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## **Recurrent miscarriage and the subsequent risk of cardiovascular disease**

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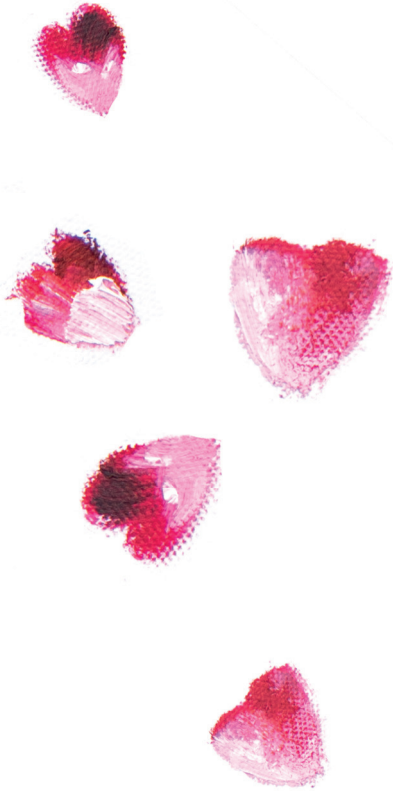


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English summary

## Recurrent miscarriage and the subsequent risk of cardiovascular disease

Cardiovascular disease (CVD) is the leading cause of death in women in the Western world. There is increasing evidence that women with adverse pregnancy outcomes are at increased risk of CVD. A history of preeclampsia, gestational diabetes or pregnancy-induced hypertension is mentioned as an important factor for cardiovascular disease in women in the American Heart Association guideline. The association between recurrent miscarriage and CVD is less clear. Recurrent miscarriage is affecting 0.5-3% of the fertile couples and is commonly defined as three or more consecutive pregnancy losses before 22 weeks of gestation. It is a highly heterogeneous condition. Possible etiologic factors include genetic disorders, uterine anomalies, endocrine factors, maternal autoimmune disorders, metabolic disorders, maternal thrombophilia, obesity and toxic factors such as smoking and alcohol consumption. In about 50% of the cases the cause remains unknown. Recurrent miscarriage might be a first sign of subsequent CVD in women. Several hypotheses are possible for an association between both diseases; shared common risk factors such as obesity and smoking, endothelial dysfunction and a genetic predisposition is assumed. Early identification of women at increased risk of CVD from their reproductive history may enable them to benefit from screening and preventive interventions. In this thesis we investigated the possible association between recurrent miscarriage and future cardiovascular disease.

**Chapter 1** provides an introduction and outline of this thesis.

**Chapter 2** reports a large retrospective cohort study with a long follow-up which assessed whether consecutive miscarriage is associated with an increased risk of cardiovascular disease later in life. Data from the Aberdeen Maternity and Neonatal Databank was used. 60105 women were analysed; 9419 with non-, 940 with two, 167 with three or more consecutive miscarriages and 49579 women with no miscarriage. Women were linked to Scottish Morbidity Records for hospital admissions for cardiovascular conditions, cardiac surgery and death registrations. A sensitivity analysis was performed dividing the women into those who had one, two or  $\geq$  three miscarriages irrespective of these were consecutive or not. In the multivariate analyses (including maternal age, BMI, social class and smoking) a significant association was found between ischemic heart disease and women with two (HR 1.75 (95%CI 1.22-2.52) or  $\geq$  three (HR 3.18 (95%CI 1.49-6.80) consecutive miscarriages. Similar patterns of risk were observed in the sensitivity analysis. The risk for ischemic heart disease was even slightly lower in women with consecutive miscarriages compared to women with 2 or more non-consecutive miscarriages. This suggests that the number of events (2 or more) is more important than the consecutive nature of events. We conclude that women with a history of two or more miscarriages, irrespective of whether consecutive or not, appear to have an increased risk of ischemic heart disease.

**Chapter 3** describes a follow-up study which determined cardiovascular risk factors and predicted long term cardiovascular disease risk in women with a history of recurrent miscarriage. Women who visited the recurrent miscarriage clinic at Leiden University Medical Center (between 2000-2010) and had their third consecutive miscarriage before the age of 31 years of age were invited to participate (between 2012-2014). The reference group consisted of women with at least one uncomplicated pregnancy and no miscarriage, matched on zip code, age, and date of pregnancy. All women were invited for risk factor screening, including physical examination and blood collection. Main outcome measures were the (extrapolated) 10- and 30-year cardiovascular risk scores using the Framingham risk score. A sub analysis was performed for women with idiopathic recurrent miscarriage. 36 women were included in both groups, with a mean follow-up of 7.5 years. Women with recurrent miscarriage had a significantly higher extrapolated 10-year cardiovascular risk score (mean 6.24%, SD 5.44) compared to women with no miscarriage (mean 3.56%, SD 1.82,  $p=0.007$ ) and a significantly higher 30-year cardiovascular risk score (mean 9.86%, SD 9.10) compared to women with no miscarriage (mean 6.39%, SD 4.20,  $p=0.04$ ). Similar results were found in women with idiopathic recurrent miscarriage ( $n=28$ ). Therefore, we concluded that women with a history of recurrent miscarriage differ in cardiovascular risk profile at young age compared to women with no miscarriage. The findings support an opportunity to identify women at risk of cardiovascular disease later in life and a possible moment for intervention.

**Chapter 4** describes novel cardiovascular biomarkers in women with a history of recurrent miscarriage at time of follow-up. The inclusion criteria of the exposed (women with recurrent miscarriage) and unexposed (women with no miscarriage) women were already described in *chapter 3*. Biomarkers were assessed, regarding the following mechanisms; inflammation (HsCRP, Lp-PLA2), thrombosis (homocysteine, folate, anti-Cardiolipin antibodies and anti- $\beta$ -2-Glycoprotein antibodies), lipid metabolism (Lipoprotein (a)), renal function (creatinine, microalbuminuria), myocardial damage (NT-proBNP, hscTroponine T), multiple mechanisms (albumin, 25-OH-Vitamin D). Women with a history of recurrent miscarriage had a significantly higher HsCRP, and significantly lower values of albumin and vitamin D compared to women with no miscarriage which indicates a proinflammatory response in women with recurrent miscarriage. Inflammation plays an important pathogenic role in all stages of atherosclerosis and therefore in the development of cardiovascular disease. No differences were found in more specific biomarkers, for example regarding renal function and myocardial damage. Therefore, we conclude that routine screening of novel cardiovascular biomarkers on patient level is not warranted. Women with a history of recurrent miscarriage should be given healthy lifestyle advises. More research is needed regarding the association between recurrent miscarriage and vitamin D.

**Chapter 5** presents a matched case control study to assess if a family history of cardiovascular disease was more prevalent in women with recurrent miscarriage. Is so,

this association indicates shared risk factors, including genetics. 103 women who visited the recurrent miscarriage clinic at Leiden University Medical Centre (between 2000-2014) and had their third consecutive miscarriage  $\leq 35$  years were included. 143 controls were included, women with at least one uncomplicated pregnancy and no miscarriage, matched on zip code, age and date of pregnancy. All women filled out a questionnaire. Family history of premature myocardial infarction and/or stroke was defined as having a first-degree relative with myocardial infarction and/or stroke  $< 60$  years. Family history of cardiovascular disease as having a first-degree relative with myocardial infarction, stroke, hypertension or thrombosis, irrespective of age at event. We did not find an increased prevalence in women with recurrent miscarriage compared to women with no miscarriage. Therefore, our data does not confirm the assumption that a link exists between familial cardiovascular disease and recurrent miscarriage when measured by proxy family history. A family history of hypertension seems more prevalent in women with recurrent miscarriage, although not significant (multivariate analysis: OR 1.71 (0.94-3.11)), which urge more investigation.

**Chapter 6** presents a meta-analysis which describes genetic variants reproducibly associated with recurrent miscarriage. The association between genes and recurrent miscarriages was assessed at the allele level and a pooled odds ratio was estimated in a random-effects model. The literature search yielded 4050 articles; a total of 241 studies were included. We identified 25 reproduced genetic variants, of which 16 remained significantly associated with recurrent miscarriage in a random-effects meta-analysis. Several of these variants are also identified as risk factors for cardiovascular disease; F2 G20210A, FVL, FXIIIa Val34Leu, MTHFR A1298C, MTHFR C677T and PAI1 -675 4G/5G polymorphism, all involved in coagulation and fibrinolysis, and NOS3 Glu298Asp polymorphism, involved in oxidative stress. This meta-analysis suggests that recurrent miscarriage and cardiovascular disease share genetic risk factors.

**Chapter 7** describes a retrospective cohort study which assessed whether women with secondary recurrent pregnancy loss (SRPL) (defined as having  $\geq 3$  consecutive miscarriages before 22 weeks of gestation, with a previous birth  $\geq 22$  weeks of gestation) (N=172) have a more complicated first pregnancy compared to all Dutch nullipara (N=1.196.178). Some women experience a complication during pregnancy, for instance pregnancy induced hypertension, preeclampsia, intrauterine growth restriction and pre-term delivery, events which may increase the risk of CVD later in life. Recurrent miscarriage might share pathophysiological pathways with other pregnancy complications. It is unclear whether these pregnancy complications are on the causal pathway between miscarriage and cardiovascular disease, they are possibly a confounding factor. Outcomes were the occurrence of preeclampsia, preterm birth, post-term birth, intrauterine growth restriction, breach position, induction of labor, delivery by Caesarean section, congenital abnormalities, perinatal death and severe hemorrhage in the first ongoing pregnancy. Subgroup analyses were performed for women with idiopathic SRPL and for women  $\leq 35$

years at first pregnancy. Women with SRPL more often had a post-term birth (OR 95%CI 1.86 (1.10-3.17)) and more perinatal deaths occurred in women with SRPL compared to the control group (OR 95%CI 5.03 (2.48-10.2)). Similar results were found in both subgroup analyses. More research is needed to reveal possible links between SRPL and these pregnancy complications as this might lead to a better understanding of the underlying pathophysiology.

**Chapter 8** provides a general discussion and discusses remaining questions, suggestions for clinical implementation and future research. We conclude, that given the consistent reporting of an association between miscarriages and later ischemic heart disease (and possibly other CVD), it is time to update current guidelines and add a history of two miscarriages to the risk factors for CVD. Women with recurrent miscarriage should be made aware of their increased risk for cardiovascular disease later in life and given healthy lifestyle advises including discontinuing smoking, improving dietary habits, healthy weight and adequate physical exercise. Individual cardiovascular risk estimation in women with a history of recurrent miscarriage should be considered.

Future research is needed to determine whether women with a history of two or more miscarriages will benefit from screening and preventive interventions.

