Recurrent miscarriage and the subsequent risk of cardiovascular disease

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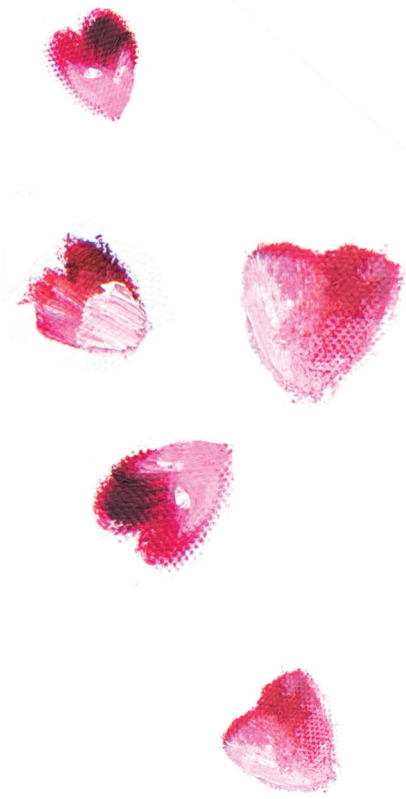

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General discussion

In this thesis, several studies are presented examining the association between recurrent miscarriage and cardiovascular disease. Main aim of this thesis was to assess whether miscarriages are independently associated with an increased risk of cardiovascular disease later in life. And, if this was true, to identify cardiovascular risk factors and predict long term cardiovascular disease risk in women with a history of recurrent miscarriage.
We found an increased risk of ischemic heart disease in women with a history of two (multivariate analysis HR 1.82) and three or more miscarriages (HR 3.18), irrespective whether consecutive or not (*chapter 2*). Women with a history of recurrent miscarriage have significantly higher 10- and 30-year cardiovascular risk scores compared to women with a history of no miscarriage. These results indicate an opportunity for the early identification of women prone to cardiovascular disease later in life. Women with a history of two or more miscarriages must be made aware of their increased cardiovascular risk and appropriate risk factor modifications will have to be offered, for example life style advises; weight management and smoking control.
In this chapter, I give an interpretation of the findings of the studies described in the previous chapters and propose remaining questions. Suggestions for clinical implementation and future research will be discussed.

(Recurrent) miscarriage; a new cardiovascular risk factor

Studies regarding novel cardiovascular risk factors, including pregnancy complications such as (recurrent) miscarriage are hampered by the nature of the events in question. The events during pregnancy and the development of cardiovascular disease are often separated by decades and observational studies are the best used method to increase our understanding of these novel risk factors. We performed a large cohort study (including 60105 women with a median follow-up of 17 years) and demonstrated an association between miscarriage and ischemic heart disease *(chapter 2)*, independent of classical cardiovascular disease risk factors (maternal age, BMI, social class and smoking). The association between both events was already clinically relevant from 2 miscarriages onwards (multivariate analysis HR 1.82 (95%CI 1.30 to 2.54)). The risk for cardiovascular disease increases with increasing number of miscarriages and was, surprisingly, independent of the consecutive nature of the miscarriages. Our research is in line with a large Danish cohort study of 1 million women, which found a dose-dependent association between miscarriage and future risk of ischemic heart disease and other atherosclerotic endpoints [1]. Overall, at present, several studies have established that (recurrent) miscarriage is associated with ischemic heart disease in the future and possibly other cardiovascular outcomes ([1-4] *chapter 2*).
There are two challenges, which I will discuss in the next paragraphs. Firstly, trying to understand the underlying mechanisms for the association between recurrent miscarriage and cardiovascular disease. This might also contribute to our knowledge of the aetiology of recurrent miscarriage, of which the cause often remains unknown. And

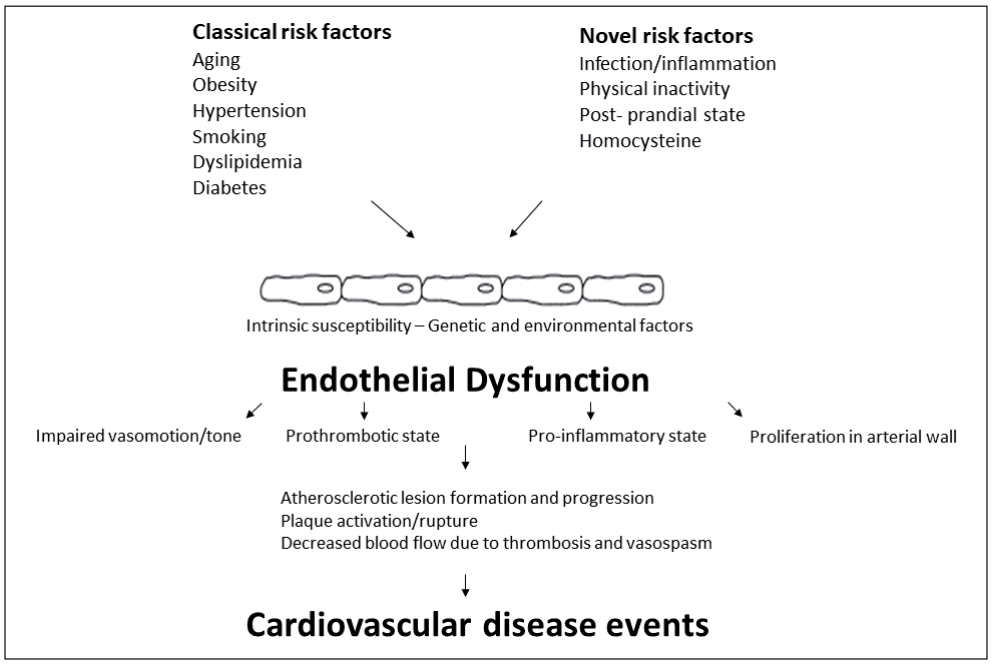

Figure 1. Endothelial dysfunction and Cardiovascular disease. Based on [11]

secondly, how to incorporate (recurrent) miscarriage as a new risk factor in the algorithm for future cardiovascular disease, especially since novel risk factors for cardiovascular disease are rising.

Mechanisms possible involved in the association between recurrent miscarriage and cardiovascular disease

Many underlying mechanisms for the association between recurrent miscarriage and cardiovascular disease are hypothesized. The following mechanisms will be discussed; endothelial dysfunction, shared classic cardiovascular risk factors, antiphospholipid syndrome and immunologic disbalance, genetics and novel cardiovascular biomarkers. Finally, the relation between recurrent miscarriage, other pregnancy complications and cardiovascular disease will be discussed.

Endothelial dysfunction

A unifying mechanism between recurrent miscarriage and cardiovascular disease could be the presence of endothelial dysfunction. Endothelial cells form the inner surface of blood vessels and have many important regulatory functions in the cardiovascular system such as vasoconstriction and dilatation. Healthy endothelium also has anti-thrombotic (through prostacyclin's), anti-inflammatory (through developmental endothelial locus-1) and anti-proliferative (through nitric oxide and prostaglandin I2) functions [5] [6].

In normal pregnancies, maternal uterine arteries are remodelled to create a high-flow, low-resistance uteroplacental vascular system that provides adequate blood flow needed for fetal growth[7]. Placentation starts in the first trimester of pregnancy. The needed invasion of extra villous trophoblasts into the uterine spiral arteries could be impaired by endothelial dysfunction. Dysregulation of the placental vasculature is thought to be the pathophysiologic mechanism leading to multiple pregnancy complications such as miscarriage, preeclampsia, intrauterine growth restriction, and perinatal death[8]. Further, endothelial dysfunction is the initial step in the pathogenesis of atherosclerosis. [9, 10] leading to cardiovascular disease events (Figure 1).
In conclusion endothelial dysfunction is a plausible explanation for the association between miscarriage and cardiovascular disease. It is likely that the endothelium is already damaged before the miscarriages, caused by diverse maternal predisposing factors. Possibly the pregnancy itself leads to endothelium damage (second hit), or it is a combination of both. Underlying maternal factors associated with endothelial dysfunction will be discussed in more detail.

Classic cardiovascular risk factors

Classic cardiovascular risk factors include age, obesity, hypertension, smoking, dyslipidaemia, and diabetes. Cardiovascular disease risk factors adversely affect a diverse range of endothelial homeostatic functions (under influence of environmental and genetic factors) resulting in endothelial dysfunction (Figure 1) which can lead to both recurrent miscarriage and cardiovascular disease. A remarkable higher prevalence of pre-existing hypertension and pre-existing diseases of circulatory system was found in women with miscarriages (dose-dependent) (*chapter 2)*. All women with pre-existing morbidity related to cardiovascular disease (hypertension, type one diabetes mellitus, kidney disease and any disease of circulatory system) were excluded from main analysis. The association between miscarriages and future cardiovascular disease was independent of classical cardiovascular risk factors such as age, BMI, social class and smoking.
In *chapter 3* we determined classical cardiovascular risk factors and calculated cardiovascular disease risk in women after recurrent miscarriage (mean follow-up 7.5 years) and found an increased (extrapolated) 10 and 30-year cardiovascular disease risk compared to women with no miscarriage, calculated by Framingham risk scores. We are not able to answer the question on causal effect as we were only able to look at cardiovascular risk factors in women after they experienced recurrent miscarriage.
The high number of women who smoked in the recurrent miscarriage group was remarkable. Women with recurrent miscarriage were more often smokers during at least one pregnancy (38.9%) compared to women with no miscarriage (13.9%), p=0.05. Active smoking is a known risk factor for recurrent miscarriage; a meta-analysis describes an increased risk of miscarriage (risk ratio 1.23, 95% CI 1.16-1.30) [12]. It is hypothesized that the vasoconstrictive and anti-metabolic properties of some components of cigarette

smoke (nicotine, carbon monoxide, cyanide) could lead to placental insufficiency and embryonic and fetal growth restriction and demise, other studies suggest that smoking results in an increase of mature oocytes leading to miscarriages [13]. Smoking was still more common in women with a history of recurrent miscarriage at time of follow-up (*chapter 3*) although not significant. Also, other values of classical cardiovascular risk factors were higher in women with recurrent miscarriage compared to no miscarriage, although only significant for systolic blood pressure. A lack of power is likely when investigating the individual risk factors as our preliminary sample size analysis was based on the Framingham risk score. It would be interesting to investigate the individual risk factors in a larger study group, and perform multivariate analyses as well, to answer the question which risk factors are contributing the most to the elevated cardiovascular risk score in women with a history of recurrent miscarriage.
In conclusion, women with recurrent miscarriage seem to have a higher prevalence of classical cardiovascular risk factors before, and after their miscarriages. However, this is not the overall explanation for the association between miscarriages and future cardiovascular disease, as the association was found to be independent of classical cardiovascular risk factors such as age, BMI, social class and smoking *(chapter 2)*.

Antiphospholipid syndrome and immunology

Acquired thrombophilia (antiphospholipid syndrome) is clearly related to recurrent miscarriage as well as cardiovascular disease. Antiphospholipid syndrome is an autoimmune disorder characterized by the occurrence of venous and arterial thrombosis and pregnancy complications (such as recurrent miscarriage and early preeclampsia), in the presence of antiphospholipid antibodies. Women with antiphospholipid syndrome are at increased risk for accelerated atherosclerosis and cardiovascular disease events [14]. The exact mechanisms by which the antibodies cause these morbidity is not fully understood. It is suggested that endothelial cells play a central role and represent the common pathway between autoimmunity and inflammation in the pathogenesis of antiphospholipid syndrome. Circulating antibodies and underlying endothelial dysfunction are a necessary 'first hit' for the development of thrombosis, pregnancy complications and cardiovascular disease, an inflammatory 'second hit' by up-regulation of β2-glycoprotein (an apolipoprotein, member of the complement control family, considered to be a natural inhibitor of coagulation) receptors is needed to precipitate the thrombotic event [14]. These inflammatory factors may include infection, immunological and other non-immunological procoagulant factors, such as oestrogen-containing contraceptive pills, surgery and immobility [15].

Acquired thrombophilia is included in the work-up of recurrent miscarriage to identify any causes. Together with: a standardized history of the couple, evaluation of hyperhomocysteinemia, heritable thrombophilia, karyotyping of the couple and

checking the presence of uterus anomalies by ultrasound or hysteroscopy. If no abnormalities are found; a woman is diagnosed with idiopathic recurrent miscarriage. In contrast to the large cohort study described in *chapter 2*, information about causes of recurrent miscarriage was available in our follow-up study in cardiovascular disease risk (*chapter 3*). We performed a subgroup analysis including women with idiopathic recurrent miscarriage which showed comparable results to the results of the total group. The calculated risk scores were even slightly higher in women with idiopathic recurrent miscarriage. Therefore, in our study, the increased cardiovascular disease risk scores in women with recurrent miscarriage cannot be explained by the presence of antiphospholipid syndrome. Recently, the first case control study regarding the association between pregnancy loss and premature arterial thrombosis, which adjusted for both classic cardiovascular risk factors and the presence of antiphospholipid antibodies, was published [16]. An increased risk of arterial thrombosis, independent of the presence of antiphospholipid syndrome, was found in women with ≥ 3 pregnancy losses (miscarriage and stillbirth together), OR 1.95, (95%CI 0.92–4.14). However, it cannot be excluded that other immunological factors will play a role. The maternal immune system plays an important role in the success of pregnancy, optimal regulation is essential to tolerate the allogeneic foetus. As in more than 50% of the cases the cause of recurrent miscarriage remains unknown, it is thought that maladaptation of the maternal immune system could explain part of its pathophysiology. Research shows that in specific cases immunotherapy might benefit pregnancy outcome, although there is no clear evidence yet [17]. On the other hand the activation of the immune system plays a significant role in the pathogenesis of atherosclerosis and other cardiovascular diseases[18]. This possible link between recurrent miscarriage and cardiovascular disease has not been further elaborated in this thesis, but it is an interesting starting point for future research. Vitamin D, that could act as an immune regulator during implantation will be discussed later in this chapter (subheading: novel cardiovascular biomarkers).

Genetic link

A shared genetic background could be a link between recurrent miscarriage and cardiovascular disease. Both diseases have a familial aggregation[19, 20]. The degree of endothelial damage (leading to both conditions) may be in part, related to intrinsic and environmental factors such as genetic polymorphisms (Figure 1 [11]). We were not able to confirm this hypothesis in our matched case-control study concerning family history of premature cardiovascular disease in *chapter 5*; no increased prevalence was found in women with recurrent miscarriage. In *chapter 6* our findings do suggest shared genetic risk factors between recurrent miscarriage and cardiovascular disease. Several of the 16 genetic variants which remained significantly associated with recurrent miscarriage after meta-analysis, are also identified as risk factors for cardiovascular disease.

A higher prevalence of family history of ischemic heart disease and other atherosclerotic

disease (not premature) in women with recurrent miscarriage was found in two other, large cohort, studies [21, 22]. Limitations of our study are the relatively small number of included women with recurrent miscarriage (N=103) and the lack of information about the age of their parents. Some parents will not have reached the age of 60 years at time of questionnaire and are still at risk to develop premature myocardial infarction and/or stroke. In the same study (*chapter 5)* we find that women with recurrent miscarriage had more often hypertension at time of questionnaire. It was interesting to see this reflected in family history of hypertension as well, which seems more often present in women with recurrent miscarriage: OR 1.71 (95%CI 0.94-3.11). Based on our results we cannot rule out a shared genetic background between both conditions, and we conclude that the design of our research probably is not the best to investigate our hypothesis.

In *chapter 6* genetic variants associated with recurrent miscarriage are described of which several, are also identified as risk factors for cardiovascular disease. Most of them are involved in pathways concerning coagulation and fibrinolysis; factor II (prothrombin), factor V Leiden, FXIIIa Val34Leu, MTHFR A1298C, MTHFR C677T and PAI1 -675 4G/5G polymorphism [23-25], and NOS3 Glu298Asp polymorphism [26] is involved in oxidative stress and plays a crucial role in regulating endothelial function [27].

Heritable thrombophilia (defined by the presence of a factor II (prothrombin) gene mutation, factor V Leiden mutation, protein C or S deficiency or antithrombin deficiency) has been an important topic of research in women with recurrent miscarriage for years. It is included in the work-up to identify possible causes of recurrent miscarriage. A strong association exists between heritable thrombophilia and venous thrombosis[28]. Several meta-analyses have reported an increased risk of recurrent miscarriage in women with heritable thrombophilia; however, heterogeneity between studies is significant and the definition of recurrent miscarriage limits firm conclusions[29, 30]. Overall, heritable thrombophilia appears to be only a weak contributor to recurrent miscarriage (and therefore as well to the association between recurrent miscarriage and cardiovascular disease). In line with this is, at first; the lack of association between a family history of venous thrombosis and recurrent miscarriage (*chapter 5*) [21]. And second, the result of a meta-analysis of randomized controlled trials (including eight trials and 483 patients); no increased live birth rate was found with the use of low-molecular-weight heparin in women with recurrent miscarriage and heritable thrombophilia[31]. Suggesting no benefit of low-molecular-weight heparin in preventing recurrent miscarriage in women with inherited thrombophilia. Perhaps, the ongoing study; the Alife2 study, which is evaluating the efficacy of low-molecular-weight heparin on pregnancy outcome, in women (aged 18-42) with heritable thrombophilia and a history of two or more miscarriage and/or intra-uterine fetal death, adds information to this discussion in the future.

MTHFR A1298C and MTHFR C677T polymorphisms reduce the activity of the MTHFR enzyme, causing elevated concentration of homocysteine. Hyperhomocysteinemia is

related to recurrent miscarriage [32] and increases risk of cardiovascular disease. Despite this, we found lower values of homocysteine in women with a history of recurrent miscarriage compared to women with no miscarriage, which could be a confounding effect of the folate and vitamin B supplementation in the recurrent miscarriage group as described in *chapter 4*.

Meanwhile many new studies have been conducted regarding the association between genetic polymorphisms and recurrent miscarriage. Therefore, it could be helpful to repeat meta-analysis with newly added studies to find possible new involved pathways in the aetiology of recurrent miscarriage and their relationship with future cardiovascular disease. And moreover, genetic and more in depth genetic studies such as epigenetics in families with a heavy burden of both miscarriage and cardiovascular disease could help to identify a likely (possibly immunological) link between the two conditions, which could potentially lead to a better understanding of the underlying pathology and possibly new treatment options.

Novel cardiovascular biomarkers

In c*hapter 4* we focused on non- classical cardiovascular risk factors, the so called novel cardiovascular biomarkers, in women with recurrent miscarriage as knowledge about these markers might contribute to a better understanding of the association between recurrent miscarriage and cardiovascular disease. We found that women with recurrent miscarriage had significantly higher values of HsCRP and lower values of albumin and vitamin D compared to women with no miscarriage at time of follow-up. These cardiovascular biomarkers are involved in mechanisms regarding inflammation; indicating a proinflammatory state in women with recurrent miscarriage and will adversely affect a diverse range of endothelial homeostatic functions (Figure 1). No differences were found in more specific cardiovascular biomarkers, for example regarding renal function and myocardial damage.

Especially the decreased concentration of vitamin D is interesting. Vitamin D is inversely associated with cardiovascular disease risk [33] via several mechanisms; increased inflammation, endothelial dysfunction, elevated blood pressure, decreased insulin sensitivity and secretion, arterial stiffness and degradation of atherosclerotic plaque [34]. Over the last decade, the role of vitamin D in human reproduction has been increasingly considered as important. Adverse outcomes linked to vitamin D insufficiency in pregnancy includes pre-eclampsia, gestational diabetes, small-for-gestational age and preterm birth [35-37]. Many potential underlying mechanisms of vitamin D in regulating each of the outcomes are hypothesized, including that vitamin D could act as an immune regulator during implantation [38]. Research showed that trophoblasts produce and response to vitamin D in early pregnancy [39, 40]. Furthermore, it has been established that vitamin D influences local anti-inflammatory responses (via inhibition of TNF-alpha-induced inflammatory cytokines) and induces decidualization for success-

ful pregnancy[41-43]. We assessed vitamin D levels only at follow-up. In addition, it is possible that women with recurrent miscarriage already have decreased values of vitamin D during and/or before pregnancy. Only one study assessed vitamin D levels and immunological implications, such as presence of several autoantibodies and cytokine production, in women with recurrent miscarriage and found that a high proportion of women had a vitamin D deficiency (<30 ng/ml) with immunological implications [44]. With this knowledge, supplementation of vitamin D might be a potential treatment in women with recurrent miscarriage. At first, there is need for more observational studies to investigate the association between vitamin D and recurrent miscarriage (adjusting for ethnicity and seasonal variations). And secondly, if an association is established, intervention studies (randomized controlled trials) are needed to evaluate the effect of vitamin D supplementation on pregnancy outcome in women with recurrent miscarriage. Next to a possible treatment option in women with recurrent miscarriage, vitamin D might be useful in cardiovascular risk estimation. Vitamin D deficiency is a strong risk marker for cardiovascular disease[45]. In the prevention of cardiovascular disease, no significant and consistent protective effect of vitamin D supplementation was found in randomized controlled trials.

Recurrent miscarriage, other pregnancy complications and cardiovascular disease

In *chapter 7* we investigated whether women with secondary recurrent miscarriage had a more complicated first pregnancy compared to all Dutch nullipara. Approximately 40% of the women with recurrent miscarriage have a previous ongoing pregnancy and are as a consequence diagnosed with secondary recurrent miscarriage [46]. We found that women with secondary recurrent miscarriage had higher rates of post-term birth and perinatal death in their first ongoing pregnancy preceding recurrent miscarriage. Causes of perinatal death varied from intrauterine fetal demise, intrauterine growth restriction, placental abruption, preterm birth to congenital abnormalities. The higher rate of perinatal death supports the hypothesis that placental vasculopathy is an underlying pathophysiologic mechanism linking an array of pregnancy complications [8, 47]. Preeclampsia is also mentioned in this hypothesis; however, we did not find an increased risk of preeclampsia in the first ongoing pregnancy for women with secondary recurrent miscarriage, in contrast to the (larger) studies of Weintraub and Nielsen[48, 49]. Shared maternal risk factors for recurrent miscarriage and still birth, the single major determinant of perinatal death, are; maternal age ≥ 40 years, smoking, obesity and diabetes mellitus [50]. An association between increasing maternal BMI and post-term birth has also been described [51], although the mechanisms are not fully understood. These common risk factors are also (classical) risk factors for developing cardiovascular disease[52], contributing to endothelial dysfunction and linking recurrent miscarriage to cardiovascular disease.

In sum, (recurrent) miscarriage and cardiovascular disease are both diseases with a multifactorial aetiology. Previous mentioned mechanisms are involved in the association between both diseases. Although none of them gives a clear explanation on its own, and the contribution of the described mechanisms seems present but not substantial. It is supposed that a unifying mechanism between recurrent miscarriage and cardiovascular disease is the presence of endothelial dysfunction. Described mechanisms of shared classic cardiovascular risk factors, antiphospholipid syndrome, genetic polymorphisms and novel cardiovascular biomarkers involved in inflammation all contribute to this phenomenon. Genetic and immunologic etiology need further elucidation.
It remains unknown if women with recurrent miscarriage have an increased cardiovascular disease risk due to pre-existing common risk factors, due to the complicated pregnancies that leads to permanent (endothelial) damage, or, perhaps the most likely; a combination of these two (second hit) as illustrated in figure 2. For preeclampsia, in which the association with cardiovascular disease is well investigated, this discussion is still ongoing.

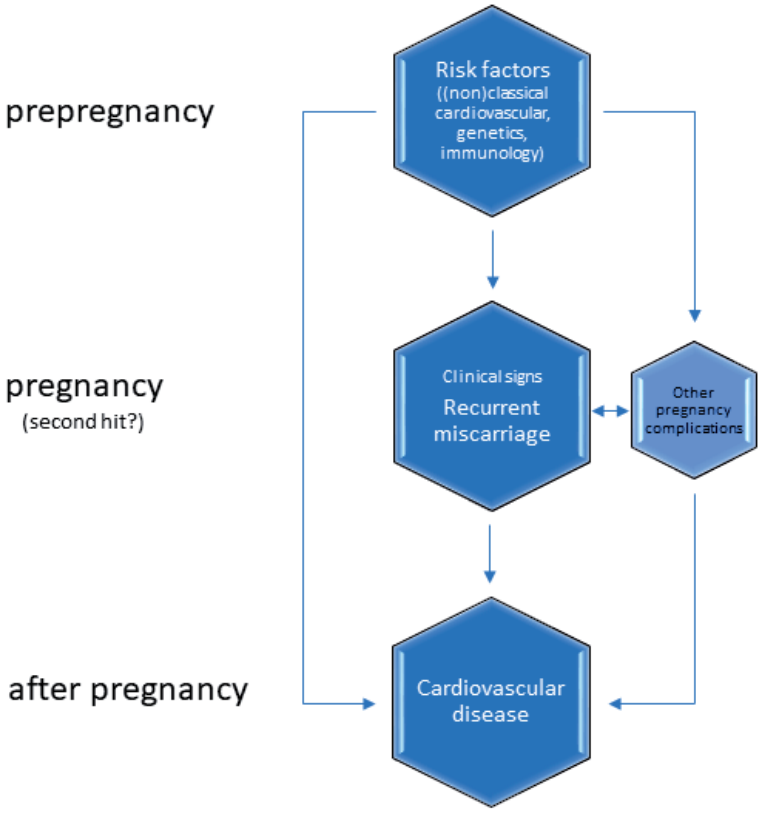

Figure 2. Incorporate (recurrent) miscarriage as a new risk factor in the algorithm for future cardiovascular disease

Definition of recurrent miscarriage

The variation in the definition of recurrent miscarriage, between two and three and consecutive versus non-consecutive miscarriages [53, 54] complicates the incorporation of recurrent miscarriage as a new risk factor for cardiovascular disease. Also, there is disagreement on gestational age at time of miscarriage; early or late, and whether detection of fetal heart activity by ultrasound is obliged or biochemical pregnancies are included as well. Generally, in the international literature, recurrent miscarriage is defined as three or more consecutive pregnancy losses before 22 weeks of gestation[55]. For this reason, we have chosen this definition setting up our research protocols. In the Netherlands, a woman is diagnosed with recurrent miscarriage after two pregnancy losses before 20 weeks of gestation, irrespective whether consecutive or not [53].

As this lack of consensus makes it difficult to compare study results between different centres, the ESHRE special interest group early pregnancy, published a consensus statement in 2015, during the writing of this thesis[54]. They recommend the term recurrent pregnancy loss be used to describe repeated pregnancy demise, and the term recurrent miscarriage be used when all pregnancy losses have been confirmed as intrauterine miscarriages, by ultrasound or histology. For this reason, we changed the term recurrent miscarriage into recurrent pregnancy loss in *chapter 7*, according to the comments of the reviewers, as we included also non-visualized miscarriages. In future research we recommend using this terminology as well [54]. In this thesis, we kept to our predefined definition and terminology of recurrent miscarriage.

Probably we should make a distinction between the most useful definition of recurrent miscarriage regarding aetiology and subsequent pregnancy prognosis on the one hand, and the most useful definition to point out a woman at future risk for cardiovascular disease on the other hand. In this thesis, we focus on the last mentioned. The results in *chapter 2* showed that women who have experienced two or more miscarriages, irrespective of whether consecutive or not, have an increased risk of ischemic heart disease. In subgroup analysis, the risk for ischemic heart disease was lower in women with consecutive miscarriages compared to women with two or more non-consecutive miscarriages. This suggests that the number of events (two or more) is more important than the consecutive nature of events.

Current guidelines

Given the world-wide health problem of cardiovascular disease in women, and its economic implications there is a strong rationale for the prevention of cardiovascular disease in women. More gender specific analyses have been published making it possible to do more definitive recommendations [52], Wilson and Jonner set up ten criteria to determine the suitability for establishing screening programs including for example; the condition should be an important health problem, there should be an accepted treatment recognized for the disease and diagnosis and treatment should be cost-effective [56].

In recent years, pregnancy complications are incorporated in guidelines as novel risk factors for cardiovascular disease in women. The 2011 guidelines for the prevention of cardiovascular disease of The American Heart Association indicate a history of gestational diabetes or hypertensive complications of pregnancy as a major risk factor for developing cardiovascular disease and advises monitoring and control of risk factors in these women postpartum [52]. In 2014, the first Dutch guideline on cardiovascular risk management after reproductive and pregnancy-related disorders was published [57]. This guideline states no increased risk for ischemic heart disease in women with recurrent miscarriage, RR1.99 (95%CI 0.94,4.19). However, only 3 cohort studies were included (up to 2012) and several studies were published afterwards, including a meta-analysis which found a significant increased risk (*chapter 2*) [1-4]. Optimization of modifiable cardiovascular risk factors, by giving lifestyle advices, is recommended to reduce the risk of future cardiovascular disease for all reproductive and pregnancy-related disorders mentioned in this guideline. Follow-up is only recommended for women with a history of preeclampsia, (relative risk CVD; 2.15 (95%CI 1.76–2.61). This includes that at the age of 50 years, women are offered a full cardiovascular risk profile performed according to the Dutch guideline for cardiovascular risk management. The most recent European Guidelines on cardiovascular disease prevention (2016) states that there is no data to suggest that recurrent pregnancy loss is associated with an increased cardiovascular disease risk [58]. They recommend that periodic screening (not further specified) for hypertension and diabetes mellitus should be considered in women with gestational diabetes and hypertensive complications of pregnancy.
Recently published data, including this thesis, suggest it is time to update these mentioned guidelines. As the hazard ratio for ischemic heart disease in women with two or more miscarriages is comparable with the hazard ratio for cardiovascular disease in women with hypertensive disorders of pregnancy [59] an equal approach for women with two or more miscarriages seems justified and I recommend to add a history of two or more miscarriage to the risk factors for cardiovascular disease.

Future perspectives
The important and growing field of the utilization of big data analysis in healthcare is very interesting. In the future, the increased use of statistical machine learning techniques will probably help us to interpret all variables involved in the association between two heterogeneous conditions such as miscarriage and cardiovascular disease. It may be helpful in teasing out subtle information from observational datasets and provide reliable interpretations for individualizing care decisions and personalized medicine.

With current knowledge, women with two or more miscarriage should be made aware of an increased cardiovascular risk and advised lifestyle advises including discontinuing smoking, improving dietary habits, healthy weight and adequate physical exercise

(reducing endothelial damage) to prevent cardiovascular disease events. Appropriate risk factor modifications can lower their risk for future cardiovascular disease. In women with a history of preeclampsia estimates showed that lifestyle interventions after this pregnancy complication have the potential to decrease cardiovascular risk by 4-13%[60]. Individual cardiovascular risk estimation in women with a history of two or more miscarriages should be considered. Evidence on costs and cost-effectiveness of cardiovascular screening in women with miscarriages is lacking. To start, a comparable approach, such as advised in the Dutch guideline on cardiovascular risk management in women with a history of preeclampsia can be applied. At the age of 50 years, performance of a full cardiovascular risk profile according to the Dutch guideline for cardiovascular risk management could be offered. Although this age limit is up for discussion. Evidence is suggesting that screening and prevention should be offered earlier in life to women with a complicated pregnancy. For example, the mean age of stroke onset was about 10 years earlier in women with a history of pregnancy complications (preeclampsia, HELLP syndrome and placental abruption), compared to women without such a history [61]. A suggested new approach is to start screening for cardiovascular risk factors postpartum and repeat it every 10 years. The ideal age of screening should be studied further.
Future research is needed to determine whether women with a history of two or more miscarriages will benefit from screening and preventive interventions. A cohort study with a long follow-up is suggested to evaluate the results of these life style advises and interventions.

Conclusions

In conclusion, given the consistent reporting of an association between miscarriages and later ischemic heart disease (and possibly other cardiovascular disease), it is time to update current guidelines and add a history of two or more miscarriages to the risk factors for cardiovascular disease.
Future studies should aim to determine how the inclusion of information on miscarriages (and other adverse pregnancy events) could improve cardiovascular disease risk evaluation in women.
Women with recurrent miscarriage must be made aware of their increased risk for cardiovascular disease later in life and given lifestyle advises. Individual cardiovascular risk estimation in women with a history of recurrent miscarriage must be implemented.

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