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ORIGINAL RESEARCH

History of pre-eclampsia does not appear to be a risk factor for vascular phenotype in women with systemic sclerosis

Claire De Moreuil ,[1,2] Elizabeth Diot,[3] Christian Agard,[4,5] Nicolas Belhomme,[6,7] Alain Lescoat,[6,7] Viviane Queyrel,[8] Nathalie Tieulie,[9] Marie-Elise Truchetet ,[10] Grégory Pugnet,[11,12] Sabine Berthier,[13] Perrine Smets,[14] Benjamin Subran,[15] Olivier Lidove,[15] Jeremy Keraen,[16] Arsène Mekinian ,[17] Emmanuel Chatelus,[18] Elisabeth Pasquier,[1] Emilie Brenaut,[19] Bénedicte Rouvière,[20] Mathieu Delplanque,[1] Sandy Lucier,[21] Emmanuelle Courtois-Communier,[21] Valérie Devauchelle-Pensec,[22,23] Eric Hachulla[24]

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For numbered affiliations see end of article.

Correspondence to
Dr Claire De Moreuil;
claire.demoreuil@chu-brest.fr

ABSTRACT

Background Vascular phenotype is associated with a poor prognosis in systemic sclerosis (SSc). The identification of its risk factors could facilitate its early detection.

Objectives To explore risk factors for a vascular phenotype of SSc, among them a history of pre-eclampsia.

Methods This observational multicentre case–control study enrolled adult women fulfilling European Alliance of Associations for Rheumatology 2013 diagnosis criteria for SSc and having a pregnancy history≥6 months before SSc diagnosis in 14 French hospital-based recruiting centres from July 2020 to July 2022. Cases had specific vascular complications of SSc defined as history of digital ischaemic ulcers, pulmonary arterial hypertension, specific cardiac involvement or renal crisis. Women with SSc were included during their annual follow-up visit and filled in a self-administered questionnaire about pregnancy. A case report form was completed by their physician, reporting data on medical history, physical examination, clinical investigations and current medication. The main outcome was the presence/absence of a personal history of pre-eclampsia before SSc diagnosis, according to the validated pre-eclampsia questionnaire.

Results 378 women were included: 129 cases with a vascular phenotype and 249 matched controls. A history of pre-eclampsia was reported in 5 (3.9%) cases and 12 (4.8%) controls and was not associated with a vascular phenotype (OR=0.96, 95% CI 0.28 to 3.34, p=0.9). Besides, Rodnan skin score and disease duration≥5 years were risk factors for vascular phenotype.

Conclusions In women with SSc and a pregnancy history≥6 months before SSc, a history of pre-eclampsia is not associated with a vascular phenotype.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Vascular phenotype is associated with a poor prognosis in systemic sclerosis (SSc).

WHAT THIS STUDY ADDS

⇒ This study investigated whether a history of pre-eclampsia could be a risk factor for vascular phenotype in SSc.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ It does not seem relevant to investigate obstetric history prior to SSc diagnosis to predict vascular complications.

INTRODUCTION

Pre-eclampsia, defined as the association of an arterial hypertension and significant proteinuria after 20 weeks of gestation (WG), complicates 1%–2% of pregnancies in developed countries.[1] Its pathophysiology involves maternal angiogenesis impairment, upregulated systemic inflammatory response, activation of oxidative stress and endothelial dysfunction.[2–5] Furthermore, it is associated with an increased risk of cardiovascular events later in life.[6 7]

In a Danish nationwide cohort study published in 2018, pre-eclampsia was also associated with a 69% increased risk of developing a systemic sclerosis (SSc).[8]

Moreover, a case–control study on 103 women diagnosed with SSc compared with 103 controls found an increased incidence of previous vasculo-placental disorders in women with SSc.[9] In this study, women had developed SSc on average 27 years after their first pregnancy.[9]

SSc is a rare connective tissue disease affecting especially women. It is characterised by vascular and inflammatory phenomena, along with tissue fibrosis, resulting in

Raynaud's phenomenon and thickening of the skin and organs.[10] Its pathophysiology is complex and not fully understood. One of the theories on the genesis of this disease is the feto-maternal microchimerism theory, which stipulates that fetal cells would cross the placenta during pregnancy and stay in the mother's body for decades. These fetal cells would trigger an immune reaction years after, resulting in the development of an autoimmune disease.[11–15] Vascular phenotype or 'generalised vasculopathy' is a particular clinical expression of SSc, which can be defined as the presence of vascular complications such as digital ischaemic ulcers, pulmonary arterial hypertension (PAH), cardiac dysfunction or renal crisis.[16] This specific phenotype could be associated with a poorer prognosis and could justify the search for clinical and biological associated features, especially if these features can be identified early in the course of the disease.[17 18]

The aim of this observational multicentre case–control study was to determine if a history of pre-eclampsia before SSc diagnosis was an independent risk factor for specific vascular phenotype in women with SSc. The secondary objective was to describe other potential risk factors for vascular phenotype in women with SSc.

MATERIALS AND METHODS

Participants

This case–control study took place between July 2020 and July 2022 in 14 French hospital-based recruiting centres, which are reference centres for SSc (Brest, Bordeaux, Clermont-Ferrand, Dijon, Lille, Nantes, Nice, Paris La Croix Saint Simon, Paris Saint Antoine, Quimper, Rennes, Strasbourg, Toulouse and Tours).

Participants in the study were adult women followed up in 1 of the 14 recruiting centres by a physician specialised in internal medicine, dermatology or rheumatology, diagnosed with SSc, fulfilling European Alliance of Associations for Rheumatology 2013 diagnosis criteria for SSc and having a pregnancy history of 6-month duration or more (≥28 WG) before SSc diagnosis.[19]

Cases were defined as women with SSc and specific vascular complications (a history of ischaemic digital ulcers, specific cardiac involvement or renal crisis). Specific cardiac involvement was defined as one of the two following conditions: PAH, diagnosed according to the European guidelines prevailing at the time of assessment and systematically confirmed by right heart catheterisation[20 21] and microvascular ischaemic and fibrotic myocardium damage confirmed by cardiac MRI and named myocarditis.

Controls were defined as women with SSc and no specific vascular complication.

For each case, two controls were included in the same recruiting centre.

Exclusion criteria were women under the age of 18 years, women under legal protection, women with no history of pregnancy of 6-month duration or more before SSc diagnosis, women unable to fill in a questionnaire in French and women unwilling to participate in the study.

After oral and written information on the study by their physician during an annual follow-up visit, women were included and were invited to fill in a self-administered questionnaire about pregnancy. A case report form was completed simultaneously by the physician, with detailed data on medical history, physical examination, clinical investigations and current medication. Clinical investigations included the results of the most recent biological tests, echocardiography, pulmonary function tests (lung volumes, carbon monoxide transfer factor), CT scan of the chest and right heart catheterisation in case of PAH. Interstitial lung disease (ILD) was classified as limited or extensive according to Goh Score based on the evaluation of CT scan of the chest.[22]

The questionnaire about pregnancy consisted in two parts (Pregnancy questionnaire PREVASCLERO, online supplemental material):

- A validated pre-eclampsia questionnaire, looking for a history of pre-eclampsia.
- A second part with additional questions on previous pregnancies, especially questions looking for a history of vasculo-placental disorders.

Outcomes

The primary outcome was the presence or the absence of a personal history of pre-eclampsia before SSc diagnosis, according to the responses of the woman to the pre-eclampsia questionnaire. A positive response for a pre-eclampsia history was defined as a self-report of any of the following items:

1. A history of pre-eclampsia, eclampsia or toxaemia, with or without hypertension, during the index pregnancy.
2. Hypertension and proteinuria during, but not before the index pregnancy.
3. Hypertension and seizures during, but not before the index pregnancy.

The questionnaire used is the French translation of a self-administered questionnaire designed and validated in English by Diehl *et al*, looking for a history of pre-eclampsia.[23] Its validity has been demonstrated in a French prospective study, with a 95.2% sensitivity and a 98.0% specificity in verifying a pre-eclampsia history.[24]

The secondary outcomes were all the other potential variables associated with specific vascular phenotype in women with SSc: age at SSc diagnosis, diffuse/limited pattern of SSc, Rodnan skin score, disease duration≥5 years, anti-centromere antibodies positivity, anti-topoisomerase antibodies positivity, anti-RNA polymerase III antibodies positivity, persistent antiphospholipid (aPL) antibodies positivity (including antiβ2GP1 immunoglobulin M (IgM) and IgG antibodies, anticardiolipin IgM and IgG antibodies and/or lupus anticoagulant, found positive at least twice, at least 12 weeks apart, according to Sydney laboratory criteria for antiphospholipid syndrome (APS)), APS, ILD, smoking status, chronic arterial hypertension

and a history of vasculo-placental disorder.[25] A history of vasculo-placental disorder was defined as a history of pre-eclampsia, eclampsia, haemolysis, elevated liver enzymes and low platelet syndrome, intrauterine growth restriction and placental abruption or stillbirth, in any of the pregnancies that occurred before SSc diagnosis, according to the responses of the woman to the 'pregnancy questionnaire'. Last, upper digestive tract involvement was defined as symptoms affecting oesophagus and/or stomach and lower digestive tract involvement as symptoms related to bowels and/or anus.

Statistics

Hypothesising that the frequency of a pre-eclampsia history would be of 2% in controls, that the OR for the association between a pre-eclampsia history and a vascular phenotype would be of 5, for a power of 80%, the number of women to include was calculated to be 378, that is, 126 cases and 252 controls.

All continuous variables were summarised as mean with SD and median with IQR, minimum and maximum values. Categorical variables were summarised as absolute number and percentage of non-missing data. Missing data were not replaced. Participants' characteristics were compared between cases and controls with χ^2 test or Fisher test for categorical variables and with Student's test or Wilcoxon test for continuous variables.

Univariable logistic regression analysis was used to assess the association between a vascular phenotype of SSc and each potential risk factor. ORs were calculated and reported with their 95% CI. The factors included in the multiple regression model were chosen among the significant factors in the univariable analyses that were of clinical interest, supplemented by clinically relevant variables that did not reach statistical significance.

A sensitivity analysis was performed, testing the variable 'history of vasculo-placental disorder' instead of the variable 'history of pre-eclampsia' in the univariable analysis and then in the multivariable analysis.

All statistics analyses were performed with SAS software V.9.4.

RESULTS

Between July 2020 and July 2022, 378 women diagnosed with SSc and with a pregnancy history≥6 months before SSc diagnosis were included in 14 French recruiting centres: 129 cases with a specific vascular phenotype and 249 SSc controls matched for recruiting centre. Of note, after verification of all the completed case report forms, three women with SSc initially included in the study as controls were redefined as cases because of a history of ischaemic digital ulcers and were then analysed in the case group.

General characteristics of participants

Table 1 summarises available clinical data on participants' characteristics.

Median (IQR) age at inclusion was 61.5 (53–70) years. Median (IQR) age at SSc diagnosis was 52 (IQR 42–61) years. In 128 (33.9%) women, disease duration was <5 years.

In the study population, 72 (19%) women had diffuse SSc, 293 (77.5%) had limited SSc and 13 (3.4%) had SSc sine scleroderma. Most women (>70%) had a low Rodnan skin score, comprised between 1 and 8 points. Anti-topoisomerase antibodies were positive in 68 (18%) women, anti-RNA polymerase III antibodies in 16 (4.2%) women, anti-centromere antibodies in 198 (52.4%) women and persistent aPL antibodies in 14 (3.7%) women (table 2). Among women carrying persistent aPL antibodies, only three had a lupus anticoagulant and none was triple positive. An overlap with another autoimmune disease was present in 88 (23.3%) women.

Among the 378 participants, 113 (29.9%) had ILD diagnosed on CT scan of the chest: 32.1% extensive and 67.9% limited.

Regarding medication, 102 (27%) women were on immunosuppressant at inclusion in the study: 74 on steroids, 33 on mycophenolate mofetil, 28 on methotrexate, 3 on azathioprine, 4 on cyclophosphamide and 3 on anti-CD20 antibodies.

Among cases, 108 (83.7%) had a history of ischaemic digital ulcers, 34 (26.4%) had active ischaemic digital ulcers, 20 (15.5%) had PAH, 2 (1.6%) had myocarditis and 6 (4.7%) had a history of renal crisis.

Pregnancy history of participants

Online supplemental table S1 details the pregnancy history of participants. Median (IQR) number of live births was 2 (2–3) in the study population. A history of pre-eclampsia was deducted from pre-eclampsia questionnaire's answers in 17 (4.5%) women: 12 (4.8%) in controls and 5 (3.9%) in cases with a vascular phenotype. Median (IQR) term at pre-eclampsia diagnosis was 6.0 (6.0–8.0) months and median (IQR) term at delivery was 8.0 (8.0–9.0) months. In four women, pre-eclampsia occurred in two pregnancies and two women experienced three pregnancies complicated with pre-eclampsia. Besides, 33 (9.4%) women reported a history of vasculo-placental disorder: 21 (9.1%) in controls and 12 (10.0%) in cases. Among them, in addition to a pre-eclampsia history, 6 (1.6%) women reported a history of placental abruption, 13 (3.4%) reported a history of intrauterine growth restriction and 3 (0.8%) reported a history of stillbirth.

Risk factors for vascular phenotype of SSc

Univariable analysis

Online supplemental table S2 illustrates the univariable analysis for variables associated with a vascular phenotype of SSc.

Among all studied variables, seven were significantly associated with a vascular phenotype of SSc: age at SSc diagnosis (OR=0.97, 95% CI 0.96 to 0.99),

Table 1 Clinical data on participants' characteristics

Variables		Total (n=378)	Control (n=249)	Case (n=129)	P value*
Age at inclusion (years)	Mean±SD	61.3±11.9	61.5±12.2	60.8±11.4	0.64
	Median (q1–q3)	61.5 (53.0–70.0)	61.0 (53.0–70.0)	62.0 (53.0–70.0)	
	Min–max	27.0–88.0	30.0–88.0	27.0–84.0	
Smoking history	n (%)	134 (35.6%)	86 (34.7%)	48 (37.5%)	0.59
	Unweaned, n (%)	41 (30.6%)	27 (31.4%)	14 (29.2%)	
	Weaned, n (%)	93 (69.4%)	59 (68.6%)	34 (70.8%)	
Chronic arterial hypertension	n (%)	103 (27.2%)	61 (24.5%)	42 (32.6%)	0.10
	Untreated, n (%)	6 (5.8%)	3 (4.9%)	3 (7.1%)	
	Treated, n (%)	97 (94.2%)	58 (95.1%)	39 (92.9%)	
Diabetes	n (%)	11 (2.9%)	8 (3.2%)	3 (2.3%)	0.76
Treated hypercholesterolemia	n (%)	37 (9.8%)	25 (10.0%)	12 (9.3%)	0.82
Type of SSc	Diffuse SSc, n (%)	72 (19.0%)	39 (15.7%)	33 (25.6%)	0.04
	Limited SSc, n (%)	293 (77.5%)	199 (79.9%)	94 (72.9%)	
	Sine scleroderma SSc, n (%)	13 (3.4%)	11 (4.4%)	2 (1.6%)	
Overlap with another autoimmune disease†	n (%)	88 (23.3%)	60 (24.1%)	28 (21.7%)	0.60
Age at SSc diagnosis (years)	Mean±SD	51.7±12.8	53.2±12.8	49.0±12.5	0.003
	Median (q1–q3)	52.0 (42.0–61.0)	54.0 (43.0–63.0)	48.0 (40.0–56.0)	
	Min–max	11.0–85.0	11.0–85.0	22.0–78.0	
Disease duration (years)	Mean±SD	9.9±9.1	8.7±8.6	12.1±9.6	0.0006
	Median (q1–q3)	7.0 (3.0–14.0)	6.0 (2.0–13.0)	10.0 (5.0–16.0)	
	Min–max	0.0–47.0	0.0–47.0	0.0–42.0	
Disease duration in class (years)	<5 years	128 (34.5%)	100 (41.2%)	28 (21.9%)	0.0002
	≥5 years	243 (65.5%)	143 (58.8%)	100 (78.1%)	
Raynaud's phenomenon	n (%)	374 (98.9%)	245 (98.4%)	129 (100.0%)	0.30
Age at start of Raynaud's phenomenon (years)	Mean±SD	44.5±15.5	45.1±15.7	43.3±15.3	0.31
	Median (q1–q3)	45.0 (34.0–56.0)	46.0 (35.0–56.0)	43.5 (32.0–54.5)	
	Min–max	0.0–84.0	8.0–84.0	0.0–74.0	
Diffuse interstitial lung disease	n (%)	113 (29.9%)	62 (24.9%)	51 (39.5%)	0.003
Limited ILD	n (%)	76 (67.9%)	44 (71.0%)	32 (64.0%)	
Extensive ILD	n (%)	36 (32.1%)	18 (29.0%)	18 (36.0%)	
PH (all types)	n (%)	29 (7.7%)	7 (2.8%)	22 (17.1%)	
PAH	n (%)	20	0	20	
Group 1 PAH	n (%)	2	1	1	
Group 2 PAH	n (%)	9	5	4	
Group 3 PAH	n (%)	5	1	4	
Chronic pericarditis	n (%)	7 (77.8%)	4 (80.0%)	3 (75.0%)	
Myocarditis	n (%)	2 (22.2%)	0	2 (50.0%)	
History of ischaemic digital ulcers	n (%)	108 (28.6%)	0	108 (83.7%)	
History of mechanical digital ulcers	n (%)	20 (5.3%)	3 (1.2%)	17 (13.2%)	
History of digital ulcers with calcinosis	n (%)	38 (10.1%)	14 (5.6%)	24 (18.6%)	
Upper digestive tract involvement	n (%)	277 (73.3%)	177 (71.1%)	100 (77.5%)	0.18
Lower digestive tract involvement	n (%)	81 (21.4%)	46 (18.5%)	35 (27.1%)	0.05
History of acute renal crisis	n (%)	6 (1.6%)	0	6 (4.7%)	
	With dialysis, n (%)	4	0	4	
BMI	Mean±SD	24.7±4.9	24.9±4.9	24.4±4.8	0.37
	Median (q1–q3)	24.0 (21.2–27.3)	24.2 (21.3–27.5)	23.4 (20.7–27.2)	
	Min–max	16.0–46.8	16.8–46.8	16.0–43.6	

Continued

Table 1 Continued

Variables		Total (n=378)	Control (n=249)	Case (n=129)	P value*
Rodnan skin score	Mean±SD	6.3±6.5	4.8±5.1	9.0±8.0	<0.0001
	Median (q1–q3)	4.0 (2.0–9.0)	4.0 (2.0–6.0)	7.5 (3.0–12.0)	
	Min–max	0.0–38.0	0.0–32.0	0.0–38.0	
Active digital ulcerations	n (%)	41 (10.8%)	7 (2.8%)	34 (26.4%)	
If present, number of ulcerations	Mean±SD	2.1±2.2	1.4±0.8	2.2±2.4	
	Median (q1–q3)	1.0 (1.0–2.0)	1.0 (1.0–2.0)	1.0 (1.0–2.0)	
	Min-max	1.0–13.0	1.0–3.0	1.0–13.0	
Dyspnoea (NYHA 2–4 functional class)	n (%)	234 (61.9%)	146 (58.6%)	88 (68.2%)	
Immunosuppressant	n (%)	102 (27.0%)	60 (24.1%)	42 (32.6%)	
Anti-endothelin receptor therapy	n (%)	35 (9.3%)	1 (0.4%)	34 (26.4%)	
Antiplatelet therapy	n (%)	55 (14.6%)	25 (10.0%)	30 (23.3%)	
Anticoagulant	n (%)	24 (6.3%)	12 (4.8%)	12 (9.3%)	
Oxygenotherapy	n (%)	5 (1.3%)	1 (0.4%)	4 (3.1%)	

*χ^2 or Fisher test for categorical variables or Student's or Wilcoxon test for continuous variables.
†43 with Sjögren disease, 10 with rheumatoid arthritis, 7 with myositis, 5 with systemic lupus erythematosus and 2 with antiphospholipid syndrome.
BMI, body mass index; ILD, interstitial lung disease; NYHA, New York Heart Association; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; SSc, systemic sclerosis.

disease duration≥5 years (OR=2.50, 95% CI 1.53 to 4.08), diffuse pattern of SSc (OR=1.85, 95% CI 1.10 to 3.12), Rodnan skin score (OR=1.11, 95% CI 1.06 to 1.15), anti-topoisomerase antibodies (OR=2.25, 95% CI 1.31 to 3.87), anti-centromere antibodies (OR=0.57, 95% CI 0.36 to 0.90) and ILD (OR=1.97, 95% CI 1.25 to 3.11).

In our data, there was no statistically significant association between a history of pre-eclampsia and a history of vasculo-placental disorder before SSc (OR=0.80, 95% CI 0.27 to 2.31, p=0.68 and OR=1.12, 95% CI 0.53 to 2.35, p=0.77, respectively).

Multivariable analysis

Table 3 illustrates the multivariable analysis for variables associated with a vascular phenotype of SSc.

The Rodnan skin score and not the type of SSc was incorporated into the final model, these two variables being related to each other.

In the multivariable analysis, a disease duration≥5 years (OR=2.07, 95% CI 1.11 to 3.87) and Rodnan skin score (OR=1.11, 95% CI 1.06 to 1.16) were associated with a vascular phenotype of SSc. Persistent aPL antibodies (OR=3.24, 95% CI 0.96 to 10.98) had no statistical significance (p=0.059) in our population, but compared with the others variables of the model, it appeared to increase the risk of vascular phenotype.

The same variables were associated with a vascular phenotype for SSc when a history of vasculo-placental disorder was taken into account in the multivariable analysis (table 4). In this sensitivity analysis, the association of persistent aPL antibodies (OR=3.48, 95% CI 1.02 to 11.89, p=0.046) with a vascular phenotype reached statistical significance.

DISCUSSION

Main findings

In this multicentre case–control study including 378 women with SSc and a pregnancy history≥6 months before SSc diagnosis, two variables were associated with a vascular phenotype: disease duration≥5 years and Rodnan skin score. Conversely, a history of pre-eclampsia or of vasculo-placental disorder before SSc diagnosis was not associated with a vascular phenotype of SSc.

Strengths and limitations

Besides its multicentre design, this study has several strengths. First, the topic is original and has not been studied before. Second, the recruitment of participants was performed by specialists of SSc in referral hospital centres, which guarantees the validity of collected data, especially the assessment of Rodnan skin score. These specialists mostly followed the French guidelines for the therapeutic management and follow-up of their patients with SSc, what resulted, among others, in a low percentage of missing data, that is, inferior to 10%.[26] Last, we used a validated self-administered questionnaire to assess a history of pre-eclampsia in the women included in our study.[23 24]

However, our study has some limitations. Some clinical investigations were collected retrospectively, in particular immunological investigations which are not performed annually in routine in patients with SSc, unless a new clinical symptom occurs. Furthermore, a pregnancy history was reported by women themselves and the accuracy of their statement could not be checked in their obstetric files, as some of them were more than 80 years old at inclusion. Last, the low number of pre-eclampsia history

Table 2 Clinical investigations in participants

Variables		Total (n=378)	Control (n=249)	Case (n=129)	P value*
Autoantibodies					
Antinuclear antibodies positivity	n (%)	338 (99.1%)	221 (99.5%)	117 (98.3%)	0.28
Anti-centromere antibodies positivity	n (%)	198 (58.6%)	140 (63.3%)	58 (49.6%)	0.01
Anti-topoisomerase antibodies positivity	n (%)	68 (20.1%)	34 (15.4%)	34 (29.1%)	0.003
Anti-RNA polymerase III antibodies positivity	n (%)	16 (4.8%)	11 (5.0%)	5 (4.3%)	0.80
Anti-RNP antibodies positivity	n (%)	18 (5.3%)	13 (5.9%)	5 (4.3%)	0.53
Persistent aPL antibodies positivity	n (%)	14 (4.0%)	7 (3.0%)	7 (5.9%)	0.25
If positive:					
Anticardiolipin IgM	(%)	5 (38.5%)	2 (33.3%)	3 (42.9%)	
Anticardiolipin IgG	n (%)	2 (15.4%)	2 (33.3%)	0	
Antiβ2GP1 IgM	n (%)	8 (61.5%)	4 (66.7%)	4 (57.1%)	
Antiβ2GP1 IgG	n (%)	2 (15.4%)	0	2 (28.6%)	
Lupus anticoagulant	n (%)	3 (23.1%)	1 (16.7%)	2 (28.6%)	
Echocardiography					
Left ventricular ejection fraction (%)	Mean±SD	64.6±6.1	64.5±6.3	64.9±5.8	0.60
	Median (q1–q3)	65.0 (60.0–68.0)	65.0 (60.0–68.0)	65.0 (60.0–68.0)	
	Min–max	38.0–85.0	38.0–85.0	53.0–84.0	
Left ventricular diastolic function	Normal, n (%)	347 (92.0%)	229 (92.0%)	118 (92.2%)	
	Abnormal, n (%)	30 (8.0%)	20 (8.0%)	10 (7.8%)	0.94
Total pulmonary arterial pressure (mm Hg)	Mean±SD	30.6±11.3	29.0±9.5	33.4±13.6	
	Median (q1–q3)	28.0 (24.0–33.0)	28.0 (24.0–33.0)	29.0 (25.0–35.0)	
	Min–max	6.0–93.0	6.0–93.0	20.0–90.0	
Pericardial effusion	n (%)	22 (5.8%)	14 (5.6%)	8 (6.3%)	
Pulmonary function tests					
TLC (%)	Mean±SD	99.8±18.7	103.0±16.0	93.3±22.0	<0.0001
	Median (q1–q3)	101.0 (89.0–113.0)	104.0 (94.0–115.0)	94.5 (83.0–109.0)	
	Min–max	4.0–138.0	54.0–138.0	4.0–138.0	
FEV (%)	Mean±SD	101.9±24.1	104.9±21.3	95.8±27.8	0.002
	Median (q1–q3)	104.0 (89.0–115.0)	106.0 (92.0–119.0)	98.0 (83.0–110.0)	
	Min–max	1.6–182.0	3.0–182.0	1.6–175.0	
FEV1 (%)	Mean±SD	97.2±23.5	100.4±20.9	91.1±27.0	0.0009
	Median (q1–q3)	98.0 (85.0–110.0)	102.0 (88.0–112.0)	92.0 (78.0–104.0)	
	Min–max	1.2–177.0	2.5–173.0	1.2–177.0	
TLco (%)	Mean±SD	69.3±22.6	72.0±23.1	63.8±20.6	0.001
	Median (q1–q3)	69.0 (57.0–82.0)	72.0 (60.0–84.0)	65.5 (51.5–75.0)	
	Min–max	7.4–283.0	19.0–283.0	7.4–129.0	

*χ^2 or Fisher test for categorical variables or Student's or Wilcoxon test for continuous variables.
aPL, antiphospholipid; FEV_1, forced expiratory volume in one second; IgM, immunoglobulin M; RNP, RiboNucleoProtein; TLC, total lung capacity; TLco, carbon monoxide transfer factor.

does not allow to provide a narrow estimate for its OR. Although the estimate is near 1, the wide CI does not exclude the possibility that a pre-eclampsia history can be a risk factor for SSc vascular phenotype, even if the univariable as well as the multivariable analyses suggest that it is not. Multivariable model building can be discussed.[27] However, we used a variable selection procedure that takes into account the research question and the substantial knowledge. This should be distinguished from solely automated selection procedures such as stepwise selection.

Interpretation

Our study explored, among other variables, a history of pre-eclampsia as a potential risk factor for vascular phenotype in women with SSc. Indeed, pre-eclampsia and vascular complications of SSc share common features, in particular the presence of anti-angiotensin II

Table 3 Multivariable analysis for variables associated with a vascular phenotype of SSc

Variables	OR	CI	P value
Smoking history	1.07	0.60 to 1.89	0.82
Chronic arterial hypertension	1.63	0.89 to 2.99	0.11
History of pre-eclampsia	0.98	0.28 to 3.43	0.98
Age at SSc diagnosis	0.98	0.96 to 1.01	0.19
SSc duration≥5 years	2.07	1.11 to 3.87	0.02
Rodnan skin score	1.11	1.06 to 1.16	<0.0001
Anti-topoisomerase antibodies	1.67	0.75 to 3.73	0.21
Anti-centromere antibodies	1.16	0.58 to 2.32	0.67
Persistent antiphospholipid antibodies	3.24	0.96 to 10.98	0.059
Interstitial lung disease	1.11	0.56 to 2.19	0.77

SSc, systemic sclerosis.

type 1 receptor antibodies. During the third trimester of pregnancy, these autoantibodies are found in up to 89% of pre-eclamptic women.[28] They are also found in up to 85% of patients with SSc and high titres seem to be associated with the severity of the disease, especially with digital ulcers, PAH, pulmonary fibrosis and SSc-related death.[29] While it has been previously demonstrated that a history of pre-eclampsia is a risk factor for developing SSc, it was not associated with a vascular phenotype of the disease in our study.[8] The calculation of the number of subjects was based on a prevalence of pre-eclampsia history of 2% in controls. Our study of patients with SSc showed a higher prevalence of pre-eclampsia history. We can therefore consider that the absence of results on the association between a pre-eclampsia history and a vascular phenotype of SSc is not due to a lack of power.

Persistent aPL antibodies were more frequent in SSc women with a vascular phenotype than in controls in our study, with an OR of 3.24, while not reaching statistical significance. The prevalence of aPL antibodies was quite low in our study (around 6% in cases and 3% in controls). A systematic review and meta-analysis on the clinical significance of aPL antibodies in SSc reported in 2017 that the pooled prevalence of aPL antibodies, especially anticardiolipin antibodies, was higher in SSc patients with PAH, renal disease, digital ischemia or thrombosis (either arterial or venous) than in SSc patients without these clinical features.[30] Two observational studies published since found an association between aPL antibodies and ischaemic digital ulcers (aOR=8.71, 95% CI 1.31 to 55.43 for antiβ2GP1 all isotypes) or ischaemic heart disease (OR=1.89, 95% CI 1.04 to 3.45 for antiβ2GP1 IgM and OR=3.72, 95% CI 1.25 to 11.11 for anti-cardiolipin IgA) in patients diagnosed with SSc.[31 32] Another observational study with systematic review and meta-analysis found no association between aPL antibodies (considered all together) and arterial complications (considered one by one) in patients with SSc, but noted though an association between anticardiolipin antibodies (all isotypes) and PAH (aOR=6.35, 95% CI 0.99 to 41.1).[33] If the question of the association between persistent aPL antibodies and vascular complications remains uncompletely answered

Table 4 Multivariable analysis for variables associated with a vascular phenotype of SSc, taking into account a history of vasculo-placental disorder

Variables	OR	CI	P value
Smoking history	1.04	0.57 to 1.87	0.91
Chronic arterial hypertension	1.57	0.84 to 2.94	0.16
History of vasculo-placental disorder	1.26	0.50 to 3.16	0.63
Age at SSc diagnosis	0.98	0.96 to 1,01	0.16
SSc duration≥5 years	2.1	1.11 to 3.99	0.02
Rodnan skin score	1.1	1.06 to 1.16	<0.0001
Presence of anti-topoisomerase antibodies	1.75	0.78 to 3.92	0.17
Presence of anti-centromere antibodies	1.11	0.54 to 2.24	0.78
Presence of antiphospholipid antibodies	3.48	1.02 to 11.89	0.046
Interstitial lung disease	1.14	0.57 to 2.26	0.72

SSc, systemic sclerosis.

among patients with SSc, the low prevalence of aPL antibodies in the SSc population makes it not a good candidate for the prediction of vascular complications of SSc.

In our study, Rodnan skin score and a diffuse pattern of SSc were both associated with vascular phenotype of SSc. For every point of Rodnan skin score, there was an 11% increase in the risk of vascular phenotype. We chose to take into account the Rodnan skin score as a continuous variable instead of the type of SSc in the multivariable analysis because the corresponding model had the best performances. A systematic review of the literature on predictive factors for digital ulcers in patients with SSc concluded that a diffuse pattern of SSc was one of the most frequent risk factors for digital ulcers, what is in line with our results.[34]

Our study highlighted that a disease duration≥5 years was a risk factor for vascular phenotype of SSc, with an OR of 2.07. A longer disease duration is a known risk factor for PAH in the context of SSc, as illustrated by a recent systematic review.[35] Besides, a recently published registry-based Asian study on 171 patients with SSc also noted that a disease duration>3 years was associated with digital ulcers, with an OR of 4.4.[36] Considering this, physicians in charge of women with SSc should follow them regularly in order to detect and treat these vascular complications. Furthermore, implementation of preventive strategies is needed to avoid the occurrence of these complications and should be a priority goal in future interventional trials on patients with SSc.

CONCLUSIONS

In women with SSc and a pregnancy history≥6 months before SSc, a history of pre-eclampsia was not associated with a vascular phenotype in our case–control study. Conversely, Rodnan skin score and a disease duration≥5 years were independent risk factors for vascular phenotype of SSc. Medical preventive strategies are needed to avoid the occurrence of these complications and should be addressed in future interventional trials on patients with SSc.

Author affiliations
[1]Internal Medicine, Vascular Medicine and Pneumology Department, Brest University Hospital, Brest, France
[2]Inserm, Univ Brest, CHRU Brest, UMR 1304, GETBO, Brest, France
[3]Internal Medicine, Regional University Hospital Centre Tours, Tours, France
[4]Internal Medicine, Nantes University Hospital, Nantes, France
[5]Nantes University, Pole Santé, Nantes, France
[6]Department of Internal Medicine and Clinical Immunology, Rennes University Hospital, Rennes, France
[7]Institut de Recherche en Santé, Environnement et Travail (IRSET), UMRS 1085, Univ Rennes, Rennes, France
[8]Internal Medicine, Nice Cote d'Azur University, Nice, France
[9]Rheumatology, Pasteur Hospital, Nice University Hospital, Nice Sophia Antipolis University, Nice, France
[10]Rheumatology, Bordeaux University Hospital, Bordeaux, France
[11]INSERM UMR1027, Toulouse, France
[12]Internal Medicine, Toulouse University Hospital, Toulouse, France
[13]Internal Medicine, Bocage Hospital, Dijon, France
[14]Internal Medicine Department, Centre Clermont-Ferrand University Hospital, Clermont-Ferrand, France
[15]Internal Medicine Department, La Croix Saint-Simon Hospital, Paris, France
[16]Internal Medicine, Hospital Centre Cornouaille, Quimper, France
[17]Internal Medicine, DHUi2B, Saint Antoine Hospital, AP HP, Université Pierre et Marie Curie, Paris, France
[18]Rheumatology, Strasbourg University Hospital, Strasbourg, France
[19]Dermatology, Brest University Hospital, Brest, France
[20]UMR1227, Lymphocytes B et Autoimmunité, Université de Brest, INSERM, CHU de Brest, Brest, France
[21]CIC 1412, INSERM, Brest University Hospital, Brest, France
[22]Rheumatology, Brest University Hospital, Brest, France
[23]EA 22-16,INSERM ESPRI, ERI29, Brest, France
[24]Internal Medicine Department, Centre de Référence des Maladies Auto-immunes Systémiques Rares Du Nord et Nord-Ouest de France, Lille, France

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ORCID iDs
Claire De Moreuil http://orcid.org/0000-0003-1142-0978
Marie-Elise Truchetet http://orcid.org/0000-0001-8045-0180
Arsène Mekinian http://orcid.org/0000-0003-2849-3049

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