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

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Abstract

Introduction: 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.

Material and methods: Women who visited the recurrent miscarriage clinic at Leiden University Medical Center between 2000 and 2010 and who had their third consecutive miscarriage before the age of 31 years, were invited to participate in this follow-up study (between 2012 and 2014). The reference group consisted of women with at least one uncomplicated pregnancy and no miscarriage, matched by 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 subanalysis was performed for women with idiopathic recurrent miscarriage.

Results: Thirty-six 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 with women with no miscarriage (mean 3.56%, SD 1.82, P = .007) and a significantly higher 30-year cardiovascular risk score (mean 9.86%, SD 9.10) compared with women with no miscarriage (mean 6.39%, SD 4.20, P = .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 a young age compared with 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.

KEYWORDS
cardiovascular disease, Framingham, pregnancy, prevention, recurrent miscarriage

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1 | 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 with men.[2] Pregnancy can be considered 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 that guideline.

Recurrent miscarriage (RM) is commonly defined as 3 or more consecutive pregnancy losses before 22 weeks of gestation [4] and affects 0.5%-3% of all fertile couples.[5] Observational studies suggest that women with a history of RM also have an increased risk of CVD.[6–9] Several hypotheses are possible for the association between both diseases; shared common risk factors such as obesity and smoking,[10] endothelial dysfunction,[11] and a genetic predisposition is assumed.[12]

We hypothesize that women with a history of RM have a more unfavorable cardiovascular risk profile already at a young age compared with women with no miscarriage. If so, women with RM represent an ideal target population for preventive strategies. Worldwide multivariable risk assessment tools have been developed to detect apparently healthy individuals at high risk for CVD.[13] At present the most common externally validated risk model is the Framingham risk score.[14]

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

2 | MATERIAL AND METHODS

2.1 | Study design

Follow-up study.

2.2 | Exposed

Women who visited the RM clinic at Leiden University Medical Center 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. RM was defined as ≥3 consecutive miscarriages before 22 weeks of gestation. All women had a routine RM work-up to identify possible causes of the RM: a standardized history of the couple was performed, karyotyping of the couple (this was offered routinely before 2005 to all couples and after 2005 only in the presence of low maternal age and/or positive family history for RM),[15] presence of uterine anomalies by ultrasound or hysteroscopy, and presence of acquired and heritable thrombophilia were assessed. For 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;[16] after revision of the

Key Message

An increased cardiovascular disease risk was found in women with a history of recurrent miscarriage compared with women with no miscarriages. Our results support an opportunity to identify women at increased risk of future cardiovascular disease early in life.

classification criteria, the presence of anti-β2 glycoprotein-I was added to the work-up.[17] 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 births before miscarriage) were included. The time interval between the RM diagnosis and the time of follow up had to be at least 2 years.

2.3 | 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 take care of low-risk women (with no medical or obstetrical history) during pregnancy and childbirth. The zip code of each woman with RM was used to contact the nearest midwifery practice to take the impact of socioeconomic status into account. Women with the same zip code and the same age (difference in birth date a maximum of 1 year) and for whom 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 RM were included in the study before the matched controls were invited to participate; a small difference in follow-up time was therefore expected. In both groups, pregnant and lactating women (within the last 3 months) were excluded. Enrollment took place between 2012 and 2014.

2.4 | Procedures and definitions

After enrollment, all women were asked to fill out a web-based questionnaire and were invited for risk factor screening. The questionnaire covered 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 hyperglycemia with onset during pregnancy.[18] Preeclampsia was defined as systolic blood pressure above 140 mm Hg and/or diastolic pressure above 90 mm Hg combined with proteinuria;[19]

pregnancy-induced hypertension as systolic blood pressure above 140 mm Hg and/or diastolic pressure above 90 mm Hg or higher measured on 2 occasions (after 20 weeks of gestation);[20] and preterm birth as a delivery before 37 weeks of gestation, intrauterine growth restriction as birthweight below the 10th percentile for gestational age and sex according to the Netherlands Perinatal Registry birthweight percentiles.[21] Assessment of classic cardiovascular risk factors was performed by trained research nurses or doctors at the Leiden University Medical Center or at the participants' home. Blood pressure was measured manually in sitting position with a validated sphygmomanometer on the left upper arm with the appropriate cuff size; the mean of 2 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, hemoglobin A1c [HbA1c], total cholesterol, high-density lipoprotein [HDL] cholesterol, triglycerides). Insulin resistance was assessed by the homeostasis model assessment.[22] 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 analyzer using reagents of Roche Diagnostics (Mannheim, Germany). Analytical variation of all analytes was well below 5%. Insulin was analyzed on an Immulite 2000 Xpi immunoanalyzer (Siemens Healthcare Diagnostics; Tarrytown, NY, USA). Analytical variation varied between 5% and 8%. HbA1c was analyzed 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 and/or stroke was defined as having at least one parent with myocardial infarction and/or stroke before the age of 60 years.

The 10- and 30-year CVD risk by the Framingham score[23,24] 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, myocardial infarction, coronary insufficiency, angina pectoris, ischemic stroke, hemorrhagic stroke, transient ischemic attack, peripheral artery disease, or heart failure. The 10-year CVD risk score was calculated twice, once 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.[25] The risk estimation was repeated in a subgroup analysis including women with idiopathic RM. RM was defined as idiopathic when the work-up for causes of RM showed no abnormalities.

2.5 | 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.[26] We planned to include women in 1:1 ratio, that is, a woman who had RM matched to one control. 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%).

2.6 | Statistical analyses

Data were analyzed using SPSS software version 22.0 (SPSS, Chicago, IL, USA). Comparisons of normal distributed data were performed using paired t test. Comparisons of continuous data were performed using McNemar's test. For all tests, a P-value < .05 is considered statistically significant.

2.7 | Ethical approval

Approval from the medical ethics committee of Leiden University Medical Center (P04-020; 3 October 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 RM.

3 | RESULTS

A flowchart of the inclusion of the participants is shown in Figure 1. Thirty-six matched pairs were included.

Women with RM had a significantly higher gravidity and lower parity than those in the no miscarriage group (Table 1). Women with RM were more often smokers during pregnancy (P = .05). On all other variables, groups were comparable.

Of the women with RM (n = 28), 78% were diagnosed with idiopathic RM. Parental chromosomal abnormality was found in 1 case, antiphospholipid syndrome in 1 case, hyperhomocysteinemia in 3 cases, and heritable thrombophilia in 3 cases.

Mean follow-up time was 6.8 years (SD 3.0) in women with RM and 8.1 years in women with no miscarriage (SD 2.9), (P < .001). Classical cardiovascular risk factors are described in Table 2. Women with RM were slightly younger at time of follow-up than women with no miscarriage (P < .001). Values of classical cardiovascular risk factors were higher in women with RM compared with women no miscarriage, although the values were only significant for systolic blood pressure.

Women with RM had significantly higher mean CVD risk scores compared with women with no miscarriage (Table 3), whether using the lipids or the BMI model. In the subgroup analysis including women with idiopathic RM, comparable results to those of the total group were found (Table 3).
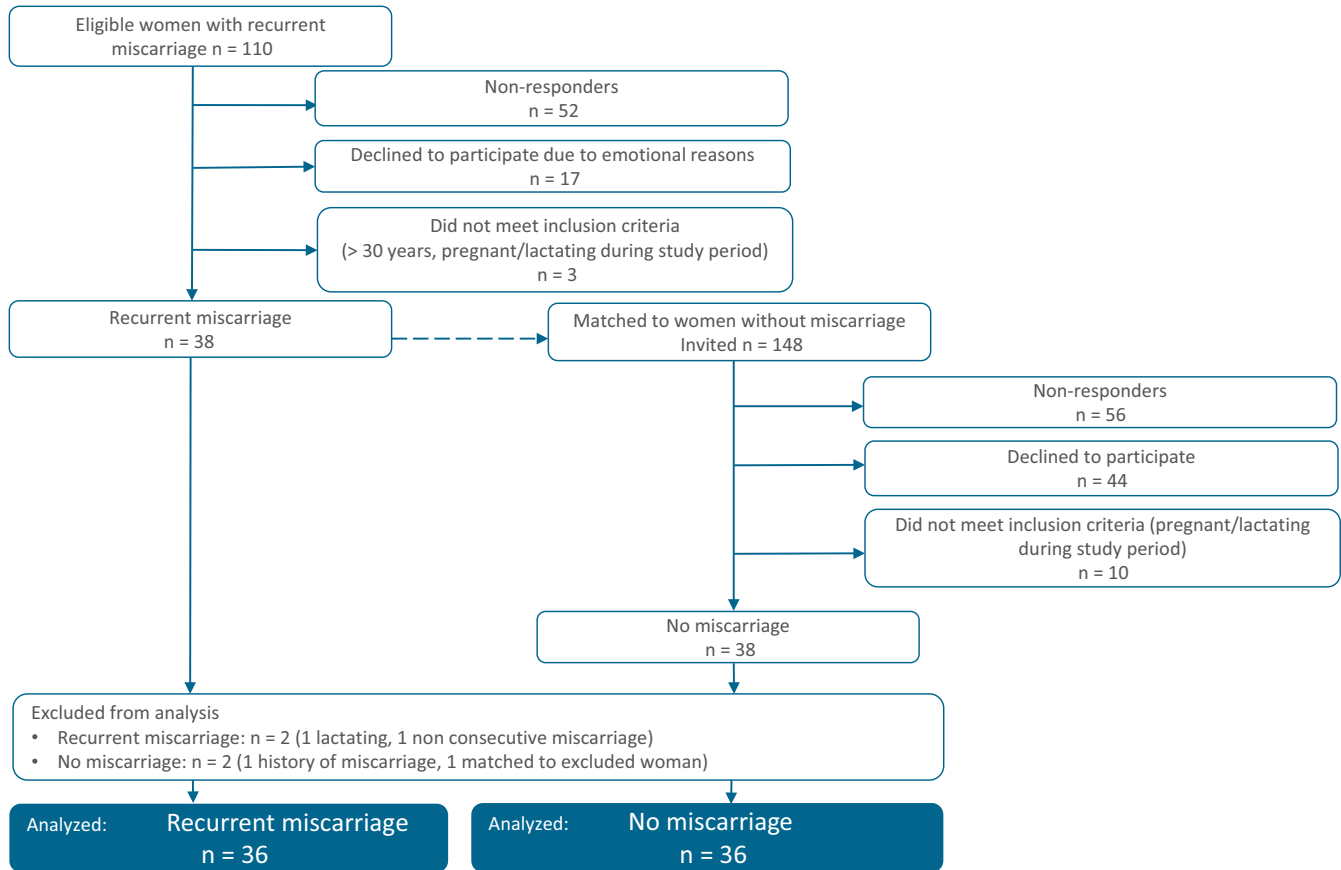
FIGURE 1 Flow chart: selection of participants. [Color figure can be viewed at wileyonlinelibrary.com]

4 | DISCUSSION

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

The Framingham risk score is the most externally validated risk score and is widely used in North American countries.[14] 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 using SCORE, which assesses only mortality risk and therefore is less useful in our young population.[27] Overestimation of the risk of CVD is possible using the Framingham score in a European cohort.[14] If so, an overestimation of the risk occurred in both groups and therefore would not change 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 to guidelines for young women with elevated risk factor levels.[25] The new method of "cardiovascular risk age"[28] was not applicable to our young cohort (age below 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 why we found quite a large difference between the extrapolated 10-year CVD risk and the 30-year CVD scores in women with an RM mean risk of 6.24% and 9.86%, respectively.

Few studies have been performed regarding cardiovascular risk factors in women with RM. A summary is given in Table 4. Our findings are inconsistent with the results of the study from Mahendru et al.,[29] which found no difference in cardiovascular function and risk factors between women with unexplained RM and women with uncomplicated pregnancy. Explanations for this may be a lack of power, short follow-up time or a difference in the selection of the women with RM. Our findings are in line with the report by Germain et al. [11], who found an altered cardiovascular risk profile in women with unexplained RM compared with women with uncomplicated pregnancy. Their methods differed from ours, as they excluded all women with preexisting markers of endothelial dysfunction, introducing a high level of selection bias. The explanation for this is that they were investigating the hypothesis that endothelial dysfunction could be the link between miscarriage and CVD. We performed a subgroup analysis including only women with idiopathic RM (n = 28) (Table 3), which showed comparable results to the results of the total group. Therefore, in the present study, the increased risk of CVD in women with RM 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 with RM

	No miscarriage, n = 36	Recurrent miscarriage, n = 36	P-value
Maternal age at index pregnancy[a]	26.36 (2.65)	26.47 (2.69)	.70
Caucasian, %	32 (88.9)	30 (83.3)	.63
University level education, %	16 (44.4)	8 (22.2)	.08
Gravidity	2.28 (0.62)	7.11 (2.07)	<.001
Parity	2.25 (0.60)	1.64 (0.83)	.001
Primary miscarriages, %	–	27 (75.0)	–
At least one continuing pregnancy,[b] %	36 (100)	35 (97.2)	.31
Smoking during pregnancy,[c] %	5 (13.9)	14 (38.9)	.05
Gestational diabetes,[c] %	0 (0)	0 (0)	–
Preeclampsia/gestational hypertension,[b,c] %	0 (0)	3 (8.3)	.08
Preterm birth,[c] %	1 (2.8)	4 (11.1)	.38
Intrauterine growth restriction,[c] %	4 (11.1)	4 (11.1)	1.00

TABLE 1 Characteristics of participants

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

	No miscarriage, n = 36	Recurrent miscarriage, n = 36	P-value
Maternal age at follow up	34.50 (3.59)	33.28 (3.51)	<.001
Smoking at follow up, %	5 (13.9)	10 (27.8)	.23
BMI at follow up	23.78 (3.49)	25.89 (7.08)	.09
Systolic blood pressure, mm Hg	101.11 (10.72)	111.11 (13.06)	<.001
Diastolic blood pressure, mm Hg	67.22 (7.62)	70.64 (9.54)	.08
Antihypertensive medication use,[a] %	0 (0)	3 (8.33)	.08
HOMA score	2.28 (1.95)	3.40 (6.20)	.31
HbA1c, mmol/mol Hb	29.89 (2.45)	32.25 (8.36)	.13
Total cholesterol, mmol/L	4.89 (0.76)	4.76 (0.68)	.46
HDL cholesterol, mmol/L	1.71 (0.39)	1.59 (0.49)	.25
Triglycerides, mmol/L	0.98 (0.29)	1.12 (0.61)	.24
Family history of premature MI and/or stroke, %	9 (25.7) missing = 1[b]	8 (22.9)	1.00

TABLE 2 Classical cardiovascular risk factors

Data are presented as mean (SD).
BMI, body mass index; HbA1C, hemoglobin A1c; HOMA, homeostasis model assessment; HDL, high-density lipoproteins; MI, myocardial infarction.
[a]Chi-square test. McNemar's test not possible (at least 1 variable in each two-way table is a constant).
[b]Due to the matched analysis, the associated women with RM were excluded, leaving n = 35 in both groups.

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)	.03	1.06 (0.73)	2.28 (2.72)	1.21 (0.11-2.31)	.03
BMI	1.12 (0.65)	2.03 (2.42)	0.91 (0.10-1.71)	.03	1.12 (0.68)	2.16 (2.66)	1.04 (0.01-2.07)	.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)	.007	3.59 (1.99)	6.73 (6.00)	3.14 (0.72-5.57)	.01
BMI	4.67 (2.13)	8.57 (7.85)	3.90 (1.22-6.58)	.006	4.74 (2.31)	9.07 (8.65)	4.33 (0.91-7.75)	.02
30-year Framingham risk score (%)								
Lipids	6.39 (4.20)	9.86 (9.10)	3.47 (0.25-6.70)	.04	6.54 (4.52)	10.68 (10.00)	4.14 (0.02-8.27)	.05
BMI	7.31 (4.08)	11.9 (12.1)	4.56 (0.53-8.56)	.03	7.46 (4.41)	12.43 (13.27)	4.96 (-0.16-10.1)	.06

Data are presented as mean (SD).

compared with those with 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. As we were only able to look at cardiovascular risk factors in women after they experienced RM, we cannot answer the question about cause and effect. Although preexisting CVD risk factors are associated with an increased risk of developing miscarriages, it is not known whether miscarriages merely unmask risk or contribute 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.

To our knowledge this is the first study which investigated and calculated CVD risk scores in women with a history of RM. A strength of our research is the unique, well-defined cohort. RM is a highly heterogenic condition; to strive for more homogeneity, in the present study we only included women who had their third consecutive miscarriage below the age of 31. A younger age at diagnosis makes a maternal cause of RM more plausible and reduces the chance of miscarriages due to fetal abnormalities.[30] Another strength is the availability of a wide range of covariates in both groups (Table 1). Some covariates have an effect on our outcome of interest. It would not make sense to adjust for BMI or smoking as confounding factors, since both are included as variables in the risk estimation.[31] On the other hand, it is interesting to verify whether the increased cardiovascular risk score in women with RM persists after adjustments for smoking and hypertension, or whether the results are totally dependent on these variates. For this reason, we performed multivariate analyses including smoking and hypertension (Tables S1 and S2); we found that neither solely explains the increased risk.

Some women experienced a complication during pregnancy such as gestational diabetes and preeclampsia which may increase their risk of CVD later in life.[2, 32] We did not adjust for a history of complications of pregnancy since these events may be on the causal pathway between miscarriage and CVD.[33] 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, or preterm birth (Tables S1 and S2). Women with RM (n = 30) still had a significantly higher extrapolated 10-year cardiovascular risk score (using lipids: mean 5.31%, SD 3.96) compared with women with no miscarriage (mean 3.59%, SD 1.94, P = .03). Comparable results were found in women with idiopathic RM (n = 24) (Tables S1 and S2). Therefore, we can conclude that the elevated risk scores in women with RM cannot be explained solely by other pregnancy complications known to be risk factors in women for developing CVD.

Limitations of our study should be acknowledged. The risk for CVD in women with RM could be underestimated due to the following reasons. First, selection bias may have been introduced. Women declined to participate for emotional reasons or did not respond to the invitation to this follow-up study. It is imaginable that

TABLE 4 Summary of studies on cardiovascular risk factors in women with RM

	Wagner et al. (present study)	Mahendru et al. (2013)	Germain et al. (2007)
Inclusion	≥3 consecutive miscarriages <22 weeks, third miscarriage <31 years.	≥3 or more unexplained miscarriages ≤12 weeks. Women planning to conceive.	≥2 consecutive miscarriages, unexplained, except for the antiphospholipid syndrome
Exclusion			Overweight, chronic hypertension, diabetes, renal and CVD, multiple pregnancies in the index pregnancy, smokers
Number	36 28 (subgroup unexplained RM)	26	29
Follow up after RM	6.8 years (mean)	8 months (median)	11 months (mean)
Outcome measurements	Classic cardiovascular risk factors and Framingham risk scores	Brachial and central blood pressures, cardiac output, peripheral vascular resistance, aortic stiffness, blood biochemistry, and platelet aggregation	Brachial arterial reactivity and factors related to endothelial dysfunction, such as circulating cholesterol, uric acid, and nitrites.
Results	Increased Framingham risk scores an increased systolic blood pressure in women with RM	No difference in cardiovascular function and cardiovascular risk	Higher rate of endothelial dysfunction, lower serum nitrite levels, and elevated cholesterol in women with RM.

the "worst" cases, women without a live birth, were more likely to decline or not respond (only 1 woman in our study group had no live birth). Secondly, women received lifestyle advice during their consultations at the RM clinic. Individual risk factors may have been changed, which could decrease the risk profile. Finally, the increased risk could be underestimated because women with RM 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, and risk factors are likely to increase with age. On the other hand, since the unexposed group consisted of women who had at least 1 uncomplicated pregnancy, this may have resulted in a healthier cohort compared with a population-based cohort. Selection bias is also possible in the unexposed group; women with a higher education are probably 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. However, it is possible that, especially for the subgroup analyses, our study may be partly underpowered, and we should be cautious about drawing conclusions.

5 | CONCLUSION

In the present study, we show that women with a history of RM, whether idiopathic or not, differ in cardiovascular risk profile at a

young age compared with women with no miscarriage. Our study provides intriguing data which support the need for more research to find out whether women with a history of RM should be offered screening and counseling for cardiovascular risk factors.

CONFLICT OF INTEREST

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.