Cardiovascular and cardiometabolic sequela after vascular complicated pregnancies

Chapter 9

Valorisation

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

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

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

CVD prevention

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

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

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

Prediction model for hypertension

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

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

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

Desire for aftercare

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

Follow up program

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

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

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

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