

# Adverse pregnancy outcomes and subsequent risk of cardiovascular disease in women with systemic lupus erythematosus

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## ABSTRACT

**Background/objective:** Patients with systemic lupus erythematosus (SLE) are at increased risk for adverse pregnancy outcomes and cardiovascular disease (CVD). The objective of this exploratory study was to investigate the association between a history of adverse pregnancy outcomes and subsequent risk of subclinical CVD assessed by imaging studies and verified clinical CVD events in 129 women with SLE.

**Methods:** The occurrence of adverse pregnancy outcomes, specifically pre-eclampsia, preterm birth and low birth weight was ascertained by questionnaire. Subclinical CVD was assessed by coronary artery calcium (CAC) as measured by electron beam CT and carotid plaque measured by B mode ultrasound. Clinical CVD events were verified by medical record review. Logistic regression was used to estimate the association of pregnancy complications with occurrence of subclinical CVD and clinical CVD with a priori adjustment for age, which is associated with CVD and SLE disease duration as a measure of SLE disease burden.

**Results:** Fifty-six women reported at least one pregnancy complication while 73 had none. Twenty-six women had at least one pregnancy complicated by pre-eclampsia and were more likely to have a CAC score greater than or equal to 10 (adjusted OR=3.7; 95% CI 1.2 to 11.9), but the presence of plaque was not associated with this pregnancy complication, OR=1.1, (95% CI 0.4 to 2.8). Low birth weight and preterm birth were not associated with CAC or plaque.

**Conclusions:** Patients with SLE with a history of pre-eclampsia had a higher rate of subclinical CVD as measured by CAC score. Future studies are needed to confirm the relationship between adverse pregnancy outcomes and subsequent subclinical CVD and clinical CVD events.

Systemic Lupus Erythematosus (SLE) is an autoimmune disease characterised by systemic inflammation affecting predominantly young premenopausal women. Compared

## KEY MESSAGES

- ▶ Women with SLE and prior adverse pregnancy outcomes were more likely to have subsequent hypertension compared to those women with SLE and no prior adverse pregnancy outcomes.
- ▶ Women with SLE and a history of pre-eclampsia had an almost four fold increase in the rate of subclinical cardiovascular disease as measure by coronary artery scores of 10 or greater.
- ▶ Plaque score was not associated with prior adverse pregnancy outcomes in women with SLE.

with the non-lupus population, patients with SLE are at an increased risk for pregnancy related complications, including pre-eclampsia, preterm delivery and low fetal birth weight.<sup>1–3</sup> As disease-related survival has improved over the past two decades, premature cardiovascular disease (CVD) is now recognised as a serious long-term complication contributing significantly to the morbidity and subsequent mortality of patients with lupus. Women with SLE experience CVD events at a higher rate, and at earlier ages compared with the general population.<sup>4–6</sup>

Pre-eclampsia is a pregnancy syndrome marked by de novo elevations in blood pressure and proteinuria. Studies in patients without lupus suggest that cardiovascular morbidity and mortality are increased among those who had previously experienced pre-eclampsia,<sup>7–11</sup> preterm delivery<sup>9 11 12</sup> and delivery of low birthweight infants<sup>11 13 14</sup> when compared with women with uncomplicated pregnancies.<sup>15</sup>

Associations that link pregnancy complications to later life CVD are not well understood and include classic cardiovascular risk factors, inflammation and thrombosis<sup>15</sup> which are all relevant to patients with SLE.<sup>16</sup>

What is not known is whether a relationship exists between pregnancy complications and CVD in women with SLE.

The objective of this study was to evaluate the association between a prior history of pregnancy complications and subsequent risk of CVD assessed by subclinical measured and verified events in women with SLE. Two measures of subclinical CVD associated with cardiovascular morbidity in the general population,<sup>17 18</sup> coronary artery calcium (CAC) measured by ultrafast electron beam CT and carotid plaque using B mode carotid ultrasound have also been noted in women with SLE.<sup>19–21</sup> Women with SLE participating in an ongoing prospective study assessing subclinical CVD and CVD events were queried on their history of pregnancy complications, including pre-eclampsia, preterm delivery and low birth weight.

## METHODS

### Study population

The parent study, Study of Long-term Vascular and Bone Outcomes in Lupus Erythematosus (SOLVABLE), from which data for the current study are derived, is a longitudinal epidemiological study designed to assess the risk for subclinical and clinical CVD in 185 patients with lupus from the Chicago Lupus Database compared with 186 healthy controls.

### Data collection

The SOLVABLE study and this exploratory study were approved by the Institutional Review Board at Northwestern University. All patients gave informed consent prior to their participation in these studies.

Demographic information, pregnancy-related information, traditional CVD risk factors and clinical CVD events were determined through interviews, self-report pregnancy questionnaires, physical examinations and serological tests. Adverse pregnancy outcomes ascertained included the following: (1) history of pre-eclampsia or history of pregnancy induced hypertension and proteinuria not due to lupus flare using clinical definitions,<sup>22</sup> (2) preterm delivery (<37 weeks of gestation) and (3) full term low birth weight (<5.5 lbs).<sup>23</sup> The adverse pregnancy outcomes were mutually exclusive and adjudicated in the following order: pre-eclampsia, then preterm delivery, then low birth weight if full term. All pregnancy data was provided by the patients and was verified if they were available from the medical records (labour and delivery procedure notes as well as clinical notes) at Prentice Women's Hospital, Chicago, Illinois, USA. Traditional CVD risk factors included: (1) hypertension (defined as self-reported history of hypertension, systolic blood pressure  $\geq 140$ , diastolic blood pressure  $\geq 90$  or taking antihypertensive medications), (2) current smoking, (3) family history of myocardial infarction (MI) in a first degree relative before the age of 60 years, (4) diabetes (defined as self-reported history of diabetes or fasting glucose  $\geq 126$  mg/dL), (5) hypercholesterolaemia (defined as

self-reported history of high cholesterol or taking cholesterol-lowering medications). In addition, height, weight, waist and hip measurements were obtained.

To assess SLE-related characteristics, we used validated measures of lupus disease activity (Systemic Lupus Erythematosus Disease Activity Index-2000) and disease damage (Systemic Lupus International Collaborating Clinics Index (SLICC-DI)) which were completed by trained physicians. SLICC-DI was modified to remove the three items related to CVD. Disease duration was calculated using the date the subject fulfilled the fourth American College of Rheumatology classification criteria for SLE.<sup>26 27</sup> Renal disease was defined as being present if the subject had fulfilled American College of Rheumatology classification criteria for lupus renal involvement ( $>0.5$  gm/day or 3+ proteinuria and/or the presence of cellular casts)<sup>26 27</sup> or had a renal biopsy with evidence of WHO Class IIb, III, IV or V lupus nephritis.<sup>28</sup> Participants provided information on corticosteroid treatment (current use, ever use and duration of treatment), as well as current use of hydroxychloroquine and immunosuppressants (cyclophosphamide, azathioprine, methotrexate, mycophenolate mofetil, ciclosporin and tacrolimus). Prior corticosteroid use and duration of treatment were verified by review of the subject's medical chart.

Measures of subclinical CVD were presence of carotid artery plaque and CAC score. Carotid artery plaque was imaged using carotid B mode ultrasound, which was performed at the Cardiovascular Imaging Processing Laboratory at Northwestern University and read at the University of Pittsburgh Ultrasound Research Laboratory. Carotid artery plaque was defined as a distinct area protruding into the vessel lumen that was at least 50% thicker than the surrounding areas and was measured at eight sites (bilateral internal carotid, external carotid, common carotid and carotid bulb). The outcome measure used for analysis was the presence or absence of plaque (plaque  $\geq 1$  vs plaque = 0) as previously described by our group.<sup>29</sup> The reproducibility of carotid duplex scanning using this technique has been previously documented in the Pittsburgh SLE cohort and a non-SLE population.<sup>30 31</sup>

CAC score was measured using electron beam CT (Imatron C-150 Ultrafast CT Scanner) at the University of Illinois, Chicago, and CAC scores were calculated with a densitometric programme available on the Imatron C-150 scanner, using the Agatston method.<sup>32</sup> The outcome measures used for the analysis of CAC were the absence (CAC score  $< 10$ ) or presence (CAC score  $\geq 10$ ). The CAC scores were read at the University of Pittsburgh Cardiovascular Institute.

Clinical cardiovascular events assessed at the time of the baseline visit were (1) MI, (2) angina, (3) percutaneous transluminal coronary angioplasty, (4) coronary artery bypass surgery, (5) cerebrovascular accident and (6) transient ischaemic attack and were verified using the Multiethnic Study of Atherosclerosis protocol.<sup>33</sup> All

CVD events occurred after pregnancy and after the diagnosis of SLE.

Laboratory tests included fasting lipids (total cholesterol, low density lipoprotein cholesterol (LDLc), high density lipoprotein cholesterol and triglycerides), homocysteine, glucose and insulin, which were measured in the Lipid Laboratory at the University of Pittsburgh Graduate School of Public Health and Prevention. The Friedewald equation was used to estimate LDLc, unless the triglyceride level was >400. In that case, LDLc was measured directly. Plasma glucose levels were determined by enzymatic assay, and plasma insulin levels were measured by radioimmunoassay. Circulating inflammatory and endothelial markers measured included homocysteine, C reactive protein (CRP), intracellular adhesion molecule (ICAM), vascular cell adhesion molecule (VCAM) and E-selectin. Homocysteine was measured at the University of Pittsburgh Medical Center nutrition laboratory spectrophotometrically on the Olympus AU400 using reagents obtained from Carolina Liquid Chemistries (Brea, California, USA). The intra-assay and interassay coefficients of variation (CVs) are 2.8% and 6.3%, respectively. CRP, ICAM, VCAM and soluble E-selectin were measured at the University of Vermont. CRP was measured using the BNII nephelometer from Dade Behring using a particle enhanced immunonephelometric assay. Intra-assay CVs range from 2.3% to 4.4% and inter-assay CVs range from 2.1 to 5.7%. ICAM, VCAM and E-selectin were measured using ELISA assays (R&D Systems, Minneapolis, Minnesota, USA). The intra-assay and interassay CVs for VCAM range from 4.3–5.9% and 8.5–10.2%, respectively and the interassay CV for E-selectin range from 5.7% to 8.8%. For ICAM, the interassay laboratory CV is 5.0%. Antiphospholipid antibodies: anticardiolipin (ACL) antibodies (IgG and IgM; Diasorin, Stillwater, Minnesota, USA) and lupus anticoagulant (partial thromboplastin time or Russell's viper venom time with mix) were measured at the Coagulation Laboratory at University of Pittsburgh Medical Center. ACL IgG was considered positive if the result was >10 units and ACL IgM was considered positive if >15 units, as per laboratory standards.

### Statistical methods

Descriptive statistics (eg, means, SDs, centiles, ranges) were used to determine distributions of the measures of subclinical CVD, cardiovascular risk factors (eg, smoking history, cholesterol, blood pressure) and inflammatory/endothelial markers. Differences between women with and without pregnancy complications were examined using *t* tests for normally distributed continuous variables, Wilcoxon's rank sum test for non-parametric comparison of continuous variables with skewed distributions and  $\chi^2$  analyses or small sample methods for proportions. Logistic regression was used to estimate the associations of pregnancy complications with occurrence of subclinical CVD and clinical CVD, with a priori adjustment for age, which is associated with

CVD and SLE disease duration as a measure of SLE disease burden. We also performed a sensitivity analysis substituting disease duration for disease damage using the SLICC-DI excluding the CVD-related variables as a measure of SLE disease burden in our logistic regression model. Since the results obtained were similar using either model, we present the results from the a priori model design which used disease duration as the measure of disease burden.

### RESULTS

The clinical characteristics of the 185 SLE participants who were enrolled in the SOLVABLE parent study have been previously described.<sup>29–34</sup> Of the 185 SLE participants, 51 had never been pregnant or only had elective terminations and 5 women refused to participate, leaving 129 subjects included in this exploratory study.

The women with adverse pregnancy outcomes were similar with respect to mean age at study visit (44.5±9.7 vs 44.4±9.7 years), current smoking, body mass index, waist-hip ratio, family history of MI, hypercholesterolaemia and diabetes, but more had hypertension (66% vs 47%, *p*=0.027) compared with women without adverse pregnancy outcomes (table 1). There were no differences in SLE characteristics (disease duration, medications, renal disease, ACL antibody status or Systemic Lupus Erythematosus Disease Activity Index-2000 score) or circulating markers of inflammation and endothelial activation in women with and without adverse pregnancy outcomes. In contrast, women with SLE and adverse pregnancy outcomes compared with those without adverse pregnancy outcomes had more SLE disease damage (SLICC-DI 2.1±1.8 vs 1.4±1.7, *p*=0.042) and menopause onset at an earlier mean age (37.4±8.0 vs 43.8±6.7, *p*=0.005), but the percentage of those who were postmenopausal at the baseline visit was similar, 38% vs 43% (table 1).

There were 331 pregnancies in the 129 women participating in this study and 66% of the pregnancies occurred before the diagnosis of SLE. Of the 33% of pregnancies occurring after the diagnosis of SLE, the mean disease duration between SLE diagnosis and pregnancy was 6.8±6.0 years and 7.3±5.9 years in those without and with adverse pregnancy outcomes, respectively. Of the 56 women who reported adverse pregnancy outcomes, 26 had at least one pregnancy complicated by pre-eclampsia during pregnancy; 36 had at least one pregnancy resulting in preterm birth; and 28 had at least one low birthweight infant. Seventy-three women had no adverse pregnancy outcomes.

Two women with adverse pregnancy outcomes, one preterm and one with a low birthweight infant, were excluded from the analysis for CAC, but included in the analysis for the presence of plaque because the former measure was not available. A higher percentage of women with an adverse pregnancy outcome had a CAC score greater than or equal to 10 and the presence of plaque compared with women without an adverse

**Table 1** Characteristics and traditional cardiovascular risk factors in patients with SLE (n=129) with and without history of adverse pregnancy outcomes\*

Characteristics/CVD risk factors at baseline SOLVABLE visit	Patients with adverse pregnancy outcomes n=56	Patients with no adverse pregnancy outcomes n=73	p Value
<b>Demographics</b>			
Age (years, mean±SD)	44.5±9.7	44.4±9.7	0.948
Age at menopause (years, mean±SD)	37.4±8.9	43.8±6.9	0.005
<b>Traditional CVD risk factors</b>			
Body mass index, kg/m <sup>2</sup> , mean±SD	29.4±8.5	27.7±7.4	0.225
Waist-hip ratio, mean±SD	0.86±0.12	0.86±0.16	0.713
Hypertension†, n (%)	37 (66.1)	34 (46.6)	0.027
Hypercholesterolaemia†, n (%)	17 (30.4)	21 (28.8)	0.844
Diabetes†, n (%)	8 (14.3)	4 (5.5)	0.088
Current smoker, n (%)	10 (17.9)	8 (11.0)	0.109
Family history of MI, n (%)	23 (41.1)	28 (38.4)	0.957
Total cholesterol, mg/dL, mean±SD	188.3±41.3	191.8±36.7	0.602
LDLc, mg/dL, mean±SD	105.6±30.4	112.0±32.8	0.263
HDLc, mg/dL, mean±SD	54.9±16.6	55.8±14.5	0.727
Triglycerides, mg/dL, mean±SD	141.0±99.2	124.1±75.6	0.276
Median (IQR)	110.5 (83.3, 172.5)	102 (81.5, 151)	0.287
<b>SLE characteristics</b>			
SLE disease duration, years, mean±SD	13.2±8.6	11.4±7.4	0.204
Current CS use, n (%)	30 (53.6)	29 (39.7)	0.118
CS use ever, n (%)	46 (82.1)	53 (72.6)	0.176
Duration of CS use, years, mean±SD	8.5±7.7	6.9±5.9	0.253
Current HCQ use, n (%)	37 (66.1)	53 (72.6)	0.423
Current immunosuppressant use‡, n (%)	23 (41.1)	19 (26.0)	0.71
Immunosuppressant‡ use ever, n (%)	28 (50)	35 (47.9)	0.817
SLICC-DI, mean±SD	2.1±1.8	1.4±1.7	0.042
Median (IQR)	2 (0.25, 3)	1 (0, 2)	0.032
SLEDAI, mean±SD	4.8±4.3	3.8±3.5	0.145
Median (IQR)	4 (2, 6)	4 (0.5, 6)	0.184
Renal disease§, n (%)	16 (28.6)	21 (28.8)	0.981
Anti-phospholipid status¶, n (%)	12 (21.8)	22 (30.1)	0.292
<b>Inflammatory markers</b>			
CRP, median (IQR)	1.6 (0.6–6.2)	1.2 (0.5–5.1)	0.277
HCY, mean±SD	13.0±8.3	11.1±3.9	0.082
ICAM, mean±SD	270.2±150.9	292.3±96.8	0.317
VCAM, mean±SD	1087.7±671.0	1038.2±48.5	0.630
E-selectin, mean±SD	69.7±30.1	65.8±35.3	0.515

Data presented as mean±SD for normally distributed continuous variables, median (IQR) for skewed continuous variables, and n (%) for categorical variables.

\*Adverse pregnancy outcomes include pre-eclampsia, low birthweight infants or preterm birth.

†Hypertension present if any of the following: self-reported history of hypertension, systolic blood pressure>140, diastolic blood pressure>90, or taking antihypertensive medications; present if any of the following: self-reported history of high cholesterol or taking cholesterol lowering medications; diabetes present if self-reported history of diabetes or fasting glucose >126 mg/dL.

‡Immunosuppressants included: cyclophosphamide, azathioprine, methotrexate, mycophenolate mofetil, ciclosporin and tacrolimus.

§Renal disease was defined as being present if the subject had fulfilled ACR classification criteria for lupus renal involvement or renal biopsy with WHO Class IIb, III, IV or V lupus nephritis.

¶Anti-phospholipid status included any one of the following positive at the study visit: anticardiolipin antibody IgG or IgM isotype or lupus anticoagulant.

ACR, American College of Rheumatology; CRP, C reactive protein; CS, corticosteroid; CVD, cardiovascular disease; HCQ, hydroxychloroquine; HCY, homocysteine; HDLc, high density lipoprotein cholesterol; ICAM, intracellular adhesion molecule; LDLc, low density lipoprotein cholesterol; MI, myocardial infarction; SLE, systemic lupus erythematosus; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; SLICC-DI, Systemic Lupus International Collaborating Clinics Damage Index; VCAM, vascular cell adhesion molecule; SOLVABLE, Study of Long-term Vascular and Bone Outcomes in Lupus Erythematosus.

pregnancy outcome, 25.9% vs 17.8% and 46.4% vs 38.4%, respectively. However these increases in the frequency of CAC score and the presence of plaque were not statistically significant after adjusting for age and

SLE disease duration as noted in table 2. When evaluating the different types of adverse pregnancy outcomes individually, women with a history of pre-eclampsia were more likely to have a CAC score greater than or equal to

**Table 2** Association between subclinical cardiovascular disease imaging of the coronary and carotid arteries in patients with SLE with and without adverse pregnancy outcomes

	Adverse pregnancy outcomes	No adverse pregnancy outcomes	OR (95% CI) Age and disease duration adjusted
CAC score $\geq$ 10, n (%)	14/54*(25.9)	13/73 (17.8)	1.5 (0.6 to 3.9)
Carotid plaque=1, n (%)	26/56 (46.4)	28/73 (38.4)	1.5 (0.7 to 3.2)
	<b>Pre-eclampsia</b>	<b>No adverse pregnancy outcomes</b>	
CAC score $\geq$ 10, n (%)	10/26 (38.5)	13/73 (17.8)	<b>3.7 (1.2 to 11.9)</b>
Carotid plaque=1, n (%)	10/26 (38.5)	28/73 (38.4)	1.1 (0.4 to 2.8)
	<b>Low birthweight infant</b>	<b>No adverse pregnancy outcomes</b>	
CAC score $\geq$ 10, n (%)	8/27*(30.0)	13/73 (17.8)	2.2 (0.7 to 7.4)
Carotid plaque=1, n (%)	14/28 (50.0)	28/73 (38.4)	2.0 (0.8 to 5.1)
	<b>Preterm birth</b>	<b>No adverse pregnancy outcomes</b>	
CAC score $\geq$ 10, n (%)	8/35*(22.9)	13/73 (17.8)	1.0 (0.3 to 3.2)
Carotid plaque=1, n (%)	18/36 (50.0)	28/73 (38.4)	1.6 (0.7 to 3.8)

Adverse pregnancy outcomes include pre-eclampsia, low birthweight infants or preterm birth.

\*Two women with adverse pregnancy outcomes (one each preterm and low birth weight) did not have a coronary calcium score calculated. CAC, coronary artery calcium; SLE, systemic lupus erythematosus.

10 (adjusted OR=3.7, 95% CI 1.2 to 11.9), but not carotid plaque (adjusted OR=1.1, 95% CI 0.4 to 2.8) compared with those without adverse pregnancy outcomes. The ORs for CAC score greater than equal to 10 and the presence of carotid plaque for women with at least one pre-term birth and low birth weight were not statistically significant as noted in table 2.

Clinical cardiovascular events occurred in four (7.14%) women with pregnancy complications and in six (8.22%) without pregnancy complications (OR=0.6, 95% CI 0.2 to 3.2). Of the four women with pregnancy complications, three had transient ischaemic attacks and one had percutaneous transluminal coronary angioplasty and of the six women without pregnancy complications four had cerebrovascular accidents, one had a MI, one had a MI and percutaneous transluminal coronary angioplasty.

## DISCUSSION

Women with SLE have been reported to have more pregnancy complications,<sup>1-3</sup> as well as a higher cardiovascular risk.<sup>16</sup> This report describes the relationship between adverse pregnancy outcomes and subsequent subclinical CVD and CVD events in women with SLE. In this study, women with a history of pre-eclampsia had almost a fourfold increased risk of having subsequent subclinical CVD based on the presence of CAC score greater than or equal to 10.

One factor that may underlie the relationship between pregnancy complications and CVD is that pregnancy complications, such as pre-eclampsia, low birth weight and preterm delivery share several common risk factors with CVD, including obesity, cigarette smoking, hypertension, diabetes and lipid abnormalities<sup>35-43</sup> as recently reviewed by Rich-Edwards and colleagues.<sup>15</sup> These traditional CVD risk factors are associated with an increased

risk of developing pregnancy complications, and conversely, pregnancy complications are also associated with an increased susceptibility for the subsequent development of traditional CVD risk factors, including hypertension, increased insulin resistance, obesity and lipid abnormalities.<sup>9 11 44-46</sup> In our study, we also found a significant association between a history of pregnancy complications and hypertension ( $p=0.027$ , table 1), as well as an association for diabetes ( $p=0.088$ , table 1). However, we did not distinguish between type 1 and type 2 diabetes in this study. Similar associations between cardiovascular risk factors and pre-eclampsia have also been noted in women with polycystic ovarian syndrome, another population of women with premature atherosclerosis.<sup>47</sup>

Recent studies have demonstrated that women with pre-eclampsia continue to have adverse metabolic and vascular abnormalities even years after delivery despite normalisation of blood pressure. When examined years after their affected pregnancy, women with a history of pre-eclampsia have worse lipid profiles,<sup>48</sup> more hyperinsulinemia<sup>49</sup> and more microalbuminuria<sup>50</sup> than women with normotensive pregnancies. In addition, women with a history of pre-eclampsia had impaired endothelial function when examined 3 years after their pre-eclamptic episode.<sup>51</sup> In women with SLE, there may be lupus-related factors such as autoantibodies that are contributing to vascular abnormalities in the endothelium as possible underlying risk factors for developing pre-eclampsia and CVD,<sup>52</sup> however we were not able to demonstrate such an association with the autoantibodies measured in this study, likely due to our limited sample size and cross-sectional study design.

Since inflammation plays a role in atherosclerosis<sup>53</sup> and SLE<sup>54</sup> and the inflammatory response is altered in pre-eclampsia compared with normal pregnancies, with elevated levels of cytokines and vascular adhesion

molecules,<sup>55–58</sup> it portends a potentially detrimental combination for the future risk of CVD in women with SLE. Furthermore, inflammation has also been implicated in preterm birth<sup>59</sup> and fetal growth restriction.<sup>12 60</sup>

The inflammatory response is triggered as the result of endothelial damage caused by risk factors such as hypertension, diabetes and cigarette smoking. Consequently, there is activation of inflammatory cells which release cytokines, chemokines and growth factors, as well as altered endothelial function. Propagation of the ensuing inflammatory response may result when exposures to these injurious factors persist or if the immune system becomes dysregulated. The physiological maternal inflammatory responses become exaggerated in pre-eclampsia compared with normal pregnancy<sup>61</sup> irrespective of SLE. Elevated levels of tumour necrosis factor  $\alpha$  and interleukin 6, as well as adhesion molecules, VCAM and E-selectin<sup>46 56 58–60 62–64</sup> have been found in pregnancies complicated by pre-eclampsia, low birth-weight infants and preterm births compared with normal pregnancy. In this study we were not able to document an association between inflammatory markers or adhesion molecules likely due to the small sample size and the cross-sectional nature of the study design.

The results from this study have some additional limitations. We also evaluated possible misclassification errors. The number of subjects in this study was small compared with the numbers studied in the general population evaluating associations between pregnancy complications and subclinical CVD and events which limit the precision of our results. Maternal recall regarding certain pregnancy details have been shown to be reliable many years postpartum.<sup>65</sup> We verified the self-reported pregnancy data for those subjects who had given birth at Prentice Women's Hospital, Chicago, Illinois and found 100% accuracy using a similar strategy in a previous study,<sup>66</sup> so maternal recall is not likely to be a problem for self-reported adverse pregnancy outcomes. Although we verified pregnancy outcomes, we were not able to document smoking or alcohol history at the time of pregnancy. We verified cardiovascular events, but we do not have biological samples nor did we perform detailed clinical assessments of SLE disease activity and medications used or tested for autoantibodies, inflammatory or endothelial markers during pregnancy, at the time subclinical CVD disease was assessed or when the cardiovascular events occurred. This study did not enrol and follow subjects prior to pregnancies. This precludes evaluation of autoantibodies, inflammatory markers and endothelial activation markers prior to pregnancy and a possible role in the occurrence of adverse pregnancy outcomes. The cross-sectional study design does not permit us to assess causality between autoantibodies, inflammatory markers, and endothelial activation markers, pregnancy outcomes and subclinical CVD and clinical CVD events nor can we eliminate the possibility that covariates measured after pregnancy could have changed over time and could also

be confounders influencing pregnancy outcomes. We controlled for SLE duration in our models and performed a sensitivity analysis substituting disease damage measured by the modified SLICC-DI (data not shown) for disease duration with similar results, making it less likely that SLE was acting as a mediating factor for the occurrence of pregnancy outcomes.

In summary, patients with SLE with a history of pre-eclampsia had an almost fourfold increase in the rate of subclinical CVD as measured by CAC score greater than or equal to 10, but the presence of plaque was not associated with this adverse pregnancy outcome. Neither low birth weight nor preterm birth was associated with CAC or plaque. The results reported here are preliminary. To explore these findings further larger, prospective studies are needed to examine the incidence of subclinical CVD and clinical CVD events in women with SLE who have a history of adverse pregnancy outcomes similar to observations in the general population<sup>15</sup> and also other groups with premature CVD such as women with polycystic ovarian syndrome.<sup>47</sup>

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**Data sharing statement** Any investigator who wishes to obtain data from this Project will do so with a Resource Sharing Agreement that provides for (1) a commitment to using the resources only for research purposes and not to identify an individual participant, (2) a commitment to securing resources using appropriate computer technology, and (3) a commitment to destroy or return the resources after analyses are completed. There is no additional unpublished data from the pregnancy project from SOLVABLE.

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