk published by Mograw-Chaffin et al. An explanation might be that Mongraw-Chaffin studied women with preeclampsia who delivered after 34 weeks' gestation, while we included women with both gestational hypertension and preeclampsia after 36 weeks' gestation. These differences in both gestational age and hypertensive disorder might explain the small discrepancy between the risks. A second explanation might be that hypertensive pregnancy disorders are independent risk factors for cardiovascular disease later in life and as a consequence current cardiovascular risk prediction models underestimate women's cardiovascular disease risks, as obstetric history is not included as a variable in the models. Further large prospective studies have to evaluate whether hypertensive pregnancy disorders have to be included as an independent variable in cardiovascular risk prediction models for women to improve their assessment of reliable cardiovascular risk estimation for the long term CVD outcome.

**Strengths and Limitations**

The major strength of this longitudinal follow-up study is that we used a unique prospective cohort from a randomized controlled trial, which consisted of women with a history of term gestational hypertension or term preeclampsia. Hypertensive pregnancy disorders at term are common disorders and therefore of great interest for health care providers. These disorders may be used as a discriminating test whether or not the clinician has to screen for cardiovascular risk factors and calculate subsequent individual cardiovascular risk.

This study has also potential limitations. First, due to the young age of our study participants, 10-year overall cardiovascular disease risk in our cohort was < 5% in all normotensive term pregnancy women and in 95% of hypertensive

term pregnancy women in the Framingham Risk Score. For this reason we extrapolated the risk to an age of 60 years. Between current age and the age of 60 years, individual cardiovascular risk factors might change over time. In our study, risk factors were determined at a relatively young age and extrapolation of the age does not account for possible changes in risk factors over time. However, our study method seems an appropriate method considering that both charts of 10-year prediction after extrapolation to 60 years and charts of 30-year prediction at current age show similar effects.

Second, we performed a cohort study, in which pregnancy data of women with a history of gestational hypertension or preeclampsia were collected at baseline while index pregnancy data of normotensive term pregnancy women were reviewed in detail from medical records at the time of inclusion in the study. However, the information on pregnancy data addressed in this manuscript was nearly all complete in the medical charts.

Third, due to refusal to participate in the follow-up study, pregnant and lactating women at the time of follow-up, and women who were lost to follow-up, we were not able to include the total of 342 women with a history of gestational hypertension or term preeclampsia as described in our power analysis.

Finally, all normotensive term pregnancy women had one or more uncomplicated pregnancies, which might have resulted in a "cardiovascular healthier" cohort compared with a population based cohort and subsequently this relative healthy cohort might have resulted in overestimation of the effect in women with a history of term gestational hypertension or term preeclampsia. However, the mean 10-year cardiovascular disease risk in the Framingham risk study in women of 60 years was 6.4%. The mean extrapolated 10-year cardiovascular disease risk of women with a history of term gestational hypertension or term preeclampsia was higher, namely 7.2%. Assuming that levels of cardiovascular risk factors in women with a history of term gestational hypertension or term preeclampsia, without intervention or prevention, will worsen over time until the age of 60, the real estimated 10-year cardiovascular risk at the age of 60 years of women with a history of term gestational hypertension or term preeclampsia may be even higher than our reported 7.2%. Thus, even without comparison with women with a history of normotensive term pregnancies, a mean 10-year cardiovascular event risk of 7% is of interest for physicians, as it is a higher risk compared with the reported risk of the population based cohort of the Framingham Heart Study.

## Conclusions

In conclusion, women with a history of gestational hypertension or preeclampsia at term have higher (extrapolated) 10-year cardiovascular event risks and 30-year cardiovascular event risks compared with women with a history of

uncomplicated pregnancies. Our study results strongly suggest that women with a history of hypertensive pregnancy disorders *at term* may be offered screening and counseling for cardiovascular risk factors after their pregnancy to calculate and estimate cardiovascular event risks.

## Reference List


(1) Jacobs AK, Eckel RH: Evaluating and managing cardiovascular disease in women: understanding a woman's heart. *Circulation* 2005, 111:383-384.

(2) Gleeson D, Crabbe DL: Emerging concepts in cardiovascular disease risk assessment: where do women fit in? *J Am Acad Nurse Pract* 2009, 21:480-487.

(3) Haukkamaa L, Salminen M, Laivuori H, Leinonen H, Hiilesmaa V, Kaaja R: Risk for subsequent coronary artery disease after preeclampsia. *Am J Cardiol* 2004, 93:805-808.

(4) Irgens HU, Reisaeter L, Irgens LM, Lie RT: Long term mortality of mothers and fathers after pre-eclampsia: population based cohort study. *BMJ* 2001, 323:1213-1217.

(5) Jonsdottir LS, Arngrimsson R, Geirsson RT, Sigvaldason H, Sigfusson N: Death rates from ischemic heart disease in women with a history of hypertension in pregnancy. *Acta Obstet Gynecol Scand* 1995, 74:772-776.

(6) Ramsay JE, Stewart F, Greer IA, Sattar N: Microvascular dysfunction: a link between pre-eclampsia and maternal coronary heart disease. *BJOG* 2003, 110:1029-1031.

(7) Sattar N, Greer IA: Pregnancy complications and maternal cardiovascular risk: opportunities for intervention and screening? *BMJ* 2002, 325:157-160.

(8) Smith GC, Pell JP, Walsh D: Pregnancy complications and maternal risk of ischaemic heart disease: a retrospective cohort study of 129,290 births. *Lancet* 2001, 357:2002-2006.

(9) Wilson BJ, Watson MS, Prescott GJ, Sunderland S, Campbell DM, Hannaford P, Smith WC: Hypertensive diseases of pregnancy and risk of hypertension and stroke in later life: results from cohort study. *BMJ* 2003, 326:845.

(10) Williams D: Pregnancy: a stress test for life. *Curr Opin Obstet Gynecol* 2003, 15:465-471.

(11) Conroy RM, Pyorala K, Fitzgerald AP, Sans S, Menotti A, De BG, De BD, Ducimetiere P, Jousilahti P, Keil U, Njolstad I, Oganov RG, Thomsen T, Tunstall-Pedoe H, Tverdal A, Wedel H, Whincup P, Wilhelmsen L, Graham IM: Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. *Eur Heart J* 2003, 24:987-1003.

(12) Cui J: Overview of risk prediction models in cardiovascular disease research. *Ann Epidemiol* 2009, 19:711-717.

(13) Hippisley-Cox J, Coupland C, Vinogradova Y, Robson J, May M, Brindle P: Derivation and validation of QRISK, a new cardiovascular disease risk score for the United Kingdom: prospective open cohort study. *BMJ* 2007, 335:136.

(14) Hippisley-Cox J, Coupland C, Robson J, Brindle P: Derivation, validation, and evaluation of a new QRISK model to estimate lifetime risk of cardiovascular disease: cohort study using QResearch database. *BMJ* 2010, 341:c6624.

(15) Pencina MJ, D'Agostino RB, Sr., Larson MG, Massaro JM, Vasan RS: Predicting the 30-year risk of cardiovascular disease: the framingham heart study. *Circulation* 2009, 119:3078-3084.

(16) Ridker PM, Buring JE, Rifai N, Cook NR: Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: the Reynolds Risk Score. *JAMA* 2007, 297:611-619.

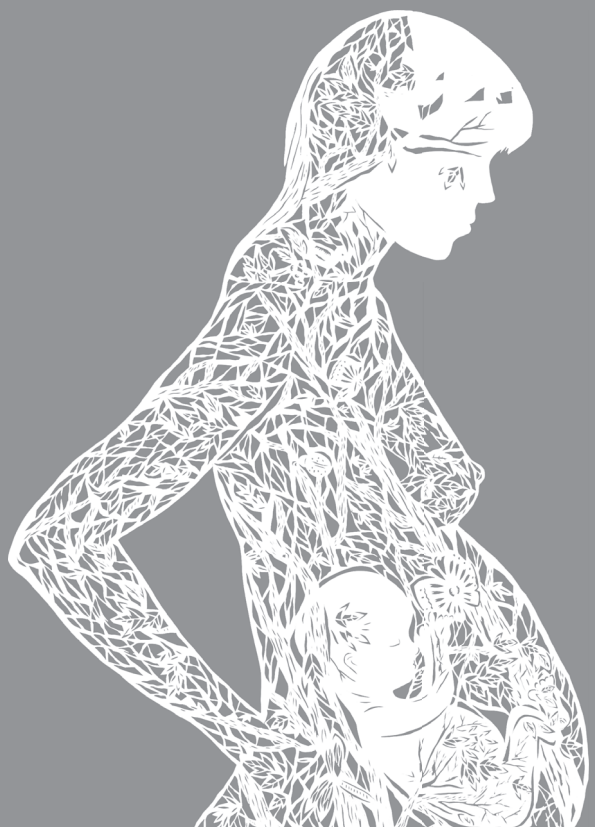
(17) Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB: Prediction of coronary heart disease using risk factor categories. *Circulation* 1998, 97:1837-1847.

(18) Siontis GC, Tzoulaki I, Siontis KC, Ioannidis JP: Comparisons of established risk prediction models for cardiovascular disease: systematic review. *BMJ* 2012, 344:e3318.
(19) Perk J, De BG, Gohlke H, Graham I, Reiner Z, Verschuren M, Albus C, Benlian P, Boysen G, Cifkova R, Deaton C, Ebrahim S, Fisher M, Germano G, Hobbs R, Hoes A, Karadeniz S, Mezzani A, Prescott E, Ryden L, Scherer M, Syvanne M, Scholte Op Reimer WJ, Vrints C, Wood D, Zamorano JL, Zannad F, Cooney MT, Bax J, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S, Funck-Brentano C, Sirnes PA, Aboyans V, Ezquerra EA, Baigent C, Brotons C, Burell G, Ceriello A, De SJ, Deckers J, Del PS, Diener HC, Fitzsimons D, Fras Z, Hambrecht R, Jankowski P, Keil U, Kirby M, Larsen ML, Mancia G, Manolis AJ, McMurray J, Pajak A, Parkhomenko A, Rallidis L, Rigo F, Rocha E, Ruilope LM, van d, V, Vanuzzo D, Viigimaa M, Volpe M, Wiklund O, Wolpert C: European Guidelines on cardiovascular disease prevention in clinical practice (version 2012): The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts) * Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J* 2012, 33:1635-1701.
(20) Mosca L, Benjamin EJ, Berra K, Bezanson JL, Dolor RJ, Lloyd-Jones DM, Newby LK, Pina IL, Roger VL, Shaw LJ, Zhao D, Beckie TM, Bushnell C, D'Armiento J, Kris-Etherton PM, Fang J, Ganiats TG, Gomes AS, Gracia CR, Haan CK, Jackson EA, Judelson DR, Kelepouris E, Lavie CJ, Moore A, Nussmeier NA, Ofili E, Oparil S, Ouyang P, Pinn VW, Sherif K, Smith SC, Jr., Sopko G, Chandra-Strobos N, Urbina EM, Vaccarino V, Wenger NK: Effectiveness-based guidelines for the prevention of cardiovascular disease in women--2011 update: a guideline from the American Heart Association. *J Am Coll Cardiol* 2011, 57:1404-1423.
(21) McDonald SD, Malinowski A, Zhou Q, Yusuf S, Devereaux PJ: Cardiovascular sequelae of preeclampsia/eclampsia: a systematic review and meta-analyses. *Am Heart J* 2008, 156:918-930.
(22) Mosca L, Mochari H, Christian A, Berra K, Taubert K, Mills T, Burdick KA, Simpson SL: National study of women's awareness, preventive action, and barriers to cardiovascular health. *Circulation* 2006, 113:525-534.
(23) De Backer G, Ambrosioni E, Borch-Johnsen K, Brotons C, Cifkova R, Dallongeville J, Ebrahim S, Faergeman O, Graham I, Mancia G, Manger C, V, Orth-Gomer K, Perk J, Pyorala K, Rodicio JL, Sans S, Sansoy V, Sechtem U, Silber S, Thomsen T, Wood D: European guidelines on cardiovascular disease prevention in clinical practice. Third Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice. *Eur Heart J* 2003, 24:1601-1610.
(24) Koopmans CM, Bijlenga D, Groen H, Vijgen SM, Aarnoudse JG, Bekedam DJ, van den Berg PP, de BK, Burggraaff JM, Bloemenkamp KW, Drogtrop AP, Franx A, de Groot CJ, Huisjes AJ, Kwee A, van Loon AJ, Lub A, Papatsonis DN, van der Post JA, Roumen FJ, Scheepers HC, Willekes C, Mol BW, van Pampus MG: Induction of labour versus expectant monitoring for gestational hypertension or mild pre-eclampsia after 36 weeks' gestation (HYPITAT): a multicentre, open-label randomised controlled trial. *Lancet* 2009, 374:979-988.

(25) Hermes W, Franx A, van Pampus MG, Bloemenkamp KW, van der Post JA, Porath M, Ponjee G, Tamsma JT, Mol BW, de Groot CJ: 10-Year cardiovascular event risks for women who experienced hypertensive disorders in late pregnancy: the HyRAS study. *BMC Pregnancy Childbirth* 2010, 10:28.
(26) Hermes W, Franx A, van Pampus MG, Bloemenkamp KW, Bots ML, van der Post JA, Porath M, Ponjee GA, Tamsma JT, Mol BW, de Groot CJ: Cardiovascular risk factors in women who had hypertensive disorders late in pregnancy: a cohort study. *Am J Obstet Gynecol* 2013.
(27) D'Agostino RB, Sr., Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, Kannel WB: General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation* 2008, 117:743-753.
(28) Spaan JJ, Houben AJHM, Musella A, Ekhart T, Spaanderman MEA, Peeters LLH: Insulin resistance relates to microvascular reactivity 23years after preeclampsia. *Microvasc Res* 2010, 80:417-421.
(29) Smith GN, Walker MC, Liu A, Wen SW, Swansburg M, Ramshaw H, White RR, Roddy M, Hladunewich M: A history of preeclampsia identifies women who have underlying cardiovascular risk factors. *Am J Obstet Gynecol* 2009, 200:58.
(30) Nijdam ME, Timmerman MR, Franx A, Bruinse HW, Numans ME, Grobbee DE, Bots ML: Cardiovascular risk factor assessment after pre-eclampsia in primary care. *BMC Fam Pract* 2009, 10:77.
(31) Cui J: Overview of risk prediction models in cardiovascular disease research. *Ann Epidemiol* 2009, 19:711-717.
(32) Siontis GC, Tzoulaki I, Siontis KC, Ioannidis JP: Comparisons of established risk prediction models for cardiovascular disease: systematic review. *BMJ* 2012, 344:e3318.
(33) Fraser A, Nelson SM, Macdonald-Wallis C, Cherry L, Butler E, Sattar N, Lawlor DA: Associations of pregnancy complications with calculated cardiovascular disease risk and cardiovascular risk factors in middle age: the avon longitudinal study of parents and children. *Circulation* 2012, 125:1367-1380.
(34) Smith GN, Pudwell J, Walker M, Wen SW: Ten-year, thirty-year, and lifetime cardiovascular disease risk estimates following a pregnancy complicated by preeclampsia. *J Obstet Gynaecol Can* 2012, 34:830-835.
(35) Mongraw-Chaffin ML, Cirillo PM, Cohn BA: Preeclampsia and cardiovascular disease death: prospective evidence from the child health and development studies cohort. *Hypertension* 2010, 56:166-171.

# *Chapter 8*

## Differences in estimated cardiovascular risk between hypertensive pregnancy disorders at term and severe early onset preeclampsia



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## Abstract

**Objective:** Hypertensive pregnancy disorders are associated with an increased risk of cardiovascular disease. Women with early onset preeclampsia have the highest risk. The aim of this study was to compare 10-year and 30-year estimated cardiovascular event risks between the extremes of severity of hypertensive pregnancy disorders between very early onset preeclampsia and late onset hypertensive pregnancy disorders.

**Methods:** We studied 20 women with previous severe very early onset preeclampsia (SPP cohort), 300 women with previous term hypertensive pregnancy disorders (HTP cohort) and 94 women with previous normotensive pregnancies (NTP cohort). All participants were assessed at least 2 years postpartum for cardiovascular risk factors, including BMI, blood pressure, glucose, total cholesterol, HDL cholesterol, triglycerides and hsCRP. Subsequently we calculated their 10- and 30 year cardiovascular event risks using Framingham risk scores.

**Results:** 10-year and 30-year cardiovascular risks were comparable in SPP women and HTP women after adjustment for age. Compared to NTP women, SPP women had a 6-fold higher extrapolated risk of >10% (p=.02, IRR 6.3 95% CI (1.4-28)) and HTP women had an almost 6-fold higher extrapolated risk of >10% (p=.003, IRR 5.5 95% CI (3.3-9.1)) to suffer from cardiovascular disease within 10-years. For 30-year cardiovascular event risks the results were comparable.

**Conclusions:** Women with previous very early onset preeclampsia and women with previous late onset hypertensive pregnancy disorders appear to have comparable estimated cardiovascular event risks. Hypertensive pregnancy disorders and their severity might be included as an independent variable in cardiovascular risk prediction models for more accurate cardiovascular risk prediction in women.

## Introduction

Cardiovascular disease continues to be the leading cause of death in women in the western world[1]. Yearly, women are more likely to die of heart disease compared to men. Signs and symptoms of heart disease in women are different than in men and diagnostic tools in women seem to be less sensitive and specific compared to men. As a consequence, women are less likely to receive appropriate cardiovascular treatment and (preventive) care.

Several epidemiological studies have demonstrated an association between preeclampsia and an increased risk of cardiovascular disease in later life. It has been suggested that preeclampsia acts as an early "natural" stress test for preclinical future cardiovascular risk. Women with previous preeclampsia have a 2-fold higher risk of ischemic heart disease[2]. Women with a history of *early onset preeclampsia* before 37 weeks' gestation are of the highest risk and have even an 8-fold higher risk of ischemic heart disease compared to women with a history of normotensive pregnancies[2;3]. The underlying mechanisms of the association between cardiovascular disease and preeclampsia remain unclear. Endothelial dysfunction is suggested to play a central role. Whether preeclampsia itself damages the vascular endothelium resulting in an increased risk for cardiovascular disease later or whether unfavourable underlying cardiovascular risk factors predispose to both preeclampsia and cardiovascular disease later, or a combination of the two hypotheses mentioned above, is not clear. In all probability, early onset preeclampsia and term hypertensive pregnancy disorders have a different pathogenesis of the linkage between cardiovascular disease and preeclampsia[4]. It is well described that women with a history of early severe preeclampsia exhibit more cardiovascular risk factors after their pregnancy compared with women with uncomplicated normotensive pregnancies[5-10]. Recently, we have shown in a longitudinal follow-up study of the HYPITAT trial that not only women with severe early preeclampsia exhibit cardiovascular risk factors after pregnancy, but also women with term gestational hypertension and term preeclampsia[11]. As women with a history of severe early preeclampsia have the highest risk of dying from cardiovascular disease[2], it is likely that women with severe early onset preeclampsia exhibit more cardiovascular risk factors long before the first cardiovascular event compared with women with hypertensive pregnancy disorders at term.

The aim of this study is to compare cardiovascular risk factors between the extremes of severity of hypertensive pregnancy disorders; women with a history of severe very early onset preeclampsia and women with a history of term hypertensive pregnancy disorders, using 10-year and 30-year cardiovascular event risks calculated with the Framingham risk score.

## Methods

### Participants

*1. Severe Very Early Onset Preeclampsia Cohort (SPP Cohort)*

From January 1993 until January 2003 all consecutive women (n=26) who had been admitted for the diagnosis severe preeclampsia with onset before 24 weeks' gestation into the University Medical Center Rotterdam, the Netherlands, were selected for the severe very early onset preeclampsia cohort (SPP cohort) to assess their cardiovascular risk factors. Maternal and perinatal outcome data of this cohort have been published previously[12]. Preeclampsia was defined as blood pressure ≥ 140 mmHg systolic or ≥ 90 mmHg diastolic measured on at least two occasions in women who were normotensive before 20 weeks' gestation and proteinuria ≥ 300 mg/ 24 hours (or ≥ 2+ on dipstick of voided specimen). Superimposed preeclampsia was defined as a rise of blood pressure ≥ 30 mmHg systolic or ≥ 15 mmHg diastolic over values in the first 20 weeks and proteinuria ≥ 300 mg/24 hours (or 2+ (1g/L) on a voided specimen or ≥ 1+ (0.3 g/L) on a catheterized specimen (ISSHP)[12]. Severe preeclampsia was defined as an absolute diastolic blood pressure of ≥ 110 mmHg and proteinuria (2+ (1g/L) on a catheterized specimen on admission, or the occurrence of preeclampsia described above in combination with eclampsia or HELLP syndrome. HELLP syndrome was defined as thrombocytes < $100x10^9$/l, and both aspartate aminotransferase (ASAT) and alanine aminotransferase (ALAT) > 70 U/l and lactate dehydrogenase > 600 U/L.[12]

*2. Hypertensive Term Pregnancy Cohort (HTP cohort)*

From June 2008 until November 2010 we included women with a history of gestational hypertension or preeclampsia between $36^{+0}$ and $41^{+0}$ weeks' gestation in the hypertensive term pregnancy cohort (HTP cohort). These women were identified from a randomized controlled trial (the HYPITAT trial). Three academic hospitals and 17 non-academic hospitals across four geographical regions in the Netherlands (Leiden, Groningen, Amsterdam, and Brabant) participated in the follow-up study. The inclusion and exclusion criteria of the HYPITAT trial are previously published elsewhere[13;14].

In short, gestational hypertension was defined as a diastolic blood pressure of 95 mmHg or higher, measured on two occasions at least six hours apart. Preeclampsia was defined as diastolic blood pressure of 90 mmHg or higher measured on two occasions at least six hours apart, combined with proteinuria (two or more occurrences of protein on a dipstick, ≥ 300 mg total protein within a

24 hours urine collection, or ratio of protein to creatinine > 30 mg/mmol). Patients were excluded if they had severe gestational hypertension or severe preeclampsia before randomization, defined as systolic blood pressure of 170 mmHg or higher, diastolic blood pressure of 110 mmHg or higher, or proteinuria of 5 gram or higher in 24 hours. Other exclusion criteria included antihypertensive medication use for chronic hypertension, diabetes mellitus, gestational diabetes treated with insulin, renal disease, heart disease, previous caesarean section, hemolysis elevated liver enzymes and low platelets syndrome (HELLP syndrome), oliguria of less than 500 mL per 24 hours, pulmonary edema or cyanosis, human immunodeficiency virus (HIV) seropositivity, use of intravenous antihypertensive medication, fetal anomalies, suspected intrauterine growth restriction (IUGR), and abnormalities detected during fetal- heart rate monitoring[15].

*3. Normotensive Term Pregnancy Cohort (NTP cohort)*

Women with a history of uncomplicated normotensive term pregnancies were included in the control group, the normotensive term pregnancy cohort (NTP cohort). These control women were friends of the women who were included in the HTP cohort or these control women were identified from midwifery practices from three different locations in the Netherlands (Groningen, Leiden and The Hague). Women in the NTP cohort were required to have only previous uncomplicated normotensive pregnancies. Baseline characteristics, medical history and information of previous pregnancies were collected from their medical records and studied in thorough detail.



Pregnant and lactating women (within the last 3 months) were excluded from all three cohorts.

The study was approved by the Institutional Review Board of the University of Leiden and by the Medical Ethics Committee of the University Medical Center Rotterdam. The study was locally approved by the hospital board of the participating hospitals.

**Data collection**

All participants were invited for examination at their local hospital. Information on medical and obstetrical history, medication use and smoking habits was obtained by means of questionnaires and interviews by the local research nurses. All women were assessed for length, weight, and blood pressure. Fasting blood samples were drawn for measurements of biochemical cardiovascular risk factors including, glucose, total cholesterol, HDL cholesterol, triglycerides and high sensitive C- reactive protein (HsCRP). A detailed description of the examination and laboratory methods at least two years after pregnancy are previously

published elsewhere[15;16]. In short, the laboratory of the Erasmus University Medical Center (SPP cohort), Rotterdam, used a Hitachi 917 chemistry analyzer and corresponding reagents (Roche Diagnostics) to determine blood plasma levels of glucose, total cholesterol, HDL cholesterol and triglycerides. The laboratory of Medical Center Haaglanden (HTP and NTP cohort), The Hague, used a Modular P800, E170 analyzer and corresponding reagents (Roche Diagnostics) to determine blood plasma levels of glucose, total cholesterol, HDL cholesterol and triglycerides.

Hypertension 2.5 years postpartum was defined as a systolic blood pressure ≥ 140 mmHg, or a diastolic blood pressure ≥ 90 mmHg or current use of antihypertensive medication.

The Framingham Heart Study provides a 10-year general cardiovascular disease risk prediction model and a 30-year full cardiovascular disease risk prediction model. We used both short- and long prediction models for our study as the 10-year risk prediction model is the most used and compared score in literature and the 30-year risk prediction model might be the most useful score in our specific relatively young cohort. For the prediction of the 10-year general cardiovascular disease risk by the Framingham risk score, cardiovascular risk factors were used according to the methodology reported by D'Agostino et al.[17], i.e. age, total cholesterol, HDL cholesterol, systolic blood pressure, treatment for hypertension, and smoking. 10-Year general cardiovascular disease was defined as coronary death, myocardial infarction, coronary insufficiency, angina, ischemic stroke, hemorrhagic stroke, transient ischemic attack, peripheral artery disease, and heart failure. 30-Year full cardiovascular disease estimation by the Framingham risk score was calculated using the algorithm reported by Pencina et al.[18]. 30-Year full cardiovascular disease was defined as coronary death, myocardial infarction, fatal and non- fatal stroke, coronary insufficiency, angina pectoris, transient ischemic attack, intermittent claudication and congestive heart failure.

**Statistical Analyses**

Data were analyzed using SPSS software (version 20.0). Baseline continuous data were expressed as means and standard deviations or as medians and interquartile ranges for not normally distributed values; dichotomous data were presented as numbers and percentages. Potential differences between groups were compared using One- way ANOVA with the Bonferroni correction or the Kruskal- Wallis test for not normally distributed values. Categorical data were compared with the Chi-squared test. A poisson regression analysis was performed to calculate the incidence risk ratios ratios (IRR) and corresponding 95% confidence intervals (CI) for the different cardiovascular risk estimation categories. For all tests, a p-value < 0.05 indicated statistical significance.

## Results

### Baseline and outcome characteristics of index pregnancy and the follow-up study

Between January 2006 and November 2010, a total of 20 women with a history of severe very early onset preeclampsia, 300 women with a history of gestational hypertension or preeclampsia at term and 94 women with a history of normotensive term pregnancies were included in this study. Baseline characteristics of index pregnancy and at follow-up are shown in Table 1.

**Table 1.** Baseline characteristics at index pregnancy and clinical characteristics at follow-up.

| Baseline Characteristic | Severe Preterm Preeclampsia Cohort (n=20) | Term Hypertensive Pregnancy Cohort (n=300) | Normotensive Pregnancy Cohort (n=94) | P-value |
|---|---|---|---|---|
| *Index Pregnancy: Baseline characteristics* | | | | |
| Maternal age, years | 32.2 (28-35) | 31.0 (28-35) | 31.5 (28-35) | .80 |
| Caucasian, % | 12 (60%)¶,§ | 270 (90%) | 89 (95%) | .001 |
| Gestational age at delivery, weeks | 26.1 (25-27)¶,§ | 39.5 (38-40)* | 39.9 (39-41) | <.001 |
| Birth weight, grams | 561 (429-648)¶,§ | 3398 (3038-3710)* | 3639 (3213-3950) | <.001 |
| *Follow-up Study: Clinical characteristics* | | | | |
| Time elapsed since delivery, days | 2007 (1902-2436)¶,§ | 888 (802-997) | 890 (797-1051) | <.001 |
| Maternal age at follow-up, years | 38.8 (34-42)¶,§ | 34.0 (30-37) | 34.0 (30-37) | .002 |
| Primiparous, % | 2 (10%)¶ | 120 (41%) | 29 (31%) | .006 |
| Antihypertensive medication use, % | 7 (35%)¶,§ | 29 (10%)* | 0 (0%) | <.001 |
| Systolic blood pressure, mmHg | 130 (116-140)§ | 124 (115-130)* | 110 (105-118) | <.001 |
| Diastolic blood pressure, mmHg | 83 (76-94)§ | 80 (78-90)* | 73 (66-80) | <.001 |
| Hypertension, % | 12 (60%)¶,§ | 104 (35%)* | 1 (1%) | <.001 |
| Body mass index, kg/m$^2$ | 25.7 (22-31) | 26.6 (24-30)* | 23.2 (22-25) | <.001 |
| Smoking, % | 2 (10%) | 60 (21%) | 17 (18%) | .47 |

Statistical test: One-way ANOVA with Bonferroni correction

Data are presented as medians (IQR).

¶ SPP cohort compared with HTP cohort, P<.05

§ SPP cohort compared with NTP cohort, P<.05

* HTP cohort compared with NTP cohort, P<.05

At index pregnancy, women with severe very early onset preeclampsia were more often non-Caucasian compared to women with term hypertensive pregnancy disorders and women with normotensive term pregnancies. There were no significant differences in maternal age at the time of delivery at index pregnancy

between women with a history of severe very early onset preeclampsia and women with a history of gestational hypertension or preeclampsia at term. At follow-up, women with a history of severe very early onset preeclampsia had a longer elapsed time since delivery. As a consequence, they were older and were more often multiparous compared with women with a history of gestational hypertension or preeclampsia at term. Furthermore, women with a history of severe very early onset preeclampsia suffered more often from hypertension and they used antihypertensive medication more often compared to women with a history of gestational hypertension or preeclampsia at term and women with a history of normotensive pregnancies at term. However, after adjustment for age and follow-up period no significant differences were found in the prevalence of hypertension between the SPP and HTP cohort.
We found no significant differences in systolic and diastolic blood pressure, BMI and smoking rates at the time of the follow-up study between women with a history of severe very early onset preeclampsia and women with a history of gestational hypertension or preeclampsia at term.

**Biochemical cardiovascular risk factors**

Table 2 shows the biochemical cardiovascular risk factors measured after pregnancy. Fasting blood glucose was found to be significantly higher and HDL cholesterol was found to be significantly lower in women with a history of gestational hypertension or preeclampsia at term compared with women with a history of severe very early onset preeclampsia and women with a history of normotensive pregnancies at term. HsCRP, total cholesterol, and triglycerides were not significantly different between women with a history of severe very early onset preeclampsia and women with a history of gestational hypertension or preeclampsia at term. These outcomes could not be explained by inclusion of women with term gestational hypertension in the HTP cohort. In a subanalysis, in which we excluded women with term gestational hypertension from the HTP cohort and we compared only women with term preeclampsia (n =78) with women with severe early onset preeclampsia (n=20), similar outcomes were found. Median (IQR) glucose levels were still significantly higher in women with term preeclampsia (4.7 (4.5-5.0)) compared to women with severe very early onset preeclampsia (3.7 (3.5-4.0)), p<.001 and median (IQR) HDL cholesterol levels were still significantly lower in women with term preeclampsia (1.3(1.1-1.5)) compared to women with severe very early onset preeclampsia (1.6 (1.4-1.9)), p<.001.

**Table 2.** Postpartum biochemical cardiovascular risk factors.

| Biochemical CVD Risk Factor | SPP cohort (n=20) | HTP cohort (n=300) | NTP cohort (n=94) | P-value |
|---|---|---|---|---|
| Glucose, mmol/L | 3.7 (3.5-4.0)¶,^ | 4.7 (4.5-5.1)*,‡ | 4.7 (4.4 – 4.9)† | <.001 |
| Total cholesterol, mmol/L | 4.9 (4.3-6.1)§ | 4.7 (4.2-5.3)* | 4.6 (3.9-5.1) | =.01 |
| HDL cholesterol, mmol/L | 1.6 (1.4-1.9)¶,§ | 1.4 (1.2-1.6)* | 1.5 (1.3-1.6) | <.001 |
| Triglycerides, mmol/L | 0.86 (0.6-1.2) § | 0.91 (0.7-1.2)** | 0.71 (0.5-1.0) | <.001 |
| HsCRP, mg/L | 2.0 (1.0-3.8)§ | 2.2 (1.0-5.0)**,† | 0.93 (0.4-2.2) | <.001 |

Statistical test: Kruskal-Wallis test

Data are presented as medians (IQR).

¶ SPP cohort compared with HTP cohort, P<.001

§ SPP cohort compared with NTP cohort, P<.05

^ SPP cohort compared with NTP cohort, P<.001

* HTP cohort compared with NTP cohort, P<.05

** HTP cohort compared with NTP cohort, P<.001

‡ 9 missing values

† 6 missing values

## Cardiovascular disease risk prediction

*1. 10-year general cardiovascular disease risk prediction by the Framingham risk score.*

Figure 1A illustrates the mean (SD) risk percentage of developing general cardiovascular disease within 10 years *at current age*, calculated with the Framingham risk score. Figure 1B illustrates different risk categories of the 10-year prediction of developing general cardiovascular disease calculated with the Framingham risk score of SPP women, HTP women and NTP women at current age. Figures 2A and 2B show the results *after extrapolation of their age to 60 years*. Poisson regression analysis showed that women with a history of severe very early onset preeclampsia had a 6-fold higher extrapolated risk of >10% (p=.02, IRR 6.3 95% CI (1.4-28)) to suffer from cardiovascular disease within the next 10-years compared to women with a history of normotensive pregnancies at term. Women with a history of gestational hypertension or preeclampsia at term had an almost 6-fold higher extrapolated risk of >10% (p=.003, IRR 5.5 95% CI (3.3-9.1)) to suffer from cardiovascular disease within the next 10-years compared to women with a history of normotensive pregnancies at term. No significant differences were found in the extrapolated risk of > 10% to suffer from cardiovascular disease within the next 10 years between women with a history of severe very early onset preeclampsia and women with a history of gestational hypertension or preeclampsia at term (p=.89, IRR 1.1 (0.39-3.0)).

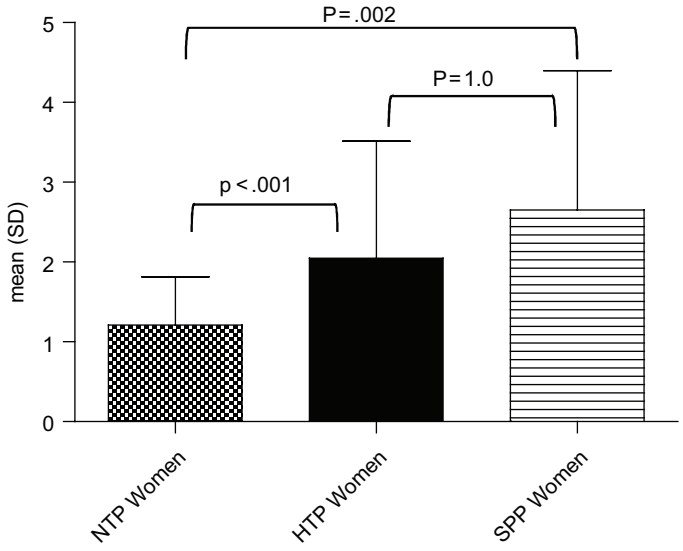


**Figure 1A.** 10-year Framingham risk score at current age

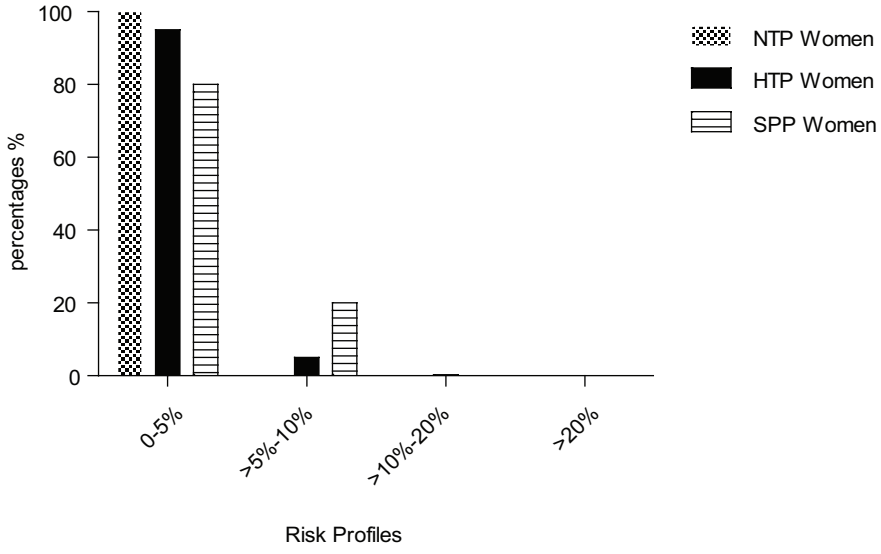


**Figure 1B.** 10-year Framingham risk score at current age

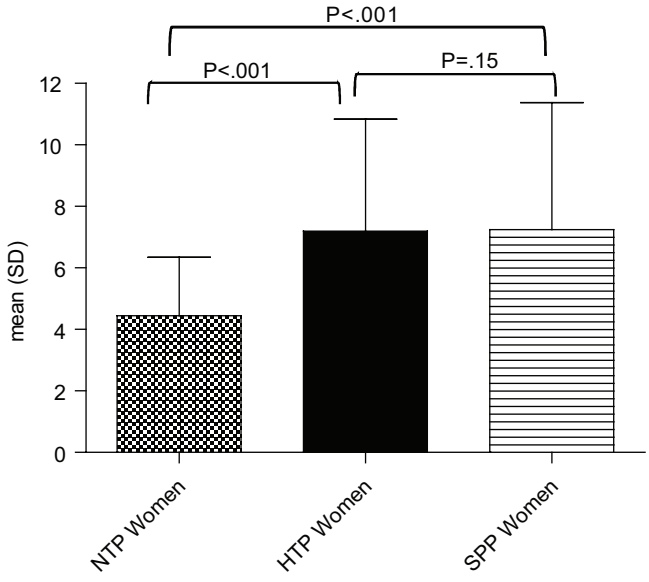


**Figure 2A**. 10-year Framingham risk score extrapolated to the age of 60 years



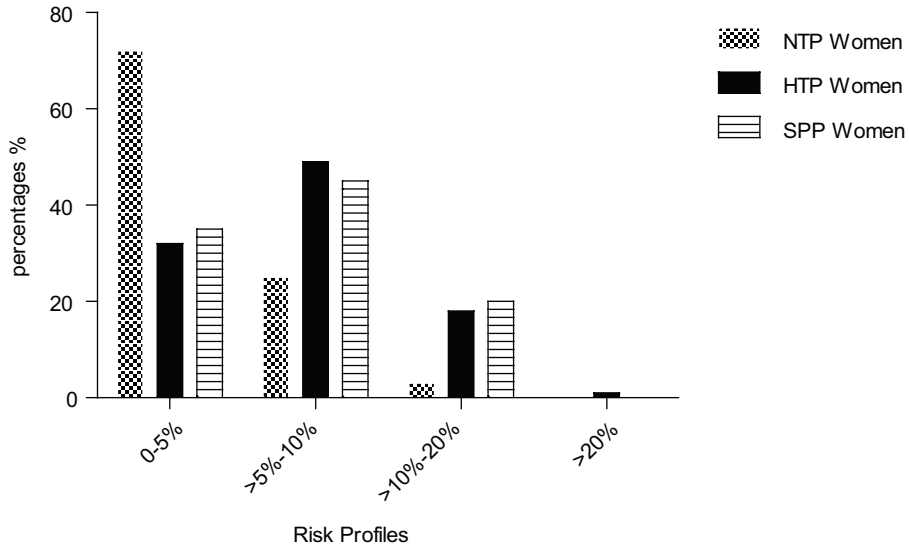


**Figure 2B.** 10-year Framingham risk score extrapolated to the age of 60 years

*2. 30-year full cardiovascular disease risk prediction by the Framingham risk score.*

Figure 3A illustrates the mean (SD) risk percentage of developing overall cardiovascular disease within 30 years at current age, calculated with the Framingham risk score. Figure 3B illustrates different risk categories of the 30-year prediction of developing general cardiovascular disease calculated with the Framingham risk score at current age. Poisson regression analyses showed that women with a history of severe very early onset preeclampsia had a 4-fold higher risk of >10% (p<.001, IRR 4.3 95% CI (2.1-8.9)) to suffer from general cardiovascular disease within the next 30 years compared with women with a history of normotensive pregnancies at term. Women with a history of gestational hypertension or preeclampsia at term had an almost 3-fold higher risk of >10% (p<.001, IRR 2.7 95% CI (1.6-4.5)) to suffer from full cardiovascular disease within the next 30 years compared to women with a history of normotensive pregnancies at term. No significant differences were found in the risk of > 10% to suffer from full cardiovascular disease within the next 30 years between women with a history of severe very early onset preeclampsia and women with a history of gestational hypertension or preeclampsia at term (p=.09, IRR 1.6 (0.93-2.8)).

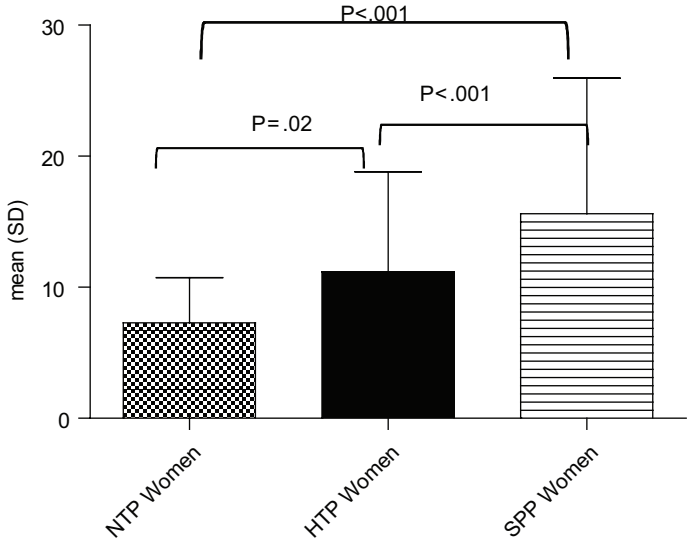


**Figure 3A.** 30-year Framingham risk score at current age

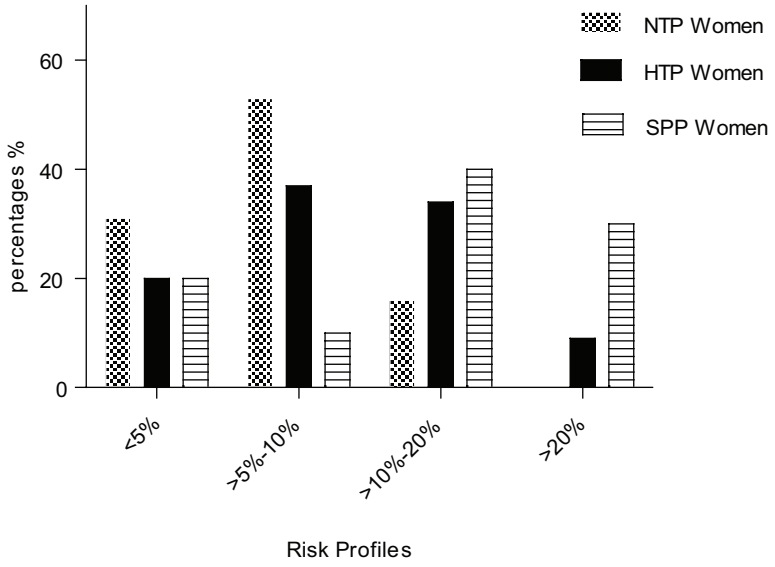


**Figure 3B.** 30-year Framingham risk score at current age



## Discussion

As expected, both women with history of severe very early onset preeclampsia and women with a history of term hypertensive pregnancy disorders exhibit more cardiovascular risk factors and have higher 10-year and 30-year cardiovascular risk estimations compared to women with a history of normotensive term pregnancies.

In our present follow-up study we found that, after adjustment for age, 10-year and 30-year cardiovascular risk estimations are comparable in women with a history of severe very early onset preeclampsia and women with a history of term hypertensive women. Women with term hypertensive pregnancy disorders exhibit more unfavourable biochemical cardiovascular risk factors compared to women with severe very early onset preeclampsia. Women with severe very early onset preeclampsia had more often hypertension and as a consequense used more often antihypertensive medication at least two years after pregnancy. However, this difference can be explained by the older age and longer follow-up period in these women.

In 2007, Bellamy et al. showed in a meta-analysis that women with a history of preeclampsia have an increased risk of cardiovascular disease, including an almost fourfold increased risk of hypertension and an approximately twofold increased risk of fatal and non-fatal ischaemic heart disease, stroke, and venous thromboembolism in later life. Women with a history of preterm preeclampsia

< 37 weeks of gestation in combination with intra uterine growth restriction and preterm delivery have even an almost 8-fold increased risk of ischemic heart disease life[2;3]. Thus, we expected that women with severe very early onset preeclampsia would have had a higher estimated extrapolated 10-year cardiovascular event risk compared to women with term hypertensive pregnancy disorders. However, no significant differences were found in the Framingham risk scores; women with severe very early onset preeclampsia only had a higher prevalence of hypertension and antihypertensive medication use compared to women with term hypertensive pregnancy disorders. However after adjustment for age and follow-up period this difference in prevalence of hypertension was not significant. This unexpected finding could be explained by the fact that we might have had an underpowered SPP cohort (n=20) and/or that SPP women were relatively "healthy". On the contrary, our HTP cohort could have been relatively "sick" as the prevalence of chronic hypertension was as high as 35%. Another explanation could be that our follow-up period was too short to find obvious differences between the two cohorts and that a longer follow-up period would reveal the differences between the two disorders. Furthermore, it is possible that, beside common cardiovascular risk factors used in the Framingham risk scores, another independent risk factor plays a key role in developing cardiovascular disease in women, for example the pregnancy complication itself, so that estimated cardiovascular risks increase with the severity of the hypertensive pregnancy disorder independent of the common measured traditional cardiovascular risk factors.

Most investigators paid attention to cardiovascular risk factor assessment after preeclampsia, especially after severe *preterm* preeclampsia, rather than after mild *term* preeclampsia or gestational hypertension. Some studies combined the severe and mild disorders without distinction and as a consequence no conclusions can be drawn from earlier follow-up studies on differences in cardiovascular risk factors between severe early and mild term preeclampsia[19].

Early onset preeclampsia has been described as "a placental disorder", also to be interpreted as a "vessel disorder". Redman et al.[20] described a two stage model explaining the pathophysiology. In the first stage, which takes place in the first half of pregnancy, the placental development is disturbed. Remodeling of the maternal spiral arteries is impaired leading to decrease of the maternal blood supply to the placenta. As the pregnancy proceeds the placenta will need more blood supply to sustain the growing workload. An underdeveloped placenta will ultimately get oxidatively stressed. This is called the second stage. The placenta then releases factors into the maternal circulation that cause the clinical features of preeclampsia. These appear to arise from a generalized systemic immune response, of which endothelial dysfunction is a prominent component. On the contrary, late onset preeclampsia has been postulated as a "maternal

constitutional disorder"[4]. It has been suggested that pre-pregnancy unfavourable cardiovascular and metabolic factors predispose for (late onset) preeclampsia[21]. The placental or vessel disorders and maternal constitutional disorders may have another underlying pathofysiology and link with cardiovascular disease later. This hypothesis is supported by the findings in our study; term hypertensive disorders were associated with more unfavourable metabolic factors, including higher BMI and higher lipid and glucose levels postpartum.

*Strengths and Limitations*

Strengths of our study include a unique cohort of women with very early onset preeclampsia and a large cohort of women with term hypertensive pregnancy disorders included within an 11 year-interval, with comprehensive and reproducible measurements and assessments. In addition, for the first time, our study describes differences in cardiovascular risk factors and compares cardiovascular event risks between women with very early onset and women with late onset preeclampsia.

Our study has also a few limitations. First, we compared three cohorts from two different studies with a significant different follow-up period. The three cohorts derived from different centers and two different laboratories analyzed the blood samples. This could have biased our study results. Unexpectedly, glucose levels were significantly higher in both the HTP and NTP cohort compared to the SPP cohort. These differences might be explained by the fact that sodium- fluoride tubes were used in both the HTP and NTP cohort to collect blood for glucose and that EDTA tubes were used to collect blood for glucose in the SPP cohort. Thus, due to these two different storage methods, which could have influenced the outcomes, we may not conclude that HTP and NTP have higher glucose levels after pregnancies complicated by hypertensive pregnancy disorders. However, for the other measured cardiovascular risk factors similar standardized measurements were used and are comparable between the three cohorts.

Second, the severe very early onset preeclampsia cohort consisted of only 20 women and the term hypertensive pregnancy cohort consisted of 300 women. As a consequence, the SPP cohort could be underpowered in this study and this could be the explanation why we did not find significant differences in cardiovascular disease risk estimations. Finally, due to the relative young age of our study participants, the estimated 10-year cardiovascular disease risk at current age was low in all three cohorts. Therefore, we extrapolated the age to 60 years. We did not adjust for the fact that cardiovascular risk factors might change over time. On the contrary, the advantage of this method is that it is possible to adjust for the age difference between women in the SPP cohort and women in the HTP cohort and NTP cohort. After extrapolation no differences

were found between the estimated 10-year cardiovascular event risks between women with a history of severe very early onset preeclampsia and women with term hypertensive pregnancy disorders.

**Conclusion**

In conclusion, women with a history of severe very early onset preeclampsia have similar estimated cardiovascular event risks as compared with women with a history of term gestational hypertension or preeclampsia. Our study supports the hypothesis that the severity of hypertensive pregnancy disorders is an independent factor for cardiovascular risk in later life. Further research is warranted to investigate whether hypertensive pregnancy disorders and severity of the disorder have to be included as an independent variable in cardiovascular risk prediction models for more accurate cardiovascular risk prediction in women.

## Reference List


(1) http://www.who.int/mediacentre/factsheets/fs310/en/index.html. 11-2-2013. 11-2-2013.

(2) Bellamy L, Casas JP, Hingorani AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. BMJ 2007; 335(7627):974.

(3) Smith GC, Pell JP, Walsh D. Pregnancy complications and maternal risk of ischaemic heart disease: a retrospective cohort study of 129,290 births. Lancet 2001; 357(9273):2002-2006.

(4) Hermes W, Van KF, de Groot CJ. Preeclampsia and cardiovascular risk. Minerva Ginecol 2012; 64(4):281-292.

(5) Berends AL, de Groot CJ, Sijbrands EJ, Sie MP, Benneheij SH, Pal R et al. Shared constitutional risks for maternal vascular-related pregnancy complications and future cardiovascular disease. Hypertension 2008; 51(4):1034-1041.

(6) Chambers JC, Fusi L, Malik IS, Haskard DO, De SM, Kooner JS. Association of maternal endothelial dysfunction with preeclampsia. JAMA 2001; 285(12):1607-1612.

(7) Freeman DJ, McManus F, Brown EA, Cherry L, Norrie J, Ramsay JE et al. Short- and long-term changes in plasma inflammatory markers associated with preeclampsia. Hypertension 2004; 44(5):708-714.

(8) Laivuori H, Tikkanen MJ, Ylikorkala O. Hyperinsulinemia 17 years after preeclamptic first pregnancy. J Clin Endocrinol Metab 1996; 81(8):2908-2911.

(9) Manten GT, Sikkema MJ, Voorbij HA, Visser GH, Bruinse HW, Franx A. Risk factors for cardiovascular disease in women with a history of pregnancy complicated by preeclampsia or intrauterine growth restriction. Hypertens Pregnancy 2007; 26(1):39-50.

(10) Drost JT, Arpaci G, Ottervanger JP, de Boer MJ, van EJ, van der Schouw YT et al. Cardiovascular risk factors in women 10 years post early preeclampsia: the Preeclampsia Risk EValuation in FEMales study (PREVFEM). Eur J Prev Cardiol 2012; 19(5):1138-1144.

(11) Hermes W, Franx A, van Pampus MG, Bloemenkamp KW, Bots ML, van der Post JA et al. Cardiovascular Risk Factors in Women Who Had Hypertensive Disorders Late in Pregnancy: A Cohort Study. 2013.

(12) Gaugler-Senden IP, Berends AL, de Groot CJ, Steegers EA. Severe, very early onset preeclampsia: subsequent pregnancies and future parental cardiovascular health. Eur J Obstet Gynecol Reprod Biol 2008; 140(2):171-177.

(13) Koopmans CM, Bijlenga D, Aarnoudse JG, van BE, Bekedam DJ, van den Berg PP et al. Induction of labour versus expectant monitoring in women with pregnancy induced hypertension or mild preeclampsia at term: the HYPITAT trial. BMC Pregnancy Childbirth 2007; 7:14.

(14) Koopmans CM, Bijlenga D, Groen H, Vijgen SM, Aarnoudse JG, Bekedam DJ et al. Induction of labour versus expectant monitoring for gestational hypertension or mild pre-eclampsia after 36 weeks' gestation (HYPITAT): a multicentre, open-label randomised controlled trial. Lancet 2009; 374(9694):979-988.

(15) Hermes W, Franx A, van Pampus MG, Bloemenkamp KW, van der Post JA, Porath M et al. 10-Year cardiovascular event risks for women who experienced hypertensive disorders in late pregnancy: the HyRAS study. BMC Pregnancy Childbirth 2010; 10:28.

(16) Gaugler-Senden IP, Berends AL, de Groot CJ, Steegers EA. Severe, very early onset preeclampsia: subsequent pregnancies and future parental cardiovascular health. Eur J Obstet Gynecol Reprod Biol 2008; 140(2):171-177.
(17) D'Agostino RB, Sr., Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation 2008; 117(6):743-753.
(18) Pencina MJ, D'Agostino RB, Sr., Larson MG, Massaro JM, Vasan RS. Predicting the 30-year risk of cardiovascular disease: the framingham heart study. Circulation 2009; 119(24):3078-3084.
(19) Hermes W, Ket JC, van Pampus MG, Franx A, Veenendaal MV, Kolster C et al. Biochemical cardiovascular risk factors after hypertensive pregnancy disorders: a systematic review and meta-analysis. Obstet Gynecol Surv 2012; 67(12):793-809.
(20) Redman CW, Sargent IL. Latest advances in understanding preeclampsia. Science 2005; 308(5728):1592-1594.
(21) Magnussen EB, Vatten LJ, Lund-Nilsen TI, Salvesen KA, Davey SG, Romundstad PR. Prepregnancy cardiovascular risk factors as predictors of pre-eclampsia: population based cohort study. BMJ 2007; 335(7627):978.

# *Chapter 9*

## Induction of labour or expectant monitoring in hypertensive pregnancy disorders at term: Do women's cardiovascular risk factors postpartum differ between the two strategies?

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## Abstract

**Objective:** Cardiovascular disease (CVD) is the leading cause of death in women in the western world. Several studies have described the association between hypertensive pregnancy disorders and CVD in later life. Our aim was to compare postpartum cardiovascular risk factors in women who had a shorter and women who had a longer exposure of endothelial activation during their *term* hypertensive pregnancy.

**Study design:** We studied a subsample of women with pregnancy induced hypertension or mild preeclampsia at term, who had participated in the randomized HYPITAT trial comparing induction of labour (IOL cohort) (n=110) or expectant monitoring (EM cohort) (n=91). We asssed, 2.5 years postpartum, cardiovascular risk factors, i.e. blood pressure, anthropometrics, glucose, HbA1C, insulin, HOMA score, total cholesterol, HDL cholesterol, triglycerides, high sensitive CRP, micro-albumin and metabolic syndrome, and compared these risk factors between the induction and expectant group.

**Results:** The mean time from randomization to delivery was 3.3 days in the induction group and 10.3 days in the expectant group (P<.001), generating a difference in exposure of 7 days. After a mean follow-up period of 2.5 years, the prevalence of hypertension (IOL 34%; EM 37%, p=.66) and metabolic syndrome (IOL 26%; EM 27%, p= 1.0) were similar in both groups. Furthermore, systolic and diastolic blood pressure, BMI, waist circumference, glucose, HbA1C, insulin, HOMA score, lipids, HsCRP-levels and micro-albumin were all comparable between women who had induction of labour and those who had expectant monitoring.

**Conclusion:** In women with hypertensive disorders in pregnancy at term, induction of labour does not affect the clinical and biochemical cardiovascular profile at 2.5 years postpartum.

## Introduction

Cardiovascular disease is still the leading cause of death in women in the Western world[1]. As a consequence, physician's interest in causality, predisposing factors, screening and prevention of developing cardiovascular disease in women is rising. Several epidemiological studies have described the association between hypertensive pregnancy disorders and cardiovascular disease in later life[2].

It is well described that women with a history of early severe preeclampsia exhibit more cardiovascular risk factors after their pregnancy compared with women with uncomplicated normotensive pregnancies[3-7]. In addition, we have recently shown in a longitudinal follow-up study of the HYPITAT trial that not only women with severe early preeclampsia exhibit more cardiovascular risk factors after pregnancy, but also women with term gestational hypertension and term preeclampsia[8].

It has been suggested that pre-pregnancy unfavourable cardiovascular and metabolic factors predispose for (late onset) preeclampsia[9]. However, it is not clear whether damage to the vascular endothelium by hypertensive pregnancy disorders results in an increased risk of cardiovascular disease in later life or whether pre-existing factors underlie both the predisposition to placental disease and the later development of cardiovascular disease.

The HYPITAT trial, by Koopmans et al.,[10] showed that women with gestational hypertension or preeclampsia at term benefit from induction of labour to avoid progression to more severe disease *during* pregnancy. However, if women with hypertensive disorders at term also benefit from induction of labour *after* pregnancy, to reduce cardiovascular risk in later life, is unknown. Expectant monitoring in women with gestational hypertension and preeclampsia at term may negatively affect women's cardiovascular outcomes in later life.

The aim of this study was to compare cardiovascular risk factors at least two years postpartum in women with a history of term hypertensive pregnancy disorders who were randomized for induction of labour and women with a history of term hypertensive pregnancy disorders who were randomized for expectant monitoring in the HYPITAT trial[10]; Does exposure to a shorter or longer period of endothelial activation result in differences of cardiovascular risk factors two years postpartum?

## Materials and Methods

Between June 2008 and November 2010, women with a history of gestational hypertension or preeclampsia at term, who were randomized during their pregnancy in a parallel, open-label randomised controlled trial (HYPITAT)

between induction of labour and expectant monitoring, were included in the current longitudinal follow-up study for cardiovascular risk factor assessment 2.5 years postpartum.
Between October 2005 and March 2008, the HYPITAT trial[10] included women with a singleton pregnancy between 36+0 and 41+0 weeks of gestation who had gestational hypertension or preeclampsia. Gestational hypertension was defined as diastolic blood pressure of 95 mmHg or higher measured on two occasions at least 6 hours apart. Preeclampsia was defined as diastolic blood pressure of 90 mmHg or higher measured on two occasions at least 6 hours apart, combined with proteinuria. Proteinuria was defined as two or more occurrences of protein on a dipstick, > 300 mg total protein within a 24 hour urine collection, or ratio of protein to creatinine > 30 mg/mmol. A detailed description of the exclusion criteria has been provided earlier[10].

The aim of the HYPITAT trial was to assess whether induction of labour in women with hypertensive pregnancy disorders at term reduced the poor maternal composite outcome compared with expectant monitoring.
Before randomisation, written informed consent was obtained to participate in the HYPITAT trial and in the current longitudinal follow-up study. Both the HYPITAT trial and the longitudinal follow-up study were approved by the Institutional Review Board of the University of Leiden, and were locally approved by the participating hospitals.
Women who were allocated to induction of labour were induced within 24 hours of randomisation. Women who were allocated to expectant monitoring were intensively monitored until spontaneous onset of labour. Exceptions for expectant monitoring included: severe hypertensive disease, eclampsia or HELLP syndrome, suspected foetal distress, pre-labour rupture of membranes lasting more than 48 hours, meconium stained amniotic fluid, or a foetus with gestational age beyond 41 weeks. If a woman developed severe hypertensive disease with imminent eclampsia after inclusion in the HYPITAT trial, magnesium sulphate prophylaxis was started according to local hospital protocols and induction of labour was recommended. In 2009, the procedures and results of the HYPITAT trial have been published elsewhere.[10]

The primary aim of the longitudinal follow-up study of the HYPITAT trial was to assess 10-year cardiovascular event risks in women with a history of gestational hypertension or preeclampsia at term using the validated Framingham risk score[8;11]. A secondary aim was to compare cardiovascular risk factors at least 2 years postpartum between induction of labour and expectant monitoring in

women with a history of hypertensive pregnancy disorders who participated in the HYPITAT trial.

Three Academic hospitals and 17 non-academic hospitals across four geographical regions in the Netherlands, participated in the follow-up study of the HYPITAT trial. Between June 2008 and November 2010, 492 women of the total randomised HYPITAT cohort (n= 756) were eligible for this follow-up study. The other randomised women of the HYPITAT trial (n=264) were included in non-participating centres of the current follow-up study and were not invited for participation.

Research nurses invited and counselled the participants 2.5 years postpartum, obtained written informed consent, monitored the study protocol and collected the data. All participants were invited into their local center for cardiovascular risk factor assessment, including blood pressure, height and weight, hip and waist circumference. Venous blood samples were collected after an overnight fast and assayed for glucose, HbA1c, insulin, total cholesterol, HDL cholesterol, triglycerides and HsCRP. Urine was collected for assessment of micro-albuminuria immediately after waking up. The laboratory methods and cardiovascular risk factor assessment are described in detail and published elsewhere[8;11;12].

Furthermore, participants were asked to complete a questionnaire. This questionnaire included questions about their medical history, current use of medication, obstetric history, subsequent pregnancy after index pregnancy and family history, including CVD.

Women, who were pregnant or lactating, either at the time of enrolment or within the last 3 months, were excluded from this follow-up study, as pregnancy and lactation have influence on biochemical cardiovascular risk factor levels.



Severe gestational hypertension or severe preeclampsia were defined as either systolic blood pressure of 170 mmHg or higher, diastolic blood pressure of 110 mmHg or higher, or proteinuria of 5 gram or higher per 24 hours.

Hypertension 2.5 years postpartum was defined as systolic blood pressure ≥ 140 mmHg, or a diastolic blood pressure ≥ 90 mmHg or current use of antihypertensive medication. Metabolic syndrome was defined as waist circumference ≥ 80 cm. plus any two of raised triglycerides (> 150 mg/dL), reduced HDL cholesterol (< 50 mg/dL), raised blood pressure (systolic ≥ 130 mmHg and diastolic ≥ 85 mmHg), treatment of previously diagnosed hypertension, raised fasting plasma glucose (≥ 100 mg/dL) or previously diagnosed type 2 diabetes[13].

Data were analyzed using SPSS software (version 20.0). Continuous data are expressed as mean and standard deviation or median and interquartile ranges. Nominal data are presented as numbers and percentages. Differences at baseline

were assessed using a Chi-square test or student T-test for independent samples where appropriate. Skewed distributions were defined as values of more than two standard errors of skewness (>|1|). Non-normally distributed data were compared using the Mann-Whitney U test. Clinical parameters during pregnancy and after 2.5 years follow-up were analyzed using univariate regression analysis. All tests were two-sided and a p-value of < 0.05 was considered significant.

## Results

Of the 492 eligible women for the 2.5 year follow-up study, 19 women (4%) refused participation, 203 women (41%) were lost to follow-up, and two women (0.4%) moved abroad and 66 women (13%) were excluded because they were again pregnant or lactating. One woman had died in a car accident. We followed up with 201 women with a history of term gestational hypertension or preeclampsia, of which 110 women (55%) had been randomized for induction of labour and 91 women (45%) had been randomized for expectant monitoring.

Baseline and clinical characteristics of the index pregnancy of the subjects are shown in Table 1. At index pregnancy, women who were randomized for expectant monitoring had more often a diastolic blood pressure ≥ 110 mmHg and more often a systolic blood pressure ≥ 170 mmHg during pregnancy or immediately after delivery and they used more oral antihypertensive medication and intravenous magnesium sulfate (MgSO4) after randomization compared with women who were randomized for induction of labour. Furthermore, severe disease was more prevalent in the expectant monitoring cohort compared with the induction of labour cohort (40% vs. 20%. P=.003). Women who were randomized for expectant monitoring had a significantly longer prolongation of pregnancy with an average of seven days. There were no significant differences in maternal age, parity, ethnicity, blood pressure at first antenatal visit, smoking, blood pressure at study entry, or hypertensive-related disease (gestational hypertension or preeclampsia).

**Table 1.** Baseline and initial outcome characteristics of women who had induction of labour and expectant monitoring

| Characteristics Index Pregnancy | Induction of Labour Cohort (n=110) | Expectant Monitoring Cohort (n=91) | P value |
|---|---|---|---|
| Maternal age at the time of labour, years | 30.8 (5.3) | 31.0 (5.3) | .82 |
| Nulliparous | 73 (34%) | 62 (68%) | .88 |
| Family history of CVD < 60 years in first degree relative | 19 (18%) | 12 (14%) | .56 |
| Race, Caucasian | 90 (91%) | 76 (91%) | 1.0 |
| Diastolic blood pressure at first antenatal visit, mmHg | 73 (8.9) | 73 (9.3) | .96 |
| Systolic blood pressure at first antenatal visit, mmHg | 121 (11) | 122 (13) | .58 |
| Body mass index at first antenatal visit, $kg/m^2$ | 27 (5.6) | 26 (5.0) | .38 |
| Smoking | 17 (17%) | 13 (15%) | .84 |
| Spontaneous onset of labour | 3 (2.7%) | 43 (47%) | <.001 |
| GA delivery, weeks | 38.8 (1.2) | 39.7 (1.1) | <.001 |
| Spontaneous delivery | 76 (69%) | 59 (65%) | .55 |
| Prolongation of pregnancy after randomization (days) | 3.3 (2.9) | 10.3 (7.1) | <.001 |
| Sex, Female | 52 (47%) | 44 (48%) | .89 |
| Small for gestational age | 8 (7.3%) | 6 (6.6%) | 1.0 |
| Systolic blood pressure at study entry HYPITAT, mmHg | 146 (12) | 145 (12) | .78 |
| Diastolic blood pressure at study entry HYPITAT, mmHg | 98 (5.4) | 98 (5.3) | .45 |
| Intravenous antihypertensive medication after randomization | 5 (4.6%) | 8 (8.9%) | .26 |
| Oral antihypertensive medication after randomization | 9 (8.3%) | 22 (24%) | .003 |
| MgSO4 use after randomization | 7 (6.5%) | 15 (17%) | .04 |
| Diastolic blood pressure ≥ 110 mmHg | 15 (14%) | 27 (30%) | .01 |
| Systolic blood pressure ≥ 170 mmHg | 13 (12%) | 23 (25%) | .02 |
| Highest systolic blood pressure, mmHg | 151 (13) | 158 (17) | .001 |
| Highest diastolic blood pressure, mmHg | 99 (8.5) | 103 (9.1) | .009 |
| Hypertensive disorder, PIH* | 84 (76%) | 66 (73%) | .62 |
| Hypertensive disorder, PE* | 26 (24%) | 25 (28%) | |
| Severe disease | 22 (20%) | 36 (40%) | .003 |

Data are presented as mean (SD) or n (%).

Statistical tests: Chi-square and independent samples T-test.

Severe disease was defined as: systolic blood pressure of 170 mmHg or higher, diastolic blood pressure of 110 mmHg or higher or proteinuria of 5 gram or higher per 24 hours

* PIH= gestational hypertension, PE= preeclampsia

At 2.5 year follow-up no significant differences in clinical characteristics were found between women who were randomized for induction of labour and women who were randomized for expectant monitoring (table 2). Univariate regression analysis showed that the use of intravenous antihypertensive medication after randomization during index pregnancy was associated with a higher systolic blood pressure 2.5 years postpartum (OR 1.05, 95% CI (1.01 – 1.09). No associations were found between other maternal clinical pregnancy parameters, including intravenous antihypertensive medication use, BMI at first antenatal visit, severe disease and the use of magnesiumsulfate and clinical parameters at 2.5 years postpartum, including diastolic blood pressures and prevalence of hypertension. Both BMI 2.5 years postpartum (OR 1.05, 95% CI (1.00- 1.11)) and age at follow-up (OR 1.12, 95% CI (1.04- 1.17)) were associated with the prevalence of hypertension 2.5 years postpartum. No association was found between waist circumference 2.5 years postpartum and the prevalence of hypertension 2.5 years postpartum.

**Table 2.** Clinical characteristics of women who had induction of labour and expectant monitoring 2.5 years postpartum.

| Characteristics | Induction of labour Cohort (n=110) | Expectant Monitoring Cohort (n=91) | P value |
|---|---|---|---|
| Maternal age at follow-up, years | 33.4 (5.3) | 33.3 (5.6) | .99 |
| Primiparous | 41 (38%) | 38 (44%) | .46 |
| BMI at follow-up, kg/m$^2$ | 28 (6.0) | 28 (5.6) | .89 |
| Follow-up period, days | 929 (161) | 912 (146) | .44 |
| Waist, cm. | 91 (14) | 91 (12) | 1.0 |
| Hip, cm. | 110 (13) | 110 (13) | .98 |
| Systolic blood pressure at 2.5 years follow-up, mmHg | 125 (14) | 125 (12) | .84 |
| Diastolic blood pressure at 2.5 years follow-up, mmHg | 82 (9.9) | 84 (9.0) | .18 |
| Hypertension | 37 (34%) | 33 (37%) | .66 |
| Antihypertensive medication use at 2.5 years follow-up. | 10 (9.4%) | 12 (14%) | .37 |
| Metabolic Syndrome | 28 (26%) | 22 (27%) | 1.0 |

Data are presented as mean (SD) or n (%).

Statistical tests: Chi-square and independent samples T-test.

Table 3 shows biochemical cardiovascular risk factors 2.5 years after index pregnancy in women who were randomized for induction of labour and women who were randomized for expectant monitoring. No significant differences were found between the two cohorts. Univariate regression analysis showed that none of the maternal clinical parameters during index pregnancy, including intravenous antihypertensive medication use, severe disease and the use of

magnesiumsulfate were associated with biochemical cardiovascular risk factor levels 2.5 years postpartum.

**Table 3.** Biochemical cardiovascular risk factors in women who had induction of labour and expectant monitoring, 2.5 years postpartum.

| Biochemical Cardiovascular Risk Factor | Induction of Labour Cohort (n=110) | Expectant Monitoring Cohort (n=91) | P value |
|---|---|---|---|
| Microalbumin urine, mmol/L | 6.0 (3.3-12) | 4.5 (3.0-12) | .15 |
| Fasting blood glucose, mg/dl | 4.7 (4.5-5.1) | 4.9 (4.5-5.1) | .33 |
| Insulin, mU/L | 4.8 (2.0-8.2) | 4.6 (2.0-7.2) | .51 |
| HOMA score | 1.0 (0.4-1.8) | 1.0 (0.4-1.5) | .62 |
| HbA1c, % | 5.4 (5.2-5.6) | 5.4 (5.1-5.6) | .68 |
| Total cholesterol, mg/dl | 4.7 (4.2-5.5) | 4.9 (4.2-5.3) | .92 |
| HDL cholesterol, mg/dl | 1.3 (1.2-1.5) | 1.4 (1.2-1.5) | .87 |
| Triglycerides, mg/dl | 0.9 (0.7-1.3) | 1.0 (0.7-1.5) | .16 |
| HsCRP, mg/L | 2.5 (1.0-5.8) | 2.5 (1.3-4.6) | .85 |

Data are presented as median (IQR).

Statistical test: Mann Whitney U test.

## Comments



We found no significant differences in clinical characteristics and biochemical cardiovascular risk factors 2.5 years postpartum between the women with a history of term hypertensive pregnancy disorders who were randomized for induction of labour and those who were randomized for expectant monitoring.

This finding suggests that a prolonged exposure to hypertensive disorders in pregnancy, of almost one week, does not affect women's cardiovascular disease risk later in life. Thus, women with term hypertensive pregnancy disorders benefit from induction of labour to avoid progression to more severe disease *during* pregnancy, but it seems that they do not benefit from induction of labour to reduce cardiovascular risk factor levels *after* pregnancy.

Current hypothesis of the pathogenesis of preeclampsia suggests that the preeclampsia syndrome may result from a complex interaction between fetal placental factors and/or maternal constitutional factors and/or maternal vascular or maternal immunological maladaptation to pregnancy and that preeclampsia can be divided in two categories. In the first category, placental preeclampsia, the disorder is a result of a placenta that is under hypoxic conditions with oxidative stress[14]. This dysfunctional placenta is considered to initiate a generalized systemic immune response in which endothelial dysfunction is an important component[15]. The second category, maternal preeclampsia, is more an abnormal maternal response than an abnormal pregnancy and results

from the interaction between a normal placenta and a maternal constitutional problem, which is prone to microvascular disease as with chronic hypertension or diabetes. Furthermore, the maternal constitutional problem not only predisposes for maternal preeclampsia, but also for cardiovascular disease in later life and there might be an additional effect of persistent endothelial damage[15]. A third category is the mixture of above mentioned syndromes and combines maternal and placental contributions. A possible explanation for the fact that we did not find a difference in postpartum cardiovascular risk factors in women who had a shorter and women who had a longer exposure of endothelial activation during their *term* hypertensive pregnancy might be the relative short time interval of only 7 days between induction of labor and expectant management and / or the mild presentation of the disease. Another explanation might be that the follow-up period of 2.5 years was too short to find a difference in cardiovascular risk factors between the two cohorts. Perhaps there are differences in cardiovascular risk factors that could be found after 10 or 20 years postpartum.

Most likely, the association of term preeclampsia and cardiovascular disease in later life is mainly or only based on maternal constitutional factors. If this is the case, our findings are logical, as maternal constitutional factors are not influenced by induction of labour or expectant monitoring.

Our results and conclusions can not be translated to severe early preeclampsia, as this disorder might have a different pathogenesis and it is well known that women with severe early preeclampsia have a higher risk of cardiovascular disease later in life compared with women with term hypertensive pregnancy disorders.

To our knowledge, no other studies have focused on the effect of induction of labour or expectant monitoring on cardiovascular risk factors or cardiovascular outcomes in later life.

The major strength of our study is that we longitudinally followed-up with women who had participated in a randomized controlled trial, which has resulted in a large and strong cohort. We included women with hypertensive pregnancy disorders at term, as these are most common in daily obstetric practice.

Limitations of this study should also be pointed out. First, the lost to follow-up percentage was 41%.The majority of women who were lost to follow-up could not be reached by phone or mail (despite approaching them two times and approaching their general practioner). This may have resulted in selection bias. Comparative baseline characteristic data of women who were not included in the current follow-up study showed that women who were lost to follow-up were significantly younger during the HYPITAT trial compared to the included women (mean (SD), 29 (5.0) vs. 31y (5.4), p<.001) and more often non- Caucasian (18% vs. 9%, p=.01).

All other baseline characteristics including systolic and diastolic blood pressure at booking, BMI at booking, parity, and gestational age at delivery, severity of hypertensive disorder during pregnancy and medication use during pregnancy (antihypertensive and anticonvulsive medication) were comparable between included and non-included women. A possible explanation for the high lost to follow-up percentage is that women either moved after starting a young family, or changed their cell phone numbers.

A second limitation is the relatively short follow-up period. We assessed young women for cardiovascular risk factors, which are surrogate endpoints for cardiovascular disease. Therefore, we cannot draw a proper conclusion on prolonged exposure to hypertensive pregnancy disorders and its long term cardiovascular disease outcome in this specific cohort.

Third, this study was not conducted to prove a causal link between term hypertensive pregnancy disorders and cardiovascular disease in later life. Instead, we used a pragmatic approach to test our hypothesis that women with a longer exposure to endothelial activation during pregnancy would exhibit more unfavourable cardiovascular risk factors. Finally, the current study might be underpowered as the comparison of cardiovascular risk factors 2.5 years postpartum between induction of labour and expectant monitoring in women with a history of hypertensive pregnancy disorders was a secondary aim of the HYPITAT follow-up study. A post-hoc power analysis of the current study showed that we had had to include 11634 women (5817 women in each group) for 80% power and a 5% type 1 error probability (two sided), for inclusion in 1:1 ratio to reach statistical significance for the cardiovascular risk estimates calculated by the Framingham risk score. For the outcome prevalence of hypertension, we had had to include 7986 women (3993 women in each group) for 80% power and a 5% type 1 error probability (two sided), for inclusion in 1:1 ratio to reach statistical significance.

In conclusion, cardiovascular risk factors do not differ 2.5 years postpartum in women with a history of term hypertensive pregnancy disorders, who were randomized for induction of labour or expectant monitoring.

## Reference List

(1) Jacobs AK, Eckel RH. Evaluating and managing cardiovascular disease in women: understanding a woman's heart. Circulation 2005 Feb 1;111(4):383-4.
(2) Bellamy L, Casas JP, Hingorani AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. BMJ 2007 Nov 10;335(7627):974.
(3) Smith GN, Walker MC, Liu A, et al. A history of preeclampsia identifies women who have underlying cardiovascular risk factors. Am J Obstet Gynecol 2009 Jan;200(1):58.
(4) Manten GT, Sikkema MJ, Voorbij HA, Visser GH, Bruinse HW, Franx A. Risk factors for cardiovascular disease in women with a history of pregnancy complicated by preeclampsia or intrauterine growth restriction. Hypertens Pregnancy 2007;26(1):39-50.
(5) Forest JC, Girouard J, Masse J, et al. Early occurrence of metabolic syndrome after hypertension in pregnancy. Obstet Gynecol 2005 Jun;105(6):1373-80.
(6) Berends AL, de Groot CJ, Sijbrands EJ, et al. Shared constitutional risks for maternal vascular-related pregnancy complications and future cardiovascular disease. Hypertension 2008 Apr;51(4):1034-41.
(7) Barden AE, Beilin LJ, Ritchie J, Walters BN, Michael C. Does a predisposition to the metabolic syndrome sensitize women to develop pre-eclampsia? J Hypertens 1999 Sep;17(9):1307-15.
(8) Hermes W, Franx A, van Pampus MG, et al. Cardiovascular risk factors in women who had hypertensive disorders late in pregnancy: a cohort study. Am J Obstet Gynecol 2013 Jun;208(6):474-8.
(9) Magnussen EB, Vatten LJ, Lund-Nilsen TI, Salvesen KA, Davey SG, Romundstad PR. Prepregnancy cardiovascular risk factors as predictors of pre-eclampsia: population based cohort study. BMJ 2007 Nov 10;335(7627):978.
(10) Koopmans CM, Bijlenga D, Groen H, et al. Induction of labour versus expectant monitoring for gestational hypertension or mild pre-eclampsia after 36 weeks' gestation (HYPITAT): a multicentre, open-label randomised controlled trial. Lancet 2009 Sep 19;374(9694):979-88.
(11) Hermes W, Tamsma JT, Grootendorst DC, et al. Cardiovascular risk estimation in women with a history of hypertensive pregnancy disorders at term: a longitudinal follow-up study. BMC Pregnancy Childbirth 2013 Jun 4;13(1):126.
(12) Hermes W, Franx A, van Pampus MG, et al. 10-Year cardiovascular event risks for women who experienced hypertensive disorders in late pregnancy: the HyRAS study. BMC Pregnancy Childbirth 2010;10:28.
(13) Alberti KG, Zimmet P, Shaw J. The metabolic syndrome--a new worldwide definition. Lancet 2005 Sep 24;366(9491):1059-62.
(14) Roberts JM, Lain KY. Recent Insights into the pathogenesis of pre-eclampsia. Placenta 2002 May;23(5):359-72.
(15) Redman CW, Sargent IL. Latest advances in understanding preeclampsia. Science 2005 Jun 10;308(5728):1592-4.

# *Chapter 10*

## Cost-effectiveness analysis of cardiovascular risk factor screening in women who experienced hypertensive pregnancy disorders at term

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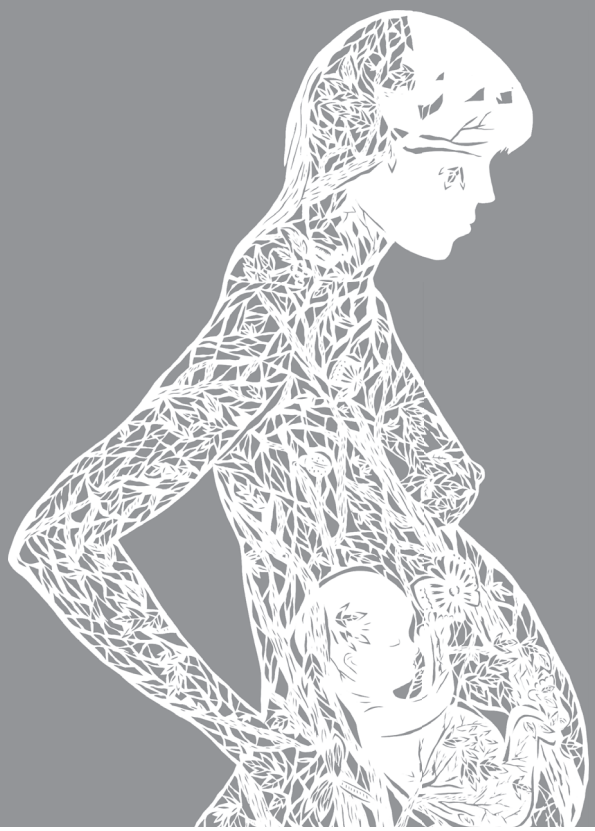


## Abstract

**Objectives:** To assess the cost-effectiveness of post-partum screening on cardiovascular risk factors and subsequent treatment in women with a history of gestational hypertension or pre- eclampsia at term.

**Study design:** Two separate Markov models evaluated the cost-effectiveness analysis of hypertension (HT) screening and screening on metabolic syndrome (MetS), respectively, as compared to current practice in women with a history of term hypertensive pregnancy disorders. Analyses were performed from the Dutch health care perspective, using a lifetime horizon. One-way sensitivity analyses and Monte Carlo simulation evaluated the robustness of the results.

**Results**: Both screening on HT and MetS in women with a history of gestational hypertension or pre-eclampsia resulted in increase in life expectancy (HT screening 0.23 year (95%CI -0.06 to 0.54); MetS screening 0.14 years (95%CI -0.16 to 0.45)). The gain in QALYs was limited, with HT screening and MetS screening generating 0.04 QALYs (95%CI -0.12 to 0.20) and 0.03 QALYs (95%CI -0.14 to 0.19)), resulting in costs to gain one QALY of €4,228 and €28,148, respectively. Analyses for uncertainty showed a chance of 74% and 75% respectively that post-partum screening is cost-effective at a threshold of €60,000/QALY.

**Conclusions:** According to the available knowledge post-partum screening on cardiovascular risk factors and subsequent treatment in women with a history of gestational hypertension or pre-eclampsia at term is likely to be cost-effective.

## Introduction

Hypertensive disorders are common complications of pregnancy, as 6-8% of all pregnancies are complicated by gestational hypertension or pre-eclampsia.[1;2] Accumulating evidence suggests that women experiencing hypertensive pregnancy disorders are at increased risk for cardiovascular disease later in life.[3] It has been suggested that pregnancy acts as a "natural stress test" and pregnancy offers an opportunity to identify women who are at high risk for cardiovascular disease later in life.[4]

Several studies have assessed cardiovascular risk factors after pregnancy in women who experienced hypertensive pregnancy disorders.[5;6] Women with a history of hypertensive pregnancy disorders appear to exhibit more cardiovascular risk factors compared to women with a history of normotensive pregnancies.[6] Cardiovascular disease in women may be reduced by early detection of presence of cardiovascular risk factors after their complicated pregnancy and subsequent lifestyle interventions, including smoking cessation, being active, avoiding overweight or weight reduction, and by having a blood pressure, glucose or blood cholesterol check if indicated (and intervention if abnormal results).

The American Heart Association guidelines (2011) recommend for cardiovascular risk screening in women to assess obstetric history in all asymptomatic women and consider pre-eclampsia as risk factor for later life maternal cardiovascular disease.[7] However, these guidelines still lack detailed advice and recommendations for subsequent screening with preventive treatments for cardiovascular disease (CVD), as, at present, evidence on costs and cost-effectiveness of cardiovascular screening and intervention programs in women who suffered from hypertensive pregnancy disorders is lacking.

The Hypertension Risk Assessment Study (HyRAS) aimed to identify cardiovascular risk factors post-partum and subsequently estimate individual cardiovascular event risks in women with a history of term gestational hypertension or term pre-eclampsia. The present study reports a model based economic evaluation performed alongside the HyRAS study.[8]



## Methods

### HyRAS study

Full details of the Hypertension Risk Assessment Study (HyRAS study) have been reported previously.[8;9] In short, two-and-a-half year post-partum a cardiovascular risk factor assessment was performed in women who developed gestational hypertension or pre-eclampsia at term. Women were identified from the Hypertension and Pre-eclampsia Intervention Trial at Term (HYPITAT).[10]

These women either had pregnancy induced hypertension with a diastolic blood pressure of at least 95 mmHg during pregnancy, measured on two occasions at least six hours apart; or had a pre-eclampsia, defined as diastolic blood pressure of 90 mmHg or higher measured on two occasions at least six hours apart, combined with proteinuria (two or more occurrences of protein on a dipstick, ≥ 300 mg total protein within a 24 hours urine collection, or ratio of protein to creatinine > 30 mg/mmol).

The cardiovascular risk factor assessment included measurements of blood pressure, weight, height, hip and waist circumference. Venous blood samples were taken after an overnight fast for glucose, HbA1c, insulin, total cholesterol, HDL cholesterol, triglycerides and HsCRP and micro-albuminuria and all participants were asked to fill out a medical questionnaire, including medical history, current use of medication, obstetric history, subsequent pregnancy after index pregnancy and family history, including CVD. Hypertension was defined as systolic blood pressure ≥ 140 mmHg, or a diastolic blood pressure ≥ 90 mmHg or current use of antihypertensive medication. For metabolic syndrome we used the definition of the International Diabetes Federation.[11]

Women with a history of hypertensive pregnancy disorders at term had a higher prevalence of hypertension (34% versus 1%, OR 51.5, 95% CI 7.1-374) and metabolic syndrome (25% versus 5%, OR 6.0, 95% CI 2.3-15) 2.5 years post-partum, and they had more often unfavorable cardiovascular risk factors compared to women with a history of uncomplicated normotensive pregnancies.[8]

**Model development**

We developed two separate Markov models: the first model focuses on hypertension screening and subsequent treatment with antihypertensive medication (Supplemental Figure 1); the second model focuses on screening for metabolic syndrome and subsequent lifestyle intervention (Supplemental Figure 2). Detailed descriptions of Markov decision analysis are available elsewhere.[12;13] Briefly, a hypothetical cohort of patients can move through a number of health states over a number of time cycles. In our models, cycles represent a period of one year, after which patients can move to one of the other health states according to predefined probabilities. Individuals may move from one state to another (for example, when a patient is well but then has a cardiovascular event) or may remain in the same health state (for example, remaining well or remaining functionally dependent after a cardiovascular event). Health states from which no movement is possible (in this case, death) are known as 'absorbing' health states. Taking a life-time perspective, each model was run until all individuals had died. Markov models were developed and analyzed in TreeAge Pro 2009 Suite software (TreeAge Software, Inc, Williamstown, MA).

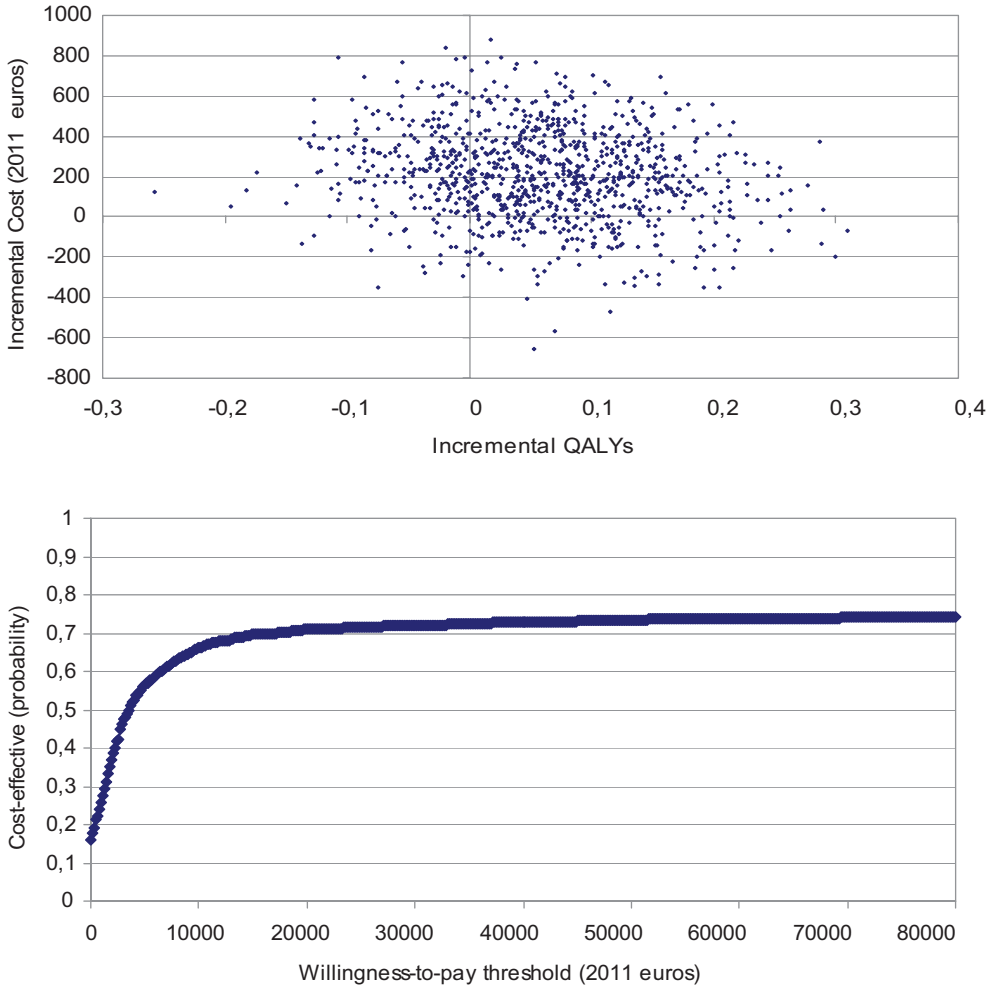



**Figure 1**. Probabilistic sensitivity analysis and cost-effectiveness acceptability curve (hypertension screening)

Caption: Top: Each dot represent 1 iteration of the model where the results are based on a random combination of possible values for the model parameter. Y-axis represents incremental costs of hypertension screening compared with current practice. X-axis represents incremental QALYs with hypertension screening compared with current practice. Below: Y-axis represents probability that cost per QALY gained is less than or equal to values on X-axis.

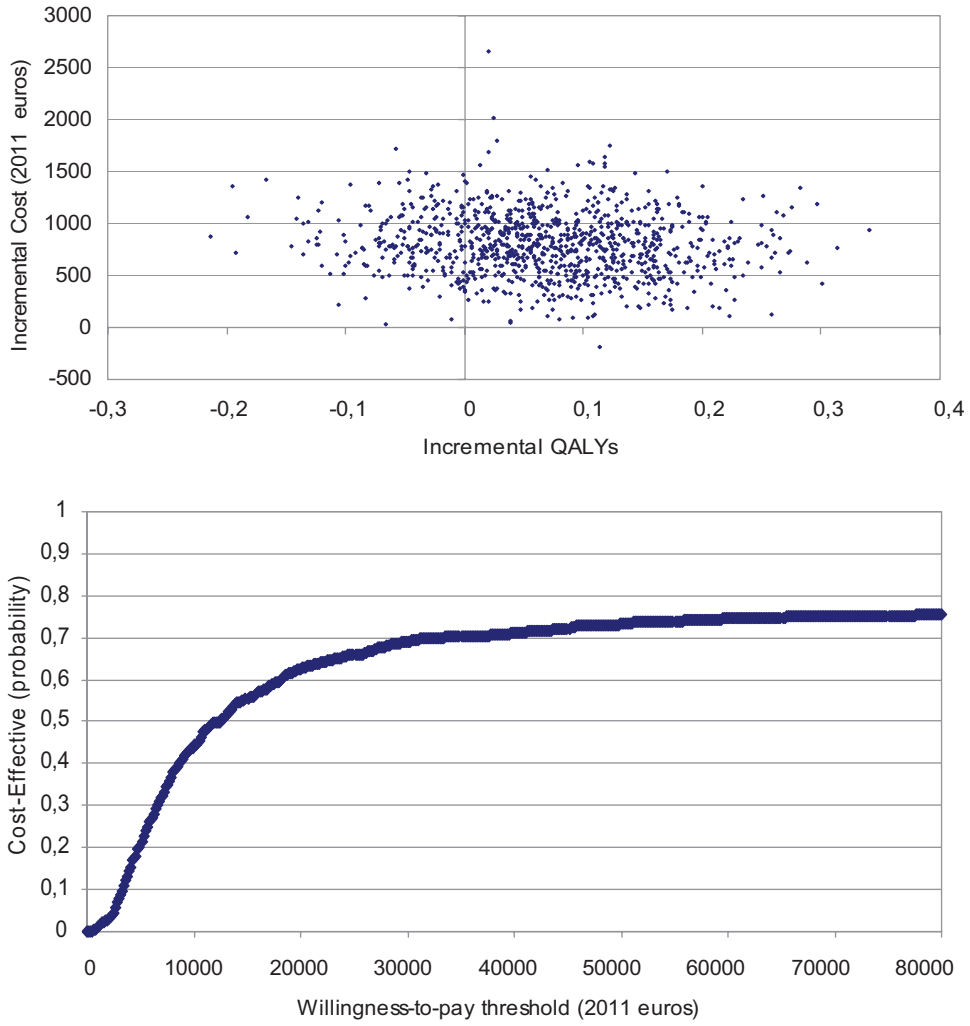



**Figure 2**. Probabilistic sensitivity analysis and cost-effectiveness acceptability curve (metabolic syndrome screening)

Caption: Top: Each dot represent 1 iteration of the model, where the results are based on a random combination of possible values for the model parameter. Y-axis represents incremental costs of metabolic syndorme screening compared with current practice. X-axis represents incremental QALYs with matabolic syndrome screening compared with current practice. Below: Y-axis represents probability that cost per QALY gained is less than or equal to values on X-axis.

**Model parameters**

Women with a history of term gestational hypertension or term pre-eclampsia were eligible to enter the model at pregnancy at 31.7 years of age, the average age at delivery of women in the HyRAS database. The probabilities to develop hypertension or metabolic syndrome within two-and-a-half years after delivery were obtained from the same database, as were the probabilities to be treated for hypertension or metabolic syndrome without screening. The risk to develop hypertension or metabolic syndrome later in life is unknown for women with a history of term gestational hypertension or term pre-eclampsia, and is no subject of analyses.

Annual risks on a cardiovascular event (CVE) in women with hypertension or metabolic syndrome were calculated using the 10-year general cardiovascular disease risks score by Framingham.[14] Other parameters included in this algorithm were also based on the HyRAS database.[8] Although women's age as the most important predictor for a CVE increased with every Markov cycle, all parameters were constant over time. Data on how these parameters develop over time in these women are unavailable. The parameters included in the Framingham risk score of each risk group are summarized in Table 1.

In the hypertension model, treatment consisted of antihypertensive medication. Blood pressure lowering treatment is recommended ≥140/90 mmHg. This is in line with the European Society of Hypertension and the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, which recommends treatment of a blood pressure ≥140/90 mm Hg in adolescents.[15-17] Relative risks to develop a CVE was 0.65 in women with good blood pressure regulation (systolic blood pressure <140 mm), and 0.83 in women with poor blood pressure regulation (systolic blood pressure ≥ 140 mm)[18-23]. The influence of side effects and compliance was accounted for in the model.[23;24]

In the metabolic syndrome model, treatment consisted of a lifestyle intervention, which comprised intensive exercise programs, dietary counseling and smoking cessation programs during the first 8 weeks from experts. Participants are offered follow-up mentoring, which can continue as long as they wish. At regular intervals, the prevention manager collects objective measurements on participants, ie, blood pressure, weight, and waist and hip circumferences.[25;26] Women participating in the lifestyle program have beneficial effects on the risk parameters included in the Framingham score according to a recent literature review. The authors of this review included studies reporting on the effects of lifestyle intervention in women aged 30 -60 years.[25] We assumed that all women

with metabolic syndrome participate in either intervention until CVE or death. Sensitivity analyses will stress this assumption.

Probabilities of a CVE include (fatal) myocardial infarction, (fatal) cerebrovascular event, or a cerebrovascular event resulting in functional dependence or a recurrent CVE were obtained from published literature and national health surveys. If possible these probabilities were differentiated by age strata.[24;27-36] Any second CVE was considered to be fatal. An overview of all probabilities can be found in Supplemental Table 1

Utilities were obtained directly with the standard gamble method using data from 148 hypertensive patients who participated in an observational study (n = 52) and in a randomized controlled trial of decision analysis in newly diagnosed hypertensive patients (n = 96). Since utilities were not normally distributed we used median values (Supplemental Table 2).[24;37]

The cost of antihypertensive medication were obtained from a Dutch drug registry.[38;39] Cost data for lifestyle intervention, stroke care, and myocardial infarction care were obtained from published literature.[24;26;40;41] All cost estimates were updated to 2011 Euros with the Dutch consumer price indices (http://statline.cbs.nl), and are listed in Supplemental Table 3.[42]

**Model analysis**

Analyses were performed from the Dutch health care perspective. In both models we compared current practice, in which women are not routinely screened post-partum, with a screen-and-treat strategy starting 2.5 years post-partum. First, we compared the strategies in terms of event free survival and life expectancy. Secondly, life expectancy was adjusted for reduced health-related quality of life using utilities, to estimate quality adjusted life years (QALYs). The economic evaluation was set up as a cost-utility analysis, expressing the cost-effectiveness of each strategy in terms of costs per QALY. Comparative effects were expressed as incremental cost-effectiveness ratios (ICER), defined as the ratio of the difference in costs and the difference in effectiveness between two interventions, i.e. the costs per additional QALY gained. To correct for time preference, we used a 1.5% annual discount rate for effectiveness and a 4% annual discount rate for the costs according to the Dutch Costing Guidelines.[39] Half cycle corrections were used, because it is plausible that events could occur at any time within each cycle. One-way sensitivity analyses were performed to estimate the impact of various assumptions. The interval between the delivery and post-partum screening was varied, because treatment in young relatively low risk women may be abundant until they reach a certain age. Both models were analyzed with a 0%, 3% and 4% discount rate for both costs and effects. In the metabolic syndrome model we varied the duration of the therapeutic effect of lifestyle intervention, because

**Table 1.** Model input; Framingham parameters and annual cardiovascular risk scores per age

| | Age (yrs) | Blood pressure (mmHg) | Cholesterol Total (mg/DL) | Cholesterol HDL(mg/DL) | Smoking | Diabetes | Annual risk on CVE (%) | Annual risk on CVE if treated (%) |
|---|---|---|---|---|---|---|---|---|
| Hypertension (> 140/90) | 30 | 135,8 | 192,7 | 55,4 | 17,1% | 2,0% | 0,17 | 0,13 |
| | 40 | x | x | x | x | x | 0,34 | 0,25 |
| | 50 | x | x | x | x | x | 0,56 | 0,41 |
| | 60 | x | x | x | x | x | 0,86 | 0,64 |
| | 70 | x | x | x | x | x | 1,23 | 0,91 |
| | 80 | x | x | x | x | x | 1,68 | 1,38 |
| No hypertension | 30 | 118,3 | 180,9 | 53,0 | 22,2% | 0% | 0,11 | |
| | 40 | x | x | x | x | x | 0,22 | |
| | 50 | x | x | x | x | x | 0,37 | |
| | 60 | x | x | x | x | x | 0,57 | |
| | 70 | x | x | x | x | x | 0,82 | |
| | 80 | x | x | x | x | x | 1,11 | |
| Metabolic syndrome* | 30 | 131,3 | 186,0 | 44,2 | 17,1% | 2,0% | 0,18 | 0,16 |
| | 40 | x | x | x | x | x | 0,34 | 0,32 |
| | 50 | x | x | x | x | x | 0,58 | 0,54 |
| | 60 | x | x | x | x | x | 0,88 | 0,82 |
| | 70 | x | x | x | x | x | 1,26 | 1,17 |
| | 80 | x | x | x | x | x | 1,72 | 1,59 |
| No metabolic syndrome | 30 | 122,1 | 184,3 | 56,8 | 22,2% | 0% | 0,12 | |
| | 40 | x | x | x | x | x | 0,24 | |
| | 50 | x | x | x | x | x | 0,40 | |
| | 60 | x | x | x | x | x | 0,61 | |
| | 70 | x | x | x | x | x | 0,87 | |
| | 80 | x | x | x | x | x | 1,18 | |

CVE = cardiovascular event

the effectiveness on lifestyle intervention on its own, the duration of beneficial effect and compliance are subject of discussion. Adherence problems during anti-hypertensive treatment are known, and incorporated in the hypertension model, making one-way sensitivity analysis unnecessary.
Robustness of the results was evaluated in multivariate sensitivity analysis, using probabilistic Monte Carlo simulations to determine the simultaneous effect of uncertainty across multiple parameters. We used beta distributions for probabilities, log-normal distributions for relative risks, triangular distributions for utilities and gamma distributions for costs. From this analysis 95% confidence intervals (CI) were derived. The results were visually presented as a scatter plot of incremental cost-effectiveness ratios (cost-effectiveness plane) and as cost-effectiveness acceptability curves (CEACs). CEACs show the probability that either screening program is cost-effective for a range of cost-effectiveness thresholds.

## Results

Costs, health outcomes and ICERs for both hypertension and metabolic syndrome screening, are reported in table 2. Overall costs between both models differed, because of different costs for screening and treatment (Supplemental Table 3), and because of the health state metabolic syndrome, which is costly and only included in the metabolic syndrome model.

**Table 2.** Life expectancy, cardiovascular event free years, quality adjusted life years (QALYs) and costs of screening strategies compared with current practice

| **Hypertension screening** | **Screening** | **Current practice** | **Incremental** | **95% CI** | | **ICER**** |
|---|---|---|---|---|---|---|
| Life expectancy* | 50.19 | 49.96 | 0.23 | -0.06 | 0.54 | |
| Event free years* | 47.38 | 46.96 | 0.42 | 0.07 | 0.76 | |
| QALYs* | 34.59 | 34.55 | 0.04 | -0.12 | 0.20 | € 4,228 |
| Costs (2011 euro's) | € 4,489 | € 4,323 | €166 | € 274- | € 605 | |
| **Metabolic syndrome screening** | **Screening** | **Current practice** | **Incremental** | **95% CI** | | **ICER**** |
| Life expectancy* | 49.95 | 49.81 | 0.14 | -0.16 | 0.45 | |
| Event free years* | 46.83 | 46.69 | 0.14 | -0.21 | 0.48 | |
| QALYs* | 34.09 | 34.06 | 0.03 | -0.14 | 0.19 | € 28,148 |
| Costs (2011 euro's) | € 9,984 | € 9,251 | € 733 | € 172 | € 1.294 | |

* additional years above the age at partus (31,74 years), **the incremental cost effectiveness ratio (ICER) represents the additional costs to gain one QALY

A strategy of screening and treatment of hypertension 2.5 year post-partum in women with a history of gestation hypertension or pre-eclampsia resulted in an increase in life expectancy (0.23 years; 95%CI -0.06 to 0.54) and event free survival (0.42 years; 95%CI 0.07 to 0.76), compared to current practice without systematic screening (Table 2). This increase in life expectancy and event free survival resulted in health gain in respectively 93 and 99% of all analyses. Screening on metabolic syndrome and lifestyle intervention resulted a somewhat lower increase in life expectancy (0.14 years; 95%CI -0.16 to 0.45) and event free survival (0.14 years; 95%CI -0.21 to 0.48). Associated health gain was seen in respectively 80 and 78% of all analyses.

The incremental effect of screening for hypertension 2.5 years post-partum and subsequent lifetime treatment was 0.04 QALYs (95%CI -0.12 to 0.20), compared to current practice in women with a history of gestational hypertension or pre-eclampsia. Because screening prevents expensive cardiovascular events the incremental costs this strategy are relatively low €166 (95%CI -€274 to €605). The costs to gain one additional QALY by hypertension screening and treatment (ICER) were €4,228. The incremental effect of screening on metabolic syndrome 2.5 years post-partum and subsequent lifestyle intervention if metabolic syndrome is present is 0.03 QALYs (95%CI -0.14 to 0.19), compared to current practice in women with a history of gestational hypertension or pre-eclampsia. Average lifetime costs per patient are higher in the screening strategy, but still relatively low (€733; 95% CI €172 to €1,294). The costs to gain one additional QALY by metabolic syndrome screening and subsequent lifestyle intervention (ICER) are €28,148.

One way sensitivity analyses are presented in table 3. Screening later in life did not influence effectiveness very much in both models, while costs reduced, resulting in favorable ICERs. Increasing the discount rates made both screen-and-treat strategies less favorable, even resulting in an ICER above the €60,000 willingness-to-pay threshold in case of discount rate of 4% for effectiveness. The same occurs in the metabolic syndrome model when we assume a shorter therapeutic effect of lifestyle intervention, especially when women participate for less than 15 years in a lifestyle program.

**Table 3.** One-way sensitivity analyses examining incremental cost-effectiveness ratio of hypertension and metabolic syndrome screening

| **Hypertension model** | | | |
|---|---|---|---|
| *Assumption* | *Incremental QALYs* | *Incremental costs (2011 euros)* | *ICER* |
| Base case | 0.04 | € 166 | € 4,228 |
| Screening at a later moment in life (base case 2,5 years post-partum) | | | |
| 5 years post-partum | 0.04 | € 122 | € 2,981 |
| 10 years post-partum | 0.04 | € 62 | € 1,488 |
| 15 years post-partum | 0.04 | € 22 | € 569 |
| 20 years post-partum | 0.03 | € 2 | € 57 |
| Discount rate (base case, costs 4%, health outcomes 1.5%) | | | |
| No discounting for both costs and health outcomes | 0.10 | € 13 | € 129 |
| 4% for both costs and health outcomes | 0.00 | € 166 | € 64,159 |
| 3% for both costs and health outcomes | 0.01 | € 161 | € 13,556 |
| **Metabolic syndrome model** | | | |
| *Assumption* | *Incremental QALYs* | *Incremental costs (2011 euros)* | *ICER* |
| Base case | 0.03 | € 733 | € 28,148 |
| Screening at a later moment in life | | | |
| 5 years post-partum | 0.02 | € 628 | € 25,564 |
| 10 years post-partum | 0.02 | € 480 | € 21,824 |
| 15 years post-partum | 0.02 | € 361 | € 19,025 |
| 20 years post-partum | 0.02 | € 268 | € 17,154 |
| Discount rate (base case, costs 4%, health outcomes 1.5%) | | | |
| No discounting for both costs and health outcomes | 0.05 | € 1,552 | € 31,414 |
| 4% for both costs and health outcomes | 0.01 | € 733 | € 74,016 |
| 3% for both costs and health outcomes | 0.01 | € 855 | € 59,522 |
| Lifestyle participation itself valued beter than non-participation* | 0.31 | € 733 | € 2,364 |
| Limited participation in life style program | | | |
| 2 years | 0.00 | € 187 | € 128,219 |
| 5 years | 0.00 | € 294 | € 84,951 |
| 10 years | 0.01 | € 444 | € 61,799 |
| 15 years | 0.01 | € 562 | € 48,966 |
| 20 years | 0.02 | € 653 | € 41,102 |

Caption: *utility = 0.9995 instead of 0.95

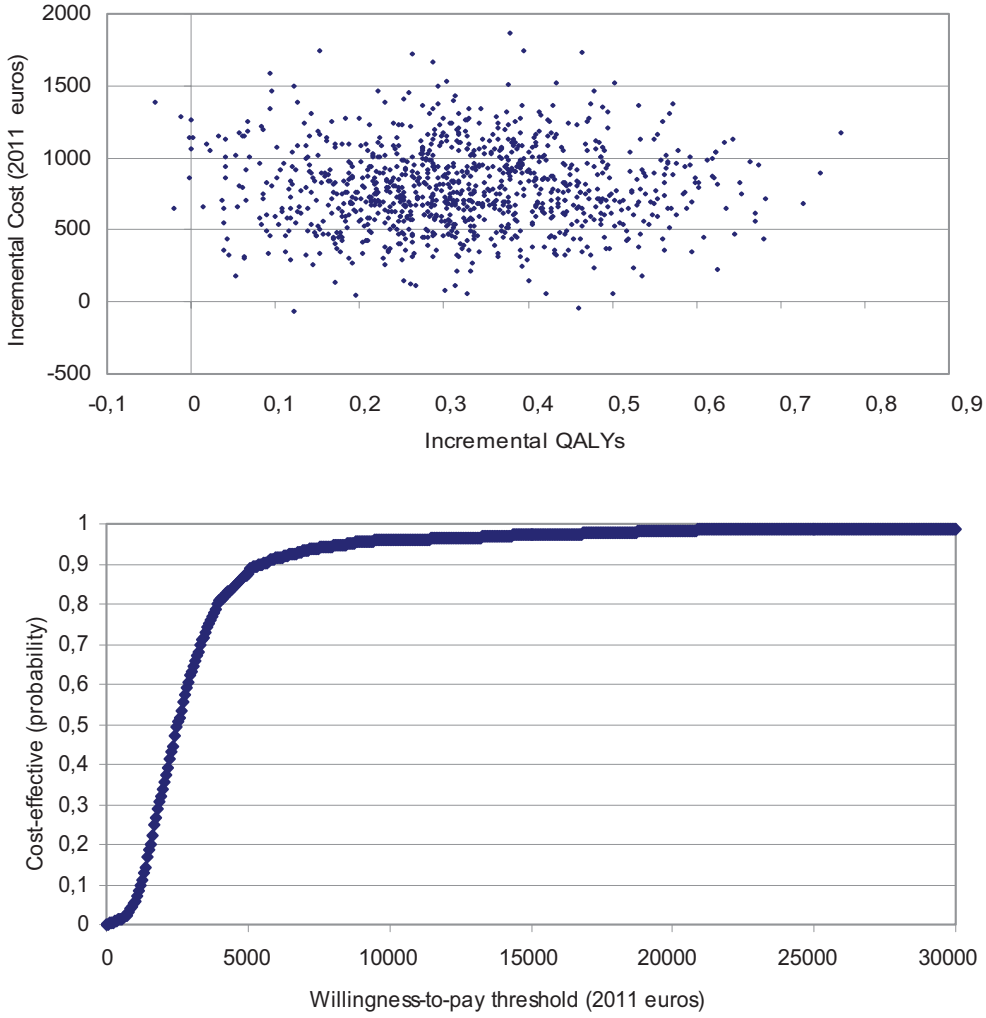



**Figure 3:** Probabilistic sensitivity analysis and cost-effectiveness acceptability curve (metabolic syndrome screening – participation in lifestyle intervention itself is valued benificial)

Caption: Top: Each dot represent 1 iteration of the model, where the results are based on a random combination of possible values for the model parameter. Y-axis represents incremental costs of metabolic syndrome screening compared with current practice. X-axis represents incremental QALYs with matabolic syndorme screening compared with current practice. Below: Y-axis represents probability that cost per QALY gained is less than or equal to values on X-axis.

The cost-effectiveness plane of screening for hypertension 2.5 years post-partum and subsequent lifetime treatment visualizes the finding that both the beneficial effect and the costs were not significantly different, and the CEAC shows that at a threshold of €20,000 per QALY the probability that hypertension screening is cost-effective is 71%. There is a 74 % chance that hypertension screening is cost-effective at a threshold of €60,000/QALY (figure 1).The CEAC of screening on metabolic syndrome 2.5 years post-partum and subsequent lifestyle intervention visualizes that at a threshold of €20,000 per QALY the probability that metabolic syndrome screening is cost-effective is 63%. There is a 75% chance that metabolic syndrome screening is cost-effective at a threshold of €60,000/QALY (figure 2).
However, if we assume that lifestyle participation itself has a positive effect on quality of life compared to non-participation, the incremental effect is 0.31 (95% CI -0.04 to 0.58), and the costs to gain one additional QALY by metabolic syndrome screening and lifestyle intervention (ICER) is €2,364. The CEAC shows that at a threshold of €20,000 per QALY the probability that metabolic syndrome screening is cost-effective is 98%. There is a 99% chance that metabolic syndrome screening is cost-effective at a threshold of €60,000/QALY (figure 3).

## Discussion

### Principal findings

This study assessed the cost-effectiveness of post-partum screening on cardiovascular risk factors and subsequent treatment in women with a history of gestational hypertension or pre-eclampsia at term, through two independent Markov models.
Both strategies – screening on hypertension and subsequent treatment with antihypertensive medication and screening on metabolic syndrome and subsequent lifestyle intervention - were found to have a substantial probability to be cost-effective. The costs to gain one QALY were respectively €4,228 and €28,148. Analyses for uncertainty showed a chance of x 71% and 63% respectively that post-partum screening is cost-effective at a threshold of €20,000/QALY. There is respectively a 74% and 75% chance that post-partum screening is cost-effective at a threshold of €60,000/QALY.
The only assumptions that stressed the results were higher discount rates, and a shorter participation (<15 years) in lifestyle intervention. Assuming that lifestyle intervention itself adds quality improved cost-effectiveness considerably. Finally, one-way sensitivity analysis suggested that screening and treatment could possibly postponed until at least 15 years post-partum without unfavorable effects on health outcomes.

**Strengths and weaknesses**

Strengths of our study are the comprehensive literature search performed to retrieve input for the Markov models and the extensive sensitivity analysis using both one-way and Monte Carlo analyses with appropriate distributions. Model parameters were based on women specific estimates. We used similar health states in both Markov models, making the models comparable.

Model-based analyses also have their limitations, as models imply a simplification of a more complex reality. Ideally, one would like to create a Markov model that incorporates screening and patient tailored care, in which multiple cardiovascular risk factors are simultaneously treated in each individual patient (according to current guidelines) allowing synergic treatment effects. As a first step towards such a highly complex model, we developed two separate Markov models: the first focusing on the occurrence of hypertension 2.5 years post-partum, the second on the occurrence of metabolic syndrome in the very same population. Other independent risk factors, such as dyslipidemia and hyperglucosemie and their treatment options were not incorporated, even as the impact of intervention on subsequent pregnancies and health outcomes.

Furthermore we were limited by the available information on cardiovascular risks and treatment options in women, and especially in women with a history of gestational hypertension or pre-eclampsia. Several assumptions and extrapolations were needed to develop this model. The most important was that we extrapolated the Framingham risk score from 2.5 years post-partum to later in life (only increasing the age in the logarithm). Gestational hypertension or pre-eclampsia was not considered as an independent risk factor for CVE, as literature on this matter is not conclusive. In addition we assumed that therapeutic results of antihypertensive treatment and lifestyle intervention can be expected at all ages, and that these therapeutic results are the same as in a regular population with hypertension or metabolic syndrome.

Another limitation that should be acknowledged is that many of the inputs for the modeling were based on a northern European population. It is quite likely that globally, the impact of screening and management of hypertension and metabolic syndrome may be even higher if African, African American, or Asian women were represented.

Finally, it remains questionable if discounting should be applied in cost-effectiveness analyses for prevention programs.[43] Health benefits in prevention programs occur later in life, while costs are made from the start of screening programs. As result health benefits are discounted more than costs, resulting in less favorable ICERs.

**Relation to other studies**

To our knowledge this is the first study that assessed the cost-effectiveness of post-partum screening on cardiovascular risk factors and subsequent treatment in women with a history of gestational hypertension or pre-eclampsia at term. The incremental effects and ICERs we found are comparable to cost-effectiveness estimates of statins and antihypertensive medication in the prevention of vascular disease.[24;41] These interventions are incorporated to a great extent in our daily practice, while post-partum screening in women with a history of gestational hypertension or pre-eclampsia is still not common practice. However, our estimates encompassed more uncertainty, resulting in lower probabilities of an intervention to be cost-effective.

**Meaning of the results**

A history of gestational hypertension or pre-eclampsia at term is associated with an increased incidence of hypertension, metabolic syndrome and unfavorable biochemical cardiovascular risk factors in young women.[8] Post-partum screening and subsequent intervention in those women might increase life expectancy, event free survival and QALYs, against acceptable costs. Concerns could be raised about the cost-effectiveness of screening and subsequent intervention in this young and relative healthy population, especially if one takes into consideration the stress of a positive test, and its impact on quality of life. Screening later in life may be more appropriate.

These study results cannot be translated to women with a history of early severe pre-eclampsia, as the HyRAS database only includes data from women with a history of term hypertensive pregnancy disorders. However, women with a history of early severe pre-eclampsia have a higher risk to suffer cardiovascular disease later in life than women with a history of term hypertensive pregnancy disorders.[44] Thus, women with a history of early severe pre-eclampsia might even more benefit from screening and intervention compared with our current study population.

**Proposal for future research**

There are still multiple gaps in our knowledge that hamper the development of these Markov models as mentioned above. Further research should involve longitudinal follow-up in women with a history of gestational hypertension or pre-eclampsia to definitively answer the question whether hypertensive pregnancy disorders are independent risk factors for cardiovascular disease, and to assess the deterioration of cardiovascular risk factors over time and the effectiveness of screening and prevention programs on the those risk factors in this specific population.

Ultimately, the best evidence would be generated by a randomized trial, which should compare individual tailored preventive programs with care as usual, to verify whether modifiable cardiovascular risk factors and absolute (long–term) cardiovascular event risks can be reduced. Depending on the cost-effectiveness analysis results of this trial, primary prevention against cardiovascular disease started at a relatively young age might be justified.

**Conclusion**

Post-partum screening on cardiovascular risk factors and subsequent intervention in women with a history of gestational hypertension or pre-eclampsia is likely to be a cost-effective strategy.

## Reference List

(1) ACOG technical bulletin. Hypertension in pregnancy. Number 219--January 1996 (replaces no. 91, February 1986). Committee on Technical Bulletins of the American College of Obstetricians and Gynecologists. Int J Gynaecol Obstet 1996; 53(2):175-183.
(2) Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. Am J Obstet Gynecol 2000; 183(1):S1-S22.
(3) Bellamy L, Casas JP, Hingorani AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. BMJ 2007; 335(7627):974.
(4) Sattar N, Greer IA. Pregnancy complications and maternal cardiovascular risk: opportunities for intervention and screening? BMJ 2002; 325(7356):157-160.
(5) Drost JT, Arpaci G, Ottervanger JP, de Boer MJ, van EJ, van der Schouw YT, Maas AH. Cardiovascular risk factors in women 10 years post early preeclampsia: the Preeclampsia Risk EValuation in FEMales study (PREVFEM). Eur J Prev Cardiol 2012; 19(5):1138-1144.
(6) Hermes W, Ket JC, van Pampus MG, Franx A, Veenendaal MV, Kolster C, Tamsma JT, Bloemenkamp KW, Ponjee G, van der Hout E, Ten HH, Loix S, Mol BW, de Groot CJ. Biochemical cardiovascular risk factors after hypertensive pregnancy disorders: a systematic review and meta-analysis. Obstet Gynecol Surv 2012; 67(12):793-809.
(7) Mosca L, Benjamin EJ, Berra K, Bezanson JL, Dolor RJ, Lloyd-Jones DM, Newby LK, Pina IL, Roger VL, Shaw LJ, Zhao D, Beckie TM, Bushnell C, D'Armiento J, Kris-Etherton PM, Fang J, Ganiats TG, Gomes AS, Gracia CR, Haan CK, Jackson EA, Judelson DR, Kelepouris E, Lavie CJ, Moore A, Nussmeier NA, Ofili E, Oparil S, Ouyang P, Pinn VW, Sherif K, Smith SC, Jr., Sopko G, Chandra-Strobos N, Urbina EM, Vaccarino V, Wenger NK. Effectiveness-based guidelines for the prevention of cardiovascular disease in women--2011 update: a guideline from the American Heart Association. J Am Coll Cardiol 2011; 57(12):1404-1423.
(8) Hermes W, Franx A, van Pampus MG, Bloemenkamp KW, Bots ML, van der Post JA, Porath M, Ponjee GA, Tamsma JT, Mol BW, de Groot CJ. Cardiovascular risk factors in women who had hypertensive disorders late in pregnancy: a cohort study. Am J Obstet Gynecol 2013; 208(6):474-478.
(9) Hermes W, Franx A, van Pampus MG, Bloemenkamp KW, van der Post JA, Porath M, Ponjee G, Tamsma JT, Mol BW, de Groot CJ. 10-Year cardiovascular event risks for women who experienced hypertensive disorders in late pregnancy: the HyRAS study. BMC Pregnancy Childbirth 2010; 10:28.
(10) Koopmans CM, Bijlenga D, Groen H, Vijgen SM, Aarnoudse JG, Bekedam DJ, van den Berg PP, de BK, Burggraaff JM, Bloemenkamp KW, Drogtrop AP, Franx A, de Groot CJ, Huisjes AJ, Kwee A, van Loon AJ, Lub A, Papatsonis DN, van der Post JA, Roumen FJ, Scheepers HC, Willekes C, Mol BW, van Pampus MG. Induction of labour versus expectant monitoring for gestational hypertension or mild pre-eclampsia after 36 weeks' gestation (HYPITAT): a multicentre, open-label randomised controlled trial. Lancet 2009; 374(9694):979-988.
(11) Alberti KG, Zimmet P, Shaw J. The metabolic syndrome--a new worldwide definition. Lancet 2005; 366(9491):1059-1062.
(12) Hunink MG, Glasziou PP, Siegel JE, Weeks JC, Pliskin JS, Elstein AS, Weinstein MC. Decision Making in Health and Medicine: Integrating Evidence and Values. Cambridge: The press syndicate of the university of cambridge, 2001.

(13) Naimark D, Krahn MD, Naglie G, Redelmeier DA, Detsky AS. Primer on medical decision analysis: Part 5--Working with Markov processes. Med Decis Making 1997; 17(2):152-159.
(14) D'Agostino RB, Sr., Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, Kannel WB. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation 2008; 117(6):743-753.
(15) Lurbe E, Cifkova R, Cruickshank JK, Dillon MJ, Ferreira I, Invitti C, Kuznetsova T, Laurent S, Mancia G, Morales-Olivas F, Rascher W, Redon J, Schaefer F, Seeman T, Stergiou G, Wuhl E, Zanchetti A. Management of high blood pressure in children and adolescents: recommendations of the European Society of Hypertension. J Hypertens 2009; 27(9):1719-1742.
(16) Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, Jr., Jones DW, Materson BJ, Oparil S, Wright JT, Jr., Roccella EJ. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 2003; 42(6):1206-1252.
(17) Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002; 360(9349):1903-1913.
(18) Cherry SB, Benner JS, Hussein MA, Tang SS, Nichol MB. The clinical and economic burden of nonadherence with antihypertensive and lipid-lowering therapy in hypertensive patients. Value Health 2009; 12(4):489-497.
(19) Degli EE, Di MM, Sturani A, Russo P, Dradi C, Falcinelli S, Buda S. Risk factors for uncontrolled hypertension in Italy. J Hum Hypertens 2004; 18(3):207-213.
(20) Grobbee DE, Tuut MK, Hoes AW. [CBO guideline 'High blood pressure' (revision)]. Ned Tijdschr Geneeskd 2001; 145(43):2071-2076.
(21) Nelson MR, Reid CM, Ryan P, Willson K, Yelland L. Self-reported adherence with medication and cardiovascular disease outcomes in the Second Australian National Blood Pressure Study (ANBP2). Med J Aust 2006; 185(9):487-489.
(22) Quan A, Kerlikowske K, Gueyffier F, Boissel JP. Pharmacotherapy for hypertension in women of different races. Cochrane Database Syst Rev 2000;(3):CD002146.
(23) Klungel OH, de BA, Paes AH, Seidell JC, Nagelkerke NJ, Bakker A. Undertreatment of hypertension in a population-based study in The Netherlands. J Hypertens 1998; 16(9):1371-1378.
(24) Montgomery AA, Fahey T, Ben-Shlomo Y, Harding J. The influence of absolute cardiovascular risk, patient utilities, and costs on the decision to treat hypertension: a Markov decision analysis. J Hypertens 2003; 21(9):1753-1759.
(25) Berks D, Hoedjes M, Raat H, Duvekot JJ, Steegers EA, Habbema JD. Risk of cardiovascular disease after pre-eclampsia and the effect of lifestyle interventions: a literature-based study. BJOG 2013; 120(8):924-931.
(26) Neumann A, Schwarz P, Lindholm L. Estimating the cost-effectiveness of lifestyle intervention programmes to prevent diabetes based on an example from Germany: Markov modelling. Cost Eff Resour Alloc 2011; 9(1):17.
(27) Statistics Netherlands. Lifetables: Dutch population by age and sex,1996-2000. Statistics Netherlands. 2002.
(28) Dutch Health Survey. www.cbs.nl. 2012.
(29) Arima H, Chalmers J, Woodward M, Anderson C, Rodgers A, Davis S, Macmahon S, Neal B. Lower target blood pressures are safe and effective for the prevention of recurrent stroke: the PROGRESS trial. J Hypertens 2006; 24(6):1201-1208.

(30) Hardie K, Hankey GJ, Jamrozik K, Broadhurst RJ, Anderson C. Ten-year risk of first recurrent stroke and disability after first-ever stroke in the Perth Community Stroke Study. Stroke 2004; 35(3):731-735.
(31) Lakhan SE, Sapko MT. Blood pressure lowering treatment for preventing stroke recurrence: a systematic review and meta-analysis. Int Arch Med 2009; 2(1):30.
(32) McNaughton H, Feigin V, Kerse N, Barber PA, Weatherall M, Bennett D, Carter K, Hackett M, Anderson C. Ethnicity and functional outcome after stroke. Stroke 2011; 42(4):960-964.
(33) Sigurdsson G, Sigfusson N, Gudmundsdottir II, Agnarsson U, Sigvaldason H, Gudnason V. The absolute risk of recurrent myocardial infarction is similar amongst both sexes: MONICA Iceland Study 1981-1999. Eur J Cardiovasc Prev Rehabil 2004; 11(2):121-124.
(34) Vaartjes I, Reitsma JB, Berger-van SM, Bots ML. Gender differences in mortality after hospital admission for stroke. Cerebrovasc Dis 2009; 28(6):564-571.
(35) Vaartjes I, van D, I, Grobbee DE, Bots ML. The dynamics of mortality in follow-up time after an acute myocardial infarction, lower extremity arterial disease and ischemic stroke. BMC Cardiovasc Disord 2010; 10:57.
(36) van der Elst ME, Buurma H, Bouvy ML, de BA. Drug therapy for prevention of recurrent myocardial infarction. Ann Pharmacother 2003; 37(10):1465-1477.
(37) Tsevat J, Goldman L, Soukup JR, Lamas GA, Connors KF, Chapin CC, Lee TH. Stability of time-tradeoff utilities in survivors of myocardial infarction. Med Decis Making 1993; 13(2):161-165.
(38) Pharmacotherapeutic Compass 2011. College voor zorgverzekeringen (CvZ) [Health Insurance Board]. 2011. College voor zorgverzekeringen (CvZ) [Health Insurance Board].
(39) Hakkaart-van Roijen L, Tan SS, Bouwmans CAM. Handleiding voor kostenonderzoek, methoden en standaard kostprijzen voor economische evaluaties in de gezondheidszorg. College voor zorgverzekeringen (CvZ) [Health Insurance Board]. 2010. Diemen, College voor zorgverzekeringen (CvZ) [Health Insurance Board].
(40) Dewilde S, Bruggenjurgen B, Nienaber C, Senges J, Welte R, Willich SN. Cost-effectiveness of adjunctive eptifibatide in patients undergoing coronary stenting in Germany. Eur J Health Econ 2012; 13(4):381-391.
(41) Greving JP, Visseren FL, de Wit GA, Algra A. Statin treatment for primary prevention of vascular disease: whom to treat? Cost-effectiveness analysis. BMJ 2011; 342:d1672.
(42) Statistics Netherlands. Statline Consumer Pricing index. [www.statline.nl]. 2-5-2008.
(43) Torgerson DJ, Raftery J. Economic notes. Discounting. BMJ 1999; 319(7214):914-915.
(44) Smith GC, Pell JP, Walsh D. Pregnancy complications and maternal risk of ischaemic heart disease: a retrospective cohort study of 129,290 births. Lancet 2001; 357(9273):2002-2006.

**Supplemental Table 1.** Model input, Probabilities

| *Both models* | | **Distribution** | **Source** | **Reference** |
|---|---|---|---|---|
| cardiovascular event (CVE) * | Framingham risk score | X | Cohort | [1, 2] |
| CVE being a stroke (based on FATAL events only) | Age 30-34: 0.600 Age 35-39: 0.353 Age 40-44: 0.341 Age 45-49: 0.467 Age 50-54: 0.554 Age 55-59: 0.506 Age 60-64: 0.574 Age 65-69: 0.550 Age 70-74: 0.507 Age 75-79: 0.461 Age 80-84: 0.442 Age 85-89: 0.435 Age 90-94: 0.404 Age 95+: 0,413 | X | Cohort | [3] |
| dying from 1st Myocardial Infarction (MI) | Age < 55: 0.058 Age 55-74: 0.128 Age 75-84: 0.298 Age 85+: 0.400 | X | Cohort | [4] |
| dying from 1st stroke | Age < 45: 0.172 Age 45-49: 0.192 Age 50-54: 0.186 Age 55-59: 0.178 Age 60-64: 0.183 Age 65-69: 0.200 Age 70-74: 0.236 Age 75-79: 0.278 Age 80-84: 0.341 age 85: 0.453 | X | Cohort | [5] |
| non-CVE mortality | see appendix S6 | X | Cohort | [6] |
| recurrent myocardial infarction with no treatment | age 40-49: 0,0067 age 50-59: 0.0295 age 60-69: 0.0252 age 70-74: 0.0388 (rate-to-prob) | X | Cohort | [7] |
| RR recurrent myocardial infarction with treatment | 0.86 (0.73 to 1.01) | Log-normal | Estimate | [8, 9] |
| recurrent stroke with no treatment | 0,43/10 (rate-to-prob) | X | Cohort | [10] |
| RR recurrent stroke with treatment | 0.71 (0.59 to 0,86) | Log-normal | Estimate | [11, 12] |
| functional dependence after 1st stroke | 0.387 (320/827) | Beta | Cohort | [13] |
| *Hypertension* | | | | |
| hypertension in patients with PIH/PE in history | 0,344 (105/305) | Beta | Cohort | [1] |
| treatment of hypertension in patients with PIH/PE in history (no screening) | 0,352 (37/105) | Beta | Cohort | [1] |
| treatment of hypertension in patients with PIH/PE in history (after screening) | Age 20-29: 0.693 Age 30-39: 0.802 Age 40-49: 0.799 Age 50-59: 0.777 | x | Cohort | [14] |
| RR CVE with treatment (systolic BP <140mmHg) | 0,65 (0.60 to 0,72) | Log-normal | Estimate | [15-19] |
| RR CVE with treatment (systolic BP > 140mmHg) | 0.83 (0,72 to 0,94) | Log-normal | Estimate | [15-19] |
| Blood pressure being controlled on treatment (systolic BP <140mmHg) | Age 20-29: 0.744 Age 30-39: 0.694 Age 40-49: 0.698 Age 50-59: 0.715 Age > 70: 0.30 | X | Cohort | [14] |

| *Both models* | | **Distribution** | **Source** | **Reference** |
|---|---|---|---|---|
| side-effects from drug therapy | First year: 0.17 Second year: 0.1 Third year 0.05 Fourth year 0.02 | X | Cost-study | [8] |
| *Metabolic syndrome* | | | | |
| Metabolic syndrome (MS) after episode of PIH/PE | 0,250 (73/292) | Beta | Cohort | [1] |
| treatment of MS in patients with PIH/PE in history (no screening) | 0,242 (16/66) | Beta | Cohort | [1] |
| Treatment of metabolic syndrome (MS) after screening | 1 | x | Estimate | Assumption |
| Lifestyle effect on Framingham parameters | | | | |
| Systolic blood pressure (mmHg) | -2.4(-5.7 to -1.3) | triangular | Review | [20] |
| Diastolic blood pressure (mmHg) | -1.8(-4.5 to -0.9) | triangular | Review | [20] |
| Total cholesterol (mg/dl) | -2 (-16 to -2) | triangular | Review | [20] |
| HDL–cholesterol (mg/dl) | 0 (-3 to 1) | triangular | Review | [20] |
| Smoking (%) | -2.2% (-7 to -0.7%) | triangular | Review | [20] |
| Diabetes mellitus (%) | x | x | Review | [20] |

* newly diagnosed angina, myocardial infarction, coronary heart disease, stroke or transient ischaemic attack

RR = relative risk; PIH = Pregnancy Induced Hypertension; PE = Pre-eclampsia

**Supplemental Table 2.** Model input, Utilities

| **Hypertension** | | **Distribution** | **Source** | **Reference** |
|---|---|---|---|---|
| Untreated, well | 1 | x | Cost-study | [8] |
| Treated, well | 0.9995 (0.9611 to 0.9995) | triangular | Cost-study | [8] |
| Treated, well, side-effects | 0.9722 (0.9000 to 0.9995) | triangular | Cost-study | [8] |
| Myocardial infarction | 0.88 (0.8 to 0.95) | triangular | Cost-study | [21] |
| Untreated, Stroke, unaffected | 0.9535 (0.8586 to 0.9982) | triangular | Cost-study | [8] |
| Treated, stroke, unaffected | 0.9600 (0.8700 to 0.9995) | triangular | Cost-study | [8] |
| Treated, side-effects, Stroke, unaffected | 0.9300 (0.7556 to 0.9975) | triangular | Cost-study | [8] |
| Untreated, Stroke, affected | 0.5000 (0.1389 to 0.8000) | triangular | Cost-study | [8] |
| Treated, Stroke, affected | 0.4998 (0.0917 to 0.7872) | triangular | Cost-study | [8] |
| Treated, side-effects, Stroke affected | 0.4995 (0.0600 to 0.7500) | triangular | Cost-study | [8] |
| Death* | 0 | x | Cost-study | [8] |
| *Metabolic syndrome* | | | | |
| Well | 1 | x | Cost-study | [8] |
| Metabolic syndrome, treated | 0,95 (0.90 to 0,98) | triangular | Cost-study | |
| Metabolic syndrome, not treated | 0,95 (0.90 to 0,98) | triangular | x | estimate |
| Myocardial infarction | 0.88 (0.8 to 0.95) | triangular | Cost-study | [21] |
| Stroke, unaffected | 0.9535 (0.8586 to 0.9982) | triangular | Cost-study | [8] |
| Stroke, affected | 0.4998 (0.0917 to 0.7872) | triangular | Cost-study | [8] |
| Death* | 0 | x | Cost-study | [8] |

**Supplemental Table 3.** Model input, Costs

| Both models | | Distribution | Source | Reference |
|---|---|---|---|---|
| **Annual costs** | | | | |
| Stroke: Mild | €1,098(€1,033 to €1,164) | gamma | Cost-study | [22] |
| Stroke: Severe | €21,374 (€21,087 to €21,663) | gamma | Cost-study | [22] |
| Myocardial Infarction | €1,067 (€1,004 to €1,131) | gamma | Cost-study | [22] |
| *One-off costs* | | | | |
| Stroke: Mild | €6,419 (€6,261 to €6,577) | gamma | Cost-study | [22] |
| Stroke: Severe | €36,604 (€36,227 to €36,981) | gamma | Cost-study | [22] |
| Stroke: Fatal | €14,651 (€12,700 to €16,500) | gamma | Cost-study | [8] |
| Myocardial Infarction | €17,548 (€17,290 to €17,813) | gamma | Cost-study | [22] |
| Myocardial Infarction: Fatal | €6,608 (€4,734 to €8,860) | gamma | Cost-study | [23] |
| Death other | €2,730 (€2,628 to €2,834) | gamma | Cost-study | [22] |
| *Hypertension* | | | | |
| Screening | €30 (€15 to €45) | gamma | Costing guideline | [24] |
| Hypertensive therapy first year | € 137 (€107 to €167) | gamma | Estimate | [6, 24, 25] |
| Hypertensive therapy following years | € 107 (€77 to €137) | gamma | Estimate | [24, 25] |
| *Metabolic syndrome* | | | | |
| Screening | € 113 (€56 -€169) | gamma | Cost-study | [26] |
| Lifestyle intervention first year | € 390 (€195 - €585) | gamma | Cost-study | [26] |
| Lifestyle intervention following years | € 190 (€95 - €285) | gamma | Cost-study | [26] |
| Metabolic syndrome | € 952 (€476 - €1428) | gamma | Cost-study | [26] |

**Supplemental Table 4.** Model input, Dutch Life Table; probability to decease per age

| | |
|---|---|
| 0 | 0,00327 |
| 0,5 | 0,00046 |
| 1,5 | 0,00024 |
| 2,5 | 0,00015 |
| 3,5 | 0,00017 |
| 4,5 | 0,00006 |
| 5,5 | 0,00004 |
| 6,5 | 0,00008 |
| 7,5 | 0,00005 |
| 8,5 | 0,00011 |
| 9,5 | 0,00007 |
| 10,5 | 0,00009 |
| 11,5 | 0,00009 |
| 12,5 | 0,00015 |
| 13,5 | 0,00006 |
| 14,5 | 0,00009 |
| 15,5 | 0,00011 |
| 16,5 | 0,0002 |
| 17,5 | 0,00021 |
| 18,5 | 0,00019 |
| 19,5 | 0,00019 |
| 20,5 | 0,00015 |
| 21,5 | 0,0002 |
| 22,5 | 0,00025 |
| 23,5 | 0,00027 |
| 24,5 | 0,00021 |
| 25,5 | 0,00032 |
| 26,5 | 0,00021 |
| 27,5 | 0,00026 |
| 28,5 | 0,00025 |
| 29,5 | 0,0003 |
| 30,5 | 0,00033 |
| 31,5 | 0,00036 |
| 32,5 | 0,00033 |
| 33,5 | 0,00038 |
| 34,5 | 0,0004 |
| 35,5 | 0,00052 |
| 36,5 | 0,00054 |
| 37,5 | 0,00062 |
| 38,5 | 0,00071 |
| 39,5 | 0,00065 |
| 40,5 | 0,00087 |
| 41,5 | 0,00103 |
| 42,5 | 0,001 |
| 43,5 | 0,00113 |
| 44,5 | 0,00139 |
| 45,5 | 0,00148 |
| 46,5 | 0,00169 |
| 47,5 | 0,00182 |
| 48,5 | 0,00212 |
| 49,5 | 0,00241 |
| 50,5 | 0,00274 |
| 51,5 | 0,00302 |
| 52,5 | 0,00291 |
| 53,5 | 0,00353 |
| 54,5 | 0,0035 |
| 55,5 | 0,00394 |
| 56,5 | 0,00428 |
| 57,5 | 0,00444 |
| 58,5 | 0,00507 |
| 59,5 | 0,0057 |
| 60,5 | 0,00607 |
| 61,5 | 0,0065 |
| 62,5 | 0,00675 |
| 63,5 | 0,00744 |
| 64,5 | 0,00855 |
| 65,5 | 0,00851 |
| 66,5 | 0,00906 |
| 67,5 | 0,0105 |
| 68,5 | 0,01108 |
| 69,5 | 0,01206 |
| 70,5 | 0,01336 |
| 71,5 | 0,01562 |
| 72,5 | 0,01695 |
| 73,5 | 0,01862 |
| 74,5 | 0,02174 |
| 75,5 | 0,02309 |
| 76,5 | 0,02681 |
| 77,5 | 0,03197 |
| 78,5 | 0,03392 |
| 79,5 | 0,04152 |
| 80,5 | 0,04623 |
| 81,5 | 0,05372 |
| 82,5 | 0,05904 |
| 83,5 | 0,06783 |
| 84,5 | 0,07557 |
| 85,5 | 0,08787 |
| 86,5 | 0,09939 |
| 87,5 | 0,1144 |
| 88,5 | 0,12676 |
| 89,5 | 0,1419 |
| 90,5 | 0,16001 |
| 91,5 | 0,18102 |
| 92,5 | 0,19719 |
| 93,5 | 0,22258 |
| 94,5 | 0,23975 |
| 95,5 | 0,26822 |
| 96,5 | 0,28454 |
| 97,5 | 0,31456 |
| 98,5 | 0,35619 |

## Reference List


(1) Hermes W, Franx A, van Pampus MG, Bloemenkamp KW, Bots ML, van der Post JA, Porath M, Ponjee GA, Tamsma JT, Mol BW, de Groot CJ. Cardiovascular risk factors in women who had hypertensive disorders late in pregnancy: a cohort study. Am J Obstet Gynecol 2013;208:474-8.

(2) D'Agostino RB, Sr., Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, Kannel WB. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation 2008;117:743-53.

(3) Dutch Health Survey. www.cbs.nl. 2012.

(4) Vaartjes I, van D, I, Grobbee DE, Bots ML. The dynamics of mortality in follow-up time after an acute myocardial infarction, lower extremity arterial disease and ischemic stroke. BMC Cardiovasc Disord 2010;10:57.

(5) Vaartjes I, Reitsma JB, Berger-van SM, Bots ML. Gender differences in mortality after hospital admission for stroke. Cerebrovasc Dis 2009;28:564-71.

(6) Statistics Netherlands. Lifetables: Dutch population by age and sex,1996-2000. Statistics Netherlands. 2002.

(7) Sigurdsson G, Sigfusson N, Gudmundsdottir II, Agnarsson U, Sigvaldason H, Gudnason V. The absolute risk of recurrent myocardial infarction is similar amongst both sexes: MONICA Iceland Study 1981-1999. Eur J Cardiovasc Prev Rehabil 2004;11:121-4.

(8) Montgomery AA, Fahey T, Ben-Shlomo Y, Harding J. The influence of absolute cardiovascular risk, patient utilities, and costs on the decision to treat hypertension: a Markov decision analysis. J Hypertens 2003;21:1753-9.

(9) van der Elst ME, Buurma H, Bouvy ML, de BA. Drug therapy for prevention of recurrent myocardial infarction. Ann Pharmacother 2003;37:1465-77.

(10) Hardie K, Hankey GJ, Jamrozik K, Broadhurst RJ, Anderson C. Ten-year risk of first recurrent stroke and disability after first-ever stroke in the Perth Community Stroke Study. Stroke 2004;35:731-5.

(11) Arima H, Chalmers J, Woodward M, Anderson C, Rodgers A, Davis S, Macmahon S, Neal B. Lower target blood pressures are safe and effective for the prevention of recurrent stroke: the PROGRESS trial. J Hypertens 2006;24:1201-8.

(12) Lakhan SE, Sapko MT. Blood pressure lowering treatment for preventing stroke recurrence: a systematic review and meta-analysis. Int Arch Med 2009;2:30.

(13) McNaughton H, Feigin V, Kerse N, Barber PA, Weatherall M, Bennett D, Carter K, Hackett M, Anderson C. Ethnicity and functional outcome after stroke. Stroke 2011;42:960-4.

(14) Klungel OH, de BA, Paes AH, Seidell JC, Nagelkerke NJ, Bakker A. Undertreatment of hypertension in a population-based study in The Netherlands. J Hypertens 1998;16:1371-8.

(15) Cherry SB, Benner JS, Hussein MA, Tang SS, Nichol MB. The clinical and economic burden of nonadherence with antihypertensive and lipid-lowering therapy in hypertensive patients. Value Health 2009;12:489-97.

(16) Degli EE, Di MM, Sturani A, Russo P, Dradi C, Falcinelli S, Buda S. Risk factors for uncontrolled hypertension in Italy. J Hum Hypertens 2004;18:207-13.

(17) Grobbee DE, Tuut MK, Hoes AW. [CBO guideline 'High blood pressure' (revision)]. Ned Tijdschr Geneeskd 2001;145:2071-6.

(18) Nelson MR, Reid CM, Ryan P, Willson K, Yelland L. Self-reported adherence with medication and cardiovascular disease outcomes in the Second Australian National Blood Pressure Study (ANBP2). Med J Aust 2006;185:487-9.

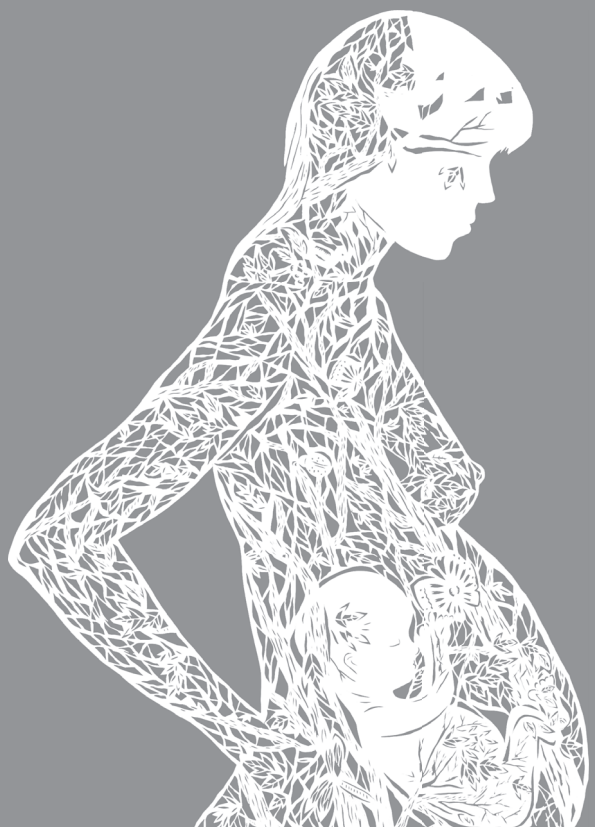
(19) Quan A, Kerlikowske K, Gueyffier F, Boissel JP. Pharmacotherapy for hypertension in women of different races. Cochrane Database Syst Rev 2000;(3):CD002146.
(20) Berks D, Hoedjes M, Raat H, Duvekot JJ, Steegers EA, Habbema JD. Risk of cardiovascular disease after pre-eclampsia and the effect of lifestyle interventions: a literature-based study. BJOG 2013;120:924-31.
(21) Tsevat J, Goldman L, Soukup JR, Lamas GA, Connors KF, Chapin CC, Lee TH. Stability of time-tradeoff utilities in survivors of myocardial infarction. Med Decis Making 1993;13(2):161-5.
(22) Greving JP, Visseren FL, de Wit GA, Algra A. Statin treatment for primary prevention of vascular disease: whom to treat? Cost-effectiveness analysis. BMJ 2011;342:d1672.
(23) Dewilde S, Bruggenjurgen B, Nienaber C, Senges J, Welte R, Willich SN. Cost-effectiveness of adjunctive eptifibatide in patients undergoing coronary stenting in Germany. Eur J Health Econ 2012;13(4):381-91.
(24) Hakkaart-van Roijen L, Tan SS, Bouwmans CAM. Handleiding voor kostenonderzoek, methoden en standaard kostprijzen voor economische evaluaties in de gezondheidszorg. Diemen, College voor zorgverzekeringen (CvZ) [Health Insurance Board]. 2010.
(25) Pharmacotherapeutic Compass 2011. College voor zorgverzekeringen (CvZ) [Health Insurance Board]. 2011.
(26) Neumann A, Schwarz P, Lindholm L. Estimating the cost-effectiveness of lifestyle intervention programmes to prevent diabetes based on an example from Germany: Markov modelling. Cost Eff Resour Alloc 2011;9(1):17.

# Part Four

# General Discussion

# *Chapter 11*

## General discussion



In this thesis we present a number of studies on cardiovascular risk in women with a history of term hypertensive pregnancy disorders that are very common. The Hypertension Risk Assessment Study (HyRAS) aims to identify cardiovascular risk factors postpartum and subsequently estimate individual cardiovascular event risks in women with a history of term gestational hypertension or term preeclampsia in order to analyze opportunities for screening and prevention of future cardiovascular disease. We found that women with a history of hypertensive pregnancy disorders at term exhibit more cardiovascular risk factors at least two years after their complicated pregnancy and that they have higher estimated individual cardiovascular event risks compared to women with a history of normotensive term pregnancies.
In this final chapter we discuss questions that remain after previous described findings and interpretations and we focus on implications for further research and clinical care.

## Outline of the problem: "pregnancy and cardiovascular disease in women"

Even though cardiovascular disease mortality has fallen considerably over recent decades in the Netherlands between 1996 - 2011 with 9% (Figure 1), cardiovascular disease still remains the most important cause of death in women in the Netherlands and the Western world[1;2]. In the Netherlands, more women than men die of heart disease each year (Figure 2). According to the Dutch mortality database, 20.238 women above the age of 20 years (29%) died of heart disease in 2011 compared to 17.858 men above the age of 20 years (28%)[3]; i.e. 55 women each day. Unfortunately, cardiovascular disease in women is still under-recognized and undertreated[4]. It has been proven that more than 50% of the reductions seen in coronary heart disease mortality relate to changes in risk factors and 40% to improved treatment[2]. Thus, cardiovascular disease is at least partly preventable.

Epidemiological studies have consistently shown that hypertensive disorders in pregnancy at least double the risk for development of hypertension and cardiovascular disease in women in later life[5-8].Pregnancy has been hypothesized as a stress test and thereby as a window for future maternal cardiovascular health[9]; during a pregnancy complicated by preeclampsia a failure to meet the physiological demands will unmask impaired organ function, e.g. hypertension will become clinical evident and most often subside after delivery. However, these failures will re-manifest in later life when the cumulative effects of aging diminish the reserves of an already vulnerable cardiovascular system. Women

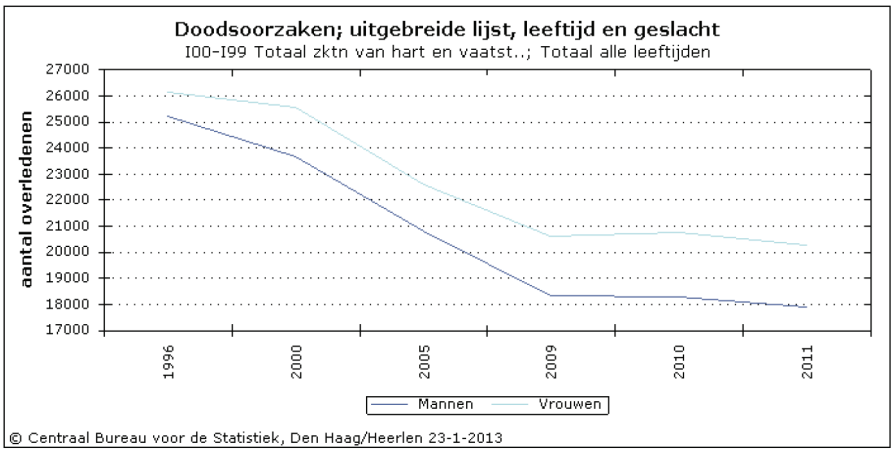



**Figure 1.** Decrease in cardiovascular mortality between 1996 - 2011

Y-axis: Total number of deaths due to cardiovascular disease, X-axis: Year

Light blue line: women

Dark blue line: men

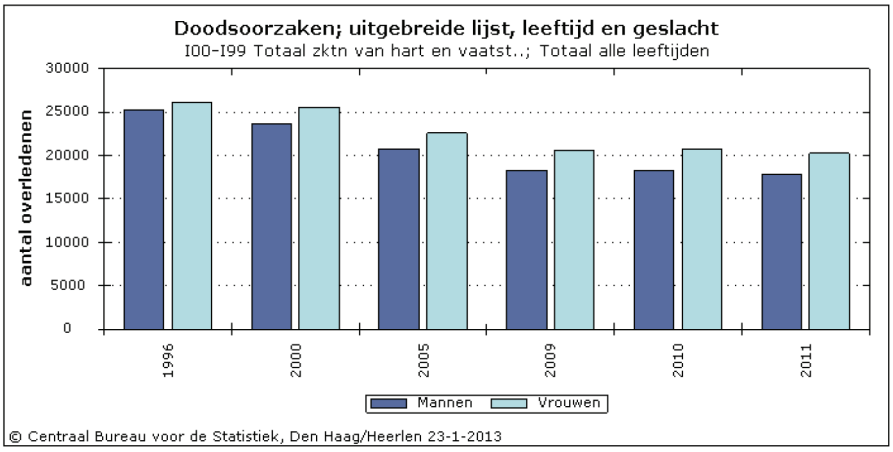



**Figure 2.** Differences in cardiovascular mortality rates from 1996 to 2011 between men and women

Y-axis: Total number of deaths due to cardiovascular disease, X-axis: Year

Light blue bars: women

Dark blue bars: men

can be identified by a complicated pregnancy as "high risk" for developing cardiovascular disease, illustrating the potential for primary prevention of premature deaths and for prolonging healthy life in this specific group of women. Cardiovascular risk factor screening after complicated pregnancies might help to identify those women who may benefit from targeted interventions for prevention of cardiovascular disease.

## Identification of traditional biochemical and non-traditional endothelial biochemical cardiovascular risk factors after hypertensive pregnancy disorders

In our meta-analysis, in chapter 3, we identified more unfavorable levels of glucose, insulin, triglycerides, total cholesterol, HDL- and LDL cholesterol and microalbumin in women with a history of hypertensive pregnancy disorders compared to women with a history of normotensive pregnancies after follow-up (range 0.5 to 32 years). In subgroup analyses for preeclampsia and gestational hypertension, versus uncomplicated pregnancies, similar associations were found. However these subgroup analyses were limited by the fact that only few studies assessed cardiovascular risk factors after gestational hypertension[10;11] and mostly focused on preterm preeclampsia[12-24]. Furthermore, the included studies did not distinguish between preterm preeclampsia and term hypertensive pregnancy disorders[10;12;14;15;18-26]. Therefore, it was impossible to perform a separate analysis of these two last mentioned hypertensive pregnancy complications. We concluded that the studied biochemical cardiovascular risk factors are potential predictors for cardiovascular disease later in life and may identify high risk women at a relative young age to benefit from screening and intervention.
However, it is important to keep in mind that the absolute levels of the assessed risk factors the absolute levels of the assessed risk factors are higher than the treshold which the international guidelines nowadays recommend pharmacological intervention or diet and lifestyle modification[2;27]. As a consequence, our study results are not sufficient to immediately advise biochemical cardiovascular risk factor screening after pregnancy in women with a history of hypertensive pregnancy disorders, according to the current guidelines.

In addition, in chapter 4, we performed a second review and meta-analysis assessing non- classical biochemical cardiovascular risk markers after hypertensive pregnancy disorders. We aimed to identify whether non-classical endothelial biomarkers are also higher in women after hypertensive pregnancy disorders and if they are potential additional, more specific predictors for cardiovascular disease later in life. The non-classical markers were selected based

on the hypothesis of a shared mechanism both in hypertensive pregnancies and cardiovascular disease. The main focus of the shared mechanism is the changed endothelial cell function. The endothelial cells are the inner lining of blood vessels between the circulating blood and vessel wall. The strategic position of the endothelial cells make them in the position of many functions including clotting system, inflammation, angiogenesis, hormone regulation, vasoconstriction and vasodilation. The meta-analysed non-classical cardiovascular risk factors included adiponectin, ICAM, VCAM, VWF, fibronectin, E-selectin, endothelin, IGF-1, IGFBP-3, IGFBP-1 and homocystein. Only homocystein appeared to be significantly higher after pregnancy in women with a history of hypertensive pregnancy disorders. Thus, homocystein might be a potential additional marker for cardiovascular risk screening in women after hypertensive pregnancy disorders. However, the magnitude of the effect of homocystein on cardiovascular risk is modest and treatment with vitamin B and folic acid to reduce homocystein levels is inefficient to reduce cardiovascular disease risk[2]. Until further evidence, it seems that homocystein might be only used as an additional marker and it is not likely that homocystein gets a more prominent role in cardiovascular risk factor screening for treatment than traditional cardiovascular risk factors in young women with a history of hypertensive pregnancy disorders. More studies are mandatory to verify whether non-classical cardiovascular risk markers are useful for cardiovascular risk factor screening in women after pregnancy in order to increase the predictive value.

## Cardiovascular risk after term hypertensive pregnancy disorders



### Implications for counseling and follow-up

The prevalence of hypertension appears to be high in women with a history of gestational hypertension or preeclampsia at term. As concluded in chapter 6, 34% of women with a history of term hypertensive pregnancy disorders suffer hypertension at least two years postpartum, of which 28% had started antihypertensive medication. Furthermore, women with a history of gestational hypertension or preeclampsia at term exhibit more unfavorable biochemical cardiovascular risk factors and even 25% has the metabolic syndrome. As described before in chapter 6, our findings are in line with results of previous studies. However, most studies focused on cardiovascular risk factors after early onset preeclampsia, or no distinction was made between early onset and term preeclampsia, making it difficult to draw a proper conclusion on absence or presence of unfavorable cardiovascular risk factors in women after term hypertensive disorders[10;12;14;15;18-26]. These data are important as term hypertensive

disorders are common complications of pregnancy and these findings might provide an opportunity in relatively young women for screening and primary prevention of cardiovascular disease later in life. Remarkably, women with a history of hypertensive pregnancy disorders have a recurrence risk of gestational hypertension in a future pregnancy ranging from 13% to 53% and a recurrence risk for preeclampsia in a future pregnancy ranging from 2% to 16%[28].This implies that, the prevalence of hypertension 2.5 years postpartum in our cohort was relatively high.

Cardiovascular disease in women may be reduced by timely detection of cardiovascular risk factors and lifestyle interventions, including smoking cessation, increased physical activity, avoiding overweight or weight reduction, and by having a blood pressure or blood cholesterol check if indicated (and intervention if abnormal results). To our knowledge, until now, evidence concerning the effectiveness of lifestyle intervention in women with a history of hypertensive pregnancy disorders is lacking. Hoedjes et al. published a systematic review in which they described that postpartum lifestyle interventions are effective in lowering cardiovascular risk factors in general populations of postpartum women, not specifically for women with a history of hypertensive disorders[29]. Furthermore, Ratner et al. showed that women with a history of gestational diabetes benefit from lifestyle interventions for delaying or preventing diabetes. It seems reasonable that similar effects might be seen on the long term for women with a history of hypertensive pregnancy disorders and development of cardiovascular disease[30].

## Cardiovascular risk prediction and prevention of cardiovascular disease in women

In common practice, prevention is mostly targeted at middle-aged or older women with established cardiovascular disease or those women who smoke or suffer hypertension, diabetes or dyslipidemia. Cardiovascular disease prevention in young women with short-term (10-year) moderate or mild risk is still limited, although pregnancy related disorders provide a unique opportunity for cardiovascular risk assessment and prevention at relatively young age, when expected lifelong health benefits are highest. Untill now, due to the lack of evidence, screening and prevention after complicated pregnancies have not yet been incorporated in national guidelines[2;27].

Individual cardiovascular risk can be estimated using several multivariable risk prediction algorithms incorporating the major risk factors for developing cardiovascular disease, including age, sex, blood pressure, smoking, dyslipidemia and diabetes[31]. Current guidelines advise multivariable assessment to estimate cardiovascular risks and to guide treatment of risk factors.

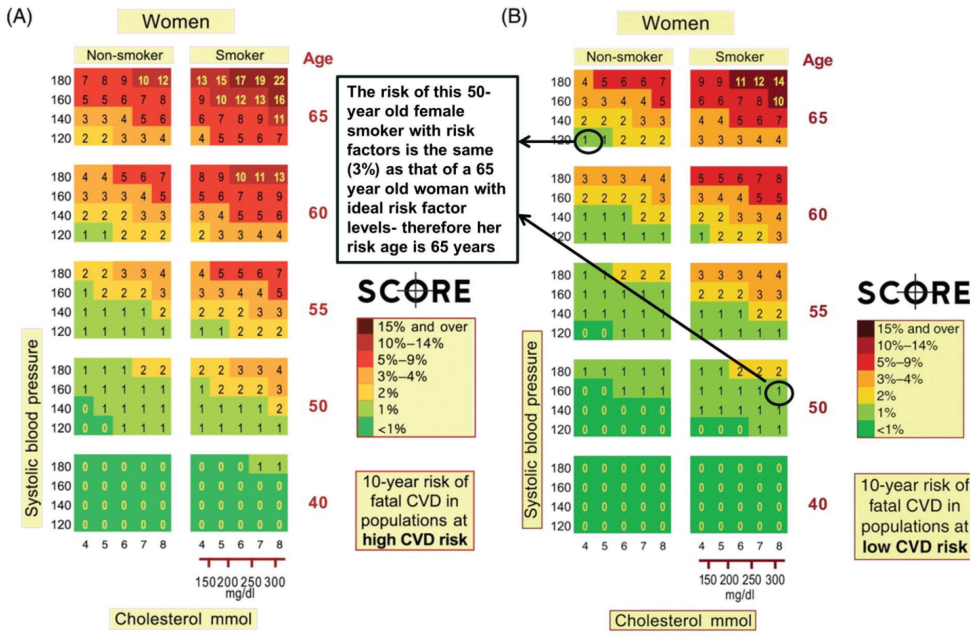



**Figure 3.** Illustration of the risk age concept in the SCORE chart

SCORE chart: 10-year risk of fatal cardiovascular disease (CVD) in countries at high CVD risk (A) and in countries at low CVD risk (B). Low CVD countries are Andorra, Austria, Belgium, Cyprus, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Luxembourg, Malta, Monaco, The Netherlands, Norway, Portugal, San Marino, Slovenia, Spain, Sweden, Switzerland, United Kingdom[2].

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A particular problem, however, relates to young men and women with unfavorable risk factors, in whom a low *absolute* risk conceals a high *relative* risk and these people remain undiagnosed and untreated. Furthermore, mostly all risk prediction models focus on relatively short-term outcomes within the next 10 years. This is also a disadvantage in young people as short-term risks underestimate their absolute long term risk.

In order to address the problem of cardiovascular risk estimation in younger persons, the European guidelines suggested in 2003[32] to extrapolate risks to the age of 60 to illustrate what would happen if preventive action was not taken. Later on, in 2012, the updated European guidelines introduced a new approach: risk age. Risk age illustrates the likely reduction in life expectance in the SCORE score that a young person with a low absolute, but a high relative risk of cardiovascular disease will be exposed to if preventive action is not taken[2]. However, it is not recommended to base treatment decisions on risk age and thus clinical judgment remains first choice in primary prevention for cardiovascular

disease in young women. Especially in young women, physicians have to keep in mind that cardiovascular disease risk is a continuous risk into the future and not a binary outcome.

In chapter 7 we analyzed cardiovascular disease risks in women with a history of term hypertensive pregnancy disorders. We used four different risk prediction models to show that women with a history of hypertensive pregnancy disorders have higher estimated (extrapolated) cardiovascular event risks compared to women with a history of uncomplicated pregnancies. Whether these women with high estimated cardiovascular event risks are the same women who develop or die from cardiovascular disease later in life remains an unanswered question. Only extensive prospective follow-up studies could provide more insight.

If current cardiovascular risk prediction models are accurate to predict cardiovascular disease risks in young women with a history of hypertensive pregnancy disorders, one would expect that women with very early onset preeclampsia would have had higher estimated extrapolated cardiovascular event risks compared to women with term hypertensive pregnancy disorders, as the relative risk for developing cardiovascular disease in women with early onset preeclampsia is higher (RR 7.7) compared to women with late onset preeclampsia (RR 2.1)[5]. This hypothesis was not supported by our findings in chapter 8 We found that after adjustment for age, 10-year and 30-year cardiovascular risk estimations are comparable in women with a history of severe very early onset preeclampsia and women with a history of term hypertensive pregnancy disorders. Furthermore, women with a history of term hypertensive pregnancy disorders had more unfavorable biochemical cardiovascular risk factors. Women with very early onset preeclampsia suffer more hypertension; however, after adjustment for age and follow-up period this difference was not significant. These findings suggest that the highest risk for cardiovascular mortality after very early onset preeclampsia cannot only be explained by unfavorable cardiovascular risk factors even before pregnancy. Probably, the severity of the pregnancy complication, the duration of the exposure of the pregnancy disease, ethnicity, or other factors still to be identified are responsible for higher risks of future cardiovascular disease in women with severe early onset preeclampsia.

**Endothelial dysfunction, hypertensive pregnancy disorders and cardiovascular disease**

Preeclampsia and atherosclerosis share a common pathway of endothelial dysfunction, possibly influenced by insulin resistance, hypertriglyceridemia and inflammation[24]. Maternal vascular endothelial cells are believed to be central to

the pathogenesis of hypertensive pregnancies[33]. Endothelial dysfunction has been demonstrated in vessels from preeclamptic women during pregnancy. Chambers et al.[13] demonstrated in vivo impaired endothelial function postpartum after a median follow-up of 3 years. Until now, it has not been clarified whether this endothelial dysfunction was already present before the hypertensive pregnancy caused by numerous maternal predisposing factors, or that the vascular endothelium is damaged during the hypertensive pregnancy, or both. It seems plausible that preexisting abnormalities, possibly genetically determined, predispose to the development of hypertensive pregnancy disorders. In contrast, it has been previously described that preeclampsia was found to be an independent risk factor for coronary artery disease later in life[34]. This suggests that the underlying link between hypertensive pregnancy disorders and cardiovascular disease is at least a combination of preexisting factors and environmental including a pregnancy complicated by hypertension. Thus, this suggests that prolonged exposure to hypertensive disease during pregnancy may negatively influence the pre-existent damaged maternal endothelium and may cause (sub clinical) permanent vascular damage.

Thus, prolonging pregnancy in women with hypertensive pregnancy disorders may negatively affect women's cardiovascular outcomes in later life. In chapter 9 we hypothesized that exposure to a shorter or longer period of endothelial activation during hypertensive pregnancies results in differences of classic cardiovascular risk factors two years postpartum. However, we could not confirm this hypothesis, which might be explained by relatively short time interval difference of only seven days, and endothelial disturbance was probabaly relatively mild in both groups. No significant differences were found between women who had induction of labour or expectant management during their term hypertensive pregnancy. It should be stressed that the comparison was not part of the primary analysis in the HyRAS study and our results should thus be regarded as an observation to prompt future study rather than a conclusion.



**Cost effectiveness of screening and intervention after hypertensive pregnancy disorders**

Evidence on costs and cost-effectiveness of cardiovascular screening and intervention programs in women who suffered from hypertensive pregnancy disorders is lacking. In chapter 10 we present the economic evaluation alongside the HyRAS study. We found that post-partum screening on cardiovascular risk factors and subsequent intervention in women with a history of gestational hypertension or pre-eclampsia is likely to be cost-effective. This study was limited by the available information on cardiovascular risks and treatment options in women, and especially in women with a history of gestational hypertension or

pre-eclampsia. Furthermore, several assumptions and extrapolations from male studies were needed to develop the Markov models.
Although there might be some assumptions and knowledge gaps, we found that post-partum screening on cardiovascular risk factors and subsequent intervention is likely to be cost-effective. More evidence is needed.

**Future Research**
Further research should focus on the effectiveness of screening and prevention programs and its cost-benefits. A randomized trial, which compares tailored preventive programs and care as usual, might answer some important and as yet unanswered questions. Such a trial should investigate whether individual tailored preventive programs, including lifestyle modification and drug treatment, compared with care as usual in women with a history of hypertensive pregnancy disorders reduces modifiable cardiovascular risk factors and reduces absolute estimated 10-year cardiovascular event risks. If these tailored preventive programs appear to be effective, their costs and cost-effectiveness should be assessed. Depending on the results of this trial, thus supported by evidence, primary prevention against cardiovascular disease started at a relatively young age might be justified, keeping in mind that this is a short term follow-up and provides evidence for surrogate endpoints, including cardiovascular risk factors and estimated cardiovascular event risks.

## Limitations of the HyRAS study, lessons for future studies?

### Discussion of limitations: warnings, recommendations and take home messages

As described above all women had participated in the Hypitat study and gave informed consent for follow-up. Therefore it seems easy to follow-up women who had already participated in a randomised controlled trial, as these women are motivated to participate in research. Women were indeed willing to participate, however due to the design of the study 101 HYPITAT women were subsequent pregnant or lactating, which was an exclusion criteria for our follow-up study (HyRAS study).
The HyRAS study was conducted in perinatal and affiliated centers that are collaborating in 27 ongoing studies in the Dutch Consortium. Due to the infrastructure of the Dutch Obstetric Consortium, research nurses and midwives in the different participating centers were able to include case subjects to participate in our study.
A major problem was to define control subjects for our follow-up study. In close collaboration with epidemiologists, the HyRAS project group discussed several


**Figure 4.** METRO advertisement for voluntary participation in the HyRAS study (June 15th 2010).

options for selecting a proper control group. The first option included women matched for date of delivery in the hospital. The disadvantage of this option is that it would not have given a good reflection of the "normal" pregnant population in the Netherlands. Dutch women who deliver in the hospital are relatively sick and therefore it would have resulted in a confounded control group with relative "sick controls" with more likely adverse outcome later. The second option was to invite women by advertising in newspapers. A major disadvantage of this method is that the background of control subjects is unknown and it would have been a great challenge to gather all the information of previous pregnancies in order not to include women with adverse pregnancy outcome including hypertensive disorders. We used a third method including women who were friend of HYPITAT women as control subject. We used this method because of expected similar age and similar potential environmental exposures (socio-economic status). However, soon after the start of the HyRAS study, it became clear that women with a history of normotensive uncomplicated pregnancies were less motivated to participate in a cardiovascular risk factor assessment study. Another explanation for the low inclusion rate of control subjects could be that the HYPITAT women (and researchers) were not able to explain the importance and need of the HyRAS study. Furthermore, young women with children have busy lives and it remains a

great effort for them to visit a hospital to attend a study, especially because they had an uncomplicated pregnancy.
Therefore, we also tried to enroll control subjects through an advertisement in one of the most read free Dutch newspapers: METRO. This newspaper places advertisements regularly to invite people for scientific research and the newspaper METRO claimed many response on this kind of advertising. Unfortunately, only one *man* (and no women) responded at our advertisement.

In order to complete the inclusions we invited women from midwifery practices form different regions in the Netherlands to attend the HyRAS study as control subject.
*From our experience, we would recommend future investigators only in exceptional circumstances to advertise in newspapers, as it was in our experience a waste of time and money.*

A second problem was that the HYPITAT trial was not designed as follow-up study; no controls were included at similar moment of inclusion of the cases. During the HYPITAT trial, the HyRAS study was conducted to follow-up HYPITAT women at least two years after pregnancy to assess their cardiovascular risk factors and to compare these outcomes with women with uncomplicated pregnancies. Once the HyRAS study was approved by the ethical committee, we could start with inviting women for the follow-up study. This is the reason we had to add a control cohort secondary to our case cohort. Controls were not simultaneously included in our study as case subjects. This limitation was one of the most frequent criticisms of the journal's referees for selection bias on our study design.

## Conclusion

Term hypertensive pregnancy disorders are common and it is important for an obstetrician to not only be aware of the risks during pregnancy, but also to be aware of the higher long term risks of developing cardiovascular disease. Structural screening, treatment and prevention programs of cardiovascular disease in young women after a pregnancy complicated by hypertensive disorders are still not incorporated in national guidelines, as essential evidence is lacking. The association between hypertensive pregnancy disorders and cardiovascular disease in later life provides a fascinating field for further research.

## Reference List


(1) http://www.who.int/mediacentre/factsheets/fs310/en/index.html. 11-2-2013. 11-2-2013. Ref Type: Unpublished Work

(2) Perk J, De BG, Gohlke H, Graham I, Reiner Z, Verschuren M et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012): The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts) * Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J 2012; 33(13):1635-1701.

(3) http://statline.cbs.nl/StatWeb/publication/?DM=SLNL&PA=7233&D1=0. CBS statline database. 8-5-2013. 8-5-2013. Ref Type: Online Source

(4) Maas AH, Appelman YE. Gender differences in coronary heart disease. Neth Heart J 2010; 18(12):598-603.

(5) Bellamy L, Casas JP, Hingorani AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. BMJ 2007; 335(7627):974.

(6) Irgens HU, Reisaeter L, Irgens LM, Lie RT. Long term mortality of mothers and fathers after pre-eclampsia: population based cohort study. BMJ 2001; 323(7323):1213-1217.

(7) Jonsdottir LS, Arngrimsson R, Geirsson RT, Sigvaldason H, Sigfusson N. Death rates from ischemic heart disease in women with a history of hypertension in pregnancy. Acta Obstet Gynecol Scand 1995; 74(10):772-776.

(8) Smith GC, Pell JP, Walsh D. Pregnancy complications and maternal risk of ischaemic heart disease: a retrospective cohort study of 129,290 births. Lancet 2001; 357(9273):2002-2006.

(9) Sattar N, Greer IA. Pregnancy complications and maternal cardiovascular risk: opportunities for intervention and screening? BMJ 2002; 325(7356):157-160.

(10) Forest JC, Girouard J, Masse J, Moutquin JM, Kharfi A, Ness RB et al. Early occurrence of metabolic syndrome after hypertension in pregnancy. Obstet Gynecol 2005; 105(6):1373-1380.

(11) Paradisi G, Biaggi A, Savone R, Ianniello F, Tomei C, Caforio L et al. Cardiovascular risk factors in healthy women with previous gestational hypertension. J Clin Endocrinol Metab 2006; 91(4):1233-1238.

(12) Barden AE, Beilin LJ, Ritchie J, Walters BN, Michael C. Does a predisposition to the metabolic syndrome sensitize women to develop pre-eclampsia? J Hypertens 1999; 17(9):1307-1315.

(13) Chambers JC, Fusi L, Malik IS, Haskard DO, De SM, Kooner JS. Association of maternal endothelial dysfunction with preeclampsia. JAMA 2001; 285(12):1607-1612.

(14) Innes KE, Weitzel L, Laudenslager M. Altered metabolic profiles among older mothers with a history of preeclampsia. Gynecol Obstet Invest 2005; 59(4):192-201.

(15) Laivuori H, Tikkanen MJ, Ylikorkala O. Hyperinsulinemia 17 years after preeclamptic first pregnancy. J Clin Endocrinol Metab 1996; 81(8):2908-2911.

(16) Lampinen KH, Ronnback M, Groop PH, Kaaja RJ. A relationship between insulin sensitivity and vasodilation in women with a history of preeclamptic pregnancy. Hypertension 2008; 52(2):394-401.

(17) Nisell H, Erikssen C, Persson B, Carlstrom K. Is carbohydrate metabolism altered among women who have undergone a preeclamptic pregnancy? Gynecol Obstet Invest 1999; 48(4):241-246.
(18) Portelinha A, Belo L, Cerdeira AS, Braga J, Tejera E, Pinto F et al. Lipid levels including oxidized LDL in women with history of preeclampsia. Hypertens Pregnancy 2010; 29(1):93-100.
(19) Smith GN, Walker MC, Liu A, Wen SW, Swansburg M, Ramshaw H et al. A history of preeclampsia identifies women who have underlying cardiovascular risk factors. Am J Obstet Gynecol 2009; 200(1):58.
(20) Spaan JJ, Houben AJHM, Musella A, Ekhart T, Spaanderman MEA, Peeters LLH. Insulin resistance relates to microvascular reactivity 23years after preeclampsia. Microvasc Res 2010; 80(3):417-421.
(21) Berends AL, de Groot CJ, Sijbrands EJ, Sie MP, Benneheij SH, Pal R et al. Shared constitutional risks for maternal vascular-related pregnancy complications and future cardiovascular disease. Hypertension 2008; 51(4):1034-1041.
(22) He S, Silveira A, Hamsten A, Blomback M, Bremme K. Haemostatic, endothelial and lipoprotein parameters and blood pressure levels in women with a history of preeclampsia. Thromb Haemost 1999; 81(4):538-542.
(23) Manten GT, Sikkema MJ, Voorbij HA, Visser GH, Bruinse HW, Franx A. Risk factors for cardiovascular disease in women with a history of pregnancy complicated by preeclampsia or intrauterine growth restriction. Hypertens Pregnancy 2007; 26(1):39-50.
(24) Sattar N, Ramsay J, Crawford L, Cheyne H, Greer IA. Classic and novel risk factor parameters in women with a history of preeclampsia. Hypertension 2003; 42(1):39-42.
(25) Hubel CA, Snaedal S, Ness RB, Weissfeld LA, Geirsson RT, Roberts JM et al. Dyslipoproteinaemia in postmenopausal women with a history of eclampsia. BJOG 2000; 107(6):776-784.
(26) Wolf M, Hubel CA, Lam C, Sampson M, Ecker JL, Ness RB et al. Preeclampsia and future cardiovascular disease: potential role of altered angiogenesis and insulin resistance. J Clin Endocrinol Metab 2004; 89(12):6239-6243.
(27) Mosca L, Benjamin EJ, Berra K, Bezanson JL, Dolor RJ, Lloyd-Jones DM et al. Effectiveness-based guidelines for the prevention of cardiovascular disease in women--2011 update: a guideline from the American Heart Association. J Am Coll Cardiol 2011; 57(12):1404-1423.
(28) NICE clinical guideline; Hypertension in pregnancy: the management of hypertensive disorders during pregnancy. 1-1-2011. 12-8-2013. Ref Type: Online Source
(29) Hoedjes M, Berks D, Vogel I, Franx A, Visser W, Duvekot JJ et al. Effect of postpartum lifestyle interventions on weight loss, smoking cessation, and prevention of smoking relapse: a systematic review. Obstet Gynecol Surv 2010; 65(10):631-652.
(30) Ratner RE, Christophi CA, Metzger BE, Dabelea D, Bennett PH, Pi-Sunyer X et al. Prevention of diabetes in women with a history of gestational diabetes: effects of metformin and lifestyle interventions. J Clin Endocrinol Metab 2008; 93(12):4774-4779.
(31) D'Agostino RB, Sr., Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation 2008; 117(6):743-753.

(32) De BG, Ambrosioni E, Borch-Johnsen K, Brotons C, Cifkova R, Dallongeville J et al. European guidelines on cardiovascular disease prevention in clinical practice. Third Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice. Eur Heart J 2003; 24(17):1601-1610.
(33) Vickers M, Ford I, Morrison R, Prescott G, Watson S, Hannaford P et al. Markers of endothelial activation and atherothrombosis in women with history of preeclampsia or gestational hypertension. Thromb Haemost 2003; 90(6):1192-1197.
(34) Haukkamaa L, Salminen M, Laivuori H, Leinonen H, Hiilesmaa V, Kaaja R. Risk for subsequent coronary artery disease after preeclampsia. Am J Cardiol 2004; 93(6):805-808.
(35) Zandstra M, Stekkinger E, van der Vlugt MJ, van Dijk AP, Lotgering FK, Spaanderman ME. Cardiac diastolic dysfunction and metabolic syndrome in young women after placental syndrome. Obstet Gynecol 2010; 115(1):101-108.
(36) Melchiorre K, Sutherland GR, Baltabaeva A, Liberati M, Thilaganathan B. Maternal cardiac dysfunction and remodeling in women with preeclampsia at term. Hypertension 2011; 57(1):85-93.

# English summary

## Cardiovascular Assessment after Hypertensive Pregnancy Disorders

Term hypertensive pregnancy disorders are common obstetric complications. Several epidemiological studies have described the association between hypertensive pregnancy disorders and cardiovascular disease in later life. Compared to women with uncomplicated pregnancies, women with hypertensive pregnancy disorders have an increased risk to develop cardiovascular disease in later life. In the Netherlands, cardiovascular disease is currently the leading cause of death, namely 30% of all women who died in 2011.
Therefore, Pregnancy might be used as a "natural stress test". Cardiovascular risk factor screening after complicated pregnancies might help to identify those women who may benefit from targeted interventions for prevention of cardiovascular disease.
This thesis focused on cardiovascular risk (factors) in women with a history of (mainly term) hypertensive pregnancy disorders.
The thesis is divided into four parts. The first part describes the association between preeclampsia and cardiovascular disease. The second part consists of two systematic reviews and meta-analyses on classical and non-classical cardiovascular risk factors after hypertensive pregnancy disorders. The third part is comprised of cohort studies that assess cardiovascular risk factors and estimate individual cardiovascular event risks in women with a history of hypertensive pregnancy disorders. The fourth and final part includes the general discussion and summary of the thesis.

## Part 1

**Chapter 1** provides a general introduction and the outline of the thesis.

**Chapter 2** describes an in depth review of the association between preeclampsia and cardiovascular disease in later in life. Preeclampsia is a common pregnancy disorder and clearly associated with an elevated cardiovascular morbidity (RR 2.2) and mortality risk (RR 2.6). Women with a history of early severe preeclampsia have the highest cardiovascular mortality risks (RR 7.7). The exact underlying

link between preeclampsia and cardiovascular disease remains unclear. It is likely that both preeclampsia and cardiovascular disease share a common pathogenesis, as both preeclampsia and cardiovascular disease share the same risk factors e.g. hyperlipidemia, hyperglycemia, genetic predisposition, insulin resistance, obesity, and hypertension. Common classical and non-classical risk factors between preeclampsia and cardiovascular disease set the basis for the second and third part of this thesis.

## Part 2

**Chapter 3** presents a systematic review and meta-analysis which assessed classical biochemical cardiovascular risk factors in women with a history of hypertensive pregnancy disorders and women with a history of normotensive pregnancies. 22 Studies were included in the review of which 15 could be meta-analyzed. The meta-analyses showed that women with a history of hypertensive pregnancy disorders have higher glucose, insulin, triglycerides, total cholesterol, HDL cholesterol and LDL cholesterol- levels measured after pregnancy compared with women with a history of normotensive pregnancies. These biochemical cardiovascular risk factors are potential predictors for cardiovascular disease later in life and may identify high- risk women early enough to benefit from intervention.

**Chapter 4** presents a systematic review and meta-analysis on non-classical biochemical cardiovascular risk factors in women with a history of hypertensive pregnancy disorders and women with a history of normotensive pregnancies. 21 Studies on 16 non-classical cardiovascular biomarkers were described in this review; 12 studies on 5 biomarkers could be included in meta-analyses. Women with a history of hypertensive pregnancy disorders show endothelial dysfunction after pregnancy with higher levels of homocysteine compared with women with a history of uncomplicated pregnancies. Homocysteine is a potential non-classical cardiovascular biomaker in prediction of cardiovascular disease in women with a history of hypertensive pregnancy disorders. Other biomarkers associated with endothlium alteration, including biomarkers in areas of inflammation, altered thrombosis and angiogenesis have a similar trend, suggesting persistent changes after hypertensive pregnancy disorders.

## Part 3

**Chapter 5** provides a detailed description of the Hypertension Risk Assessment Study (HyRAS study) protocol.The HyRAS study included women who had

preeclampsia or gestational hypertension at term, who participated in the Hypertension and Pre-eclampsia Intervention Trial At Term (HYPITAT). The HYPITAT study was a national randomised clinical trial which included women with gestational hypertension or preeclampsia at (near) term and a singleton pregnancy in cephalic presentation with a gestational age between $36^{+0}$ and $41^{+0}$ weeks of gestation. Women were randomised between induction of labour or expectant monitoring. The primary outcome of the HYPITAT trial was a composite measure of poor maternal outcome. Women at study entry (randomisation) were inquired for a follow-up study at least 2 years after delivery, the Hypertension Risk Assessment Study (HyRAS).
In this cohort study (HyRAS), 306 women with a history of hypertensive pregnancy disorders ((HTP cohort (HYPITAT women)) and 99 women with uncomplicated pregnancies (NTP cohort) were both screened for established modifiable cardiovascular risk factors. Additionally, individual 10-year cardiovascular event risks were calculated using three different validated prediction models, including the Framingham risk score, SCORE score and Reynolds risk score.

**Chapter 6** presents the results of the cardiovascular risk factor screening 2.5 years postpartum of the HyRAS study. From June 2008 through November 2010, 306 women with a history of gestational hypertension or preeclampsia at term (HTP women) and 99 women with a history of normtensive pregnancies at term (NTP women) were included. Hypertension (HTP, 34%; NTP, 1%; P<.001) and metabolic syndrome (HTP, 25%; NTP, 5%; P<.001) were more prevalent in women with a history of hypertensive pregnancy disorders compared to women with a history of normotensive term pregnancies. Furthermore, women with a history of hypertensive pregnancy disorders had significantly higher systolic and diastolic blood pressure, higher BMI and waist circumference. Glucose, HbA1C, insulin, HOMA score, total cholesterol, triglycerides and high sensitive CRP-levels were significantly higher and HDL cholesterol was significantly lower in women with a history of hypertensive pregnancy disorders. Multiple risk factors were present in 18% of the women with a history of term hypertensive pregnancy disorders compared with 7% of women with a history of normotensive term pregnancies (p=0.01). Four percent of women with a history of hypertensive pregnancy disorders had more than 3 independent risk factors compared to 0% in women with a history of normotensive term pregnancies.
This study results strongly suggest that women with a history of gestational hypertension or preeclampsia at term may be offered screening and counseling for cardiovascular risk factors after their pregnancy. However, before wide implementation in practice, strategies of cardiovascular risk factor screening and

subsequent tailored preventive interventions need to be evaluated for feasibility, clinical effectiveness and cost-effectiveness.

**Chapter 7** describes the possibility of long term cardiovascular risk prediction in women with a history of hypertensive pregnancy disorders at term. The study presents estimated individual cardiovascular event risks calculated by the Framingham risk score, SCORE score and Reynolds risk score of women who were included in the HyRAS study. After a mean follow-up of 2.5 years, women with a history of hypertensive pregnancy disorders had significantly higher mean (SD) extrapolated 10-year cardiovascular event risks (HTP 7.2% (3.7); NTP 4.4% (1.9) ($p<.001$, IRR 5.8, 95% CI 1.9 to 19)) and 30-year cardiovascular event risks (HTP 11% (7.6); NTP 7.3% (3.5) ($p<.001$, IRR 2.7, 95% CI 1.6 to 4.5)) as compared to women with a history of normotensive term pregnancies calculated by the Framingham risk scores. The SCORE score and the Reynolds risk score showed similar significant results.
Further large prospective studies have to evaluate whether hypertensive pregnancy disorders have to be included as an independent variable in cardiovascular risk prediction models for women.

**Chapter 8** compares estimated individual cardiovascular event risks between women with a history of very early onset preeclampsia and women with a history of term hypertensive pregnancy disorders.
We found that after adjustment for age, 10-year and 30-year cardiovascular risk estimations are comparable in women with a history of severe very early onset preeclampsia and women with a history of term hypertensive pregnancy disorders. Furthermore, women with a history of term hypertensive pregnancy disorders had more unfavorable biochemical cardiovascular risk factors. Women with very early onset preeclampsia suffer more hypertension (60% vs. 35%); however, after adjustment for age and follow-up period this difference was not significant. These findings suggest that the highest risk for cardiovascular mortality after very early onset preeclampsia cannot only be explained by unfavorable cardiovascular risk factors. Probably, the severity of the pregnancy complication, the duration of the exposure of the pregnancy disease, ethnicity, or other factors still to be identified are responsible for higher risks of future cardiovascular disease in women with severe early onset preeclampsia.

**Chapter 9** hypothesizes that women with a longer exposure to endothelial activation during pregnancy would exhibit more unfavorable cardiovascular risk factors postpartum. The aim of the analysis was to compare postpartum cardiovascular risk factors in women who had a shorter and women who had a

longer exposure to hypertensive pregnancy disorders and therefore to endothelial activation during their *term* hypertensive pregnancy. Women who participated in the HYPITAT trial were evaluated.
At 2.5 year follow-up no significant differences in clinical characteristics and in biochemical cardiovascular risk factors were found between women who were randomized for induction of labor (n=110) and women who were randomized for expectant monitoring (n=91). Furthermore, no associations were found between other maternal clinical pregnancy parameters, including intravenous antihypertensive medication use, BMI at first antenatal visit, severe disease and the use of magnesiumsulfate and clinical parameters at 2.5 years postpartum, including diastolic blood pressures and prevalence of hypertension. Only the use of intravenous antihypertensive medication after randomization during index pregnancy was associated with a higher systolic blood pressure 2.5 years postpartum (OR 1.05, 95% CI (1.01 – 1.09).
In conclusion, we found that induction of labor, generating a difference in exposure to endothelial activation of 7 days, in women with hypertensive disorders in pregnancy at term does not affect the clinical and biochemical cardiovascular profile at 2.5 years postpartum.

**Chapter 10** shows in a cost-effectiveness analysis of the HyRAS study that postpartum screening on cardiovascular risk factors and subsequent treatment in women with a history of term gestational hypertension or pre-eclampsia is very likely to be cost-effective. Cost-effectiveness analysis was performed using two explorative Markov models, based on hypertension screening and screening on metabolic syndrome. Compared to current practice, both screening on hypertension and metabolic syndrome in women with a history of term gestational hypertension or pre-eclampsia resulted in increase in life expectancy (hypertension screening 0.19 years (95% CI -0.28 to 0.66); metabolic syndrome screening 0.05 years (95% CI -0.26 to 0.35)) and event free survival (hypertension screening: 0.42 years (95% CI -0.39 to 1.23); metabolic syndrome screening 0.09 years (95% CI -0.25 to 0.44)). The gain in QALYs was limited (hypertension screening 0.04 QALYs (95% CI -0.12 to 0.20); metabolic syndrome screening 0.03 QALYs (95% CI -0.14 to 0.19)). All incremental cost-effectiveness ratios were below the €60.000 euros/QALY.

## Part 4

Based on the findings and conclusions of the studies that formed the basis of this thesis, a number of recommendations for future research have been formulated in the discussion section (Chapter 11). Structural screening, treatment and

prevention programs of cardiovascular disease in young women after a pregnancy complicated by hypertensive disorders are still not incorporated in national guidelines, as essential evidence is lacking. Further research should mainly focus on the effectiveness of screening and prevention programs and its cost-benefits. The association between hypertensive pregnancy disorders and cardiovascular disease in later life provides a fascinating field for further research.

# Nederlandse samenvatting

## Cardiovasculaire Beoordeling na Hypertensieve Afwijkingen van de Zwangerschap

Hypertensieve zwangerschapscomplicaties rondom de uitgerekende datum zijn veelvoorkomende complicaties. Verschillende epidemiologische studies hebben de associatie beschreven tussen hypertensie in de zwangerschap en cardiovasculaire ziekte later in het leven. Hart- en vaatziekten zijn vandaag de dag de meest voorkomende doodsoorzaak bij vrouwen in Nederland. Hart- en vaatziekte was de doodsoorzaak bij 30% van alle vrouwen die in Nederland in 2011 overleden zijn.
Zwangerschap zou als "natuurlijke stress test" gebruikt kunnen worden. Screenen op cardiovasculaire risicofactoren na een gecompliceerde zwangerschap zou mogelijk vrouwen kunnen identificeren die een verhoogd risico hebben op het ontwikkelen van hart- en vaatziekten later in het leven en baat kunnen hebben bij gerichte interventie en preventie van hart- en vaatziekten.
Dit proefschrift is gericht op cardiovasculaire risicofactoren bij vrouwen met een hypertensieve zwangerschapscomplicatie rondom de uitgerekende datum.

## DEEL 1

**Hoofdstuk 1** is de algemene introductie van dit proefschrift.
**Hoofdstuk 2** beschrijft een review van de literatuur over de associatie tussen preëclampsie en hart- en vaatziekten later in het leven. Preëclampsie is een vaak voorkomende zwangerschapscomplicatie en is geassocieerd met verhoogde cardiovasculaire morbiditeit (RR 2.2) en mortaliteit (RR 2.6) later. Vrouwen met een voorgeschiedenis van vroege ernstige preëclampsie hebben het hoogste cardiovasculaire sterfterisico later (RR 7.7). Het is nog onduidelijk wat precies de link is tussen preëclampsie en cardiovasculaire ziekte later. De hypothese is dat preeclampsie en cardiovasculaire ziekte een gemeenschappelijke pathogenese. Deze hypothese wordt onderschreven doordat beide ziekte beelden gemeenschappelijke risicofactoren hebben zoals, hyperlipidemie, hyperglycemie, genetische predispositie, insuline resistentie, obesitas, en hypertensie. Gemeenschappelijke klassieke en niet-klassieke risico factoren tussen preëclampsie en cardiovasculaire ziekte vormen de basis voor het tweede en derde deel van dit proefschrift.

## DEEL 2

**Hoofdstuk 3** beschrijft een systematische review en meta-analyse naar klassieke biochemische cardiovasculaire risicofactoren bij vrouwen met een zwangerschap gecompliceerd door hypertensie in de voorgeschiedenis en vrouwen met een normotensieve zwangerschap in de voorgeschiedenis. In de review werden 22 studies geïncludeerd, waarvan 15 studies werden geïncludeerd in de meta-analyse. De meta-analyse toonde dat vrouwen met een zwangerschap gecompliceerd door hypertensie in de voorgeschiedenis, na de zwangerschap hogere glucose, insuline, triglyceriden, totaal cholesterol, HDL cholesterol en LDL cholesterol waarden hadden in vergelijking met vrouwen die een normotensieve zwangerschap hebben gehad. Deze biochemische cardiovasculaire risicofactoren zijn potentiële voorspellers voor cardiovasculaire ziekte later in het leven. Deze risicofactoren zouden gebruikt kunnen worden om "hoog risico" vrouwen al in een vroeg stadium te identificeren om te profiteren van interventie op maat voor preventie van hart- en vaatziekten.

**Hoofdstuk 4** beschrijft een systematische review en meta-analyse naar niet-klassieke biochemische cardiovasculaire risicofactoren bij vrouwen met een zwangerschap gecompliceerd door hypertensie in de voorgeschiedenis en vrouwen met een normotensieve zwangerschap in de voorgeschiedenis. In de review werden 21 studies en 16 niet-klassieke biomarkers beschreven; 12 studies over 5 biomarkers werden geincludeerd in de meta-analyse. De biomarkers zijn geselecteerd op basis van afwijkende endotheelfunctie. Vrouwen met een zwangerschap gecompliceerd door hypertensie in de voorgeschiedenis hebben na de zwangerschap hogere homocysteine waarden dan vrouwen met een normotensieve zwangerschap in de voorgeschiedenis. Homocysteine is een potentiële niet- klassieke cardiovasculaire biomaker voor het voorspellen van cardiovasculaire ziekte later in het leven. De overige geanalyseerde biomarkers, die geassocieerd zijn met endotheeel veranderingen, lieten een vergelijkbare trend zien, wat suggereert dat er blijvende schade is na hypertensieve zwangerschappen.

## DEEL 3

**Hoofdstuk 5** beschrijft gedetailleerd het studieprotocol van de Hypertension Risk Assessment Study (HyRAS studie). In de HyRAS studie werden vrouwen geïncludeerd die een zwangerschap hadden doorgemaakt die gecompliceerd werd door a terme preëclampsie of zwangerschapshypertensie en geïncludeerd waren in de Hypertension and Pre-eclampsia Intervention Trial At Term (HYPITAT studie). De HYPITAT studie was een nationaal gerandomiseerde studie die

vrouwen met preëclampsie of zwangerschapshypertensie includeerde met een eenlingzwangerschap in hoofdligging bij een amenorroeduur van $36^{+0}$ tot $41^{+0}$ weken. Deze vrouwen werden gerandomiseerd tussen inleiding van de baring of een afwachtend beleid. De primaire uitkomst van de HYPITAT studie was een samengestelde meting van slechte maternale uitkomsten.
In het vervolgonderzoek, de HyRAS studie, werden vrouwen met een voorgeschiedenis van hypertensieve aandoeningen in de zwangerschap geïncludeerd (HYPITAT vrouwen, HTP cohort) en vrouwen met een voorgeschiedenis van een ongecompliceerde (normotensieve) zwangerschap (NTP cohort). Beide groepen vrouwen werden minstens 2 jaar na de bevalling gescreend op cardiovasculaire risicofactoren, zoals microalbumine in de urine, en glucose, insuline, totaal cholesterol, HDL cholesterol, triglyceriden, en hsCRP in het bloed. Er werden bloeddrukken, gewicht, heup omtrek, en taille omtrek gemeten. Met behulp van de uitkomsten van deze waarden werden individuele 10-jaars cardiovasculaire risico's berekend met gebruik van drie verschillende gevalideerde predictiemodellen; de Framingham risk score, de SCORE score en de Reynolds risk score.

**Hoofdstuk 6** beschrijft de resultaten van de cardiovasculaire risicofactor screening 2.5 jaar na de bevalling. Tussen juni 2008 en november 2010 werden 306 vrouwen met een voorgeschiedenis van hypertensieve aandoeningen in de zwangerschap geïncludeerd (HYPITAT vrouwen, HTP cohort) en 99 vrouwen met een ongecompliceerde (normotensieve) zwangerschap in de voorgeschiedenis (NTP cohort). Bij HTP vrouwen werd een hogere prevalentie van hypertensie (HTP, 34%; NTP, 1%; P<.001) en metabool syndroom (HTP, 25%; NTP, 5%; P<.001) gevonden dan bij NTP vrouwen. Verder werd bij HTP vrouwen een significant hogere systolische bloeddruk en diastolische bloeddruk, hogere BMI en grotere heup en taille omtrek gemeten 2.5 jaar na de bevalling. Glucose, HbA1C, insuline, HOMA score, totaal cholesterol, triglyceriden and high sensitive CRP waarden waren significant hoger en HDL cholesterol was significant lager bij HTP vrouwen dan bij NTP vrouwen. Bij 18% van de HTP vrouwen werd meer dan 1 onafhankelijke risicofactor gevonden in vergelijking met 7% in de NTP groep (p=0.01). Vier procent van de HTP vrouwen had 3 of meer onafhankelijke risicofactoren in vergelijking met 0% in de NTP groep.
De resultaten van deze studie suggereren dat vrouwen met een voorgeschiedenis van a terme hypertensieve aandoening in de zwangerschap baat zouden kunnen hebben bij screening op cardiovasculaire risicofactoren na hun bevalling. Echter, voordat cardiovasculaire screening en counseling geïmplementeerd kan worden moet eerst de haalbaarheid van screening, de klinische effectiviteit en kosteneffectiviteit verder geanalyseerd worden.

**Hoofdstuk 7** beschrijft de vergelijking van de berekende cardiovasculaire risicoscores op het ontwikkelen van hart- en vaatziekten met behulp van de Framingham risk score, de SCORE score en de Reynolds risk score tussen HTP en NTP vrouwen uit de hierboven beschreven HyRAS studie. HTP vrouwen hadden significant hogere gemiddelde (SD) geëxtrapoleerde 10- jaar cardiovasculaire risico's (HTP 7.2% (3.7); NTP 4.4% (1.9) (p<.001, IRR 5.8, 95% CI 1.9 to 19)) en 30- jaar cardiovasculaire risico's (HTP 11% (7.6); NTP 7.3% (3.5) (p<.001, IRR 2.7, 95% CI 1.6 to 4.5)) in vergelijking met NTP vrouwen berekend met de Framingham risk scores. De SCORE score en de Reynolds risk score lieten vergelijkbare resultaten zien.
In de toekomst moeten grote prospectieve studies evalueren of hypertensieve zwangerschapscomplicaties toegevoegd moeten worden als onafhankelijke variabele in cardiovasculaire predictiemodellen voor vrouwen.

**Hoofdstuk 8** vergelijkt de berekende cardiovasculaire risicoscores van vrouwen met een voorgeschiedenis van ernstige vroege preëclampsie (SPP cohort) met vrouwen met een voorgeschiedenis van a terme preëclampsie of zwangerschapshypertensie (HTP cohort HyRAS studie).
Na correctie voor leeftijd zijn 10- jaar en 30- jaar cardiovasculaire risico berekeningen vergelijkbaar tussen vrouwen met een voorgeschiedenis van ernstige vroege preëclampsie en vrouwen met een voorgeschiedenis van a terme preëclampsie of zwangerschapshypertensie. Vrouwen met een voorgeschiedenis van a terme preëclampsie of zwangerschapshypertensie hadden meer ongunstige cardiovasculaire risicofactoren en vrouwen met een voorgeschiedenis van ernstige vroege preëclampsie hadden een hogere prevalentie van hypertensie postpartum (SPP 60% vs. HTP 35%), echter na correctie voor leeftijd was dit verschil niet significant. Naar aanleiding van deze bevindingen kan een hoger risico op sterfte aan hart- en vaatziekten bij vrouwen met een voorgeschiedenis van vroege ernstige preëclampsie niet verklaard worden door ongunstigere cardiovasculaire risicofactoren. Mogelijk spelen andere factoren, zoals de ernst en de duur van de hypertensieve zwangerschapscomplicatie, de etniciteit of andere, nog onbekende, factoren een rol bij het verschil in risico op cardiovasculaire mortaliteit tussen vrouwen met vroege ernstige preëclampsie en vrouwen met a terme preëclampsie of zwangerschapshypertensie.

**Hoofdstuk 9** Het doel van deze studie was om minstens 2 jaar na de bevalling cardiovasculaire risicofactoren te vergelijken tussen vrouwen die een korte en vrouwen die een langere blootstelling aan a terme hypertensieve aandoeningen in de zwangerschap hadden gehad.

Er werden 2.5 jaar na de bevalling geen verschillen gevonden in klinische karakteristieken en biochemische cardiovasculaire risicofactoren tussen de HYPITAT vrouwen die waren gerandomiseerd voor inleiding (n=110) en vrouwen die gerandomiseerd waren voor een afwachtend beleid tijdens de zwangerschap (n=91). Er werden ook geen associaties gevonden tussen maternale klinische parameters tijdens de zwangerschap, zoals intraveneus antihypertensieve medicatie, BMI bij eerste prenatale controle, ernst van de hypertensie tijdens de zwangerschap en het gebruik van magnesiumsulfaat, en klinische parameters 2.5 jaar postpartum, zoals diastolische bloeddruk en de prevalentie van hypertensie. Alleen het gebruik van intraveneuze antihypertensieve medicatie na randomisatie tijdens de zwangerschap was geassocieerd met hogere systolische bloeddruk 2.5 jaar na de bevalling (OR 1.05, 95% CI (1.01 – 1.09). Concluderend lijkt een verschil van 7 dagen aan blootstelling aan endotheel activatie tijdens a terme zwangerschappen geen effect te hebben op klinische en biochemische cardiovasculaire risicofactoren 2.5 jaar na de bevalling.

**Hoofdstuk 10** beschrijft de kosten effectiviteit analyse van de HyRAS studie waarin duidelijk wordt dat postpartum screenen op cardiovasculaire risicofactoren en aanvullende behandeling bij vrouwen met een voorgeschiedenis van a terme hypertensieve aandoeningen in de zwangerschap hoogstwaarschijnlijk kosten effectief is. De kosten effectiviteit analyse is verricht met behulp van twee Markov modellen, gebaseerd op screening naar hypertensie en naar metabool syndroom. In vergelijking met de huidige praktijk (geen follow-up na hypertensieve zwangerschappen), resulteerde zowel screening naar hypertensie als screening naar metabool syndroom bij vrouwen met een voorgeschiedenis van a terme preëclampsie of zwangerschapshypertensie in een toename in levensverwachting (hypertensie screening 0.19 jaar (95%CI -0.28 tot 0.66); metabool syndroom screening 0.05 jaar (95%CI -0.26 tot 0.35) en ziektevrije overleving (hypertensie screening: 0.42 jaar (95%CI -0.39 tot 1.23); metabool syndroom screening 0.09 jaar (95%CI -0.25 tot 0.44)). De winst in QALYs was beperkt (hypertensie screening 0.04 QALYs (95%CI -0.12 tot 0.20); metabool syndroom screening 0.03 QALYs (95%CI -0.14 tot 0.19)). Alle incrementele kosten effectiviteit ratio's waren lager dan €60.000 euro's/QALY.

## DEEL 4

Naar aanleiding van de bevindingen en de conclusies van de studies die de basis vormen van dit proefschrift, wordt in de algemene discussie van dit proefschrift een aantal aanbevelingen gedaan voor verder onderzoek (Hoofdstuk 11). Structurele screening, aanvullende behandeling en preventieve programma's van hart- en

vaatziekten bij jonge vrouwen na een zwangerschap die gecompliceerd werd door preëclampsie of zwangerschapshypertensie zijn nog niet opgenomen in nationale richtlijnen omdat essentieel bewijs nog steeds ontbreekt. Verder onderzoek moet gericht worden op de effectiviteit van screening- en preventie programma's en de kosten effectiviteit hiervan. De associatie tussen hypertensieve zwangerschap complicaties en cardiovasculaire ziekte later in het leven is een goede kans voor verbetering van kwaliteit van leven en biedt mogelijkheden voor verder onderzoek.

# Curriculum vitae

| | |
|---|---|
| 5 oktober 1980 | Geboren te Hoorn. |
| 1998 | Gymnasium, Stedelijk Gymnasium Leiden. |
| 1998 – 2005 | Geneeskunde, Universiteit Leiden. |
| *2002* | Wetenschappelijke stage, afdeling gynaecologie LUMC (Prof. Dr. A.A.W. Peeters) en Stichting Lobi Paramaribo, Suriname (Drs. A. Grunberg). *Titel: "Screening naar cervixcarcinoom in Suriname".* |
| *2004* | Co-schappen: co-schap KNO, oogheelkunde en dermatologie in Paramaribo, Suriname. |
| *2005* | Keuze co-schap gynaecologie/verloskunde Medisch Centrum Haaglanden, Den Haag (Dr. J. Lind). |
| 2005 – 2006 | Arts assistent niet in opleiding afdeling gynaecologie/ verloskunde, Medisch Centrum Haaglanden, Den Haag. |
| 2006 – heden | Opleiding gynaecologie/verloskunde, cluster Leiden. Leids Universitair Medisch Centrum (opleiders: Prof. Dr. H.H.H. Kanhai, Prof. Dr. G. Kenter, Prof. Dr. J.M.M. van Lith) en Medisch Centrum Haaglanden (opleiders: Prof. Dr. P.J. Dörr †, Dr. M.J. Kagie). |
| *2008 – 2013* | Promotie onderzoek, VU Medisch Centrum, Amsterdam (onder leiding van Prof. Dr. C.J.M. de Groot (VUMC), Prof. Dr. A. Franx (UMCU) en Dr. M.G. van Pampus (OLVG)). |
| 2010 | Getrouwd met Uko Meijer, zonen Jurre (2011) en Joppe (2013). |

# Publications

Visser VS, **Hermes W**, Ket JC, Otten RH, Van Pampus MG, Bloemenkamp KW, Franx A, Mol BW, Groot CJM. Systematic review and meta-analysis on non-classic cardiovascular biomarkers after hypertensive pregnancy disorders. Am J Obstet Gynecol. 2014 Mar 14.

Visser VS, **Hermes W**, Franx A, Koopmans CM, van Pampus MG, Mol BW, de Groot CJM. High blood pressure six weeks postpartum after hypertensive pregnancy disorders at term is associated with chronic hypertension. Pregnancy Hypertension. 2013 Oct 3;4: 242-247.

**Hermes W**, Koopmans CM, van Pampus MG, Franx A, Bloemenkamp KW, van der Post J, Porath M, Tamsma JT, Mol BW, Groot CJ. Induction of labour or expectant monitoring in hypertensive pregnancy disorders at term: Do women's cardiovascular risk factors postpartum differ between the two strategies? Eur J Obstet Gynecol Reprod Biol. 2013 Nov;171(1):30-4.

**Hermes W**, Tamsma JT, Grootendorst DC, Franx A, van der Post J, van Pampus MG, Bloemenkamp KW, Porath M, Mol BW, de Groot CJ. Cardiovascular risk estimation in women with a history of hypertensive pregnancy disorders at term: a longitudinal follow-up study. BMC Pregnancy Childbirth. 2013 Jun 4; 13(1):126.

**Hermes W**, Franx A, van Pampus MG, Bloemenkamp KW, Bots ML, van der Post JA, Porath M, Ponjee GA, Tamsma JT, Mol BW, de Groot CJ. Cardiovascular risk factors in women who had hypertensive disorders late in pregnancy: a cohort study. Am J Obstet Gynecol. 2013 Jun; 208(6):474.

**Hermes W**, Ket JC, van Pampus MG, Franx A, Veenendaal MV, Kolster C, Tamsma JT, Bloemenkamp KW, Ponjee G, van der Hout E, Ten Horn H, Loix S, Mol BW, de Groot CJ. Biochemical cardiovascular risk factors after hypertensive pregnancy disorders: a systematic review and meta-analysis. Obstet Gynecol Surv. 2012 Dec; 67(12):793-809.

**Hermes W**, Van Kesteren F, De Groot CJ. Preeclampsia and cardiovascular risk. Minerva Ginecol. 2012 Aug; 64(4):281-92.

**Hermes W**, Franx A, van Pampus MG, Bloemenkamp KW, van der Post JA, Porath M, Ponjee G, Tamsma JT, Mol BW, de Groot CJ. 10-Year cardiovascular event risks for women who experienced hypertensive disorders in late pregnancy: the HyRAS study. BMC Pregnancy Childbirth. 2010 Jun 1;10:28.

**Hermes W**, de Groot CJM, Bloemenkamp KWM. Absence of mid- pregnancy drop in prediction of preeclampsia: A myth?! BMJ (rapid response) 2008;337:699, 10.1136.

**Hermes W**, Puylaert JB, de Groot CJ.Acute abdominal pain in the third trimester of pregnancy caused by adnexal torsion based on a small cystic adenoma. Ned Tijdschr Geneeskd. 2007 Sep 8;151(36):1994-7.

**Hermes W,** Kagie MJ. Nieuwe inzichten in abdominale uterusextirpatie voor benigne afwijkingen? Nederlands Tijdschrift voor Obstetrie en Gynaecologie. 2006.

# Acknowledgments/Dankwoord

Onderzoek doen gaat niet vanzelf. Dit proefschrift is tot stand gekomen door de inzet van vele collega's, vrienden en betrokkenen. Graag wil ik een aantal personen in het bijzonder bedanken.

Speciale dank gaat uit naar alle vrouwen die hebben deelgenomen aan de HyRAS studie en verder naar:

- Mijn promotores, Prof. Dr. C.J.M. de Groot en Prof. Dr. A. Franx
- Mijn co-promotor, Dr. M. G. van Pampus
- Prof. Dr. Ben Willem Mol, Dr. J.T. Tamsma, Dr. K.W.M. Bloemenkamp, Dr. G.A.E. Ponjee, Dr. M. Porath
- De leescommissie: Prof. Dr. J.I.P. de Vries, Prof. Dr. J.M.M. van Lith, Prof Dr. J.A.M. van der Post, Prof. Dr. E.A. Spaanderman
- Leden van de wetenschapscommissie van het Medisch Centrum Haaglanden en het Landsteiner Instituut
- Alle medewerkers van het Consortium Verloskunde en in het bijzonder: Clara Kolster, Birgit van der Goes, Jannet Bakker, Corine Verhoeven, Lida Ulkeman, José Keurentjes, Marjolein Verhart, Maija Kruijt en Zelda van Dijk
- Piet Sturm en laboratorium Medisch Centrum Haaglanden
- Mijn opleiders Marjolein Kagie en Jan van Lith
- Alle deelnemende verloskundigenpraktijken
- Corine Koopmans
- Johannes C.F. Ket, Marjolein Veenendaal, Evelien van der Hout, Hilde ten Horn, Stéphanie Loix, Femke de Bok, Suzanne Peeters
- Gert- Jan van Baaren
- Floortje van Kesteren
- Ingrid Gaugler- Senden
- Jan Willem Borleffs
- Charlotte Severijns, Anne Hanschke en Judith Allen
- Diana Grootendorst
- Maatschap Gynaecologie Medisch Centrum Haaglanden
- Karin Karmerood
- Arts assistenten Gynaecologie/Verloskunde cluster Leiden
- Mijn Paranimfen: Mignon van Gent en Sanne Visser
- Mijn vrienden

– Willy Bruheim
– Mijn schoonouders, Ate, Pamela en Augusta
– Mijn ouders, Noortje, Janneke, Marten, Hyke en Lise
– Uko en mijn twee lieve zoontjes Jurre en Joppe

Beste Christianne, wat ben jij een prettige en betrokken promotor! Ik ben onder de indruk van je inzet voor de wetenschap en hoe jij promovendi begeleidt. Je wist altijd de goede dingen te zeggen waardoor ik weer gemotiveerd werd om door te gaan. Ik wil je vooral bedanken voor je vertrouwen in mij als onderzoeker, je laagdrempeligheid, de vele uren die je in je eigen tijd aan mij besteed hebt om dit proefschrift tot een goed einde te brengen, maar ook voor je geduld, je oprechte interesse en je vriendschap.

Beste Clara, jij hebt je vanaf het begin voor de volle 100% ingezet voor de HyRAS studie. Je controleerde de voortgang, checkte alle labuitslagen en metingen en je hebt ervoor gezorgd dat de studie een succes is geworden. Zonder jouw enthousiasme en inzet was dit proefschrift er niet. Veel dank voor de prettige samenwerking!

Lieve Mama, bijna alles heb ik aan jou te danken. Je liefdevolle opvoeding, je motivatie, ondersteuning en je vertrouwen hebben mij gebracht waar ik nu ben. Ook nu maak je het ons nog steeds gemakkelijk door er altijd voor ons en de kinderen te zijn. Ik kan je niet genoeg bedanken voor de afgelopen 33 jaar. Je bent een schat!

Lieve, lieve Uko, eindelijk, mijn "scriptie" is af! Je was de eerste die zei dat ik dit promotieonderzoek moest doen. Dank voor al je steun, liefde en vertrouwen.
Wat kunnen we samen lachen, wat hebben we het leuk samen en wat verheug ik me op alles wat nog komen gaat, samen met jou en de kinderen!

Wietske Hermes