Cardiovascular and cardiometabolic sequela after vascular complicated pregnancies

Chapter 10

Summary

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

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

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

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

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

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

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

Chapter 8 elaborates on the findings of this manuscript.