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The impact of systemic sclerosis on women's health evaluated with an ad hoc-developed patient-reported questionnaire

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Abstract

Objective: The impact of disease on women's health-related quality of life has become increasingly important in patients with rheumatic diseases (RDs). Systemic sclerosis (SSc) mostly affects women with a broad spectrum of clinical presentations and severity, and a variable impact on daily living. The objective of the present study was to specifically address "women's health" in systemic sclerosis patients through a dedicated questionnaire.

Methods: An anonymous self-reported questionnaire (only in Italian) was developed in collaboration with obstetricians and gynecologists and subsequently revised and approved by five patient representatives. The questionnaire was administered to SSc patients during scheduled visits in an outpatient Rheumatology SSc Clinic.

Results: Between April 2021 and March 2023, 168 patients accepted to participate; among them, 44.1% had received their SSc diagnosis during reproductive age ($<$45 years). The questionnaire was composed of 44 questions and included 5 sections encompassing different topics. A high rate of adherence to female cancer screening programs was recorded (86.9% for cervix and 93.6% for breast cancer), while a non-regular gynecological follow-up was observed in 36.4%, mostly in patients with more severe disease phenotype. Only 42.3% accepted to compile the Female Sexual Function Index (FSFI), which indicated a sexual dysfunction (score $\leqslant$ 26.55) in 66.2% of patients. A worse sexual function was shown to be associated with different disease manifestations, including digital ulcers. More than 90% of patients who expressed a desire for pregnancy after diagnosis received medical pre-conception counseling and were satisfied with the information provided. In contrast, discussion about contraception occurred in 37.8% of patients who had been diagnosed during fertile age. Family planning still represents an unmet need, as 43.6% of patients did not achieve their desired family size, mainly due to concerns about their capacity to care for their children.

Conclusion: The newly developed questionnaire provides a unique opportunity to comprehensively assess the experience of women with SSc. Disease burden was shown to negatively impact sexual function and adherence to regular gynecological visits. Furthermore, receiving a diagnosis during reproductive age may increase the likelihood of a reduced family size. Clinicians who take care of women with SSc should implement these domains into routine management, thus improving the health literacy of their patients.

Keywords

Women, female, gynecological, systemic sclerosis, reproduction, pregnancy, questionnaire, patients reported

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Introduction

Systemic sclerosis (SSc) is a rare and complex systemic autoimmune condition characterized by a diverse range of clinical presentations, organ involvement, and disease courses.[1] Like many other autoimmune diseases, SSc exhibits a significant female predominance, with reported female-to-male ratios ranging from 3:1 to 15:1. While disease onset is commonly observed during the perimenopausal age, it can also be observed in younger women.[1,2]

Until a few decades ago, women with SSc were advised against pregnancy due to concerns about maternal and fetal risks.[3] However, advancements in disease understanding and treatment have resulted in the availability of therapeutic options compatible with pregnancy, enabling more patients to successfully carry out pregnancies, particularly when managed within multidisciplinary clinics at specialized referral centers.[4]

As a consequence, reproductive issues and the impact of disease on women's quality of life (QoL) and health have become increasingly important in SSc and all rheumatic diseases (RDs).[5–7] A large multicentric Italian study coordinated by our Unit (Rheumatology and Clinical Immunology Unit—ASST Spedali Civili of Brescia, Italy) in 2015 proposed a newly created questionnaire that was directly administered by rheumatologists during scheduled visits of 477 consecutive RD patients allowing to collect data regarding 398 patients and their 349 pregnancies.[8] In addition, a "disease knowledge index" (DKI) was created using six key questions, in order to assess the level of patients' understanding regarding the implications of their RD on reproductive issues. The study revealed several unmet needs among RD women, indicating a lack of optimal patient-physician communication on these crucial topics.[9]

The aim of the present study was to evaluate "women's health" as a broad field encompassing various topics, including different gynecological issues, such as the menopausal period and its implications, and sexual dysfunction. A high prevalence of sexual dysfunction has been previously reported in SSc women,[10,11] as the direct involvement of the genital tract can lead to vaginal tightness and dryness, but other SSc manifestations causing disability and pain, such as digital ulcers (DUs), joint contractures, and gastrointestinal issues, have also been shown to significantly impact sexual function.[12,13]

Overall, low Female Sexual Function Index (FSFI) scores indicating sexual dysfunction have been observed in women with various RDs, suggesting shared challenges such as living with a chronic disease, reactive depression, reduced hand function, and pain.[14] These findings underscore the significant burden that the complex spectrum of SSc manifestations determines on women's lives through various pathways that may not always be considered by clinicians.

For this purpose, we have developed a new questionnaire specifically tailored to the experiences of women with SSc. This questionnaire, developed in Italian, was created in collaboration with gynecologists and patient representatives, encompassing a wide range of questions aimed at offering a comprehensive perspective from the patients' point of view.

Patients and methods

Design of the study

The study was a single-center prospective study, conducted in the Rheumatology and Clinical Immunology Unit of the ASST Spedali Civili of Brescia, Italy, between April 2021 and March 2023.

Inclusion criteria

Adult female patients (⩾18 years) regularly followed for SSc according to 2013 ACR/EULAR classification criteria[15] and attending our outpatient clinic for scheduled visits or infusions in the time interval indicated were proposed to fulfill a questionnaire.

Questionnaire

A self-reported questionnaire was developed in collaboration with obstetrics and gynecologists and subsequently revised and approved by five patients' representatives who voluntarily accepted to collaborate. The questionnaire is composed of 44 total questions, including 38 multiple-choice and 6 open-questions, and is provided as Supplementary File 1.

The newly created questionnaire included demographic information and five main sections on different topics regarding women's health:

- Gynecological issues.
- Sexual dysfunction evaluated through one entry question plus the Female Sexual Function Index (FSFI).[16]
- Contraception and family planning.
- Patient knowledge about the implications of SSc on reproductive issues (further evaluated with the "disease knowledge index").
- Pregnancy outcomes.

The FSFI is a 19-item multidimensional questionnaire, with a validated available Italian version, that was used to assess sexual function in women. Each item is scored from 0 to 5 except for questions 1, 2, and 13–16 (which are scored from 1 to 5), and then the items are scaled to achieve a maximum score of 36. A score ⩽26.55 is the cut-off proposed as the criterion for impaired sexual function.[15]

Disease knowledge index. The DKI, previously developed in the study by Andreoli et al,[8] includes six key questions (Box 1) identified as the most relevant to summarize patient's knowledge regarding the impact of RD on

Box 1. Questions and answers considered correct for the creation of the "disease knowledge index" (DKI).

Can women with rheumatic diseases get pregnant? Yes.
Can women with rheumatic diseases get pregnant through medical assisted procreation procedures? Yes.
Is it possible that disease activity can worsen during pregnancy? Yes.
Can women with rheumatic diseases take safe medications for SSc during pregnancy? Yes.
Can women with rheumatic diseases breastfeed? Yes.
Can women with rheumatic diseases have healthy children? Yes.

reproductive issues. The score is determined as follows: for each correct answer, 1 point was attributed; not given or incorrect answers were scored 0. Finally, the total score was normalized to obtain an indicator with values between 0 and 1, where 0 corresponds to the lack of knowledge and 1 to the highest knowledge.

Data collection

Data on clinical, serological, and therapeutic approach for SSc were retrospectively retrieved from the clinical charts of the patients and registered in a specific Excel data form by the Clinicians involved in the study. The answers collected through the paper questionnaire administered to the patients were registered in a separate sheet of the Excel data form. The questionnaires were anonymized, and patient identification was achieved through an alphanumeric code that cannot be traced back to individual patients. A single file containing patient identification was managed by one investigator (MGL).

Statistical analysis

Results of the answers were reported as descriptive statistics using absolute numbers and percentages (calculated according to the total number of available data) for categorical variables and mean ± SD (in case of a normal distribution), or medians, interquartile range (IQR), and min/max (in case of a skewed distribution) for continuous variables. For comparisons between two groups, the chi-square test for categorical data (or the Fisher exact test in case of a limited number of observations) and the Mann–Whitney test for continuous data were used. Statistical significance was set at a p-value less or equal to 0.05.

Ethical statement

The study was approved by the Ethical Committee (EC) of the University Hospital in Brescia (ASST Spedali Civili of Brescia; NP4876) and performed according to the principles of the Declaration of Helsinki.

Results

Between April 2021 and March 2023, the survey was proposed to 205 SSc Italian women regularly attending our outpatient clinic for scheduled visits or infusions. Among them, 168 (81.9%) accepted to participate. Most of them were Caucasian (95.8%), with a median age at the questionnaire of 58.0 (44.0–67.0) years and a median disease duration of 9.0 (5.0–17.0) years. The description of the cohort is reported in Supplementary Table 1.

Patients were divided into two groups according to the age of SSc diagnosis and are identified below as patients with diagnosis during reproductive age when ⩽45 years of age (n = 74, 44.1%) and after reproductive age when >45 years of age (n = 94, 55.9%).

Demographic data

The majority of SSc women were married (72.0%) and half of them had a high education level (secondary school and/or university diploma in n = 84/160, 52.5%); 61.1% were never-smokers. Fifty-nine (35.9%) were active workers, while 58 (35.3%) were retired and 47 (28.7%) were unemployed or housewives; more than one-third declared they had to reduce or modify their workload due to SSc. One-third (32.8%) did regular physical activity, while one-third had to reduce it, especially for arthralgias, fatigue, and dyspnea due to SSc-related-Interstitial Lung Disease (ILD) or Pulmonary Arterial Hypertension PAH.

Sexual dysfunction

Half of the patients (51.3%) reported that SSc had negatively affected their sexual activity, subjectively impacted by vaginal dryness (70.1%), gastrointestinal involvement (41.6%), DUs (33.8%), dyspnea (29.9%), cutaneous tightness (28.6%), and esthetical changes (22.1%).

FSFI questionnaire was completed by 71/168 (42.3%) patients; among the remaining subjects, 47.8% did not complete the questionnaire because considered not relevant to QoL, 36.2% because of sexual inactivity in the previous month, and 15.9% did not want to share this kind of information. Patients who did not fulfill FSFI questionnaire were older (both at disease onset and at questionnaire), more frequently in menopause state, with a higher rate of anti-topoisomerase positivity, joint contractures, and microstomia, lower percent of predicted diffuse capacity of carbon monoxide (%pDLCO), and more frequently treated with intravenous prostanoid analogs (Supplementary Table 2), suggesting a more severe SSc phenotype and damage accrual.

The median score of the FSFI questionnaire was 21.9 (9.1–30.1) and 66.2% had a score ⩽ 26.55 indicating sexual dysfunction. By comparing women reporting sexual dysfunction to the others, they were older and with higher frequency of menopause and comorbidities. Regarding SSc features, they had longer disease duration, higher rates of esophageal involvement, higher systolic pulmonary arterial pressures (PAPs) on echocardiography, lower %pDLCO, and received more therapies, especially intravenous prostanoid analogs (Table 1).

Gynecological issues

Most patients ($n = 103/162$, 63.6%) declared a regular gynecological follow-up with annual frequency in 47/103 (45.6%) and every 2–3 years in the remaining 56/103 (54.4%). Patients who did not undergo regular controls, as compared to the others, were older, more frequently on menopause at the time of the questionnaire, and presented a more severe SSc phenotype, characterized by a higher prevalence of anti-topoisomerase I positivity, higher rates of PAH, diastolic left ventricle (LV) dysfunction, DUs, pitting scars, and microstomia, and requiring a more aggressive therapeutic approach (Table 2).

A high rate of adherence to the free female national cancer screening programs was recorded: 86.9% for cervical cancer ($n = 86/99$; women aged 25–64 years: $n = 105$) and 93.6% for breast cancer ($n = 103/110$; women aged 45–74 years: $n = 111$). Moreover, among 43 patients aged < 45 years not eligible for mammography screening, 48.6% spontaneously underwent ultrasound examination for breast cancer screening.

At the time of the questionnaire, 70.2% of patients had reached menopause. Median age at menopause was 49.5 (46.4–52.0) years; 93 out of 113 (82.3%) women had spontaneous menopause; 21/113 (18.6%) were treated with hormone replacement therapy for a median of 5.0 (3.5–5.5) years.

Contraception and family planning

Considering 74 patients who received SSc diagnosis during potentially reproductive age, two-thirds declared they never discussed contraceptive methods with their SSc clinicians, mainly because they thought contraception was not related to SSc or was not of interest for their rheumatologist ($n = 28/46$, 69.9%), while half of them discussed the topic with their gynecologist ($n = 25/46$, 54.3%). Seventy percent of patients ($n = 46/65$) reported that they ever used a contraceptive method, most frequently condom (65.2%), followed by estrogen–progestogen pill (47.8%), progesterone-only pill (36.9%), and intrauterine device (13.0%).

Half of the patients who received SSc diagnosis during reproductive age desired a pregnancy after this event ($n = 39/74$, 52.5%). Almost all of them (94.9%) discussed this with their SSc clinicians, with 97.3% reporting they were satisfied with the counseling received and felt adequately informed about the potential risks. Among patients with pregnancy desire after SSc diagnosis, 43.6% were not satisfied with their family size and had less children than desired. Regarding the reasons, patients were mostly concerned of not being able to care for their children ($n = 8/17$, 45.1%) and of medications potentially harmful to the baby ($n = 4/17$, 23.5%).

Pregnancy

Among 168 SSc patients who compiled the questionnaire, 137 reported 312 pregnancies with a median of 2 (IQR 1-3) pregnancies *per* woman, including 4 twin pregnancies. Regarding the outcomes, 63/312 (20.2%) had a miscarriage, while the majority ($n = 249/312$, 79.8%) yielded live births ($n = 253$). Preterm births were reported in 42/197 (21.3%) cases, of which 8/42 (19.0%) before 34 gestational weeks; overall adverse pregnancy outcomes were recorded in 17/194 (8.8%) women, namely, hypertensive disorders ($n = 10/194$, 5.2%), fetal growth restriction ($n = 6/194$, 3.1%), and gestational diabetes ($n = 4/194$, 2.1%). Maternal characteristics and obstetric outcomes were compared between pregnancies conducted after ($n = 48$) and before ($n = 264$) diagnosis (Table 3) and showed higher maternal age at conception, higher rate of cesarean sections, and a lower weight of the babies at birth in the first group. The same results were confirmed by comparing pregnancies that occurred before ($n = 96$) and after ($n = 48$) SSc diagnosis in patients who received the diagnosis during potentially reproductive age ($n = 74$) (Supplementary Table 3).

Most of the SSc women having pregnancies (72% limited cutaneous subset, 47% former or current DUs, 50% esophageal involvement, 6% interstitial lung disease, and 3% previous scleroderma renal crisis) after the diagnosis reported improvement (especially of Raynaud phenomenon and DUs) or stability of their disease manifestations during pregnancy ($n = 25/30$, 83.3%).

Disease knowledge index

The disease knowledge index was evaluated for the subgroup of 74 patients who received SSc diagnosis during reproductive age and showed a high rate of correct answers regarding the possibility for SSc women to become pregnant ($n = 57/68$, 83.8%), intermediate regarding the possibility to breastfeed and have healthy children ($n = 39/68$, 57.4% for both), while lower levels regarding medically assisted procreation procedures, disease worsening, or medications allowed during pregnancy (Figure 1). The median value of the DKI was 0.57 (0.29–0.61). Patients who received medical counseling on reproductive issues

Table 1. Comparison of demographic, clinical, and therapeutic features: patients presenting sexual dysfunction versus no sexual dysfunction.

	No sexual dysfunction (FSFI > 26.55) (*N* = 24)	Sexual dysfunction (FSFI ⩽ 26.55) (*N* = 47)	*p-value*
Age at disease onset[a], years	32.5 (29.0–43.0)	44.0 (31.5–51.0)	0.048
Age at questionnaire, years	42.5 (35.5–50.8)	56.0 (43.5–66.5)	<0.001
Disease duration, years	6.0 (2.8–9.5)	12.0 (6.0–18.5)	0.006
Menopause at questionnaire	5/24 (20.8)	31/47 (65.9)	<0.001
CCI	1.0 (1.0–1.0)	2.5 (3.0–4.8)	0.004
Anti-centromere+	12/24 (50.0)	24/47 (51.1)	0.932
Anti-topo1+	4/24 (16.7)	10/47 (21.3)	0.759
Anti-RNAP3+	3/24 (12.5)	1/47 (2.1)	0.109
Other auto-antibodies+	5/24 (20.8)	12/47 (25.5)	0.661
Limited cutaneous involvement	20/24 (83.3)	41/47 (87.2)	0.724
mRSS	2.5 (2.0–5.5)	2.5 (2.0–6.0)	0.858
Digital ulcers (ever)	8/24 (33.3)	25/46 (54.3)	0.095
Pitting scars	10/24 (41.7)	18/46 (39.1)	0.837
Telangiectasia	11/24 (45.8)	26/45 (57.7)	0.343
Calcinosis	4/24 (16.7)	8/46 (17.4)	1.000
Esophageal involvement	12/24 (50.0)	36/47 (76.6)	0.023
Synovitis	4/24 (16.7)	7/47 (14.9)	1.000
Joint contractures	3/24 (12.5)	4/47 (8.5)	0.682
Microstomia	1/24 (4.2)	5/47 (10.6)	0.656
Sicca	5/24 (20.8)	11/47 (23.4)	0.806
Myositis (ever)	0/24 (0.0)	1/47 (2.1)	1.000
Heart involvement (ever)	4/24 (16.7)	12/47 (25.5)	0.398
Myocarditis (ever)	1/24 (4.2)	2/47 (4.3)	1.000
Arrythmia (ever)	0/24 (0.0)	2/47 (4.3)	0.546
Abnormal LV relaxation (ever)	2/24 (8.3)	11/47 (23.4)	0.195
Last EF%	60.0 (60.0–66.3)	60.0 (57.0-64.0)	0.251
Last PAPs	25.0 (24.5–25.5)	30.0 (26.0–32.0)	0.001
Pulmonary arterial hypertension (PAH) (ever)	0/24 (0.0)	4/47 (8.5)	0.292
Scleroderma renal crisis (ever)	1/24 (4.2)	0/47 (0.0)	0.338
Interstitial lung disease (ILD) (ever)	4/9 (44.4)	16/30 (53.3)	0.716
Last %pFVC	96.0 (88.0–112.0)	103.0 (94.0–118.0)	0.317
Last %pDLCO	76.0 (70.0–81.0)	71.0 (58.0–79.0)	0.048
Last %pDLCO/VA	81.5 (74.0–87.5)	80.0 (71.0–84.5)	0.528
Major organ involvement[b] (ever)	4/24 (16.7)	18/46 (39.1)	0.055
Synchronous[c] cancer	1/24 (4.2)	2/47 (4.3)	1.000
Calcium channel blockers	12/24 (50.0)	27/47 (57.4)	0.551
Antiplatelets	18/24 (75.0)	34/47 (72.3)	0.811
Iloprost	2/24 (8.3)	15/47 (31.9)	0.028
Anti-endothelin receptor	0/24 (0.0)	3/47 (6.4)	0.546
PDE5 inhibitors	0/24 (0.0)	3/47 (6.4)	0.546
Selexipag	0/24 (0.0)	1/47 (2.1)	1.000
PPI	14/24 (58.3)	37/47 (78.7)	0.071
Nintedanib	0/24 (0.0)	1/47 (2.1)	1.000
Oxygen supply	0/24 (0.0)	0/47 (0.0)	1.000
IVIG	0/24 (0.0)	1/47 (2.1)	1.000
Steroid	3/24 (12.5)	15/47 (31.9)	0.075
Steroid dose, mg/week	17.5 (16.3–26.3)	32.5 (19.4–35.0)	0.432
Hydroxychloroquine	5/24 (20.8)	6/47 (12.7)	0.490
Immunosuppressive therapy	5/24 (20.8)	11/47 (23.4)	0.806
Number of therapies for SSc	2.0 (2.0–3.0)	3.0 (2.0–4.0)	0.036

Continuous variables are presented as median (first–third quartile) and compared with the Mann–Whitney test; categorical variables are presented as number/number available data (%) and compared with the Chi-square test/Fisher's exact test.

[a]SSc onset = onset of first non-Raynaud manifestation.

[b]Major organ involvement = heart, lungs, kidney involvement.

[c]Synchronous malignancy = ± 3 years from SSc onset.

Abbreviations: FSFI = female sexual function index, CCI = Charlson Comorbidity Index, topo1 = topoisomerase 1, RNAP3 = RNA polymerase 3, mRSS = modified Rodnan Skin Score, EF = ejection fraction, PAPs = systolic pulmonary arterial pressure, pFVC = predicted forced vital capacity, pDLCO = predicted lung diffusion of carbon monoxide, VA = alveolar volume, PDE5 = phosphodiesterase 5, PPI = proton pump inhibitor, IgIV = intravenous immunoglobulin, SSc = Systemic Sclerosis.

Table 2. Comparison of demographic, clinical, and therapeutic features: patients declaring regular versus not regular gynecological controls.

	Patients (*N* = 168)	Regular gynecological follow-up (*N* = 103)	Not regular gynecological follow-up (*N* = 59)	*p*
Age at disease onset[a], years	46.0 (33.0–55.0)	43.5 (32.0–53.8)	50.0 (40.3–58.0)	0.024
Age at questionnaire, years	58.0 (44.0–67.0)	57.0 (43.0–65.3)	65.0 (54.5–69.5)	0.005
Disease duration, years	9.0 (5.0–17.0)	9.0 (5.0–17.0)	10.5 (6.0–15.5)	0.802
Menopause at questionnaire	111/159 (69.8)	63/101 (62.4)	48/58 (82.8)	0.007
CCI	3.0 (1.5–4.0)	3.0 (1.0–4.0)	4.0 (2.3–4.0)	0.409
Anti-centromere+	83/168 (49.4)	51/103 (49.5)	29/59 (49.2)	0.965
Anti-topo1+	48/168 (28.6)	23/103 (22.3)	22/59 (37.3)	0.041
Anti-RNAP3+	7/168 (4.2)	6/103 (5.8)	1/59 (1.7)	0.424
Other auto-antibodies+	30/168 (17.9)	23/103 (22.3)	7/59 (11.9)	0.099
Limited cutaneous involvement	136/168 (80.9)	87/102 (84.5)	44/59 (74.6)	0.092
mRSS	4.0 (2.0–6.0)	3.0 (2.0–6.0)	4.0 (2.0–7.0)	0.163
Digital ulcers (ever)	87/165 (52.7)	43/102 (42.2)	41/57 (71.9)	<0.001
Pitting scars	79/166 (47.6)	41/103 (39.8)	35/57 (61.4)	0.009
Telangiectasia	99/165 (60.0)	60/103 (58.3)	37/56 (66.1)	0.334
Calcinosis	26/166 (15.7)	14/103 (13.6)	12/57 (21.1)	0.221
Esophageal involvement	118/167 (70.7)	68/103 (66.0)	46/58 (79.3)	0.075
Synovitis	23/167 (13.8)	11/103 (10.7)	10/58 (17.2)	0.235
Joint contractures	27/167 (16.2)	13/103 (12.6)	13/58 (22.4)	0.105
Microstomia	24/167 (14.4)	11/103 (10.7)	13/58 (22.4)	0.045
Sicca	41/166 (24.7)	25/102 (24.5)	15/58 (25.9)	0.849
Myositis (ever)	2/167 (1.2)	2/103 (1.9)	0/58 (0.0)	0.536
Heart involvement (ever)	40/167 (23.9)	20/103 (19.4)	18/58 (31.0)	0.096
Myocarditis (ever)	5/167 (2.9)	2/103 (1.9)	3/58 (5.2)	0.352
Arrythmia (ever)	10/167 (5.9)	6/103 (5.8)	4/58 (6.9)	0.748
Abnormal LV relaxation (ever)	35/167 (20.9)	16/103 (15.5)	17/58 (29.3)	0.038
Last EF%	60.0 (57.0–64.0)	60.0 (57.0–64.0)	60.0 (55.5–61.0)	0.251
Last PAPs	27.0 (25.0–30.5)	27.0 (25.0–30.0)	30.0 (25.8–33.5)	0.094
Pulmonary arterial hypertension (ever)	6/167 (3.6)	1/103 (1.0)	5/58 (8.6)	0.023
Scleroderma renal crisis (ever)	3/167 (1.8)	3/103 (2.9)	0/58 (0.0)	0.554
Interstitial lung disease (ever)	53/95 (55.8)	27/53 (50.9)	25/39 (64.1)	0.208
Last %pFVC	103.0 (89.3–117.0)	104 (91.0–119.0)	101.5 (78.8–116.3)	0.084
Last %pDLCO	69.0 (57.0–79.0)	75.0 (64.0–83.0)	60.0 (49.0–69.8)	0.000
Last %pDLCO/VA	79.0 (68.0–89.0)	80.0 (73.0–88.0)	74.0 (65.5–92.0)	0.213
Major organ involvement[b] (ever)	60/165 (36.4)	32/102 (31.4)	26/57 (45.6)	0.067
Synchronous[c] cancer	6/167 (3.6)	4/103 (3.9)	2/58 (3.4)	1.000
Calcium channel blockers	95/167 (56.9)	55/103 (53.4)	37/58 (63.8)	0.201
Antiplatelets	123/167 (73.7)	80/103 (77.7)	39/58 (67.2)	0.148
Iloprost	56/167 (33.5)	22/103 (21.4)	33/58 (56.9)	<0.001
Anti-endothelin receptor	14/167 (8.4)	4/103 (3.9)	10/58 (17.2)	0.004
PDE5 inhibitors	7/167 (4.2)	1/103 (1.0)	6/58 (10.3)	0.005
Selexipag	1/167 (0.6)	1/103 (1.0)	0/58 (0.0)	1.000
PPI	130/167 (77.8)	79/103 (76.7)	48/58 (82.8)	0.366
Nintedanib	5/167 (2.9)	2/103 (1.9)	3/58 (5.2)	0.352
Oxygen supply	3/167 (1.8)	0/103 (0.0)	3/58 (5.2)	0.045
IVIG	1/167 (0.6)	1/103 (1.0)	0/58 (0.0)	1.000
Steroid	48/167 (28.7)	25/103 (24.3)	21/58 (36.2)	0.108
Steroid dose, mg/week	25.0 (17.5–35.0)	30.0 (17.5–35.0)	25.0 (17.5–35.0)	0.656
Hydroxychloroquine	17/167 (10.2)	11/103 (10.7)	6/58 (10.3)	0.947
Immunosuppressive therapy	48/167 (28.7)	25/103 (24.3)	20/58 (34.5)	0.166
Number of therapies for SSc	3.0 (2.0–4.0)	3.0 (2.0–4.0)	4.0 (2.4–5.0)	0.001

Continuous variables are presented as median [first–third quartile] and compared with the Mann–Whitney test; categorical variables are presented as number/number available data (%) and compared with the Chi-square test/Fisher's exact test.

[a]SSc onset = onset of first non-Raynaud manifestation.

[b]Major organ involvement = heart, lungs, kidney involvement.

[c]Synchronous malignancy = ± 3 years from SSc onset.

Abbreviations: CCI = Charlson Comorbidity Index, topo1 = topoisomerase 1, RNAP3 = RNA polymerase 3, mRSS = modified Rodnan Skin Score, EF = ejection fraction, PAPs = systolic pulmonary arterial pressure, pFVC = predicted forced vital capacity, pDLCO = predicted lung diffusion of carbon monoxide, VA = alveolar volume, PDE5 = phosphodiesterase 5, PPI = proton pump inhibitor, IgIV = intravenous immunoglobulin, SSc = Systemic Sclerosis.

Table 3. Comparison of pregnancy occurred before versus after SSc diagnosis.

	Pregnancies (*n* = 312)	Pregnancies after SSc diagnosis (*n* = 48)	Pregnancies before SSc diagnosis (*n* = 264)	*p*
Maternal age, years	28.0 (24.0–32.0)	32.0 (29.0–36.0)	27.0 (23.0–30.0)	<0.001
ARTs	2/312 (6.4)	0/48 (0.0)	2/264 (7.6)	1.000
Twin pregnancies	4/312 (1.3)	1/48 (2.0)	3/264 (1.1)	0.489
Miscarriages/IUDs	63/312 (20.2)	12/48 (25.0)	51/264 (19.3)	0.367
Hesitated in live births	249/312 (79.8)	36/48 (75.0)	213/264 (80.7)	0.367
Live births	253	37	216	—
Cesarean sections	55/228 (24.1)	15/35 (42.9)	40/193 (20.6)	0.005
Gestational age, weeks	39.0 (37.0–40.0)	39.0 (37.0–40.0)	39.0 (37.0–40.0)	0.310
Preterm births	42/197 (21.3)	7/36 (19.4)	35/161 (21.7)	0.761
Severe preterm birth (<34 GW)	8/42 (19.0)	3/7 (42.9)	5/35 (14.3)	0.113
Weight at birth, kg	3.2 (2.9–3.6)	2.9 (2.7–3.2)	3.3 (3.0–3.7)	0.002
Adverse pregnancy outcomes	17/194 (8.8)	4/36 (11.1)	13/158 (8.2)	0.527
Gestational hypertension	7/194 (3.6)	2/36 (5.6)	5/158 (3.2)	0.616
Preeclampsia	2/194 (1.0)	0/36 (0.0)	2/158 (1.3)	1.000
Eclampsia	0/194 (0.0)	0/36 (0.0)	0/158 (0.0)	1.000
HELLP syndrome	1/194 (0.5)	0/36 (0.0)	1/158 (0.6)	1.000
Gestational diabetes	4/194 (2.1)	2/36 (5.6)	2/158 (1.3)	0.157
FGR	6/194 (3.1)	0/36 (0.0)	6/158 (3.7)	0.595
Perinatal deaths	3/225 (1.3)	1/35 (2.9)	2/190 (1.1)	0.399
Admissions to neonatal ICU	17/225 (7.6)	4/35 (11.4)	13/190 (6.8)	0.312
Perinatal infections	11/225 (4.9)	3/35 (8.6)	8/190 (4.2)	0.384
Breastfeeding	164/227 (72.2)	23/35 (65.7)	141/192 (73.4)	0.348
Breastfeeding duration, months	6.0 (3.0–12.0)	8.5 (6.0–12.0)	6.0 (3.0–11.8)	0.200

Continuous variables are presented as median (first–third quartile) and compared with the Mann–Whitney test; categorical variables are presented as number/number available data (%) and compared with the Chi-square test/Fisher's exact test.
Abbreviations: ART = assisted reproductive technique, IUD = intrauterine death, GW = gestational week, HELLP = hemolysis, elevated liver enzymes and low platelets, FGR = fetal growth restriction, ICU = intensive care unit.

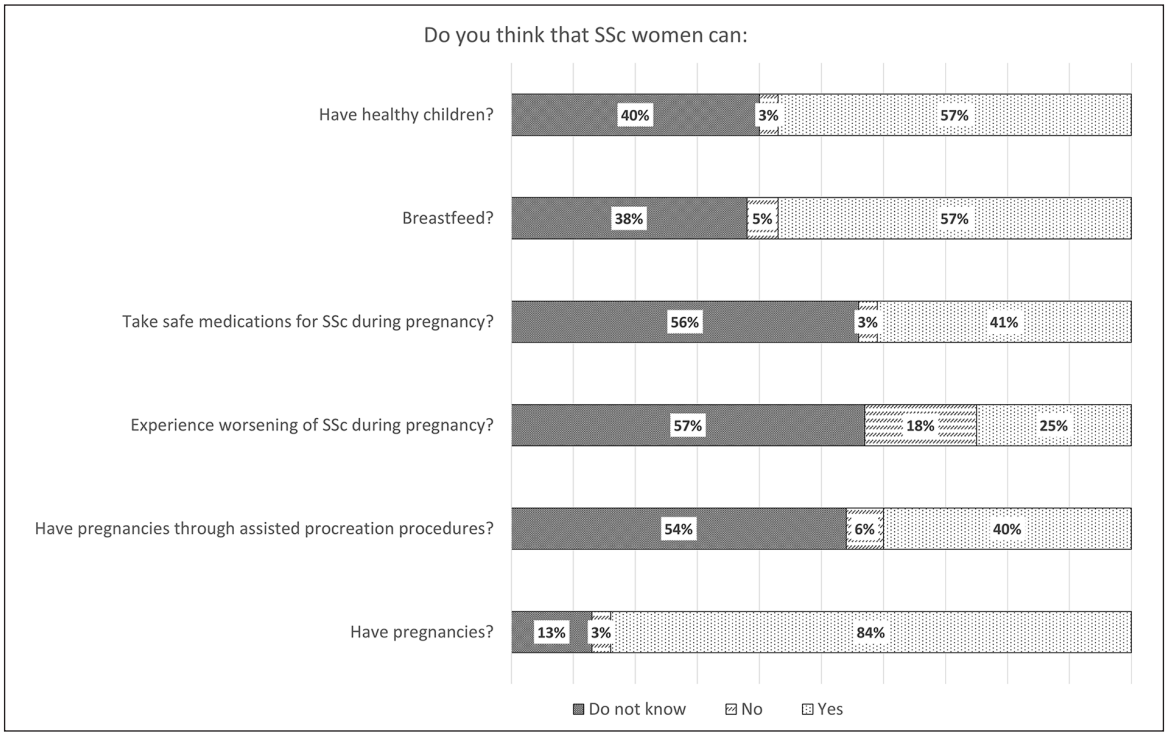

Figure 1. Patients' knowledge index about reproductive issues.

exhibited a significantly higher score at DKI as compared with those who did not receive it (0.57 (0.43–0.71) vs 0.43 (0.14–0.57), *p*: 0.004). Notably, 31/68 (45.6%) women declared to have collected information about SSc and its implications from other sources in addition to those provided by the referral SSc clinicians. In particular, 83.4% declared to consult websites, 35.5% to share information with other SSc patients, and 22.6% to have received information from patients' associations.

Discussion

Gender medicine is a growing field of interest in clinical research, with an increasing number of studies focusing on understanding the implications of RDs on women's lives.

In the present study, the collaboration with gynecologists-obstetricians and patients' representatives allowed the development of a specific questionnaire for SSc women, by adapting and extending a previous one focusing on women's health in different RDs.[8] This questionnaire was administered to a large number of patients with confirmed SSc diagnosis, during scheduled visits or infusions. Noteworthy, 44% of our interviewed patients received their diagnosis below 45 years of age, thus allowing the evaluation of their perspective on reproductive issues.

One notable observation was the high rate of adherence to female cancer screening (cervix and breast cancer), with an additional group of patients spontaneously undergoing regular controls. This was likely to be influenced by well-organized screening programs in Italy, actively recruiting subjects, and offering free exams.[17] However, about one-third of patients reported a lack of regular gynecological consultations, a subgroup mostly represented by menopausal women with severe disease phenotype. This lack of consultations could potentially be attributed to the burden of SSc-related exams and complications, which have a significant impact on patients' health and QoL. Moreover, preventive screening exams may not have been perceived as essential within the context of a severe SSc phenotype.

The burden of SSc on sexual function has also been emphasized, as indicated by the FSFI showing sexual dysfunction in over half of cases. Patients reported that various disease manifestations negatively affected sexual function by causing functional impairment, embarrassment, or impacting esthetical appearance, reinforcing previous reports.[12,18]

It is notable that only 40% of the women interviewed accepted to complete the FSFI questionnaire and that some of them reported feelings of shame and discomfort in sharing such information, even within the context of medical research conducted through an anonymous questionnaire. This could be related to a topic that is still perceived as a taboo and for this reason should be further investigated and discussed during follow-up consultations.

This underscores the importance of addressing sexual health concerns as part of a comprehensive care for individuals with SSc and highlights the need for tailored interventions to improve both physical and emotional well-being in SSc patients. It also underlines the importance of creating a supportive context for patients to feel comfortable sharing their experiences and concerns and, mainly, to plan a pregnancy with the referral clinicians.[19,20]

The data collected regarding patients who received their diagnosis during their reproductive age revealed that 94% of those desiring pregnancy discussed it with their SSc clinicians, and nearly all expressed satisfaction with the counseling received and felt well-informed about potential risks. This rate is significantly higher than that recently reported in a Chinese cross-sectional study conducted by the Chinese Organization for Scleroderma, in which more than half of patients reported they did not receive counseling before pregnancy.[21]

SSc women who had previously received medical counseling on reproductive issues demonstrated significantly higher scores in the DKI. This may be attributed, in part, to the presence of a Pregnancy Clinic within our center, which has fostered expertise among specialists and influenced our approach to patient care. These findings, based on patient perspectives, underscore the importance of comprehensive pre-conception counseling, as supported by existing recommendations and expert opinions in RDs,[17] but here confirmed in a real-life scenario.

On the contrary, we observed that SSc women rarely raised the discussion on contraception with their rheumatologists, primarily due to a lack of awareness regarding the importance of this topic in relation to their SSc. While estrogens are not absolutely contraindicated in SSc as they are in other RDs like anti-phospholipid syndrome and active systemic lupus erythematosus,[18] it is crucial to conduct a comprehensive medical evaluation. This should include testing for anti-phospholipid antibodies and assessing the overall thrombotic risk before prescribing estrogen-containing compounds, whether for contraceptive purposes or hormonal replacement therapy.[4]

Moreover, our questionnaire revealed the persistence of concerns on medications prescribed during pregnancy, which was reported as a reason contributing to the restriction of family size in about 20% of cases. A similar scenario was highlighted in a recent Chinese study, in which 24% of a group of 22 SSc patients did not carry out their family plan due to worries mainly about heredity or aggravation of the disease.[21] Nonetheless, the Chinese social and cultural context possibly represents a bias and should be carefully considered when taken as a comparison.

Furthermore, knowledge levels regarding medications compatible with pregnancy were among the lowest when evaluated through the DKI score, with 41% of patients reporting a lack of sufficient information on this topic. Importantly, nearly half of women with their diagnosis during reproductive age declared to collect information about their disease or implications on reproductive issues from other sources, mainly web-based.

The questionnaire also offered the unique opportunity to collect information regarding pregnancy and compare the outcomes of those conducted before and after SSc diagnosis. Data collected from patients' reports were mostly aligned with previous literature, confirming higher rates of cesarean sections and lower birth weight in pregnancies after diagnosis, while contrary to expectations, the frequency of preterm delivery was found to be similar in both groups. The majority of women noted stability or improvement in disease manifestations during pregnancy, possibly driven by the beneficial vasodilatory effect of estrogens on vascular manifestations, such as Raynaud's phenomena and DUs.[4]

However, it is important to acknowledge several limitations that may have impacted our study:

- Possible recall and self-reported data bias, particularly in the pregnancy section for individuals of older age at the time of questionnaire completion.
- Only Italian-speaking patients have been included.
- Potential selection bias, as patients with lower educational status or non-Italian background may have been underrepresented.
- The length of the questionnaire, which required approximately 30 min for completion, could have affected the reliability of responses. However, the DKI consisting of only six key questions may be improved in the future to serve as a screening tool for assessing SSc women's health in everyday clinical practice.
- Our data derive from the context of an academic referral center with specialized clinics for SSc and pregnancy. Results may vary for SSc patients in different countries with diverse healthcare systems or in non-referral centers for SSc. Further research in varied settings is warranted to confirm the generalizability of our findings.
- The self-reported questionnaire *ad hoc* created and used for the present study should be validated in an external cohort.

In conclusion, our study specifically addressed SSc women's health through a newly created questionnaire, enabling a comprehensive evaluation of patients' experience. Clinicians caring for SSc women should be aware of the existing unmet needs and should enhance the discussion of these topics during daily clinical practice, keeping in mind possible difficulties due to diverse cultural contexts, where sexual life is still considered a taboo. By fostering collaboration between scientific societies and patients' associations, valuable insights could be gained and informative campaigns could be developed to enhance knowledge and awareness among both women with SSc and clinicians. Furthermore, the results of this questionnaire may be significantly influenced by various factors, including geographic and socio-economic conditions. In addition, translating and distributing the questionnaire in other countries could help identify further unmet needs.

Ultimately, this collaborative effort can lead to an improvement in the QoL for SSc patients.

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Supplemental material

Supplemental material for this article is available online.

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