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 biomarker in prediction of cardiovascular disease in women with a history of hypertensive pregnancy disorders. Other biomarkers associated with endothelium 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\textsuperscript{+0} and 41\textsuperscript{+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.