Università degli Studi di Modena e Reggio Emilia
Facoltà di Medicina e Chirurgia

Corso di Laurea Magistrale in Medicina e Chirurgia

Dipartimento di Scienze Mediche e Chirurgiche Materno-Infantili e dell'Adulto

Unità Operativa di Ginecologia Ostetricia

SCLERO-GYN: GYNECOLOGICAL HEALTH AND ULTRASOUND EVALUATION AMONG FERTILE WOMEN AFFECTED BY SISTEMIC SCLEROSIS: OBSERVATIONAL STUDY IN A REFERENCE CENTER

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Tesi di laurea di:

Denise Bertini

Anno accademico 2024-2025

A tutte le donne che giorno dopo
giorno fanno il cambiamento

"Le donne hanno sempre dovuto lottare doppiamente. Hanno sempre dovuto portare due pesi, quello privato e quello sociale. Le donne sono la colonna vertebrale delle società"
(Montalcini s.d.)

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ABSTRACT

Background

Systemic sclerosis (SSc) is a rare, immune-mediated and progressive multisystemic connective tissue disease. It is characterized by vasculopathy and abnormal collagen deposition, culminating in fibrosis of the skin and internal organs.

Ssc is predominantly observed in females, most prevalent in the third to fifth decade of life. The disease manifests itself in nearly 50% of patients during their reproductive years. SSc could affect various dimensions of women's lives, including uro-gynecological health, reproduction, and sexuality. Although endometriosis remains an enigmatic condition with under-explored aetiology, immune system alterations have been proposed as a contributing factor to the development of ectopic endometrial tissue; however, there are no data on the incidence of autoimmune gynecological conditions such as endometriosis in patients affected by SSc.

SSc is a condition recognized for its impact on blood vessels, specifically renal vessels, and may lead to severe complications such as a scleroderma renal crisis. Despite the similar capacity of the uterine and renal vessels, ultrasound evaluation and Doppler velocimetry of the uterine arteries have not yet been explored.

The aim of the study

The purpose of this study is to provide a comprehensive report on the gynecological health of SSc-affected fertile women both clinically and ultrasoundly.

Materials and Methods

The present study is an observational, cross-sectional, monocentric study performed in the scleroderma Unit of the University Hospital of Modena in collaboration with the Department of Medical and Surgical Sciences for Mothers, Children and Adults of the same institution.

The study duration was 9 months.

This study was conducted in two distinct phases. Initial phase consisted of a case-control study during which four validated questionnaires (SF-12, MEDI-Q, FSFI, USP) were administered to assess gynecological health, sexual well-being, and quality of life in both patients with systemic sclerosis and healthy controls (HC). The second phase involved a cross-sectional section, referring to a comprehensive pelvic gynecological and ultrasound evaluation exclusively in patients diagnosed with systemic sclerosis.

Inclusion criteria were the diagnosis of SSc according to the 2013 ACR/EULAR criteria, adult age (≥18 years), fertile age, non-pregnant and non-breastfeeding. The age-matched healthy controls (HC) were enrolled by routine controls in the gynecological clinic.

Results

29 Caucasian fertile patients with SSc and 33 HC gave their consent and were finally enrolled in the study. The mean age was 39.57 years, with a duration of the disease of 5.7 years. Half of the patients (53%) were diagnosed with lcSSc. The mean modified Rodnan skin score (mRSS) was 8 ±8.26, and 45% of the participants exhibited positivity for Scl/70. Scores for MEDI-Q, the FSFI full-scale score (with a cutoff of <26.5 indicating sexual dysfunction), and SF-12 were observed to be worse in patients with SSc. Furthermore, 10% of the patients reported a diagnosis of polycystic ovary syndrome (PCOS), while 17% were affected by endometriosis, -3 of whom received a diagnosis during the visit and 2 had a previous diagnosis. Notably, 14% of the patients demonstrated at least one uterine artery with increased resistance to blood flow.

Conclusions

Despite the limitations of the study, this well-selected sample for a unique referral center is considerable. The results highlight a high prevalence of gynecological, menstrual and sexual dysfunctions in patients with SSc, with a significant impact on quality of life.

In our sample, the incidence of endometriosis is 17%, compared to 10% among fertile Italian women. This suggests that the incidence may be higher in SSc patients; but it should be taken with caution given the under-diagnosis of endometriosis.

In our study, resistance in the uterine arteries exceeded 95 ° in 14% of the patients, while the expected percentage should have been 5%. This suggests a potential increase in uterine resistance in patients with scleroderma. To our knowledge, this is the first study to demonstrate the possible involvement of the uterine arteries by disease and the need for a specific and multidisciplinary gynecological framework in patients with SSc.

ABBREVIATIONS

SSc: Systemic Sclerosis

VAS: Visual Analogue Scale

IDEA: International Deep Endometriosis Analysis group

Ut-A: Uterine Artery Doppler

UtA-PIs: Pulsatility Index Uterine Artery Doppler

SF-12: Short-form-health-survey questionnaire

QoL: Qualify of Life

MEDI-Q: Menstrual Distress Questionnaire

FSFI: Female Sexual Index

USP: Urinary Symptom Profile

IcSSc: Limited cutaneous subset SSc

dcSSc: Diffuse Cutaneous subset SSc

mRss: Modified Rodman Skin Score

csDMARDs: Conventional Synthetic Disease-Modifying Antirheumatic Drug

DMARDS: Synthetic Disease Modifying Artirheumatic Drugs

ART: Assisted Reproductive Technology

ACA: Anti-Centromero Antibody

PCOS: Polycystic Ovary Syndrome

VHI: Vaginal Health Index

RP: Raynaud's Phenomenon

HC: Health Controls

BMI: Body Mass Index

ACA: Anti-nuclear antibodies

ATA: Anti-Scl-70 antibodies

CENP-1: Anti-centromere antibodies

RNAP: Anti-RNA polymerase

ESR: Erythrocyte Sedimentation Rate

CRP-C: C-reactive Protein

SU: Skin Ulcers

DU: Digital Ulcers

SRC: Scleroderma Renal crisis

DPS: Digital pitting scar

NVC: Nailfold Video Capillaroscopy

PAH: Pulmonary Arterial Hypertension

ILD: Interstitial Lung Disease

PF: Pulmonary Fibrosis

DLco: Diffusion Lung CO

HRCT: Hight Resolution Computed Tomography

GI: Gastrointestinal Involvements

GERD: Gastrointestinal Esophageal Reflux Disease

EGD: EsophagoGastroDueodenoscopy

CIPO: Chronic Intestinal Pseudo-Obstruction

SIBO: Small Intestinal Bacterial Overgrowth

GAVE: Gastric Antral Vascular Ectasia

AKI: Acute Kidney Injury

HEELPS: Hemolysis, Elevate Liver enzymes, Low Platelet count

DHEAS: Dehydroepiandrosterone

aPL: anti-Phospholipid antiantibodies

CYC: Cyclophosphamide

SS: Sjogren's Syndrome

IBD: Infiammatory Bowel Disease

RA: Rheumatoid arthritis

CLD: Coeliac Disease

MS: Multiple Sclerosis

CD: Chron's Disease

UC: Ulcerative Disease

ATD: Autoimmune Thyroid Disorder

SLE: System Lupus Erythematosus

PVOD-like: Pulmonary Veno-Occlusive Disease

CMR: Cardiovascular Magnetic Resonance

RDs: Rheumatic Diseases

RRI: Renal Resistive Index

DMARDS: Synthetic Disease Modifying Antirheumatic Drugs

INTRODUCTION

SYSTEMIC SCLEROSIS

Systemic sclerosis (SSc) is a rare, immune-mediated, rheumatic, progressive and multisystemic connective tissue disease[1,2]. It is characterized by vasculopathy and abnormal collagen deposit, leading to fibrosis of the skin and major internal organs. This pathological process is determined by 3 hallmarks: vasculopathy, immune activation and fibrosis[3,4]. The immune dysregulation affects both the adaptive and innate systems[5]. The association of vascular and immunoinflammatory aspects determines micro and macro abnormalities, activation of endothelial cells and vascular changes[5].

SSc is the most severe disease within "scleroderma-like" disorders, conditions that clinically resemble scleroderma[5,6]. This is a group with predominant features such as specific organ involvements (notably skin thickening), difficulty to treat, treatable with anti-inflammatory therapies, significant morbidity and high mortality.

Furthermore, the management of the most frequent SSc comorbidities (arterial hypertension, osteoporosis, dyslipidemia, diabetes mellitus, autoimmune hypothyroidism) is important to improve patients survival rate[7].

Unfortunately, the etiology of SSc is not known[8].

Traditional classification of SSc is based on skin extension involvement (showed in Figure 1): diffuse cutaneous subset(dcSSc) and limited cutaneous subset (lcSSc, Scleroderma or morphea)[9–11]. Localized scleroderma (lcSSc) is frequently limited to the distal limbs and often face; it does not extend proximal to the elbows, knees or involve the trunk[2].

Disease progression has been shown to occur often[12,13]. The clinical picture varies widely among patients based on skin thickening and organs involvements. Organ-based complications may occur in the lung, heart, gastrointestinal system, musculoskeletal system, kidney and skin[5,14]. The range is shown in Figure 2.

The pathological hallmarks, indeterminate aetiology and elucidated trigger events define the burden and important impact of the SSc[5].

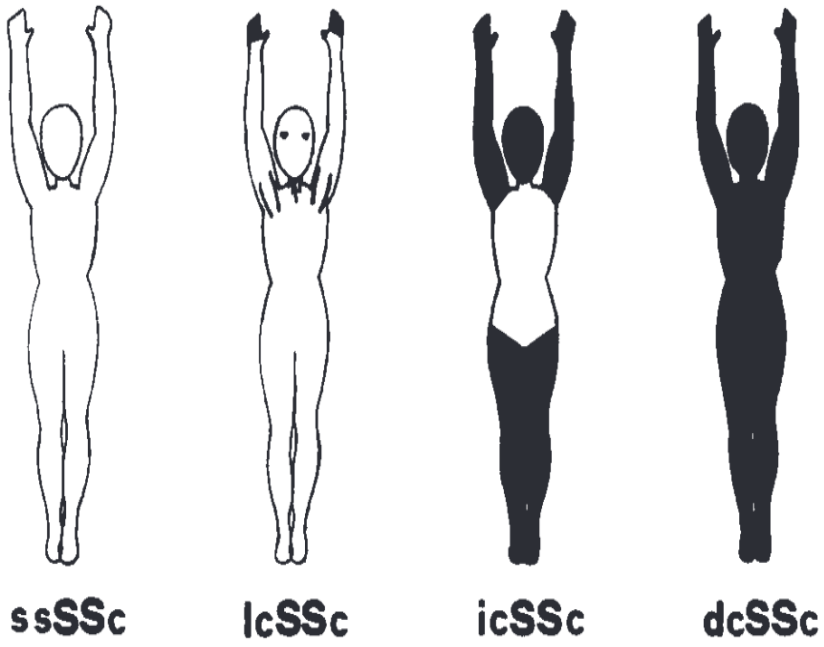

Figure 1. Classification can be particularly difficult during the early stage of the disease or in the presence of sine scleroderma SSc (ssSSc). Extrapolated from:[8].

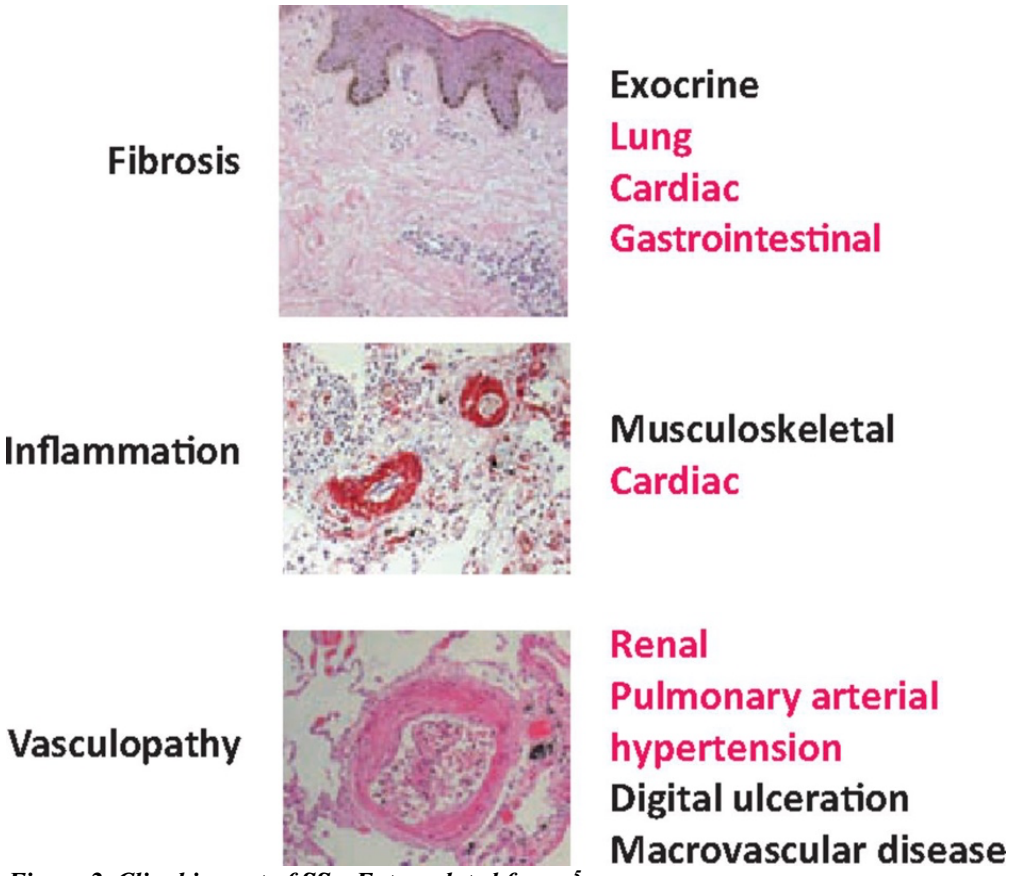

Figure 2. Clinal impact of SSc. Extrapolated from: [5].

CLINICAL PRESENTATION AND CRITERIA

SSc is a heterogeneous disease with unpredictable clinical course[15,16]. The clinical evolution of the disease is the result of a multistep and multifactorial process, including genetic, autoimmune system, triggers events (e.g. viral infections) and vascular dysfunctions[17].

Raynaud's phenomenon (vascular disease) is an almost universal symptom in patients with systemic sclerosis and is often an early manifestation of the disease. It is characterized by color change of the extremities of the body; frequently the hand and feet are more involved[8]. Often dermatologist are the first-diagnosis specialists[18].

Among patients with localized cutaneous systemic sclerosis (IcSSc), there is a specific subgroup presenting CREST syndrome. These individuals exhibit distinctive microvascular abnormalities and manifest clinical features, including systemic sclerosis, calcinosis, Raynaud's phenomenon, esophageal disease, sclerodactyly and telangiectasia[3]. Patients affected by this phenomenon incur in an increased risk of development SSc[19]. Systemic sclerosis is associated with a 2.5-fold higher mortality risk than the general population, indicating an urgent need for early diagnosis[20].

Criteria for early diagnosis to prevent organ involvement were proposed in 2001 by LeRoy and Medsger: Raynaud's phenomenon, SSc specific autoimmune antibodies and scleroderma pattern in capilloroscopy[21].

In 2011, similar criteria with the addiction of puffy fingers were proposed[22,23]. Preliminary criteria for the very early diagnosis of SSc (VEDOSS) offer a useful tool for stratify risk in patients with Raynaud's phenomenon and to determine which patients may progress to systemic sclerosis within the following 5 years[22].

Since 2013, the newer and better-performing ACR/EULAR were introduced replacing 1980 ACR criteria[24]. According to ACR/EULAR criteria, the SSc diagnosis is determined by 14 items, each carrying a different weight in the diagnostic process[24]. A total score (obtained by the sum of the maximum score for each item) equal to 9 or greater is sufficient to diagnose the patient as affected by SSc. The item 'skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints' alone can score 9 points[5,10,24].

The extensive clinical spectrum of SSc, combined with its overlap with other rheumatological conditions (e.g., rheumatoid arthritis, Sjögren syndrome, myositis, and primary biliary cholangitis), contributes significantly to a marked delay in diagnosis.

RP should be considered as a "window of opportunity" for early diagnosis, to block the progression of the disease[22,25].

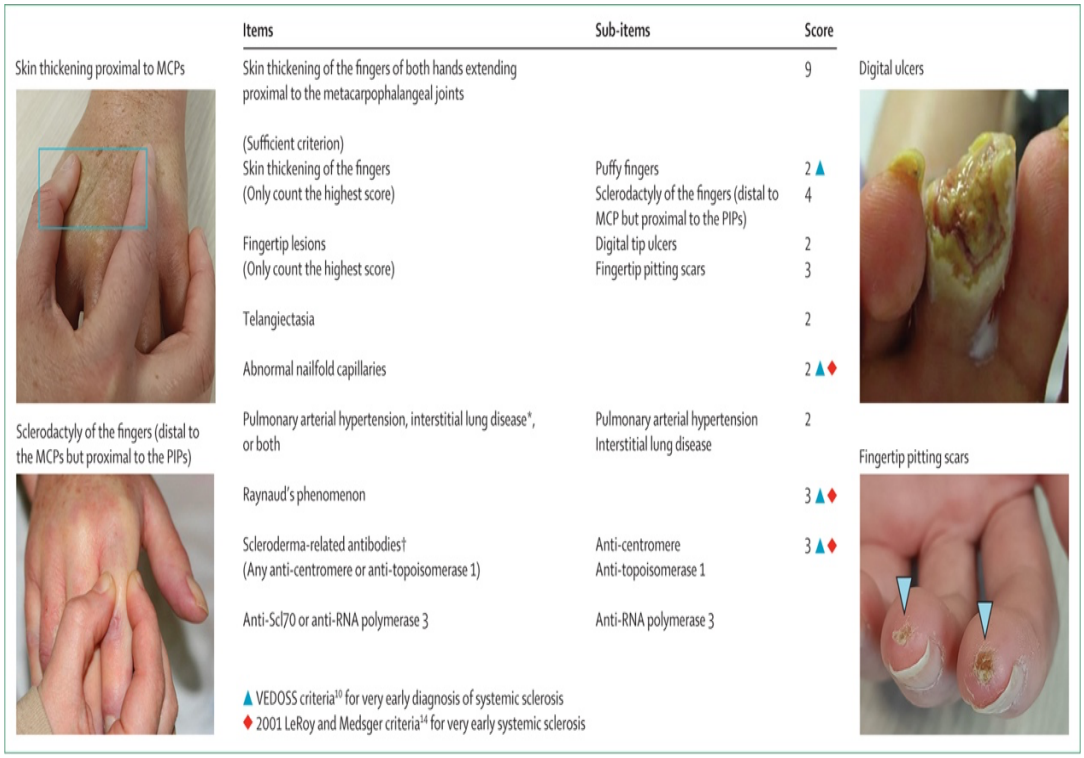

Figure 3.The 2013 American College of Rheumatology and European Alliance of Associations for Rheumatology Classification Criteria for systemic sclerosis. Extrapolated from:[19]

Table 1. The American College of Rheumatology/European League Against Rheumatism criteria for the classification of systemic sclerosis (SSc)*

Item	Sub-item(s)	Weight/score†
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints *(sufficient criterion)*	–	9
Skin thickening of the fingers *(only count the higher score)*	Puffy fingers	2
	Sclerodactyly of the fingers (distal to the metacarpophalangeal joints but proximal to the proximal interphalangeal joints)	4
Fingertip lesions *(only count the higher score)*	Digital tip ulcers	2
	Fingertip pitting scars	3
Telangiectasia	–	2
Abnormal nailfold capillaries	–	2
Pulmonary arterial hypertension and/or interstitial lung disease *(maximum score is 2)*	Pulmonary arterial hypertension	2
	Interstitial lung disease	2
Raynaud's phenomenon	–	3
SSc-related autoantibodies (anticentromere, anti–topoisomerase I [anti–Scl-70], anti–RNA polymerase III) *(maximum score is 3)*	Anticentromere Anti–topoisomerase I Anti–RNA polymerase III	3

* These criteria are applicable to any patient considered for inclusion in an SSc study. The criteria are not applicable to patients with skin thickening sparing the fingers or to patients who have a scleroderma-like disorder that better explains their manifestations (e.g., nephrogenic sclerosing fibrosis, generalized morphea, eosinophilic fasciitis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft-versus-host disease, diabetic cheiroarthropathy).
† The total score is determined by adding the maximum weight (score) in each category. Patients with a total score of ≥9 are classified as having definite SSc.

Figure 4. Extrapolate from:[24].

AUTOIMMUNE SIEROLOGY AND BIOMARKERS

Systemic sclerosis is defined by skin thickening, vasculopathy and autoantibody production, resulting from pathogenic pathways of the disease.

The biggest challenge in the fight against SSc is to detect valid predictors of disease so as to treat patients since the earliest stages of disease[22].

Raynaud's phenomenon (RP), antinuclear antibodies (ANA) positivity, and puffy fingers are indicated as the 'red flags', to suspect SSc and perform further tests to confirm the diagnosis. Confirmatory tests consist of assessing the presence of SSc autoantibodies and/or abnormal nailfold capillaries[2,22].

Approximately 95% of SSc patients are ANA positive and antibodies are more common in women[26,27].

The evaluation of specific disease antibodies includes anti-centromere antibodies (ACA), anti-topoisomerase I/Scl-70 antibodies and anti-RNA polymerase (RNAP) I-III[2]. SSc-autoantibodies outline two groups: the first positive for anti-topoisomerase antibodies Scl-70, while the second group with positivity of anti-centromere antibodies ACA. Double SSc-specific autoantibody positivity is extremely rare[28]. Furthermore, there is a correlation between skin subset, autoantibody positivity and prognosis[17,28]. In detail, the cutaneous subset limited with positivity of anti-centromere autoantibodies ACA shows a slower and more gradual evolution, while the diffuse anti-Scl-70 positive form sees a rapidly progressive course and a more severe prognosis[17]. In addition to the correlation with the SSc subsets, some demographic, clinical and organ involvement discoveries (e.g. muscle inflammation, pulmonary hypertension, pulmonary fibrosis, renal crisis) are associated with the positivity of the autoantibodies produced[26]. In 2008, a twenty-year prospective study of 586 patients demonstrates the association between microvascular damage and SSc-specific autoantibody positivity and their role in disease progression[29].

Therefore, it is essential in the case of suspicion of SSc to search for SSc-specific autoantibodies and their determination is important to predict possible organ involvement and prognosis, as well as monitoring and treatment[30].

In addition, markers of inflammation such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are used in clinical practice for their availability. CRP level helps clinicians identify patients who require more intensive monitoring and treatment and predict long-term progression such as interstitial lung disease (ILD)[31].

Increased CRP is correlated with IL-6, whose monitoring helps to assess the various stages of the disease, the monitoring of the severity of SSc and the prognosis of the patient[32,33].

IL-6 and other mediators play an important role in disease pathogenesis and their knowledge allows to modulate the therapy agents in these pathways[5].

In the future, the mediators (indicated in Figure 5) may be a target terapy[5].

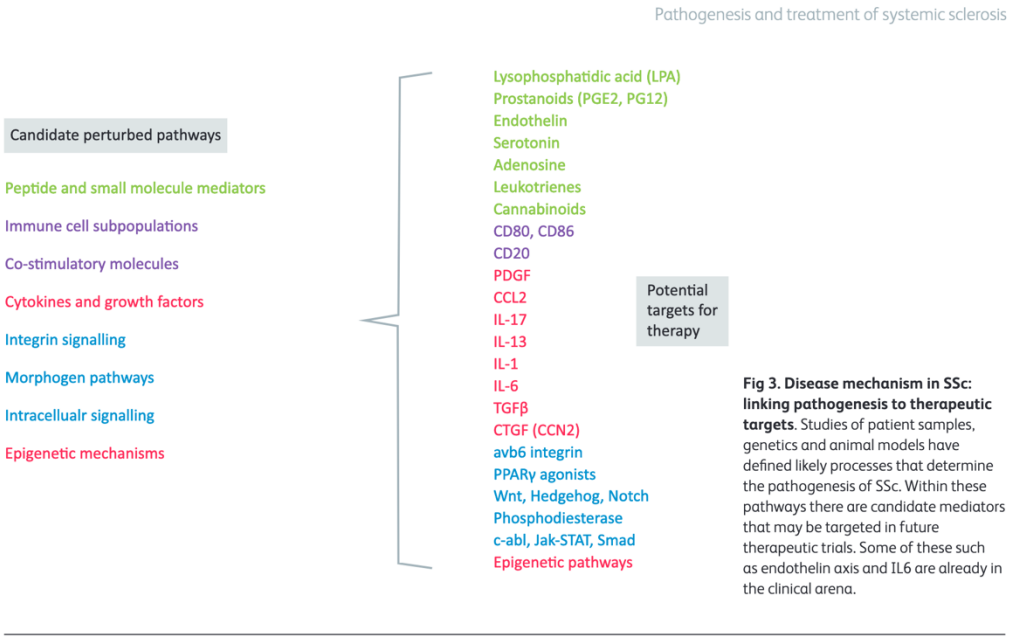

Figure 5. Extraposed from:[5]

The role played by vascular dysfunction can also be investigated by circulating markers such as endostatin. Previous studies suggest endostatin evaluation may be helpful for the association of SSc with a few complications (e.g. digital ulcers, pulmonary arterial hypertension)[34].

CLINICAL FEATURES

SSc is clinically heterogeneous[2]. Skin abnormalities are a distinctive feature and occur early in the disease course[15]. Organ-involvement is not often observed in the initial phase of the disease; it commonly arises later during SSc development: those are the manifestations that mainly increase mortality risk. The range of organ-based complications occur at different times and frequency in the two major subsets of SSc[5].

It is crucial to calculate the duration of the disease from the initial onset of no-Raynaud symptoms in relation to the presence of autoantibodies and the classification of the skin subset.

Skin involvements

The cutaneous involvement is characterized by skin ulcers (SU), early puffy hand ('sausage-like'), telangiectasis, sclerodactyly and calcifications in the extensor parts of the elbow and fingertips[6]. Fibrosis can also involve orofacial district and the main oral manifestation of the disease is microstomia, causing mask-like face, impaired speech and mastication[6,35]. SSc can also coexist with xerostomia in 30-40% of patients[35]. Sicca symptoms are believed to be a frequent complaint associated with SSc, some patients met the criteria for concurrent Sjogren syndrome[35,36].

SU refers to all ulcerative skin lesions and includes digital ulcers (DU); these usually refer to ulcers of the distal fingers and toe, very painful and often persistent and recurrent[2,37]. The digital ulcerations complicated by secondary infection may progress to osteomyelitis and require amputation, in order to prevent and improve patient's quality life the management is based on evaluation of necrotic tissue, infection/inflammation, moisture balance, and epithelization[37,38].

Dilated cutaneous bloods vessels are associated with DU and nailfold capillary changes (NVC pattern) and typically affect face, chest and palm in almost the totally of SSc patients[39].

Figure 6. Extrapoled from:[37]

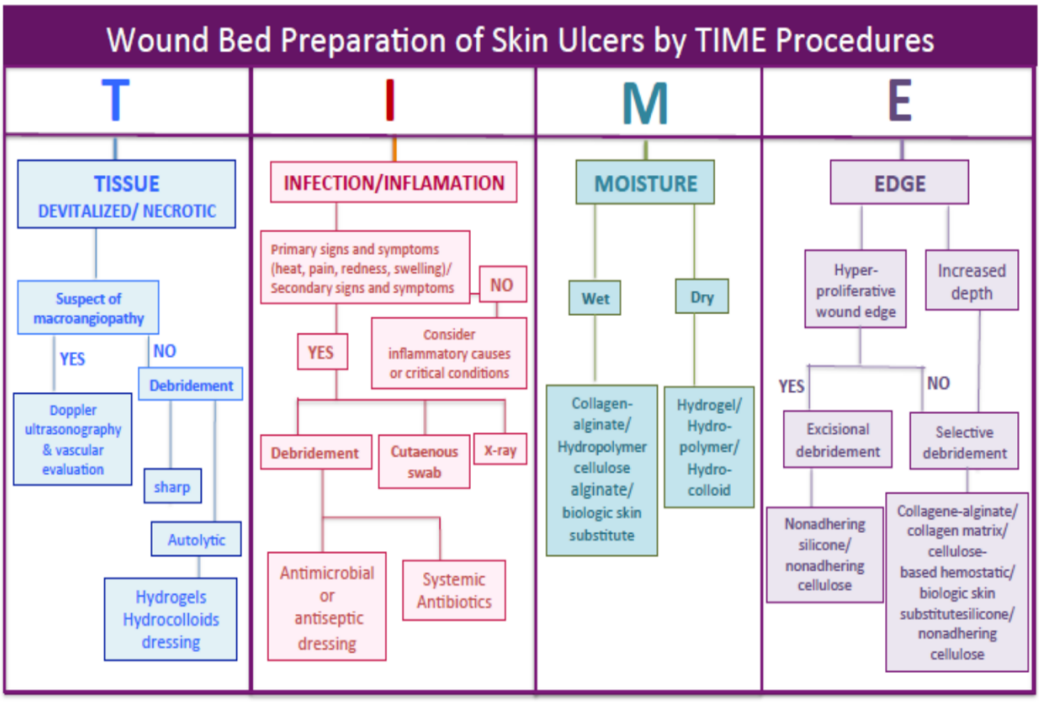

Figure 7. In detail, the Time Procedures. Extrapolate from:[37]

Calcinosis is the deposition of insoluble calcium in the skin and subcutaneous tissues. It occurs at the tips of the finger and the superface of the extensor in at least 25% of patients[40]. It may be asyntompatic[2]. SSc patients with calcinosis have a lower rate of steroid but a higher frequency of osteoporosis, particularly in non-obese patients[41].

The progression from inflammation accompanied by edema to subsequent fibrosis and atrophy is pathognomonic for systemic sclerosis[2]. Initially, due to infiammatory and impaired vascularization, patients experience pain, itching, erythema and sometimes nerve compression associated with neuropathy symptoms (e.g. carpal tunnel syndrome)[6].

The main manifestations are classified into two distinct forms: diffuse cutaneous systemic sclerosis (dcSSc) and limited cutaneous systemic sclerosis (IcSSc). In diffuse cutaneous systemic sclerosis (dcSSc), there is a tendency for an increase in skin thickness, which typically progresses through three distinct phases:

1. **Edematous phase**, generally lasting 6 to 12 months.
2. **Fibrotic or indurative phase**, persisting for 1 to 4 years or potentially longer.
3. **Atrophic phase**, which continues for the remainder of the patient's life.

The duration of each phase varies, with skin thickening in the early stages of dcSSc exhibiting a rapid progression, whereas it tends to develop gradually in a limited cutaneous systemic [42].

Skin thickness is assessed using the modified Rodman skin score (mRSS). This metric is essential in clinical practice for the diffuse cutaneous subset, as it serves as a surrogate indicator of disease severity and mortality. However, in IcSSc, it lacks sensitivity to change[42]. A baseline skin score > or =20 was associated with heart involvement at baseline and predicted mortality and SRC over the subsequent 4 years[43].

In 2011, The STPR (skin thickness progression rate) was tested and patients with rapid STPR had a higher median total skin score (34)[44]. A rapid STRP observed during the first visit, such as mRSS, was associated with higher risk of having or developing both renal and cardiac involvement in the first 3 years[44].

In conclusion, rapid STPR outperformed mRSS at the first visit in predicting both mortality and the development of renal crisis[44].

In addition to organ-based complications, skin fibrosis leads to contractures and reduced mobility, limiting the patient's life. Many patients have significant skin involvement, 50% of patients develop deformities such muscle pain on chewing, difficulty in mouth opening, headaches[35]; this has a strong impact on the quality of life, disability, social and psycho-social aspect[36,45].For example, 50 to 80% of patients affected by microstomia have psycho-social impact [46].

Furthermore, most aspects are important in self-perceived quality of life (QoL) and the most efficient factors in predicting functional disability are dyspnea, gastrointestinal symptoms, muscle weakness, the presence of DU and pain[45].

Lung Complication

Pulmonary involvement is second in frequency only to esophageal involvement as a visceral complication of systemic sclerosis (SSc) and affected patients have a significantly worse prognosis than patients with SSc who are free of pulmonary involvement[47].The most relevant lung complications are interstitial lung disease (ILD), pulmonary fibrosis (PF) and pulmonary artery hypertension (PAH).

ILD was estimated to affect ~35% of the SSc patients in Europe and ~52% in North America; the SSc-ILD is rare in Europe and North America, but it is one of the leading causes of mortality in patients with SSc[48]. To prevent that, a lot of studies are focused on predictive models and clinical tools for subdividing patient risk stratification. In SPAR predictive model, a lower SpO_2 after 6 min walk test (6MWT) and arthritis were ever identified as independent predictors for ILD progression in both cohorts and evidence-based for the stratification of risk of patients with ILD in clinical practice[12].

Some variables (e.g. dcSSc, greater age at onset, lower forced vital capacity, DLco and the presence of anti–topoisomerase I) predict clinically significant PF development and increased risk. While anticentromere antibody reduces the hazard[49].

In 2023, the Delphib study findings provide an algorithm to support effective management of the SSc-ILD patients; according to that HRCT is considered the gold standard to detection of ILD[50].

Pulmonary hypertension (PH) is defined by a mean pulmonary artery pressure ≤ 25 mm Hg at rest, measured during right heart catheterization. The term pulmonary arterial hypertension (PAH) describes a subpopulation of patients with PH characterized hemodynamically by the presence of pre-capillary PH[51].

The different clinical phenotypes of SSc-PH can be explained by different clinical phenotypes of SSc itself and by different mechanisms of pathogenesis of the SSc disease.

PH can be divided and explained by:

1. **Group 1**: Pulmonary arterial vasculopathy or by PVOD-like lesion (obstruction of the small pulmonary veins[52]).
2. **Group 2**: heart involvement.
3. **Group 3**: lung fibrosis.

These mechanisms can be combined with various other SSc elements and explain the number of possible clinical phenotypes, showed in Figure 8[53].

A given patient can be placed somewhere on this three-axis graph with the x-axis ranging from post-capillary PH to severe pre-capillary PH, the y-axis ranging from no interstitial lung disease (ILD) to extensive ILD and the z-axis ranging from limited cutaneous SSc to diffuse cutaneous SSc[53].

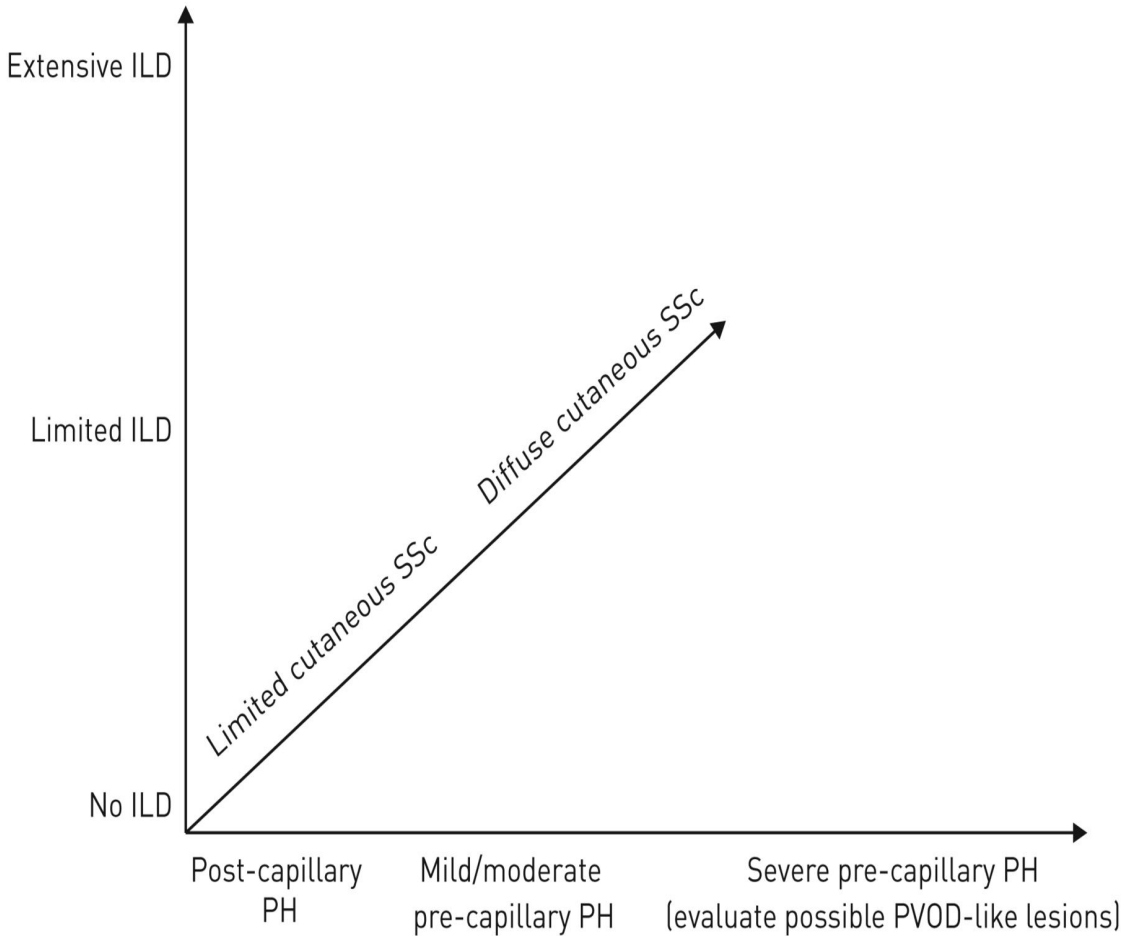

Figure 8.It is useful to consider possible pulmonary Veno-occlusive disease (PVOD)-like conditions in patients with severe pre-capillary PH .Extrapolated from:[53].

Heart involvement

In 2017, a retrospective study revealed the major contribution of the cardiopulmonary system to SSc mortality[54].

In addition to significant cardiac involvement in group 2 SSc-PH patients, the disease may cause patients to have a reduction in exercise capacity and myocardial fibrosis.

Knowing that cardiac involvement and ILD are the main determinants of patient prognosis, it is mandatory to investigate heart and lung status in all SSc patients[15].

In 2023, a study supported by the available data indicates the importance of CMR (cardiovascular magnetic resonance)-defined cardiac SSc phenotypes for a comprehensive cardiovascular evaluation and higher risk in patient with SSc-associated PH[15,55].

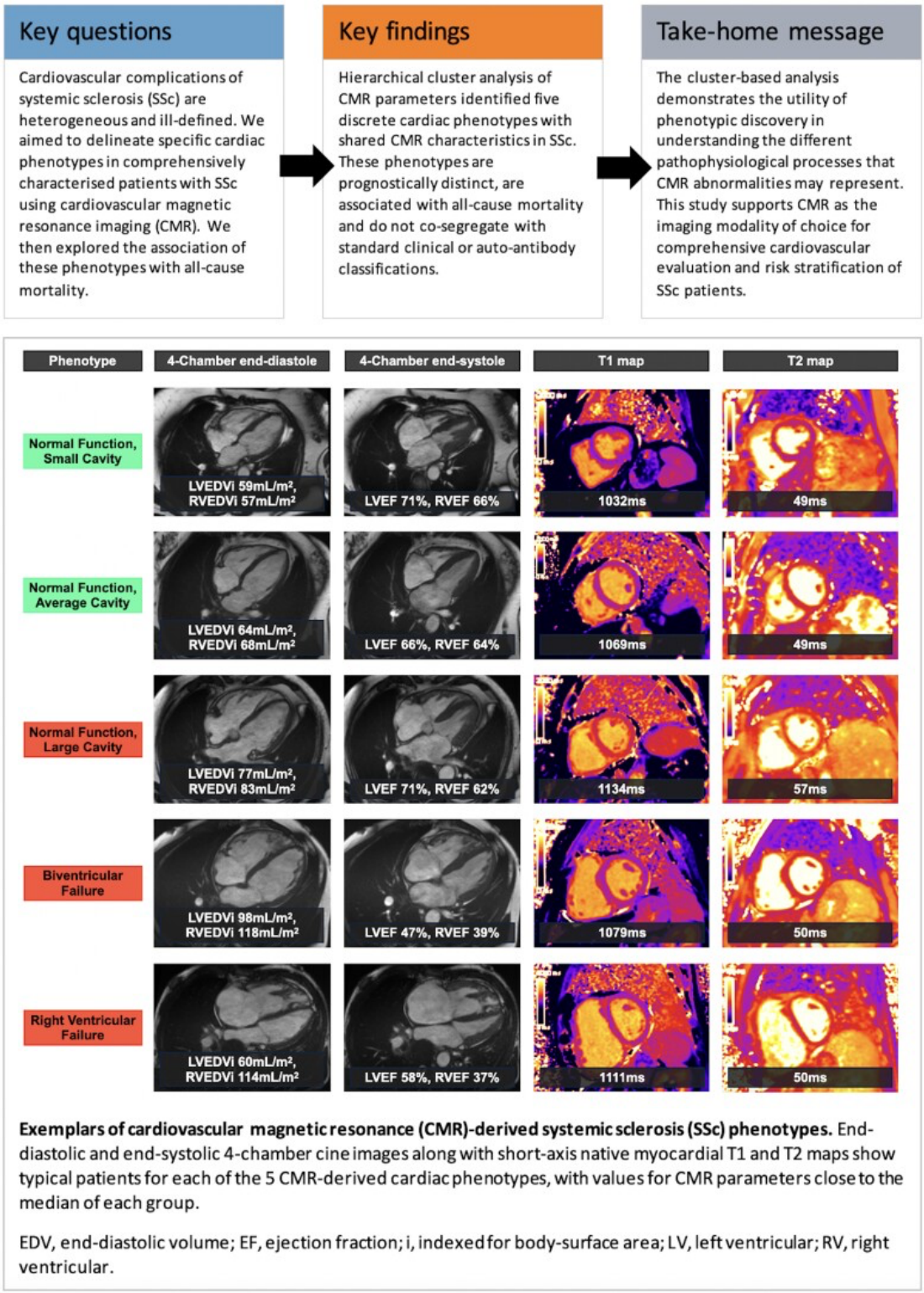

Figure 9. Extrapolate from:[55]

Gastrointestinal complications

In around 90% of all patients with scleroderma, the GI tract is involved[56]. Patients affected develop a high frequency of GI symptoms at an early stage of systemic scleroderma and manifestations' frequency vary in the anorectum, esophagus and other gastrointestinal locations[57]. GI symptoms commonly include meteorism, dysmotility of the esophagus, malabsorption, intestine dilation, heartburn, dysphagia, nausea, vomiting, diarrhea and constipation[58,59]. Meteorism and fecal incontinence have a contribute to impairment in quality life and GI dysautonomia with higher levels of emotional distress[57].

The GI involvement can be analyses by region affected:

1. **Oral Cavity**: analyzed above and often correlated with Sicca syndrome and mandibular bone resporption[36]. It is essential to educate the patient about their dental care[36,56,57].
2. **Esophagus**: its manifestation includes esophageal dysmotility, gastrointestinal reflux disease (GERD), reflux-related esophagitis, Helicobacter pylori infection, esophageal strictures, Barret esophagus, lower esophageal sphincter laxity and adenocarcinoma; Esophagogastroduodenoscopy (EGD) is important for effectively diagnosis[57]. Furthermore, subclinical involvement of esophagus, can be attributed to development of the interstitial lung[36].
3. **Stomach**: must be careful for gastroparesis, H.pylori infection, gastric antral vascular ectasia (GAVE or 'watermelon stomach'), gastric bleeding and consequent anemia[57].
4. **Small intestine**: the small bowel is the second most common organ affected in SSc, after esophagus and complications are diarrhea, malabsorption, chronic intestinal pseudo-obstruction (CIPO), small intestinal bacterial overgrowth (SIBO)[36,57].
5. **Colon and Anorectum**: colonic involvement affects 20 to 50% of SSc patients and the majority of patients are asymptomatic[36]. The main complications are costipation, megacolon, large intestine vascular ectasia, lower bleeding, diverticula, rectal prolapse and fecal incontinance[57].

The risk factors for gastrointestinal issues in SSc patients are difficult to investigate due to the lack of evidence. A cause of that, H.pylori and smoke cannot be determinate as definitive risk factors for developing GI problems in SSc patients[56].

A self-questionnaire developed to evaluated the profile of GI in SSc patients, show that GI symptoms are significant problems for patients; in IcSSc patients the upper GI are less frequently and increase in frequency for costipation and meteorism during follow-up after one year[58].

Also, in patients with other rheumatic diseases, the upper GI involvement is less frequenty.[58].

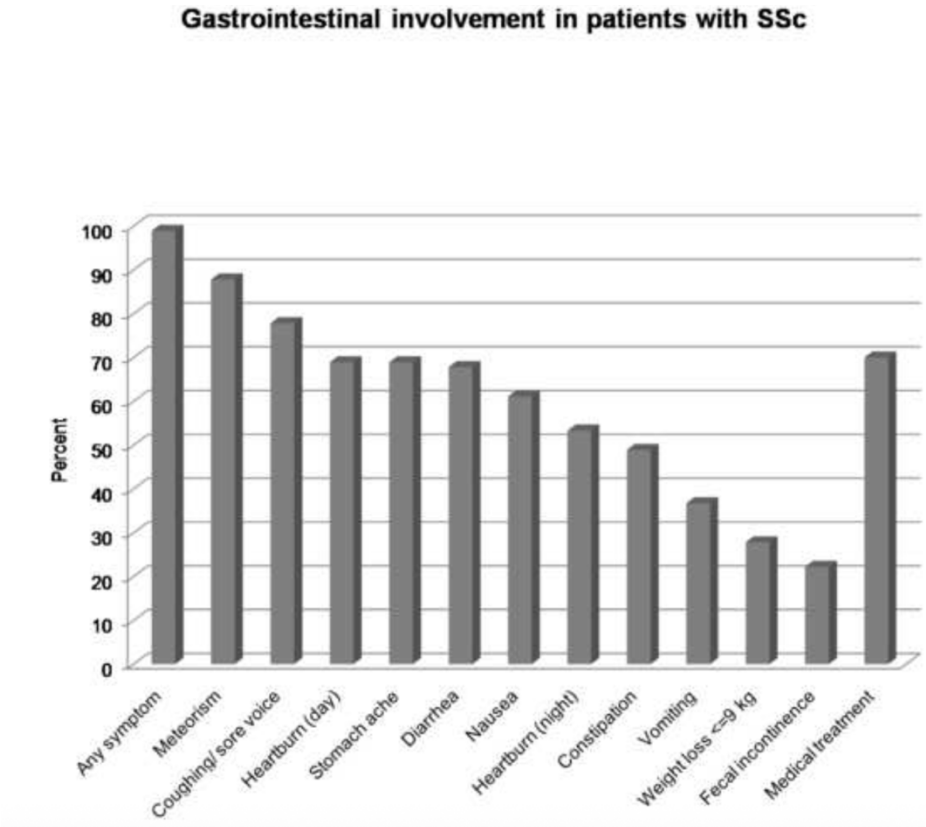

Figure 10. More frequent GI symptoms in SSc patients. Extrapolated from:[58].

Musculoskeletal complications

There are many aspects of SSc that remain difficult to treat, such as fatigue and musculoskeletal function[2]. Muscle pain, muscle weakness, reduced mobility, muscle fibrosis and atrophy can occur[6].

Kidney complications

RP, NVC and DU are not the only manifestations of SSc vasculopathy; in fact, endothelial involvement and damage are responsible for some of the most terrifying manifestations such as PAH and SRC[15].

Most cases of kidney involvement are subclinical and can be characterized by decreased renal function, glomerulonephritis, chronic vasculopathy and specific sensibility to drug toxicity, while SRC is the dramatic elements of acute kidney involment[60].

SRC classically presents with accelerated hypertension and acute kidney injury (AKI) defined as an increase in serum creatinine > 1.5 × baseline and is reported to occur in the early years of disease (<5 years from first non -Raynaud's symptoms) in patients with dcSSc subset[61].

In fertile women in the early stage of SSc, patients are advised to avoid pregnancy, preventing serious complications of pregnancy, such as pre-eclampsia and HEELP (hemolysis, elevated liver enzymes, low platelet) that can mimic SRC[62].

Pathological characteristics of SRC are recognized, but the development of sensitive biomarkers for renal disease in SSc is necessary to provide tools for the early detection and possible prognosis of SRC[61]. At regular routine clinical assessment composed of urine dipstick, serum urea and creatine should be monitored, but SSc patients are also frequently affected by arterial hypertension as a comorbidly[60]. To eliminate this problem during follow-up, ultrasound evaluation and Doppler can evaluate vascular perfusion[60,63,64].

SCLERODERMA IN WOMEN

The incidence of SSc is similar in Europe and North America[48].

SSc is a predominantly female disease with a ratio between women and men ranging from 3:1 to 15:1, most commonly in the third to fifth decade. Diagnosis occurs at a mean age of 33,5-59,8 in Europe.[48] As the disease occurs in fertile age in almost 50% of patients[11,48].

Systemic sclerosis could affect various aspects of women's lives such as the menstrual cycle, urogenital health, reproduction and sexual dysfunction, leading to an important clinical difference of SSc between genders.

Figure 11. Prevalence of SSc across Europe and North America (per 100.000 individuals) Extrapolated from:[48].

Despite the importance of this issue, data on the impact of SSc on gynecological health are very scarce. Some aspects such as reproductive health, the use of hormone therapies and sexual dysfunction have been investigated by Lazzaroni et al. in 2021[65].

Sex hormones in SSc

One of the SSc characteristics is the female predominance with the important role of sex hormones in immune and inflammatory regulation. Gender-related clinical and immunological differences in SSc may be consequences of: potential profibrotic and vasodilator activity of estrogens, lower levels of DHEAS and testosterone, increased risk of PAH in the post-menopausal period[65]**.**

Today, experts do not consider estrogen-containing compounds as absolutely contraindicated in presence of SSc, but risk profile must be done before hormone therapy including factors of general health and antiphospholipid antibodies (aPL) to evaluate thrombotic risk assesment[65].

Fertility

Women affected by SSc have normal fertility, excluding patients who receives cyclophosphamide (CYC) therapy. In patients undergoing CYC therapy, there is a reduction in ovarian reserve [66] and for teratogenic effect management of SSc-ILD, alternative treatments with comparable efficacy can be considered[65].

Sexual Dysfunction

Specific tightness and dryness caused by the 3 hallmarks of SSc affect directly the vaginal tract. Other manifestations (e.g. Raynaud's phenomenon, digital ulcers, gastrointestinal manifestation) are sources of discomfort, disability and lead to the patient's sexual dysfucntion.[65,67]. Also, physiological aspect such as body image dissatisfaction and pain reduce sexual function[68,69].

This dysfunction is showed by the reduction of clitoral blood flow documented by Doppler, correlating with no balance between pro-angiogenic and anti-

angiogenic factors[70,71]. So, a high prevalence of sexual dysfunctions is present in SSc women[60,68,72–74].

Reproductive Health Issues

Gynecological issues represent a topic of major interest for SSc women, affecting their quality of life, their personal decision about reproduction, number of pregnancies and contraception. In addition to pregnancy implications, these aspects can be managed in a multidisciplinary team, driven by gynecologists, to provide adequate elements and counseling to SSc patients[65].

Pregnancy

Preconception counseling, adjustment of treatment, and close surveillance during pregnancy by a multidisciplinary team are key points to minimize fetal and maternal risks and favor successful pregnancy outcomes[65]. The rates of spontaneous pregnancy losses are comparable to those of the general obstetric population; in detail, pregnancies ended in miscarriages 1.6 times more often than control popolation[75], except for patients with diffuse cutaneous SSc and early complicated organ involvement who may carry a higher risk of abortion. The risk of miscarriage appears to increase after the onset of SSc[76], even if the number of pregnancies is lower than before the onset. Preterm birth can frequently occur in women with SSc[77], as happens in other rheumatic diseases[65]. Overall disease activity generally remains stable during pregnancy, but particular attention should be paid to women with major organ disease such as renal and cardiopulmonary involvement and women suffering dcSSc with disease onset less than 4 years for higher risk of progression during pregnancy and purperium[65]. Women with such severe involvement should be fully informed about risks during pregnancy and possibly discouraged from getting pregnant.
Otherwise, women affected by SSc who are wishing for a pregnancy appropriately informed, should be evaluated for the presence of anti-phospholipid antibodies (aPL) to determine an increased thrombotic profile and pregnancy morbidity[78].

ENDOMETRIOSIS

Endometriosis is an estrogen-dependent disorder that can result in substantial morbidity, including pelvic pain, multiple operations, and infertility[79]. Epidemiological studies suggest an estimated prevalence of 2-10% in women within the reproductive age range[80]. It is classically defined as a chronic gynecological disease characterized by endometrial-like tissue outside of the uterus and is thought to arise from retrograde menstruation[81]. The clinical presentation is varied, and common symptoms of endometriosis often include dysmenorrhea, non-menstrual pelvic pain and infertility[82]. Up to 50% of women affected by endometriosis are infertile[83].

The disease outside of the female reproductive tract remains poorly understood, but endometriosis is now considered a systemic disease rather than a disease predominantly affecting the pelvis. In fact, this disease can affect metabolism in the liver, adipose tissue and leads to systemic inflammation[81]. Affected women have higher risk than the general female population of developing ovarian cancer and may incur in increased risk of breast cancer, as well as autoimmune and atopic disorders[79].

Although endometriosis remains an enigmatic condition with under-explored aetiology, alterations in immune system have been proposed as a contributing factor to the development of ectopic endometrial tissue[84] and an association between endometriosis and autoimmune disease has been suggested[85]. The association between endometriosis and a range of 28 autoimmune disease has been suggested, including Sjogren's syndrome (SS), inflammatory bowel disease (IBD), rheumatoid arthritis (RA), coeliac disease (CLD), multiple sclerosis (MS), Crohn's disease (CD), ulcerative colitis (UC), autoimmune thyroid disorder(ATD), systemic lupus erythematosus (SLE) and Addison's disease[85].

Probably there are shared biological pathways and autoimmune-related genes (e.g. PTPN22[86], HLA alleles[2]) between endometriosis and autoimmune disease that could explain increased comorbidity. Finally, hormonal factors play an important role in increasing the activity of autoimmune diseases[85].

Targeting dysregulated immune pathways represents a potential path to new therapeutic development that will hopefully not impact fertility[84].

There are no data regarding the incidence of gynecological pathology such as endometriosis in patients affected by SSc; furthermore, endometriosis is a major cause of disability and compromised quality of life in women and teenage girls[87].

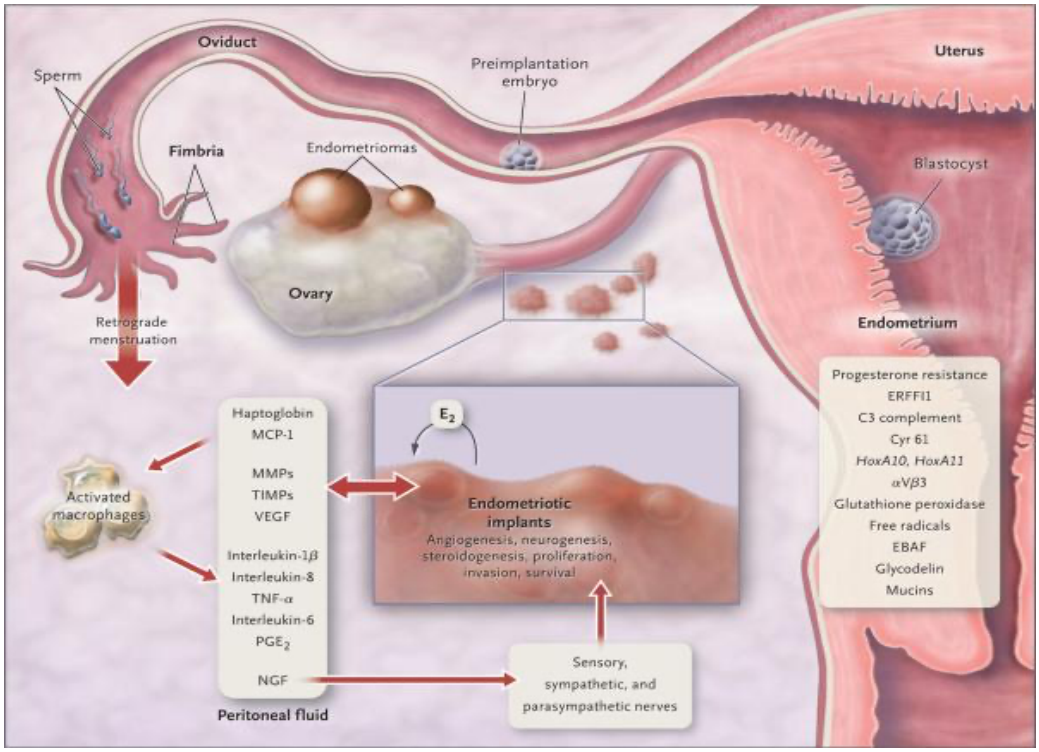

Figure 12.Pathophysiology of pain and infertility in Endometriosis. Extrapolated from:[88].

UTERINE ARTERY EVALUATION

SSc is a condition recognized for its impact on blood vessels, specifically renal vessels and may lead to life-threatening complications such as a scleroderma renal crisis[61]. Several studies examine the pattern of Renal Resistive Index (RRI) with ultrasound in SSc patients to asses kidney involvement[60].

The uterine and renal arteries are vessels of similar capacity and evaluation of uterine arteries is widely used in obstetrics related to determining the development of pregnancy diseases (e.g. preeclampsia, fetal growth restriction)[89].

In non-pregnancy women, increased resistance of the uterine arteries has been associated with infertility[90], though its clinical significance is challenging to determine due to physiological variations throughout the menstrual cycle[91].In recent studies, the UtA-PI is indirectly measured, a technique which gained popularity over other Doppler resistance index[92,93].

In Guedes-Martins research, the uterine artery (UtA) impedance, measured by its pulsatility index (PI) exhibits a regular pattern during the normal menstrual cycle (NMC) and in the same study, normative new-data-based reference ranges for the UtA-PI had been derived[91]. The UtA-PI is high during the temporal extremes and with a mid-cycle depression, showing minimal values between the 13th and 17th day. The median, 5th, and the 95th percentiles of UtA-PI (significantly dependent on age and parity) are obtained and show a decrease during the first third of the menstrual cycle. During the last two thirds of the cycle, the UtA-PI returns to the initial values[91]. The downward trend in impedance (which reaches a minimum near day 13) appears to bear reproductive benefecits[90,91].

The mechanism underlying such impedance variation is unknown, but increased myometrial tone (required to expel the endometrium) might negatively affect uterine perfusion, generating high impedance to UtA blood flow during the first third and the end of the cycle. It's suggested in this hypothesis that estrogens promote vascular smooth muscle relaxation during the follicular phase[91].

			Observed			Predicted		
Cycle (days)	n	EOD[a] (n)	5th centile	50th centile	95th centile	5th centile	50th centile	95th centile
1	50	0	1.74	3.37	5.55	2.08	3.40	5.55
2	50	0	2.00	3.04	4.59	1.99	3.24	5.29
3	49	0	1.88	3.02	4.90	1.90	3.11	5.07
4	48	0	1.83	3.17	4.60	1.83	2.99	4.89
5	51	0	1.94	3.25	5.00	1.78	2.90	4.73
6	52	1	1.88	3.15	5.77	1.73	2.82	4.60
7	46	20	1.80	3.12	5.37	1.69	2.76	4.50
8	52	46	1.59	2.41	4.03	1.66	2.71	4.42
9	50	107	1.83	2.48	4.64	1.63	2.67	4.36
10	52	110	1.09	2.21	3.93	1.62	2.64	4.31
11	49	136	1.24	2.40	4.48	1.61	2.62	4.28
12	48	131	1.05	2.60	4.10	1.60	2.61	4.27
13	49	103	1.52	2.62	4.18	1.60	2.61	4.26
14	53	209	1.81	2.33	4.09	1.60	2.62	4.27
15	46	160	1.42	2.56	3.66	1.61	2.63	4.29
16	50	71	1.43	2.60	4.87	1.62	2.65	4.32
17	52	104	1.36	2.33	3.93	1.63	2.67	4.36
18	52	103	1.93	2.99	4.66	1.65	2.70	4.40
19	49	67	1.62	2.88	3.96	1.67	2.73	4.45
20	49	99	1.89	2.74	4.78	1.69	2.76	4.51
21	50	96	1.85	2.72	4.31	1.72	2.80	4.57
22	54	61	2.14	3.01	4.18	1.74	2.84	4.64
23	48	19	2.30	2.86	5.03	1.77	2.88	4.70
24	45	21	1.56	2.91	4.81	1.79	2.92	4.77
25	51	4	1.81	3.07	4.73	1.82	2.97	4.84
26	54	0	1.87	2.96	4.30	1.84	3.01	4.91
27	46	0	2.08	2.86	4.71	1.87	3.05	4.98
28	47	0	1.67	2.94	4.52	1.89	3.09	5.04
29	47	0	2.16	2.90	4.58	1.91	3.12	5.09
30	50	0	1.97	3.00	4.61	1.93	3.15	5.14
31	43	0	2.19	2.94	4.90	1.94	3.17	5.18
32	49	0	2.16	3.25	4.95	1.95	3.19	5.21
33	48	0	2.41	3.14	4.29	1.96	3.20	5.23
34	39	0	2.11	3.21	5.42	1.96	3.20	5.23

[a]For each patient, the expected ovulation date (EOD) was calculated assuming that the luteal phase exhibited a consistent duration of approximately 2 weeks, i.e., *E0D = menstrual cycle length*—14.

Figure 13. Observed and predicted percentiles of the uterine artery pulsatility index on each cycle day. Extrapolated from:[91].

AIM OF THE STUDY

The aim of this study is to provide a comprehensive report on gynecological health in SSc fertile women both clinically and ultrasoundly.

STUDY DESIGN

PATIENTS AND STUDY DESIGN

This is an observational, cross-sectional monocentric study performed in the scleroderma Unit of the University Hospital of Modena in collaboration with the Department of Medical and Surgical Sciences for Mother, Child and Adult of the same institution. All enrolled patients and the controls gave their informed consent to the study and for the gynecological evaluation and the research project was approved by the local Institutional Ethics Committees (Modena, protocol no. 275/16). The study was conducted in two distinct phases. Initial phase comprised a case-control study during which four validated questionnaires (SF-12, MEDI-Q, FSFI, USP) were administered to evaluate gynecological health, sexual well-being and quality of life in both patients with systemic sclerosis and healthy controls. The second phase involved a cross-sectional section, concerning a comprehensive gynecological pelvic and ultrasound evaluation exclusively in patients diagnosed with systemic sclerosis.

From February to November 2014, all consecutive fertile SSc patients were enrolled in this study. The study duration was 9 months.

Inclusion criteria were the diagnosis of SSc according to the 2013 ACR/EULAR criteria[24], adult age (≥18 years), fertile age, non-pregnant and non-breastfeeding. The age-matched healthy controls (HC) were enrolled by routine controls at the gynaecological clinic

The exclusion criteria were patient's refusal to participate in the study or to undergo gynaecological evaluation, heart failure, pulmonary failure, previous uro-gynecological diseases and SSc overlap forms.

Each enrolled patient was assigned an alphanumeric code; self-administered questionnaires were administered and filled out anonymously.

Each patient underwent rheumatological assessment and complete gynecological evaluation with pelvic examination and transvaginal ultrasound with measurement of uterine resistance.

METHODS

Demographical and clinical data recording during both the rheumatological and gynaecological assessment were collected for each patient in a password protected database.

RHEUMATOLOGICAL ASSESSMENT

For all patients and controls included in the study, the following data were collected: demographic information (age, marital status, level of education), family history and lifestyle (tobacco use, occupation). For patients, an overall assessment of SSc included autoantibody profile (e.g. Anti-Scl70 antibodies, Anti-centromere CENP-1), clinical signs and symptoms of disease, disease cutaneous subset (limited cutaneous subset (lcSSc) and diffuse cutaneous subset (dcSSc)), organ involvement (gastroenteric tracts, pulmonary and heart), skin involvement (modified Rodnan skin score (mRss), calcinosis, telangiectasia, skin ulcers). Disease duration was calculated from the first non -Raynaud symptoms. Previous and current therapies were also collected, categorized as vasoactive/vasodilating drugs (Bosentan, Ambrisentan, Macitentan, Sildenafil, Tadalafil, Iloprost, Epoprostenol, PGE1, Riociguat; Calcium channel blocker), corticosteroids, conventional synthetic disease modifying antirheumatic drugs (csDMARDs, including cyclophosphamide, methotrexate, leflunomide, azathioprine, mycophenolate and cyclosporine) and biological DMARDs (bDMARDs, including rituximab, anti-tumour necrosis factor-α antagonists, tocilizumab and abatacept). In addition, comorbidities (arterial hypertension, diabetes mellitus and thyroid disorders) are also collected.

SELF-ADMINISTERED QUESTIONNAIRES

A total of four validated questionnaires were administered to each patient.
They investigated various aspects of general health and gynecological health, in particular general menstrual disorders, sexual and urinary health.

General health status

Short-form-12-health-survey

The Short-form-12-health-survey (SF -12) is a self-reported outcome measure assessing the impact of health on an individual's quality of life[94]. As the larger form (SF-36), the SF-12 uses the exact eight domains: limitations in physical activities due to health problems; limitations in social activities because of physical or emotional problems; limitations in usual role activities due to physical health problems; bodily pain; general mental health (psychological distress and well-being); limitations in usual role activities because of emotional problems; vitality (energy and fatigue) and general perceptions of health. Responses are then combined to generate two summary scores: the Physical Component Summary (PCS) and the Mental Component Summary (MCS). These summary scores provide an overall evaluation of an individual's physical and mental health status, respectively.
Range score 0 to 100 (0 = poor QoL, 100 = high QoL).

Menstrual disorders

Menstrual Distress Questionnaire

The menstrual distress questionnaire (MEDI-Q) is a newly developed tool that has been validated for a comprehensive evaluation of menstrual-related distress in an Italian population. It investigated 25 items, covering different areas of menstruation-related symptoms, such as pain, discomfort, psychic/cognitive changes, gastrointestinal symptoms, changes in physiological functions.
The level of distress caused by each symptom is evaluated by considering not only its impact on functioning and quality of life during the menstrual phase

compared to the intermenstrual and premenstrual phases, but also its frequency. The questionnaire provides a total score (MEDI-Q Total Score), which is a synthetic index of the global menstruation-related distress, and three sub-scales: Menstrual Symptoms (MS), the total number of symptoms that generate more distress during menstruation than in intermenstrual days; Menstrual Symptoms Distress (MSD), which measures the average distress related to menstrual symptoms; and Menstrual Specificity Index (MESI), which represents the proportion of symptoms for which the participant has reported an exacerbation of distress during the menstrual phase as compared to intermenstrual days and premenstrual days.
MEDI-Q Total score range from 0-125, a Score ≥ 20 indicates a clinically relevant condition[95].

Sexual health

Female Sexual Function Index

The female sexual function index (FSFI) is a 19-item multidimensional self-reporting measure that quantified female sexual dysfunction in six domains: desire, arousal, lubrication, orgasm, satisfaction, and pain; compiled only from sexually active patients (who have had intercourse in the past 4 weeks)[96]. To obtain the total FSFI score, the scores from each domain are summed up. The maximum total score is 36, with higher scores indicating better overall sexual function; SFI total scores ≤26.55 indicate an impaired sexual function.

Urinary health

Urinary Symptom Profile

The Urinary Symptom Profile (USP) is a 13-item questionnaire that explores 3 dimensions: stress urinary incontinence (SUI) (maximum score 9), overactive bladder (OAB) (maximum score 21) and low stream (LS) (maximum score 9). A score of 0 represents the absence of symptoms and 9 or 21 maximal severity symptoms. The USP has no cutoff score, and it is the only instrument to screen patients for all lower urinary tract symptoms[97].

GYNECOLOGICAL ASSESSMENT

Each patient underwent a full gynecological examination performed by the same gynecologist, divided into three parts as follows:

- **Gynecological medical history**: family history of gynecological disease, age of menarche, obstetric history, regularity of the menstrual cycle, presence of dysmenorrhea, dyspareunia, dyschezia, and dysuria (evaluated with the VAS scale), recurrent urinary or vaginal infections, last pap test evaluation, hormonal therapy (previews or current), abdominal surgery. VAS score consists of a 10 cm line, ranging from 0 as no pain and 10 as the worst experience of pain. Presence of urinary infection during the last 12 months (almost 2/year).

- **Gynecological physical examination**: The physical examination includes an abdominal and bimanual pelvic examination and evaluation of focal tenderness in the pelvic floor (trigger point). Using the speculum, the five parameters (vaginal elasticity, vaginal secretions, pH evaluated with vaginal pH test card, epithelial mucous membrane, vaginal hydration) for the Vaginal Health Index (VHI) index were scored.

- **Gynecological ultrasound examination**: The ultrasound scan was performed using a Voluson SWIFT BT23 (GE Healthcare Technologies, Milwaukee, WI, USA) ultrasound unit containing multifrequency transvaginal and transabdominal transducers. Assessments were performed by a single operator with vast experience in gynecological imaging and Doppler ultrasound to avoid inter-observer variability using a transvaginal transducer. The scan was made following the 4 steps of the IDEA[98] consensus for the diagnosis of endometriosis (routine evaluation of uterus and adnexa, evaluation of transvaginal ultrasound soft markers, assessment of the status of the pouch of Douglas “sliding sign”, assessment of deep endometriosis nodule in the anterior and posterior compartment). In addition, Uterine artery (UtA) Doppler evaluation was performed, and UtA-PIs (Pulsatility Index) were measured automatically as follows:

$$PI = \frac{sistolic\ peak\ velocity - end\ diastolic\ velocity}{mean\ velocity\ during\ cardiac\ cycle}$$

Continuous data were reported with the [mean ± standard deviation]. Dichotomous variables were reported in absolute value and percentage frequency.

RESULTS

A cohort of 38 patients was invited to participate in the study; however, 9 individuals declined undergoing gynecological evaluation (1 for personal reasons, 2 due to having already received care from another gynecologist, 1for a linguistic barrier and 5 refused to complete the questionnaire about sexual function). Furthermore, 1 un-intercourse patient was excluded due to the inability to complete the questionnaires.

Then, 29 fertile patients with SSc and 33 HC gave their consent and were finally enrolled in the study. The demographic composition consisted entirely of Caucasian participants. The two groups were comparable in ethnicity, age, body mass index (BMI), obstetric history (number of pregnancies, births, miscarriages), age of menarche and intake of hormone therapy.

RHEUMATOLOGICAL ASSESSMENT

The mean age was 39.57 ±7.86 years old, with a disease duration of 5.7 years. Half of the patients had lcSSc (54%), the mean mRSS was 8±8.66, 45% of patients had positive Scl-70 antibody. Most of them presented with a vascular phenotype of the disease characterized by digital ulcer for 46%, puffy fingers (55.6%), telangiectasis (46.2%), digital pitting scars (46.4%). None had pulmonary arterial hypertension, and 8 patients (30.7%) had interstitial lung disease. Almost all patients were in vasodilator or vasoactive treatment (94,1%) and 62.1% were undergoing immunosuppressive therapy.

All the detailed characteristics of the enrolled population were reported in Table 1.

SELF-ADMINISTERED QUESTIONNAIRES

General health status

Short-form-12-health-survey

Patients with SSc have a significantly lower quality of life than health controls in both the physical (PCS 46.80vs 54.49, p= 0.007) and psychological (MCS 34.80 vs 41.46, p=0.043) domains. A summary is shown in Table 2 and a comparison with HC in Figure 14.

Menstrual disorders

Menstrual Distress Questionnaire

Menstruation is a physiological event that is often associated with subjective distress. Dysmenorrhea was reported by 55.2% of patients and heavy menstrual bleeding was noted by 5 patients. Menstrual disorders were more frequent and associated with greater discomfort in SSc patients than in controls, as evidenced by significantly higher scores on the MEDI-Q questionnaire for both the total score (11.61 vs 5.48; p=0.048) and menstrual symptoms (MS: 5.00 vs 2.48; p=0.006). A summary and comparison with healthy controls are given in Table 5 and Figure 17.

Sexual health

Female Sexual Function Index

In our SSc population, 26 (92.9%) women were sexually active.

Regarding sexual function, 40% of patients (p=0.018) reported dyspareunia, with an FSFI full-scale score <26.5 (cut-off for sexual dysfunction[99]) worse for the patients than for HC (p=0.033). Sexual desire, the only domain that can be considered separately from the final FSFI score, was 3.40 (±1.22), lower than the cut-off value (5.00) defining the hypoactive sexual desire disorder(HSDD)[100]. A summary of FSFI questionnaire is presented in Table 4, while comparison with HC is presented in Figure 15.

Urinary health

Urinary Symptom Profile

Urinary incontinence was reported in 9/28 SSc patients (32.14%), mainly stress incontinence (77.8%). The mean USP (SUI) score was 1,26 (±1,51). Overactive symptoms were reported in 64.3% (16/28) of the patients, the mean UPS (OBS) score was 3.04 (±2,92). Urinary infections were reported in 6/28 patients (21.43%). Compared to HC, patients have a higher number of recurrent urinary infections (p=0.007) and vaginal infections (p=0.049). Urinary findings are detailed in Table 3 and Figure 14.

GYNECOLOGICAL ASSESSMENT

Seventeen patients (58.6%) had experienced at least one pregnancy, totalling 33 pregnancies, of which 9 (31,0%) resulted in miscarriage.

Infertility was reported by 17.2% of patients and 5 underwent Assisted Reproductive Technology (ART) procedures, with 3 achieving successful outcomes. Hormone therapy had been used by 86.2% of patients at some point in their lives, although only 6 were currently undergoing treatment.

Additionally, 10% of the patients reported a diagnosis of polycystic ovary syndrome (PCOS), while 17% had endometriosis—3 of whom were diagnosed during the visit and 2 with a prior diagnosis.

Dysmenorrhea was reported by 55.2% of patients and heavy menstrual bleeding was noted by 5 patients. Regarding pain assessment, 6 patients reported dysmenorrhea scores greater than 5, 4 experienced ovulation pain above 5, and 4 reported dyspareunia exceeding 5. Recurrent urinary tract infections were reported by 21% of patients, while 31% experienced recurrent vaginal infections. A summary of medical records is presented in Table 6.

The VHI was assessed in 28 patients, only 2 showing a score ≤15 and a mean score of 18.7. VHI value is shown in Table 7.

On pelvic ultrasound, adenomyosis was found in 27.5% of patients and endometriosis in 17%. Patients with endometriosis reported chronic pelvic pain more frequently (p=0.010) and had a significantly higher incidence of pelvic

adhesions (p=0.026). No significant differences were observed in the distribution of clinical forms of SSc between patients with and without endometriosis. A summary is presented in Table 6.

UtA DOPPLER EVALUATION

The date of the last menstrual period was recorded for all patients, and uterine artery (UtA) Doppler measurements were analyzed according to menstrual phase. In 6 patients, UtA Doppler assessment was not possible due to poor image quality.

An increase in uterine artery resistance (>95th percentile) was observed in 14% of patients with SSc. These patients reported dyspareunia (p=0.006) and ovulatory pain (p=0.008) more frequently than those with normal resistance. Doppler findings are detailed in Table 8.

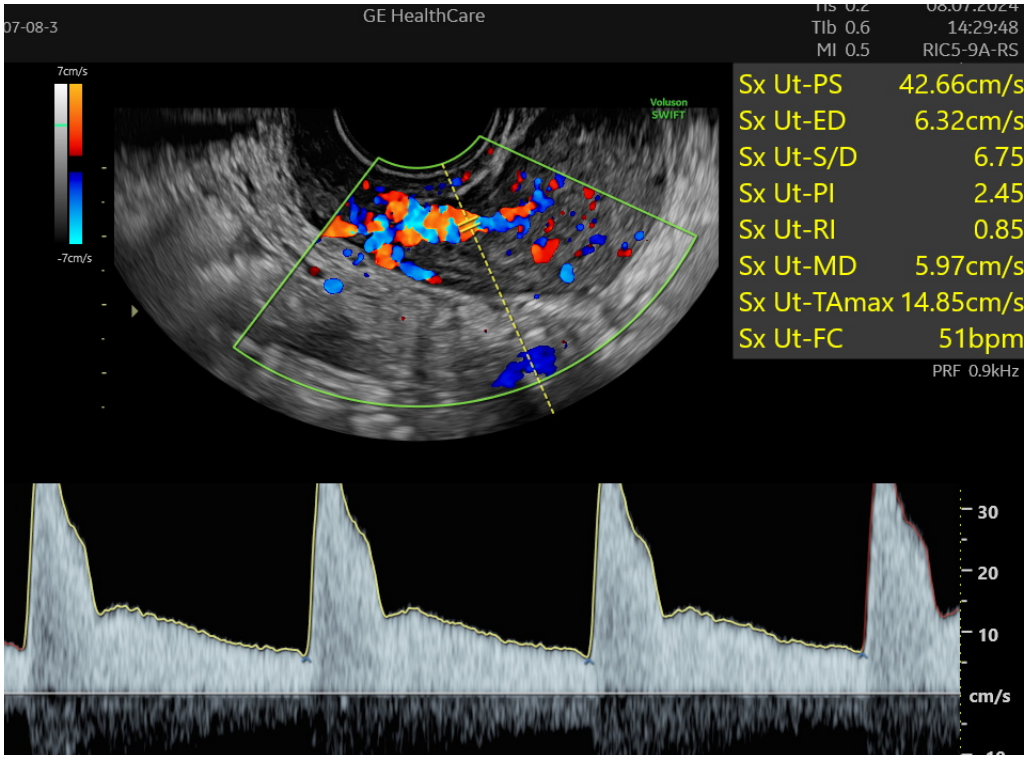

Figure 14.Example of increased Uterine Artery Resistence in enrolled SSc patients.

Table 1.Clinical characteristic of SSc patients.

Parameters	**n =29**
Demographical characteristics	
Age, (years) mean (±SD)	39,57 (±7,86)
BMI, mean (±SD)	22,70 (±4,23)
Rheumatological characteristics	
Disease duration, (years) mean (SD)	5.7 (±4.37)
lcSSc, n (%)	14 (53.84)
dcSSc, n (%)	8 (30.8)
VEDOSS, n (%)	4 (15.4)
mRSS, n (%)	8±8.64
ATA, n (%)	13 (44.8)
CENP, n (%)	7 (24.1)
ESR, mean (±SD)	18.07(±14.40)
CRP, mean (±SD)	0.51(±0.20)
Esophageal symptoms, n (%)	18 (62.1)
Gastrointestinal involvement, n (%)	5 (17.2)
Sicca Syndrome, n (%)	5 (17.2)
Sclerodactyly, n (%)	10 (37.0)
Puffy fingers, n (%)	15 (55.6)
Digital pitting scar/ulcers, n (%)	13 (46.4)
Telangiectasis, n (%)	12 (46.1)
Calcinosis, n (%)	1 (3.8)
Muscle weakness, n (%)	3 (11.5)
Arthritis, n (%)	8 (32.0)
Tendon friction rubs, n (%)	1 (4.0)
Arrhythmia, n (%)	1 (4.0)
PAH, n (%)	0 (0.0)
ILD, n (%)	8 (30.7)
NVC Scleroderma Pattern (ACTIVE), n (%)	5 (27.78)
NVC Scleroderma Pattern (EARLY), n (%)	6 (33.33)

NVC Scleroderma Pattern (LATE), n (%)	3 (16.67)
Vasodilator or vasoactive treatment (≥1), n (%)	27 (93.10)
ERA, n (%)	12 (41.38)
PDE5i, n (%)	1 (3.45)
Prostacyclins, n (%)	23 (79.31)
Immunosuppressive treatment (≥1), n (%)	18 (62,07)
Corticosteroids, n (%)	1 (3.45)
Biologic DMARDS, n (%)	6 (20.69)
Conventional DMARDs, n (%)	15 (51.72)
Comorbidity	
Arterial hypertension, n (%)	10 (35.7)
Diabetes mellitus, n (%)	0
Dyslipidemia, n (%)	13 (46.4)
Hypothyroidism, n (%)	11 (36.67)
Autoimmune hypothyroidism, n (%)	6 (54.55)

***Legend**: SD: Standard deviation; BMI: Body Mass Index; ATA: Anti-Scl-70 antibodies; CENP-1: Anti-centromere antibodies; ESR: Erythrocyte Sedimentation Rate; CRP:C-reactive Proteine; SSc: Systemic sclerosis; lcSSc: limited skin involvement; dcSSc: diffuse skin involvement; mRSS: modified Rodnan Skin Score; DPS: Digital pitting scar; DU: Digital Ulcers; SRC: Scleroderma Renal crisis; NVC: nailfold video capillaroscopy, TFR:Tendon Friction rubs PAH: pulmonary arterial hypertension; ILD: Interstitial lung disease; ERA: Early Rheumatoid Arthritis; PDE5i:Phosphodiesterase Type 5 Inhibitors; DMARDS: synthetic disease modifying antirheumatic drugs.*

Table 2.Short-form-12-health survey Questionnaire in SSc patients.

Quality of Life	**n=28**
MCS-12, mean (±SD)	34.80(±8.89)
PCS-12, mean (±SD)	46.80 (±11.98)

Legend*: PCS12: Physical Component Summary, MCS12: Mental Component Summary.*

Table 3.Urinary Symptom Profile in SSc patients.

Parameters	**n =28**
Urinary infection, n (%)	6 (21.48)
Urinary incontinence, n (%)	9(32.14)
USP (SUI) score, mean (±SD)	1.26(±1.51)
USP(SUI) score>1, n (%)	8(28.5)
USP (OBS) score, mean (±SD)	3.04 (±2.92)
USP(OBS) score>1, n (%)	18(64.3)
USP (LSS) score, mean (±SD)	0.19(±0.69)
USP(LSS) score>1, n (%)	2(7.14)

Legend*: USP: Urinary Symptom Profile; SUI: stress urinary incontinence; OBS: overactive bladder symptom and LSS: low stream symptom*

Table 4. Female Sexual Function Index in SSc patients.

Parameters	***n =28***
Dyspareunia, n (%)	11(40.74)
FSFI<26.5, n (%)	14(51.85)
FSFI total score, mean (±SD)	24.63(±9.58)
Desire, mean (±SD)	3.40 (±1.22)
Arousal, mean (±SD)	3.93 (±1.68)
Lubrication, mean (±SD)	3.91 (±2.01)
Orgasm, mean (±SD)	4.01(±1.94)
Satisfaction, mean (±SD)	4.25 (±1.73)
Pain, mean (±SD)	4.12 (±2.14)

Legend*: SD: Standard deviation; FSFI: Female Sexual Function Index; FSDS-R: Female Sexual Distress Scale Revised; USP: Urinary Symptom Profile.*

Table 5. MEDI-Q Questionnaire in SSc patients.

Menstrual Distress	**n=28**
MEDI-Q total score, mean (±SD)	11.61±10.90
MEDI-Q - MS, mean (±SD)	5.00(±4.12)
MEDI-Q - MSD, mean (±SD)	1.73 (±1,04)

Legend*: MEDI-Q: Menstrual Distress Questionnaire, MS: Menstrual Symptoms; MSD: Menstrual Symptoms Distress.*

Table 6. Gynecological evaluation in SSc patients.

Gynecological Parameters	**n=29**
Family history endometriosis, n (%)	3 (10.3)
Family history gynecological cancer, n (%)	4 (13.8)
Family history breast cancer, n (%)	7 (24.1)
Pregnancies mean (±SD)	1.17±1.15
Pregnancies, n total	33
Women with abortions, n (%)	8(27.5)
Total abortions	9
Infertility, n (%)	5 (17.2)
ART procedure, n (%)	5 (17.2)
PCOS, n (%)	3 (10.3)
Endometriosis (current or previous), n (%)	5 (17.2)
Previous endometriosis eradication, n (%)	2 (6.9)
Adenomyosis, n (%)	8 (27.5)
Myomas uterus, n (%)	4 (13.8)
Previous hormonal therapy, n (%)	25 (86.2)
Current hormonal therapy, n (%)	6 (20.7)
Vaginal infection, n (%)	9 (31.0)
Urinary infection, n (%)	6(20.06)
Urinary incontinence, n (%)	9(31.0)
Under stress incontinence, n (%)	7(24.1)
Menstruation	
Age of menarche, mean (±SD)	12,40±1,33
Regularity of menstrual cycle, n (%)	20 (76.9)
Regular amount menstrual cycle, n (%)	19 (76.00)
Spotting, n (%)	6 (20.7)
Therapy for Dysmenorrhea, n (%)	9(31.5)
Dysmenorrhea, n (%)	16(55,2)
Severe Dysmenorrhea, VAS>5, n (%)	10(34.5)
Heavy menstrual bleeding, n (%)	5(20,0)
Chronic pelvic pain, n (%)	4(13,3)
Urinary pain, n (%)	0
Pain at defecation, n (%)	4(13,7)

***Legend**: ART: Assisted Reproductive Technology; PCOS: Poly-Cystic Ovary Syndrome,*

Table 7. Gynecological physical examination in SSc patients.

Vaginal evaluation	**n=29**
Trigger points (pelvic floor), n (%)	2(6.90)
Cervix normal, n (%)	26(89.7)
Normal-Excellent Vaginal elasticity, n (%)	27(87.1)
Normal-Excellent Vaginal secretions, n (%)	19(65.5)
Ph ≥5, n (%)	26(95.0)
Normal Vaginal Hydration, n (%)	11(37,9)
Normal Epithelial integrity, n (%)	27(93.1)
Total VHI, mean (±SD)	18.68±1.98
VHI <15, n (%)	2(6.9)

***Legend**: VHI: Vaginal Health Index.*

Table 8. UtA-PI evaluation in SSc patients.

UtA Doppler	***n=29***
>95°, n (%)	4(13.8)
50-95°, n (%)	22(75.6)
5-49°, n (%)	18(62.1)
<5°, n (%)	1(3.4)

***Legend**: UtA-PI: Uterine Artery Pulsatility Index.*

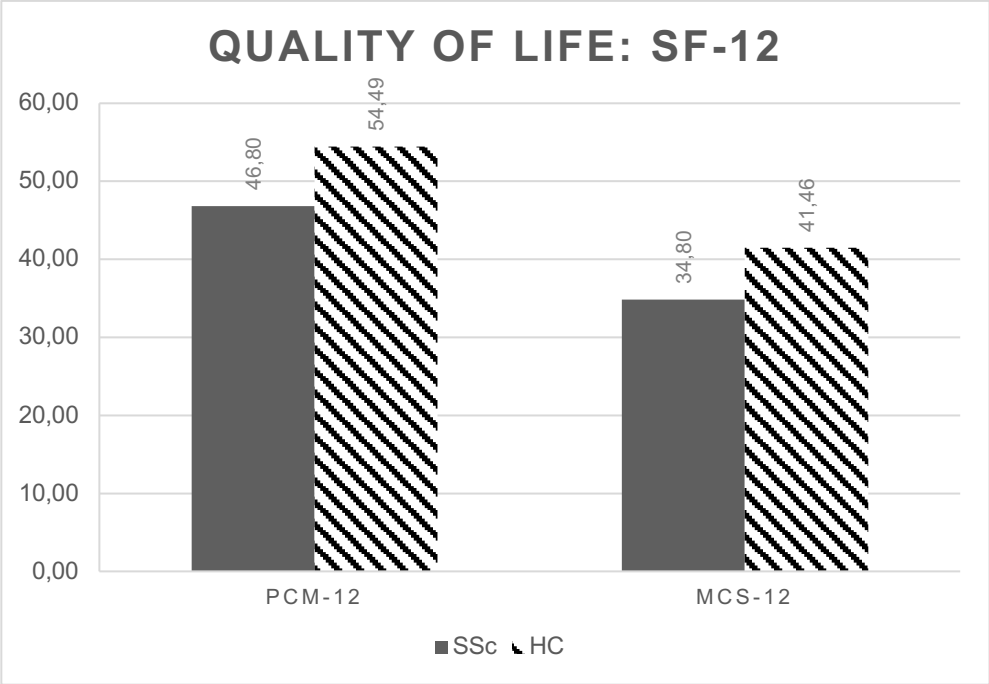

Figure 15. Quality of life: Comparison between SSc patients and HC.

***Legend**: PCS-12: Physical Component Summary; MCS-12: Mental Component Summary; SSc: Systemic Sclerosis; HC: Health Controls.*

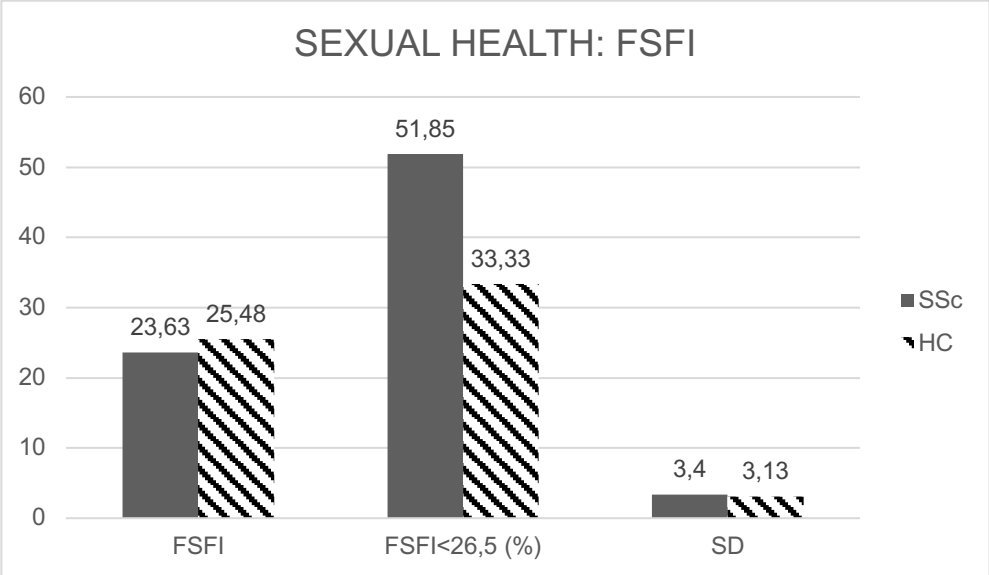

Figure 16. Sexual Health: Comparison between SSc patient and HC.

***Legend**: FSFI: Female Sexual Function Index; SD: Sexual Desire Domain; SSc: Sclerosis Systemic; HC: Health Controls.*

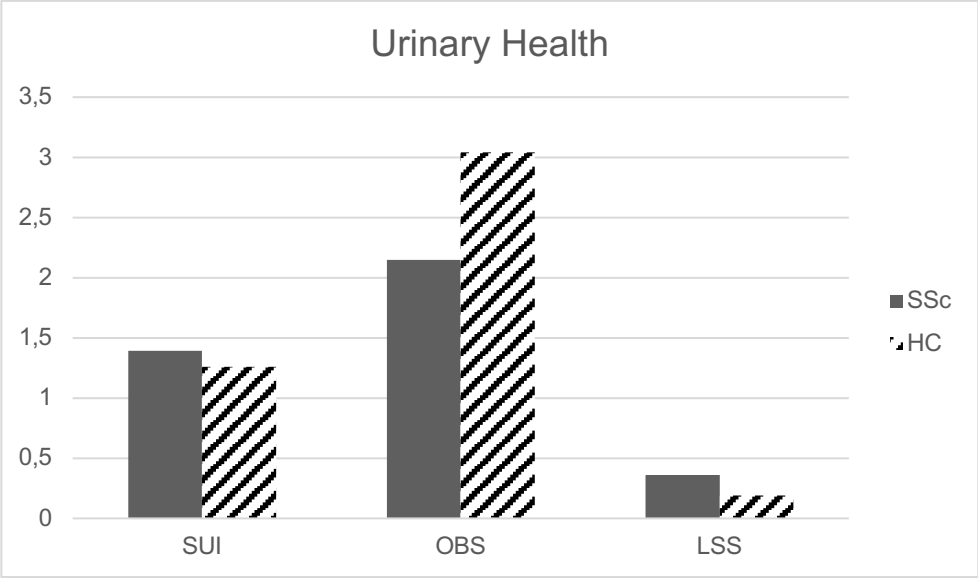

Figure 17. Urinary Health: Comparison between SSc patients and HC.

***Legend**: SUI: Stress Urinary Incontinence; OBS: Overreactive Bladder Score; LBS: Low Stream Score; SSc: Sclerosis Systemic; HC: Health Controls.*

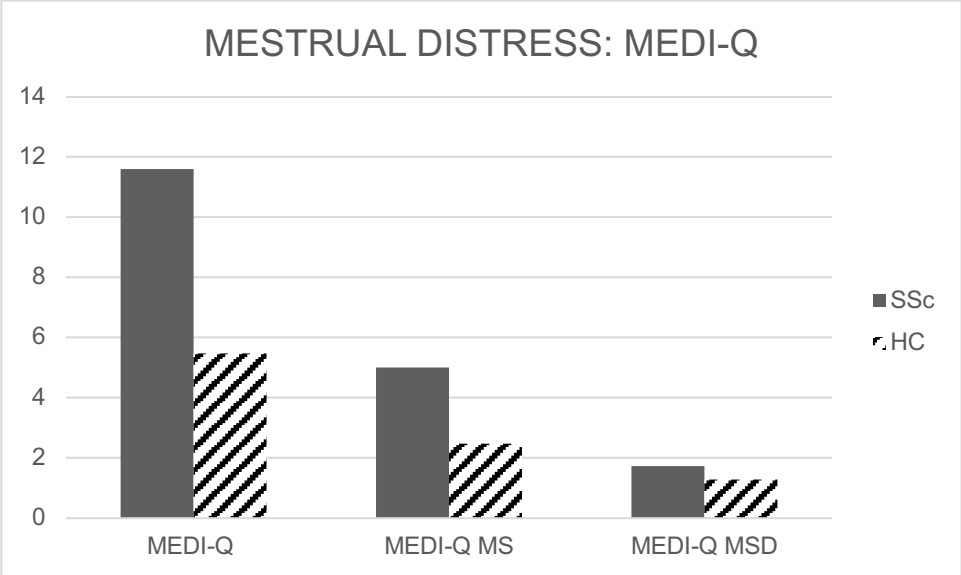

Figure 18. Menstrual Distress: Comparison between SSc patients and HC.

***Legend**: MEDI-Q: Menstrual Distress Questionnaire; MEDI-Q MS: Menstrual Symptoms; MEDI-Q MSD: Menstrual Symptoms Distress.*

DISCUSSION

Few reports are presented in literature on the uro-genital symptoms, the ultrasound evaluation of gynecological disorders and Doppler measurements, focusing on the reproductive age of patients affected by SSc.

The present study investigates the gynecological history, menstrual cycle pattern, menstrual-related symptoms/disorders, and QoL of women with RDs. At the best of our knowledge, this is the first study to extensively analyses these aspects in fertile age women with RDs.

So far, multiple studies were conducted on fertility issues and pregnancy management of women with RDs[101,102], whereas menstruation-related disorders are often neglected.

MESTRUAL DISORDERS

In our study, dysmenorrhea was reported by 55.2% of patients and heavy menstrual bleeding was noted by 5 patients. These data highlight the association between systemic sclerosis disease and relevant menstrual distress. Orlandi et al[103] reported that 56.6% of patients with connective tissue disease were also affected by dysmenorrhea and 43.4% declared heavy menstrual bleeding. As menstrual distress impact significantly on patients' QoL, for the first time in SSc patients the MEDI-Q was used to measure the global menstrual distress experienced by women[95,104]. Our patients presented a clinically relevant menstrual distress, the analysis of the MEDI-Q subscale for SSc patients presented higher discomfort than heath controls. This was evidenced by a greater number of symptoms and a higher average distress value during menstrual flow.

Gambigliani et al.[82] reported endometriosis as a complex, multifactorial condition that encompasses not only the presence of endometriotic lesions, but also involves women's sexuality, dyspareunia correlated to frequency intercourse and pelvic adhesions. In our study, endometriosis was found in 17% of SSc patients; a percentage higher than the estimated incidence in the general

Italian population (~5-10%). However, the higher incidence of endometriosis observed in our study may reflect the fact that this condition is frequently underdiagnosed, often with a diagnostic delay of 7–8 years[105]. In contrast, all patients in our cohort underwent second-level ultrasound evaluation, which may have facilitated earlier and more accurate detection. Furthermore, patients with endometriosis reported more frequently chronic pelvic pain (p=0.010) and had a significantly higher incidence of pelvic adhesions (p=0.026) that may impair infertility.

SEXUAL DISFUCTION

A high prevalence of sexual dysfunction has been described among SSc women[67,68,73,74,106]. In women affected by SSc, various factors could be involved in sexual disfunction: direct involvement of the vaginal tract determining tightness and dryness of vaginal and vulvar mucosa, musculoskeletal involvement with joint contractures, muscle weakness, joint pain and deformity but also mood disorders[68]. Bruni et al.[107] proposed genital tract alteration and general physical change as the most common factors leading to sexual impairment, often associated to psychological aspects.

In our study, significantly, sexual disfunction (cut off FSFI full scale score <26.5[99]) was present in 51.85% of patient affected by SSc, versus 33.3% in health control.

In literature, the percentage of sexual dysfunction in SSc patients (based on FSFI score) ranges from 46 to 86%[67,70,72,74,106,108].

Furthermore, isolating the sexual desire domain (cut off <5[100]), all SSc patients are affected by hypoactive sexual desire disorder (HSDD).

Most studies investigating sexual dysfunction in systemic sclerosis (SSc) have focused on populations composed predominantly of postmenopausal women. Only two studies to date have included a lower proportion of menopausal women: Levis et al.[108], who reported a 61.8% prevalence of sexual dysfunction using an FSFI total score cut-off of 22.5 and Shouffer et al.[72], who found a prevalence of 70%.

Nevertheless, both studies still included a significant number of postmenopausal women, a key factor influencing sexual function due to the genitourinary syndrome of menopause. In this context, our findings are particularly relevant, as they are based on a cohort of women in their reproductive age.

GENERAL HEALTH STATUS

The general physical change impact the sexual function, but also the general health status.

Heyne et al.[109] demonstrated the close interactions between physical limitation, high risk of depressive symptoms, pain and psychological factors in SSc, leading to a decline in health status and quality of life over the course of the disease.

In our study, SF-12 questionnaire results reported a significantly lower quality of life than controls in both the physical and psychological domains. Referring to the <50 cut-off for PCS-12 and the <42 cut-off for MCS-12[110], we can assets almost 50% of SSc patients may present physical condition and clinical depression. In detail, 16 SSc patient vs 3 HC had a PCS-12 value <50, and 25 SSc patients vs 15 HC showed MCS-12 value lower than 42.

URINARY HEALTH

Lower urinary tract symptoms are a common genitourinary complication related to SSc and the severity of symptoms can affect patients' quality of life[111–113]. Fibrosis, nervous involvement (notably dysautonomia), and functional restriction certainly play a role, but these factors are not sufficient to explain all the aspects of lower urinary tract symptoms in SSc[114]. Among the lower urinary tract symptoms, overactive bladder and urinary incontinence were described as the most frequent in SSc.

Urinary incontinence was the most reported lower urinary tract symptom in SSc, appearing more frequently in patients affected by IcSSc and affecting patient quality of life[115,116].

In our cohort, urinary incontinence was reported by 31% of patients, mainly stress incontinence. Incidence in this study might appear reduced compared to that reported in the literature, which ranges from 58-63%[116]; but it should be remembered that in our study only fertile patients were included.
Overactive bladder was remarkably reported by 64% of the patients in our study, while it was noted in 45% of patients in previous literature[115].

UtA DOPPLER EVALUATION

Several studies examined the pattern of Renal Resistive Index (RRI) using ultrasound in SSc patients to assess vascular kidney involvement[60]. The uterine and renal arteries are vessels of similar capacity, yet the relationship between SSc and uterine artery Doppler measurements has not been explored. This gap in research makes it difficult to determine whether SSc affects uterine circulation. The only available study examining Doppler ultrasound of the female genital tract in SSc focused on the microvascular integrity of the clitoral artery. Some authors reported that SSc women with digital ulcers exhibited reduced clitoral blood flow, correlated with progressive capillaroscopic damage[70].
In our study, an increase in uterine artery resistance (>95th percentile) was observed in 14% of SSc patients and these same patients more frequently reported dyspareunia and ovulatory pain. The resistance in the observed uterine arteries was greater than the expected 5%. This suggests a potential link between systemic sclerosis and microvascular impairment in the female reproductive system, requiring further investigation.

CONCLUSION

Despite the limitations of the study (i.e. small sample size, a cross-sectional design, the rarity of the disease, its infrequent onset during reproductive age), this well-selected sample for a unique center is considerable.

This is the first study to systematically analyse gynecological health in women with systemic sclerosis in childbearing age, combining the use of validated questionnaires with pelvic ultrasound examination.

The results highlight a high prevalence of gynecological, menstrual and sexual dysfunctions in patients with SSc, with a significant impact on quality of life.

Furthermore, the incidence of endometriosis among fertile Italian women is estimated at 10%, while in our sample, the incidence of the disease was found to be 17%. This suggests that the incidence of endometriosis in SSc patients may be higher; however, this finding should be interpreted with caution given the underdiagnosis of endometriosis.

For the first time, an increase in uterine artery resistance is also documented in SSc patients, with possible implications on pelvic vascularization and associated gynecological symptoms.

These data underline the need for a specific and multidisciplinary gynecological framework in the management of the patients affected systemic sclerosis.

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