The following handle holds various files of this Leiden University dissertation: 
http://hdl.handle.net/1887/63089

Author: Wagner, M.M.
Title: Recurrent miscarriage and the subsequent risk of cardiovascular disease
Issue Date: 2018-06-26
1

General introduction and outline of this thesis
Approximately 15% of clinically recognized pregnancies fail to result in a live birth (1). A miscarriage can be defined as a pregnancy that ends spontaneously before the fetus has reached a viable gestational age. Most miscarriages occur before 12 weeks, frequently caused by sporadic fetal chromosome abnormalities. It has been estimated that only 2–3% of pregnancies end spontaneously in the second trimester(2). Recurrent miscarriage is commonly defined as three or more consecutive pregnancy losses before 22 weeks of gestation(3). It is a problem affecting 0.5-3% of all fertile couples(4). Recurrent miscarriage is a highly heterogeneous condition. Whenever the diagnosis ‘recurrent miscarriage’ is established, an underlying cause is identified in only 25-50% of cases(5, 6). 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.

Cardiovascular disease is the leading cause of death in women in the Western world(7). Clinical manifestation of cardiovascular disease in women is different compared to men(8, 9). Historically, cardiovascular risk factors in women have been insufficiently recognized, diagnosed and treated(10). Most data used to develop prevention guidelines came from trials that enrolled few or no women. In 2004, the American Heart association published evidence-based guidelines for cardiovascular prevention in women(11). In the most recent guideline, pregnancy complications as a history of pregnancy induced hypertension or preeclampsia, and gestational diabetes are mentioned as important risk factors for cardiovascular disease(12). Recurrent miscarriage is not mentioned in current guidelines as a risk factor for cardiovascular disease. A woman is classified as ‘at risk for cardiovascular disease’ when she is having one or more risk factor(s). Other risk factors are, for example; cigarette smoking, high blood pressure and a family history of premature cardiovascular disease in a first-degree relative. The guidelines further call for new research to identify events during ‘periods of potential vulnerability’ such as pregnancy, across a woman’s lifespan that might influence her cardiovascular disease risk(12).

Pregnancy provides a unique opportunity to estimate a woman’s risk because of its exceptional cardiovascular and metabolic stress. Cardiac output increases enormously, there is a decrease in maternal systemic vascular resistance; the renin-angiotensin-aldosterone system is significantly activated; and the heart and vasculature undergo remodeling. These changes are already significant in the first weeks of gestation(13). Pregnancy can be considered as a vascular “stress test” (14) and can unmask early or preexisting endothelial dysfunction and vascular or metabolic disease. This suggests that women at high risk of future cardiovascular disease are identifiable during pregnancy. (Figure 1)

**Figure 1.** Pregnancy as a vascular ‘stress test’.

Women at high risk of future cardiovascular disease, indicated by the red line in figure 1, are crossing the threshold for clinical vascular disease during pregnancy. Women at low risk of future cardiovascular disease (blue line) will pass this test with an uncomplicated pregnancy.

Since the cardiovascular and metabolic changes are already significantly present in the first trimester, recurrent miscarriage might be a first sign of subsequent cardiovascular disease in women. As earlier stated recurrent miscarriage is a highly heterogenous condition. Several hypotheses are possible for an association between recurrent miscarriage and cardiovascular disease; shared common risk factors such as obesity and smoking(15), thrombophilia, and a genetic predisposition is assumed(16).

Epidemiologic studies are showing an association between both conditions; a recently published meta-analysis found an association between recurrent miscarriage and coronary heart disease: pooled odds ratio 1.99, 95%CI (1.13-3.50)(17). Though, clinical heterogeneity between studies was evident. An assessment of the association between recurrent miscarriage and cerebrovascular disease was not possible due to the small number of studies available.

In this thesis, we further want to examine the association between recurrent miscarriage and cardiovascular disease, since current research is sparse. Therefore, in **chapter 2** we report a large retrospective cohort study with a long follow-up which assessed whether consecutive miscarriage is (independently) associated with an increased risk of cardiovascular disease later in life, including ischemic heart disease and cerebrovascular disease.
Worldwide multivariable risk assessment tools are developed to detect apparently healthy individuals at high risk for cardiovascular disease and to effectively implement prevention strategies (18). At present the most common externally validated risk model is the Framingham risk score (19). We hypothesize that women with a history of recurrent miscarriage have a more unfavorable cardiovascular risk profile already at a young age compared to women with no miscarriage. If so, women with recurrent miscarriage represent an ideal target population for preventive strategies. In chapter 3 we conducted a follow-up study to determine cardiovascular risk factors and predict the long term cardiovascular disease risk using Framingham risk scores in women with a history of recurrent miscarriage compared to women with no miscarriage.

In addition to classic cardiovascular risk factors, there is a wide variety of novel cardiovascular biomarkers associated with future cardiovascular disease. Biomarkers regarding inflammation, thrombosis, lipid metabolism, renal function and myocardial damage. For example; high-sensitivity C-reactive protein (HsCRP), an inflammatory biomarker, lipoprotein(a) (Lp(a)), a lipid related biomarker and homocysteine, a thrombosis biomarker, which alters the process of hemostasis. Hyperhomocysteinemia is associated with recurrent miscarriage and with cardiovascular disease (20, 21). These novel cardiovascular biomarkers might contribute in linking recurrent miscarriage to cardiovascular disease and therefore can lead to a better understanding of the association. In chapter 4 we conducted a follow-up study to determine novel cardiovascular biomarkers in women with a history of recurrent miscarriage compared to women with no miscarriage.

We hypothesize that the association between miscarriages and cardiovascular disease indicates shared common acquired risk factors, such as smoking and antiphospholipid syndrome, and shared heritable (genetic) risk factors. A Scottish retrospective cohort study found an increased incidence of ischemic heart disease in the parents of women who experienced multiple miscarriages before their first birth, which supports the hypothesis of shared genetic factors (22). A family history of (premature) cardiovascular disease is an independent predictor of myocardial infarction and cardiovascular disease (23). We conducted a matched case-control study to investigate whether a family history of premature cardiovascular disease was more common in women who experienced recurrent miscarriage compared to women with no miscarriage, which is described in chapter 5.

As earlier stated, research suggests a multifactorial etiology in recurrent miscarriage with a role for genetics. A familial predisposition is described in literature. An increase in the risk of spontaneous miscarriage was seen in family of women with recurrent miscarriage compared to control women (23-26). In addition, a case-control study showed that women with two or more unexplained recurrent miscarriage more often had a family history of recurrent miscarriage compared to healthy control subjects, RR 3.2 (95%CI 1.3-8.1) (27). However, it is still unclear what specific genes are involved
and what individual variants contribute to the development of recurrent miscarriage. Polymorphisms have been investigated in almost 90 different genes(28). We hypothesize that there are shared genetic polymorphisms which are associated with recurrent miscarriage and cardiovascular disease. Therefore, a systematic overview of the genetic variants associated with recurrent miscarriage was described in chapter 6. A meta-analysis was performed to assess the pooled effect of the genetic variants that are repeatedly investigated and that are significantly associated with recurrent miscarriage in at least two of the performed studies (and find possible genetic links between recurrent miscarriage and cardiovascular disease).

Other pregnancy complications, for instance, pregnancy induced hypertension, preeclampsia, intrauterine growth restriction and pre-term delivery may increase the risk of cardiovascular disease later in life(29, 30). It is unclear whether these pregnancy complications are on the causal pathway between miscarriage and cardiovascular disease(31, 32), they are possibly a confounding factor. Women with recurrent miscarriage might have more complicated pregnancies prior and after their recurrent miscarriage. Not all women with recurrent miscarriage will have an ongoing pregnancy, so will not have the chance to develop pregnancy complications. Approximately 40% of the women with recurrent miscarriage have a previous ongoing pregnancy and are diagnosed with secondary recurrent miscarriage(4). Women who did not have an ongoing pregnancy prior to their recurrent miscarriage are diagnosed with primary miscarriage. The chance of a live birth in the subsequent pregnancy after recurrent miscarriage is reported to be 60-90%(33-35). A review identified an increased risk for placenta previa, premature preterm rupture of membranes, preterm delivery, intrauterine growth restriction, low birth weight and congenital abnormalities in the pregnancy subsequent to the recurrent miscarriage(36). Little is known about pregnancy outcome prior to recurrent miscarriage(5, 37, 38). Endothelial dysfunction has been hypothesized as the underlying link between recurrent miscarriage, preeclampsia, intrauterine growth restriction and future cardiovascular events(16). Other pathophysiological links could be inherited and acquired thrombophilia such as antiphospholipid syndrome. As knowledge of obstetric details regarding the pregnancy prior to miscarriage may contribute to our understanding of the development of recurrent miscarriage, or cardiovascular disease and their possible link, in chapter 7 a retrospective cohort study was performed to assess if women with secondary recurrent miscarriage have a more complicated first pregnancy compared to control women.
Reference List
