Recurrent miscarriage and the subsequent risk of cardiovascular disease

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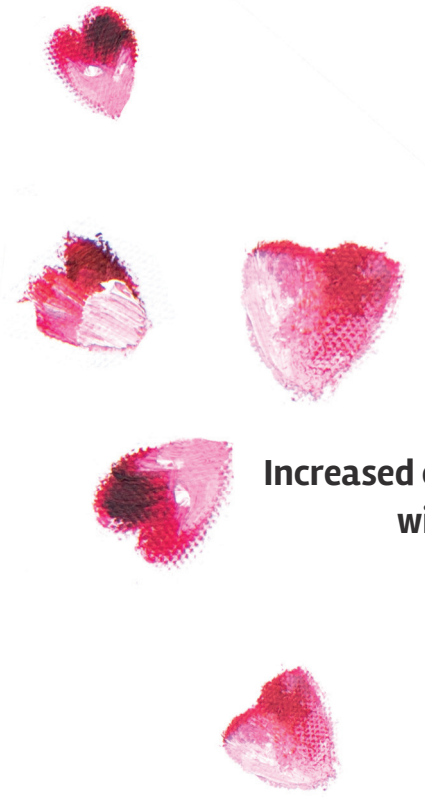

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Increased cardiovascular disease risk in women with a history of recurrent miscarriage

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Abstract

Background Cardiovascular disease is the leading cause of death in women. Observational studies suggest that women with a history of recurrent miscarriage have an increased risk of cardiovascular disease.

Methods Women who visited the recurrent miscarriage clinic at Leiden University Medical Centre (between 2000-2010) and had their third consecutive miscarriage < 31 years, were invited to participate in this follow-up study (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.

Results 36 women were included in both groups. Mean follow-up was 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).

Conclusions 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.

Introduction

Cardiovascular disease(CVD) is the leading cause of death in women in the western world[1]. Women have a unique risk profile for CVD compared to men[2]. There is increasing evidence that women with adverse pregnancy outcomes are at increased risk of premature CVD. Pregnancy can be considered as a "stress test" unmasking underlying cardiovascular defects[3]. A history of gestational diabetes, preeclampsia or pregnancy induced hypertension is mentioned as a major risk factor in women for developing CVD in the American Heart Association Guidelines[2]. Miscarriages are not considered in this guideline.

Recurrent miscarriage is commonly defined as three or more consecutive pregnancy losses before 22 weeks of gestation[4] and affects 0.5-3% of all fertile couples[5]. Recurrent miscarriage is a highly heterogeneous condition. Possible etiologic factors include genetic disorders, uterine anomalies, endocrine factors, maternal autoimmune disorders, metabolic disorders, maternal thrombophilia and lifestyle factors[6]. An underlying cause may be identified in 25-50% of cases. Observational studies suggest that also women with a history of recurrent miscarriage have an increased risk of CVD[7-10]. Several hypotheses are possible for the association between both diseases; shared common risk factors such as obesity and smoking[11], endothelial dysfunction[12], and a genetic predisposition is assumed[13].

Determining cardiovascular risk factors in women with recurrent miscarriage could be an opportunity to identify women at high risk for future CVD at a young age. Worldwide multivariable risk assessment tools are developed to detect apparently healthy individuals at high risk for CVD and to effectively implement prevention strategies[14]. At present the most common externally validated risk model is the Framingham risk score[15].

We conducted a follow-up study to determine cardiovascular risk factors and predict the long-term CVD risk using Framingham risk scores in women with a history of recurrent miscarriage.

Methods

Study design

Follow-up study.

Exposed

Women who visited the recurrent miscarriage clinic at Leiden University Medical Centre between 2000 and 2010 and had their third consecutive miscarriage below the age of 31 years were invited to participate in this follow-up study. Recurrent miscarriage was defined as ≥ 3 consecutive miscarriages before 22 weeks of gestation. All women had

a routine recurrent miscarriage work-up to identify possible causes for the recurrent miscarriage: a standardised history of the couple was performed, karyotyping of the couple (this was offered routinely before 2005 to all couples, after 2005 this was only offered in presence of low maternal age and/or positive family history for recurrent miscarriage)[16], presence of uterus anomalies by ultrasound or hysteroscopy and presence of acquired and heritable thrombophilia was assessed. Acquired thrombophilia: antiphospholipid syndrome was defined as the presence of anticardiolipin antibodies or lupus anticoagulant in repeated samples taken 3 months apart and at least 10 weeks after delivery[17], after revision of the classification criteria the presence of anti-β2 glycoprotein-I was added to the work-up[18]. Hyperhomocysteinemia was evaluated. Heritable thrombophilia was defined by the presence of a factor V Leiden mutation, factor II (prothrombin) gene mutation, protein C or S deficiency or antithrombin deficiency. Women with primary miscarriage (no live birth before miscarriage) and secondary miscarriage (live birth(s) before miscarriage) were included. The time interval between the diagnosis recurrent miscarriage and the time of follow-up had to be at least 2 years.

Unexposed

Women with one or more uncomplicated pregnancy(ies) and no miscarriages were enrolled (reference group). In the Netherlands, it is common practice that independent community midwives are taking care of low-risk women (with no medical or obstetrical history) during pregnancy and child birth. The zip code of each woman with recurrent miscarriage was used to contact the nearest midwifery practice to take the impact of socio-economic status into account. Women with the same zip code, the same age (difference in birthdate maximal 1 year) and of which the time of first delivery was close to the time of the third miscarriage of the matched exposed woman (maximum 6 months before or 6 months after) were asked to participate. Women with recurrent miscarriage were included in the study before the matched controls were invited to participate, a small difference in follow-time was therefore expected. In both groups, pregnant and lactating women (within the last 3 months) were excluded. Enrolment took place between 2012 and 2014.

Procedures and definitions

After enrolment, all women were asked to fill out a web based questionnaire and were invited for risk factor screening. The questionnaire included general information, medical history, family history of CVD, use of medication, intoxications and obstetric history. Information about medical history, use of medication, intoxications and pregnancy outcome was cross checked in obstetrical records to overcome recall bias. Gestational diabetes was defined as a glucose intolerance resulting in hyperglycaemia with onset during pregnancy[19]. Preeclampsia was defined as systolic blood pressure above 140 mmHg and/or diastolic pressure above 90 mmHg combined with proteinuria[20],

pregnancy induced hypertension as systolic blood pressure above 140 mmHg and/or diastolic pressure above 90 mmHg or higher measured on two occasions(after 20 weeks' gestation)[21], preterm birth as a delivery between 24 and 37 weeks gestation, intra-uterine growth restriction as birth weight below the 10th percentile for gestational age and sex according to the Netherlands Perinatal Registry birth weight percentiles[22]. Assessment of classic cardiovascular risk factors was performed by trained research nurses or doctors at the Leiden University Medical Centre or at the participants' home. Blood pressure was measured manually with a validated sphygmomanometer in sitting position at the left upper arm with the appropriate cuff size, the mean of two measurements was taken. Length and weight was measured wearing light clothes and without shoes; length was measured to the nearest 1 cm and weight to the nearest 1 kg. Body mass index(BMI) was calculated as weight/ length^2, Venous blood samples were collected after an overnight fast and assayed for classical risk factors of CVD (glucose, insulin, HbA1c, total cholesterol, HDL cholesterol, triglycerides), Insulin resistance was assessed by the homeostasis model assessment (HOMA)[23]. The blood samples were centrifuged, separated and frozen at -80°C within 2 hours. Routine chemistry analyses were performed on a Roche Modular P800 chemistry analyser using reagents of Roche Diagnostics (Mannheim, Germany). Analytical variation of all analytes was well below 5%. Insulin was analysed on an Immulite 2000 Xpi immunoanalyser of Siemens Healthcare Diagnostics (Tarry town, NY, USA). Analytical variation varied between 5% and 8%. HbA1c was analysed using a Boronate affinity chromatographic system (Primus Ultra^2, Trinity Biotech, Bray Ireland). Analytical variation was well below 2%. All analyses were performed by technicians blinded for obstetrical history. Family history of premature myocardial infarction (MI) and/or stroke was defined as having at least one parent with MI and/or stroke before the age of 60.

10- and 30-Year CVD risk by the Framingham score[24, 25] was calculated using information on age, systolic blood pressure, antihypertensive treatment, smoking, diabetes and lipid spectrum (total cholesterol and HDL cholesterol) or BMI (a simpler model of the risk score). Both models, using lipids and using BMI, were applied. CVD was defined as coronary death, MI, coronary insufficiency, angina pectoris, ischemic stroke, haemorrhagic stroke, transient ischemic attack, peripheral artery disease and heart failure. The 10-Year CVD risk score was calculated twice; using current age and subsequently estimating the risk as if the woman was 60 years of age (due to the young age of our participants, the estimated absolute 10-year CVD risk was likely to be low). This approach has been recommended in the cardiovascular risk factor management guidelines for young women with elevated risk factor levels [26]. During our study period a new guideline was published[27], which revised the approach to CVD in the young in using 'cardiovascular risk age'. This method was not applicable to our young cohort (age < 40 years) and we decided to follow the afore-mentioned approach. The risk estimation was repeated in a subgroup analysis including women with idiopathic recurrent miscarriage. Recurrent miscarriage was defined as idiopathic when the work-up for causes of recurrent miscarriage showed no abnormalities.

Sample size considerations

The calculation was based on results of the Hyras study: the (extrapolated) 10-year CVD risk was 4,4% (SD 1.9) in women with uncomplicated pregnancies[28]. We planned to include women in 1:1 ratio, i.e. a woman who had recurrent miscarriage matched to 1 control subject. A relative risk of 1,5 or higher was considered to be clinically relevant. A sample size of 68 women (34 exposed, 34 non-exposed) was sufficient, with a 10% drop-out rate (two sided alpha .05. power 90%).

Statistics

Data were analysed using SPSS software version 22.0 (Statistical Package for Social Science; SPSS, Chicago, Illinois, USA). Comparisons of normal distributed data were performed using paired T- test. Comparisons of continuous data were performed using the McNemar's test. For all tests, a p-value < 0.05 is indicated statistical significant.

Ethics

Approval from the medical ethics committee of Leiden University Medical Centre (P04-020; October 3, 2012) was obtained and all participants gave informed consent. The study was registered with the Dutch trial registry NTR3408. This study is part of the REMI (REcurrent MIscarriages) studies, studies which investigate consequences and causes of recurrent miscarriages.

Results

A flowchart of the inclusion of the participants is shown in Figure 1. Of the 76 included women, 4 women were excluded from analysis, because they did not meet the inclusion criteria for this study as described in Figure 1. Leaving 36 matched pairs.

Women with recurrent miscarriage had a significantly higher gravidity and lower parity than those in the no miscarriage group (Table 1). Women with recurrent miscarriage were more often smokers during pregnancy (p=0.05). On all other variables groups were comparable.

78% of the women with recurrent miscarriage (n=28) were diagnosed with idiopathic recurrent miscarriage. Parental chromosomal abnormality was found in one case, antiphospholipid syndrome in one case, hyperhomocysteinemia in three cases and heritable thrombophilia was found in three cases.

Mean follow-up time was 6.8 years (SD 3.0) in women with recurrent miscarriage and 8.1 years in women with no miscarriage (SD 2.9), (p<0.001). Classical cardiovascular risk factors are described in Table 2. Women with recurrent miscarriage were slightly younger at time of follow-up than women with no miscarriage (p<0.001). Values of classical cardiovascular risk factors were higher in women with recurrent miscarriage compared to no miscarriage, although only significant for systolic blood pressure.

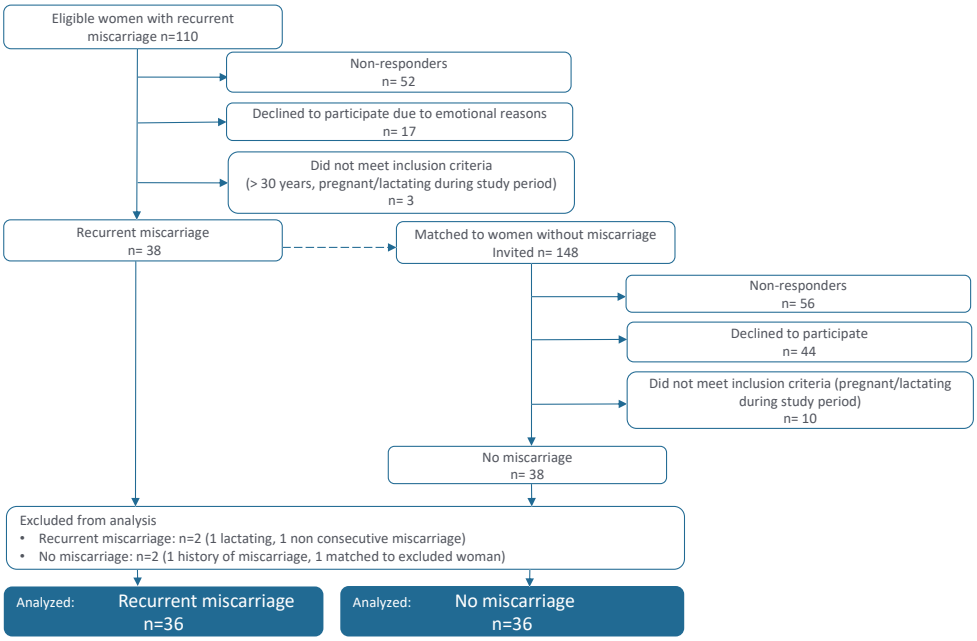

Figure 1. Flow chart Selection of participants

Table 1. Characteristics of participants

	No miscarriage n=36	Recurrent miscarriage n=36	p-value
Maternal age at index pregnancy[a]	26.36 (2.65)	26.47 (2.69)	0.70
Caucasian (%)	32 (88.9)	30 (83.3)	0.63
University level education (%)	16 (44.4)	8 (22.2)	0.08
Gravidity	2.28 (0.62)	7.11 (2.07)	<0.001
Parity	2.25 (0.60)	1.64 (0.83)	0.001
Primary miscarriages (%)	--	27 (75.0)	--
At least one continuing pregnancy[b] (%)	36 (100)	35 (97.2)	0.31
Smoking during pregnancy[c] (%)	5 (13.9)	14 (38.9)	0.05
Gestational diabetes[c] (%)	0 (0)	0 (0)	--
Preeclampsia/Gestational hypertension[b,c] (%)	0 (0)	3 (8.3)	0.08
Preterm birth[c] (%)	1 (2.8)	4 (11.1)	0.38
Intra uterine growth restriction[c] (%)	4 (11.1)	4 (11.1)	1.00

Data are presented as mean (SD)
[a]Age at first pregnancy for unexposed women, age at third consecutive miscarriage for exposed women
[b]Chi-squared test. Mc Nemars test not possible (at least one variable in each 2-way table is a constant)
[c]In at least one continuing pregnancy

Table 2. Classical cardiovascular risk factors

	No miscarriage n=36	Recurrent miscarriage n=36	p-value
Maternal age at follow-up	34.50 (3.59)	33.28 (3.51)	<0.001
Smoking at follow-up (%)	5 (13.9)	10 (27.8)	0.23
BMI at follow-up	23.78 (3.49)	25.89 (7.08)	0.09
Systolic blood pressure mmHg	101.11 (10.72)	111.11 (13.06)	<0.001
Diastolic blood pressure mmHg	67.22 (7.62)	70.64 (9.54)	0.08
Antihypertensive medication use[a] (%)	0 (0)	3 (8.33)	0.08
HOMA score	2.28 (1.95)	3.40 (6.20)	0.31
HbA1c mmol/mol Hb	29.89 (2.45)	32.25 (8.36)	0.13
Total cholesterol mmol/L	4.89 (0.76)	4.76 (0.68)	0.46
HDL cholesterol mmol/L	1.71 (0.39)	1.59 (0.49)	0.25
Triglycerides mmol/L	0.98 (0.29)	1.12 (0.61)	0.24
Family history of premature MI and/or stroke (%) ***Missing=1***	9 (25.7)	8 (22.9)	1.00

Data are presented as mean (SD)
[a]Chi-squared test. Mc Nemars test not possible (at least one variable in each 2-way table is a constant)
BMI body mass index, HOMA homeostasis model assessment, HbA1C haemoglobin A1c, HDL high-density lipoproteins, MI myocardial infarction

Women with recurrent miscarriage had significantly higher mean CVD risk scores compared to women with no miscarriage (Table 3), independent of using the lipids or the BMI model. In the subgroup analysis including women with idiopathic recurrent miscarriage comparable results to the total group were found (Table 3).

Discussion

Main findings

In this follow-up study an increased (extrapolated) 10 and 30-year CVD risk was found in women with a history of recurrent miscarriage compared to women with no miscarriages, calculated by Framingham risk scores (lipids and BMI model). Women with recurrent miscarriage had an increased systolic blood pressure compared to women with no miscarriage at time of follow-up.

Interpretation

The Framingham risk score is the most externally validated risk score and is widely used in North American countries[15]. It is the only model which can estimate the 10 and 30-year CVD risk (mortality and morbidity) and is therefore useful to estimate risks for a young population. European guidelines advise the use of SCORE, which assesses only mortality risk and therefore is less useful in our young population[29]. Overestimation of the risk of CVD is possible using the Framingham score in a European cohort[15]. If so,

Table 3 Cardiovascular disease risk estimation

		No miscarriage n=36	Recurrent miscarriage n=36	Mean difference (95% CI)	p-value	No miscarriage n=28	Idiopathic recurrent miscarriage n=28	Mean difference (95% CI)	p-value
10 year Framingham risk score (%)	lipids	1.06 (0.68)	2.05 (2.45)	0.99 (0.13-1.85)	0.03	1.06 (0.73)	2.28 (2.72)	1.21 (0.11-2.31)	0.03
	BMI	1.12 (0.65)	2.03 (2.42)	0.91 (0.10-1.71)	0.03	1.12 (0.68)	2.16 (2.66)	1.04 (0.01-2.07)	0.05
10 year Framingham risk score (%) (extrapolated to 60 years)	lipids	3.56 (1.82)	6.24 (5.44)	2.68 (0.78-4.58)	0.007	3.59 (1.99)	6.73 (6.00)	3.14 (0.72-5.57)	0.01
	BMI	4.67 (2.13)	8.57 (7.85)	3.90 (1.22-6.58)	0.006	4.74 (2.31)	9.07 (8.65)	4.33 (0.91-7.75)	0.02
30 year Framingham risk score (%)	lipids	6.39 (4.20)	9.86 (9.10)	3.47 (0.25-6.70)	0.04	6.54 (4.52)	10.68 (10.00)	4.14 (0.02-8.27)	0.05
	BMI	7.31 (4.08)	11.9 (12.1)	4.56 (0.53-8.56)	0.03	7.46 (4.41)	12.43 (13.27)	4.96 (-0.16-10.1)	0.06

Data are presented as mean (SD)

an overestimation of the risk occurred in both groups and therefore is not changing the direction of effect. Due to the young age of our participants we calculated the 10-year risk scores as if the women were 60 years of age according guidelines for young women with elevated risk factor levels[26]. The new method of 'cardiovascular risk age'[27] was not applicable to our young cohort (age < 40 years). A disadvantage of this method, extrapolating to an age of 60 years, is that the real risk could be underestimated assuming that levels of cardiovascular risk factors will increase without prevention or intervention. Perhaps this is the reason why we found a quite large difference between the 10-Year CVD risk after extrapolating the age to 60 years and the 30-Year CVD scores, in women with recurrent miscarriage mean risk 6.24% and 9.86%, respectively.

Only few studies have been performed regarding cardiovascular risk factors in women with recurrent miscarriage. Our findings are inconsistent with the results of the study from Mahendru et al[30], which found no difference in cardiovascular function and risk factors between women with unexplained recurrent miscarriage (n=26) and women with uncomplicated pregnancy before a subsequent pregnancy. Explanations for this may be a lack of power, short follow-up time (median 8 months in study from Mahendru et al) or the difference in selection of the women with recurrent miscarriage; we used an age criterion; recurrent miscarriage ≤ 30 years versus unexplained recurrent miscarriage irrespective of age in the other study. Our findings are in line with the report by Germain et al[12] who found that women with recurrent pregnancy loss (n= 29), defined as ≥ 2 consecutive miscarriages, have an altered cardiovascular risk profile compared to women with uncomplicated pregnancy (significant for total cholesterol). Their methods differed from ours as they excluded all women with: overweight, chronic hypertension, diabetes, renal and CVD at index pregnancy, smokers and women with thrombophilia except for antiphospholipid syndrome (APS), introducing a high level of selection bias. The explanation for this is that they investigated the hypothesis that endothelial dysfunction could be the link between miscarriage and CVD (and these factors alter markers of endothelial function). We performed a subgroup analysis including only women with idiopathic recurrent miscarriage (n=28) (Table 3), which showed comparable results to the results of the total group. Therefore, in this study the increased risk of CVD in women with recurrent miscarriage cannot be explained by the presence of known acquired and heritable thrombophilia.

In Table 2 we described the individual classical risk factors. Only systolic blood pressure was significantly higher in women recurrent miscarriage compared to no miscarriage. Since we did not perform a sample size analysis based on individual risk factors, a lack of power is likely when investigating the individual risk factors. It would be interesting to investigate these risk factors in a larger study group to answer the question which risk factor is contributing the most to the elevated CVD risk in women with recurrent miscarriage. As we were only able to look at cardiovascular risk factors in women after they experienced recurrent miscarriage we are not answering the question about cause

and effect. Although pre-existing CVD risk factors are associated with an increased risk of developing miscarriages, it is not known whether miscarriages merely unmask risk or contributes directly to future CVD. Miscarriages could trigger a pathophysiological mechanism or cascade that in turn leads to CVD, potentially via interactions with classical risk factors.

Strengths/limitations

To our knowledge this is the first study which investigated and calculated CVD risk scores in women with a history of recurrent miscarriage. A strength of our research is the unique, well defined cohort. Recurrent miscarriage is a highly heterogenic condition, to strive to more homogeneity, in present study we included only women who had their third consecutive miscarriage below the age of 31. A younger age at diagnosis makes a maternal cause of recurrent miscarriage more plausible and reduces the change of miscarriages due to foetal abnormalities[31]. Another strength is the availability of a wide range of covariates in both groups (Table 1). We decided not to adjust for any covariates in our CVD risk estimation as both groups were comparable at baseline, except for gravidity and parity what is a direct consequence of the exposure (recurrent miscarriage). Besides, some covariates have an effect at our outcome of interest. For example, it wouldn't make sense to adjust for BMI or smoking as both are included as variables in the risk estimation[32]. Some women experienced a complication during pregnancy, such as gestational diabetes and preeclampsia which may increase their risk of CVD later in life[2, 33]. We did not adjust for history of complications of pregnancy since these events are possibly on the causal pathway between miscarriage and CVD[34]. If we assume that they are not on this pathway and that these events are confounding factors we should have adjusted for these pregnancy complications. Therefore, we repeated the risk calculations for women who did not have a pregnancy complicated by gestational diabetes, preeclampsia, pregnancy induced hypertension and/or preterm birth (online supplementary data). Women with recurrent miscarriage (N=30) had still a significantly higher extrapolated 10-year cardiovascular risk score (using lipids: mean 5.31%, SD 3.96) compared to women with no miscarriage (mean 3.59%, SD 1.94, p=0.03). Comparable results were found in women with idiopathic recurrent miscarriage (N=24) (online supplementary data). Therefore, we can conclude that the elevated risk scores in women with recurrent miscarriage cannot be explained solely by other pregnancy complications known to be a risk factor in women for developing CVD.

Limitations of our study should be acknowledged. The risk for CVD in women with recurrent miscarriage could be underestimated due to the following reasons: At first selection bias may have been introduced. Women declined to participate due to emotional reasons or did not respond on the invitation for this follow-up study. It is imaginable that the 'worst' cases, women without a live birth, were more likely to decline or not respond (only one woman in our study group had no live birth). Secondly, women received lifestyle advice

during their consultations at the recurrent miscarriage clinic. Individual risk factors may have been changed which could decrease the risk profile. And finally, bias could have been introduced since women with recurrent miscarriage were included in the study before the matched controls were invited to participate resulting in a small difference in age (1.2 years) at follow-up. In case this small difference will influence the results, the increased risk in women with recurrent miscarriage would be an underestimate because risk factors are likely to increase with age. On the other hand, since the unexposed group consisted of women who had at least one uncomplicated pregnancy, this may have resulted in a healthier cohort compared to a population based cohort. Selection bias is also possible in the unexposed group; probably women with a higher education are more likely to participate (although no significant difference was found for university level education between both groups). Another limitation is the relatively small sample size. A preliminary calculation was performed based on the 10-year risk score with age extrapolated to 60 years, which showed that 34 women in both groups would be sufficient. Though it is possible that, especially for the subgroup analyses, our study may partly be underpowered and we should be cautious drawing conclusions.

Perspectives

In present study, we show that women with a history of recurrent miscarriage, irrespective whether idiopathic or not, differ in cardiovascular risk profile at a young age compared to women with no miscarriage. Our study provides intriguing data which support the need for more research to find out if women with a history of recurrent miscarriage should be offered screening and counselling for cardiovascular risk factors.

Reference List

1. Global status report on noncommunicable disaeses 2010. 2013.
2. Mosca, L., et al., Effectiveness-based guidelines for the prevention of cardiovascular disease in women--2011 update: a guideline from the American Heart Association. J.Am.Coll.Cardiol., 2011. 57(12): p. 1404-1423.
3. Rich-Edwards, J.W., et al., Breathing life into the lifecourse approach: pregnancy history and cardiovascular disease in women. Hypertension, 2010. 56(3): p. 331-334.
4. Stirrat, G.M., Recurrent miscarriage. Lancet, 1990. 336(8716): p. 673-675.
5. Jivraj, S., et al., Obstetric and neonatal outcome in women with a history of recurrent miscarriage: a cohort study. Hum.Reprod., 2001. 16(1): p. 102-106.
6. Branch, D.W., M. Gibson, and R.M. Silver, Clinical practice. Recurrent miscarriage. N Engl J Med, 2010. 363(18): p. 1740-7.
7. Ranthe, M.F., et al., Pregnancy loss and later risk of atherosclerotic disease. Circulation, 2013. 127(17): p. 1775-1782.
8. Oliver-Williams, C.T., et al., Miscarriage and future maternal cardiovascular disease: a systematic review and meta-analysis. Heart, 2013. 99(22): p. 1636-1644.
9. Wagner, M.M., et al., Association between miscarriage and cardiovascular disease in a Scottish cohort. Heart, 2015. 101(24): p. 1954-1960.
10. Kessous, R., et al., Recurrent pregnancy loss: a risk factor for long-term maternal atherosclerotic morbidity? Am J Obstet Gynecol, 2014. 211(4): p. 414.e1-11.
11. Appelman, Y., et al., Sex differences in cardiovascular risk factors and disease prevention. Atherosclerosis, 2015.
12. Germain, A.M., et al., Endothelial dysfunction: a link among preeclampsia, recurrent pregnancy loss, and future cardiovascular events? Hypertension, 2007. 49(1): p. 90-95.
13. Smith, G.C., et al., Recurrent miscarriage is associated with a family history of ischaemic heart disease: a retrospective cohort study. BJOG., 2011. 118(5): p. 557-563.
14. Siontis, G.C., et al., Comparisons of established risk prediction models for cardiovascular disease: systematic review. BMJ, 2012. 344: p. e3318.
15. Matheny, M., et al., Systematic Review of Cardiovascular Disease Risk Assessment Tools [Internet]. 2011.
16. Nederlandse Vereniging Obstetrie & Gynecologie. Richtlijn Herhaalde Miskraam ('Guideline Recurrent Miscarriage'). 2007.
17. Visser, J., et al., Thromboprophylaxis for recurrent miscarriage in women with or without thrombophilia. HABENOX: a randomised multicentre trial. Thromb.Haemost., 2011. 105(2): p. 295-301.
18. Miyakis, S., et al., International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J.Thromb.Haemost., 2006. 4(2): p. 295-306.
19. Baz, B., J.P. Riveline, and J.F. Gautier, ENDOCRINOLOGY OF PREGNANCY: Gestational diabetes mellitus: definition, aetiological and clinical aspects. Eur.J.Endocrinol., 2015. 174(2): p. R43-R51.
20. Tranquilli, A.L., Introduction to ISSHP new classification of preeclampsia. Pregnancy. Hypertens., 2013. 3(2): p. 58-59.
21. Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. Am.J.Obstet.Gynecol., 2000. 183(1): p. S1-S22.
22. Kloosterman, G.J., [Intrauterine growth and intrauterine growth curves]. Maandschr. Kindergeneeskd., 1969. 37(7): p. 209-225.
23. Matthews, D.R., et al., Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia, 1985. 28(7): p. 412-419.

24. D'Agostino, R.B., Sr., et al., General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation, 2008. 117(6): p. 743-753.
25. Pencina, M.J., et al., Predicting the 30-year risk of cardiovascular disease: the framingham heart study. Circulation, 2009. 119(24): p. 3078-3084.
26. De, B.G., et al., European guidelines on cardiovascular disease prevention in clinical practice. Third Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice. Eur.Heart J., 2003. 24(17): p. 1601-1610.
27. Perk, J., et al., European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). Eur.Heart J., 2012. 33(13): p. 1635-1701.
28. Hermes, W., et al., Cardiovascular risk factors in women who had hypertensive disorders late in pregnancy: a cohort study. Am.J.Obstet.Gynecol., 2013. 208(6): p. 474-478.
29. Conroy, R.M., et al., Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur.Heart J., 2003. 24(11): p. 987-1003.
30. Mahendru, A.A., et al., Cardiovascular function in women with recurrent miscarriage, pre-eclampsia and/or intrauterine growth restriction. J.Matern.Fetal Neonatal Med., 2013. 26(4): p. 351-356.
31. Franssen, M.T., et al., Selective chromosome analysis in couples with two or more miscarriages: case-control study. BMJ, 2005. 331(7509): p. 137-141.
32. Fall, T., et al., Age- and Sex-Specific Causal Effects of Adiposity on Cardiovascular Risk Factors. Diabetes, 2015.
33. Smith, G.C., J.P. Pell, and D. Walsh, Pregnancy complications and maternal risk of ischaemic heart disease: a retrospective cohort study of 129,290 births. Lancet, 2001. 357(9273): p. 2002-2006.
34. Sheiner, E., et al., Pregnancy outcome following recurrent spontaneous abortions. Eur.J. Obstet.Gynecol.Reprod.Biol., 2005. 118(1): p. 61-65.

Table 4 Cardiovascular disease risk estimation, in women with recurrent miscarriage without other pregnancy complications

		No miscarriage n=30	Recurrent miscarriage n=30	Mean difference (95% CI)	p-value	No miscarriage n=24	Idiopathic recurrent miscarriage n=24	Mean difference (95% CI)	p-value
10 year Framingham risk score (%)	lipids	1.06 (0.71)	1.44 (1.25)	0.39 (-0.12-0.90)	0.13	1.10 (0.78)	1.58 (1.35)	0.48 (-0.16-1.11)	0.13
	BMI	1.09 (0.66)	1.65 (1.73)	0.57 (-0.10-1.23)	0.09	1.12 (0.71)	1.82 (1.90)	0.70 (-0.13-1.52)	0.10
10 year Framingham risk score (%) (extrapolated to 60 years)	lipids	3.59 (1.94)	5.31 (3.96)	1.72 (0.14-3.29)	0.03	3.70 (2.12)	5.75 (4.28)	2.04 (0.09-3.99)	0.04
	BMI	4.59 (2.23)	7.38 (6.31)	2.79 (0.37-5.21)	0.03	4.77 (2.42)	8.03 (6.91)	3.25 (0.24-6.27)	0.04
30 year Framingham risk score (%)	lipids	6.50 (4.45)	8.33 (6.59)	1.83 (-0.90-4.57)	0.18	6.79 (4.80)	9.04 (7.12)	2.25 (-1.15-5.65)	0.18
	BMI	7.27 (4.27)	10.13 (9.44)	2.87 (-0.71-6.44)	0.11	7.50 (4.63)	10.92 (10.41)	3.42 (-1.05-7.88)	0.13

Data are presented as mean (SD)