Review

# Assessment of fertility and sexual dysfunction in women with systemic sclerosis: a narrative review of the literature

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## ABSTRACT

**Objective.** *The aim of this work is to review the existing literature regarding sexual and reproductive function of women affected by systemic sclerosis and to establish the impact of the disease on the gynaecological-obstetrical field.*

**Methods.** *A systematic search has been conducted by means of PubMed, Cochrane, Google Scholar, until January 2024 by the keywords "systemic sclerosis", "fertility", "sexual dysfunction" and "pregnancy".*

**Results.** *Sexual dysfunction has been described in most of the studies. This could be related to dryness and dyspareunia, but also to the psychosocial impact of SSc on body and facial appearance, which impacts on social and sexual relationships. There is conflicting evidence regarding the influence of SSc and fertility. Before the 1980s pregnancies in these patients were rare. This could be linked to the satisfied reproductive desire before the onset of SSc, or to the fact that pregnancy was labelled as high-risk, leading to counsel against it in most patients. Recently, the evidence supporting infertility is conflicting. There is no certain theory on how the disease may interfere with reproductive function, but a possible linkage can be detected in a pro-inflammatory milieu which can impair the ovarian reserve.*

**Conclusion.** *Women affected by SSc should be followed-up by a multidisciplinary team to prevent sexual dysfunction. Although there is no consensus on the impact of SSc on fertility, these patients should be provided with adequate pre-conceptional counselling and a strict follow-up in high-risk pregnancy units.*

## Introduction

Systemic sclerosis (SSc) is a rare, female-dominant, and multifactorial disease associated with several systemic manifestations caused by inflammation, vasculopathy and progressive fibrosis that compromises many organs, such as skin, lungs, kidneys, heart, gut and musculoskeletal system.

The overall pooled prevalence of SSc is 17.6 (95% CI 15.1, 20.5) per 100,000 and the overall pooled incidence rate of SSc is 1.4 (95% CI 1.1, 1.9) per 100,000 person-years (1).

SSc can be classified in limited cutaneous SSc (lcSSc), characterised by skin thickening distal to the elbows, distal to the knees, and/or face without trunk involvement, and diffuse cutaneous SSc (dcSSc) characterised by skin thickening involving the skin proximal to the elbows, the knees, face, and/or trunk. Both are associated with internal organ involvement. Antinuclear Antibodies (ANA) positivity may be present in more than 90% of cases and specific SSc antibodies such as anti-centromere, anti-SCL70, or anti-RNA polymerase III may be present in up to 70% of the cases (2-3).

The pathophysiology of the disease is very complex and involves autoimmune mechanisms and immune system dysregulation, environmental factors, predisposing genetic background and epigenetic factors (4, 5). Genetic factors are crucial in the pathogenesis of SSc, in particular genes that regulate inflammation and autoimmune response such as, for example, the HLA genes (5-7).

All these factors, added to other environmental factors (silica dust, drugs, food contaminants) can cause the onset of the disease (8).

*SSc and fertility*

Although the average onset age of SSc is around perimenopausal age and diagnosis occurs at a mean age of 33.5-59.8 in Europe and 46.1-49.1 years in North America (9), it may occur in women of childbearing age.

There is conflicting evidence in the literature regarding the impact of SSc on fertility and it is still not clear how this disease may interfere with the reproductive function. Impaired fertility in SSc patients could be linked to altered sexual function, due to vaginal dryness, dyspareunia, lack of predisposition to have sexual intercourse and/or, in some cases, premature ovarian failure and low ovarian reserve (10). Furthermore, scleroderma has a significant psychosocial impact on women due to the change in body and facial appearance, which does not encourage social and sexual relationships because of personal dissatisfaction and reduced self-esteem (11).

A possible explanation for the impaired fertility in SSc is the proinflammatory milieu which may impair the reproductive potential. As the excessive production of proinflammatory cytokines can diminish the ovarian reserve. Lliberos *et al*. in their study on mice, investigated the possibility that chronic, low-grade systemic inflammation, mediated by the inflammasome, contributes to diminished ovarian reserves and that the inflammasome activation contributes to age-related follicle depletion (12). Paradisi *et al*. demonstrated a strong negative correlation between anti-Mullerian hormone (AMH) and SIL-2R, IL-6, and IL-8 in patients with Hodgkin and non-Hodgkin lymphoma (13). TNF-α is the major actor in the inflammatory response and therefore its role in premature ovarian insufficiency (POI) was investigated in many studies. It was demonstrated that high levels of TNF-α can lead to ovarian cell apoptosis and to progressive follicular atresia (14-17). Uri-Belapolsky *et al*. demonstrated increased levels of serum AMH level and a better response of the ovaries to gonadotropins in IL-1 beta-deficient mice (18).

In conclusion, proinflammatory cytokines seem to have a possible role in the age-related process of exhaustion of ovarian reserve in SSc, possibly by enhancing the expression of inflammatory genes and promoting apoptotic pathways (13-19).

A further mechanism is the one that associates fertility to adverse obstetric outcomes; it has been suggested that trans-placental transfer of foetal cells during prior pregnancies and abortions initiates a chronic graft versus host disease which in turn may damage ovaries (20). Early menopause and a low ovarian reserve have been described in patients affected by SSc (10). Premature ovarian failure is, instead, rare but frequently associated with cyclophosphamide treatment (CYC) which has significant gonadotoxic effects crosslinking the DNA, which results in permanent damage to the finite population of germ cells present in ovaries. Moreover, CYC affects the function of granulosa cells of primordial follicles, suppressing oestrogen production and stimulating gonadotropin release, which initiates the recruitment of a new cohort of follicles to develop. This process greatly increases the number of follicles vulnerable to the toxic effects of CYC, ultimately resulting in accelerated maturation and depletion of the ovaries (21).

Treatment with CYC should be considered in a shared decision with the patient, and other alternative treatments, with comparable efficacy but not affecting fertility should be discussed (22). In case of prescription of CYC, gonadotropin-releasing hormone agonists (GnRH-a) should be suggested in order to attempt a preservation of ovarian follicles (23).

Family planning is an important issue for patients with rheumatic diseases and must be considered and discussed with the patient already at the time of diagnosis and appropriate counselling must be performed.

*SSc and sexual dysfunction*

An important aspect of SSc is the reduced quality of life, to which sexual dysfunction (SD) contributes. Currently sexual life has a significant impact on people's quality of life, influencing

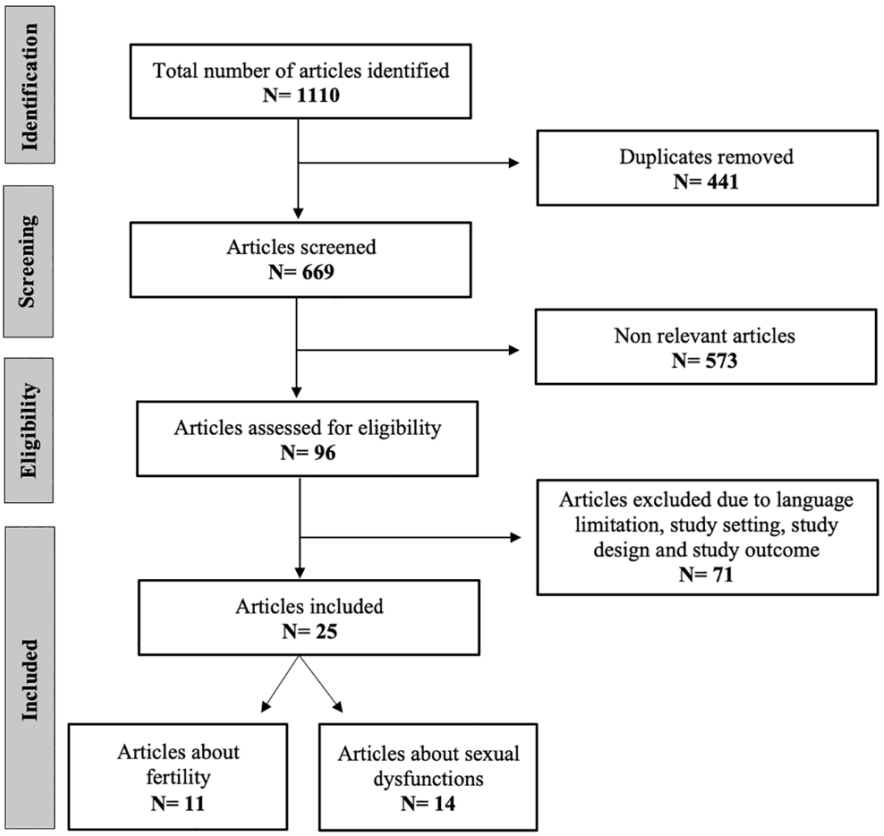


**Fig. 1.** Prisma flowchart.

**Table I.** Case series reporting fertility in SSc patients.

| Study | Year | Study design | n. of SSc patients | Rate of infertility for SSc patients | Conclusions |
|---|---|---|---|---|---|
| Slate and Graham (29) | 1968 | Case series | 66 | 31% | Infrequent association of pregnancy and scleroderma |
| Ballou *et al*. (30) | 1984 | Case series | 19 | - | Only 2 of 8 patients with onset of SSc during early childbearing years reported pregnancy |
| Giordano *et al*. (32) | 1985 | Case series | 86 | 7% | A lower number of total pregnancies in affected patients might be related to other factors |

SSc: systemic sclerosis.

the couple's relationship, social life, self-esteem and personal satisfaction (10, 12, 24).

The progressive fibrosis involving the face and body in SSc patients leads to a high body image dissatisfaction, similar to severe burn patients (12). Furthermore, vaginal dryness and dyspareunia, present in up to 37% of SSc patients, compromise sexual relationships (10).

All these features lead to a reduced self-esteem and difficulties in social and private relationships, and consequently compromised sexual function in SSc patients (20).

According to a systematic review conducted by Minopoulou *et al*. in 2022, across different systemic autoimmune rheumatic diseases, females with primary Sjögren's syndrome (pSS) and SSc seem to display higher rates of SD (24).

The mechanisms by which SSc impairs sexual function are not clear yet, but probably sexual desire disorders, arousal disorders, lubrication disorders, orgasm disorders, sexual satisfaction disorders, and sexual pain due to physical and mental reasons are important factors (25).

## Material and methods

A systematic search has been conducted by means of PubMed database, Chochrane, Google Scholar until January 2024. The keywords used for the search were: ''systemic sclerosis'' and ''fertility'', "sexual dysfunction", "pregnancy". Based on these terms, retrospective and prospective clinical studies, review articles and original articles of interest were analysed with regard to sexual function and fertility in women affected by SSc.

A total of 1110 articles were identified, and, after removal of duplicate records, two investigators screened abstracts and titles of all articles independently (n=669). After the primary screening, articles were full text screened and discussed.

We included prospective and retrospective, case-control studies, descriptive and observational studies assessing fertility and sexual dysfunction in women with SSc. We included only studies that used validated questionnaires and published in English.

We assessed the quality of all included studies using the Hoy Risk of Bias Tool, which considers both internal and external validity as well as bias related to the analysis of each study (26).

Two authors (C.M., C.G.) independently evaluated the quality of the included records. Any discrepancies were resolved by consensus.

The only articles assessed for eligibility were 96, of which 71 were excluded due to language limitations, study setting, study design and study outcomes. 9 of them were about sexual impairment and 62 of them were about fertility. We excluded articles including populations affected by overlapping other rheumatic diseases, studies using non validated questionnaires and studies that were not published in English language. There were no limitations on the patient's age and ethnicity. The inclusion criteria are female population with SSc, childbearing age or not, sexually active patients. Finally, only 25 studies were included in our review, 14 of them regarding sexual dysfunction and 11 regarding fertility (Fig. 1). Conflicts were evaluated in consensus with a third investigator.

### *Fertility issues*

The 11 studies included in this review are reported in Table I (case series) and in Table II (clinical studies).

Considering SSc rarity and the low number of clinical studies on the topic, we examined both case series with a consistent number of patients (from a minimum of 10) and clinical retrospective and prospective studies.

There is conflicting evidence in literature regarding the impact of SSc on fertility and many definitions of infertility have been proposed by different authors (*e.g*. self-reported difficulty in conception and failure to achieve a successful pregnancy by the age of 35 by Silman *et al*. (27) or by the age of 40 by Sampaio-Barros *et al*. (23).

Before the 1980s there were frequent references to the rarity of the pregnancies in patients who had established SSc. Leinwand *et al*., in 1954, did report only 2 pregnancies in 108 SSc women (28). Slate and Graham, in 1967, presented a case series in which 45 out of 66 enrolled patients had a history of pregnancy but in only 7 cases pregnancy and SSc coexisted (29). Ballou *et al*. in 1984, reported that out of their 8 patients with onset of SSc during early childbearing years, only 2 became pregnant during the course of the disease (30).

The implication was that fertility was decreased in SSc. This could be linked to the satisfied reproductive desire before the onset of SSc in that historical period or to the fact that pregnancy was labelled as high-risk for both foetal and maternal complications, leading to counsel against pregnancy in most patients (31).

More recently, the evidence supporting infertility is inconsistent, either before or after the onset of the disease.

Giordano *et al*., in 1985, stated that

**Table II.** Clinical studies reporting fertility in SSc patients.

| Study | Year | Study design | Study population | n. of sexually inactive SSc patients/patients with no pregnancy desire | Rate of infertility | Conclusions |
|---|---|---|---|---|---|---|
| Leinwand *et al*. (28) | 1954 | Retrospective study | n 108 SSc | - | 98% SSc | Only 2 pregnancies reported over 108 patients |
| Silman *et al*. (27) | 1988 | Retrospective case/ control study | n 115 SSc<br>n 115 HC | 11% | 7.8% SSc<br>2.6% HC | Fertility evaluated before SSc onset.<br>No significant infertility in SSc patients |
| Steen *et al*. (39) | 1989 | Prospective case/ control study | n 450 SSc<br>(48 with concomitant pregnancy) n 48 RA<br>n 48 HC | - | - | Fertility evaluated after SSc onset.<br>Controls had a statistically significant higher number of pregnancies than SSc patients and RA patients |
| Englert *et al*. (34) | 1992 | Retrospective case/ control study | n 204 SSc<br>n 233 PRP<br>n 189 HC | - | 7.2% (but 6 out of12 patients had other explained causes of infertility)<br>8.5% PRP<br>3.5% HC | Fertility evaluated before SSc onset.<br>Infertility rate of affected patients was comparable to that of the general population. |
| Steen and Medsger (35) | 1999 | Postal questionnaire | n 214 SSc<br>n 167 RA<br>n 105 HC | 5% | 21% SSc<br>23% RA<br>12% HC | Fertility was not significantly different when adjustments were made for possible contributing factors. |
| Sampaio-Barros *et al*. (23) | 2000 | Retrospective study | n 150 SSc | 13% | 4% SSc | Fertility evaluated before and after SSc onset.<br>Higher fertility in limited SSc patients than in diffuse SSc patients.<br>Fertility rate higher in SSc populations than in general population. |
| Kharbanda *et al*. (36) | 2021 | Retrospective study | n 75 SSc | 20% | 8.3% SSc | Fertility evaluated before and after SSc onset.<br>Very low number of pregnancies in SSc patients after disease onset. |
| Dai *et al*. (37) | 2023 | Cross-sectional study | n 342 SSc<br>n 110 HC | 20.1% before disease onset<br>69.5%after disease onset | 3.8% SSc before disease onset 11.6% SSc after disease onset | Infertility rate not increased both before and after disease onset.<br>Decrease in reproductive intention of SSc patients. |

SSc: systemic sclerosis; HC: healthy controls; RA: rheumatoid arthritis; PRP: primary Raynaud's phenomenon.

only 6 out of 86 patients in their series had no pregnancy (32).

Silman *et al*. in 1988, compared, retrospectively, fertility issues in 115 patients before the onset of the disease to the ones of 115 health controls. According to their definition, infertility was more frequent in SSc, although not in a statistically significant way (9/115 *vs*. 3/115) (27).

Steen *et al*. in 1989, prospectively examined 450 women. Among them, 225 (50%) had completed all pregnancies before the onset of SSc, 156 (35%) had never been pregnant, and 69 (15%) had one or more pregnancies after the onset of SSc (concomitant pregnancy). 48 women out of the 69 who had a pregnancy after the onset of the disease were compared to patients affected by rheumatoid arthritis (RA) and control subjects who had at least one pregnancy. Although this study did not specifically address fertility issues, Steen and her colleagues suggest that infertility could be a feature of SSc. Thirty-five percent of the SSc patients with disease onset prior to age 45 were never pregnant, and there was a significantly decreased total number of pregnancies in the group with SSc and concomitant pregnancy compared with that in NC subjects (33).

Englert *et al*. in 1992, analysed retrospectively the reproductive function of 204 SSc patients before the onset of the disease, the reproductive function of 233 patients affected by primary Raynaud's phenomenon and the one of 189 controls. Infertility was more frequent in SSc patients than in the controls (7.2% *vs*. 3.5%, odds ratio [OR]: 2.1) but no differences were found between the group of SSc patients, and the patients affected by primary Raynaud's phenomenon (7.2% *vs*. 8.5%). It is important to underline, however, that in 6 of the 12 infertile SSc patients other causes of infertility were found. In this way, the infertility rate of affected patients was comparable to the one of the general population (34).

In 1999, Steen and Medsger compared retrospectively 214 SSc patients before the onset of the disease to 167 patients affected by RA and to 105 health controls with questions about the occurrence of pregnancy and any delays in conception. There was a significantly larger number of women who had SSc, and RA who had never been pregnant (21% SSc, 23% RA, and 12% healthy controls, $p<005$). Although, when this data was corrected for factors such as no marriage, no active sexual life and no desire of pregnancy, there were no differences between the three groups. Also, the percentage of women who had at least a one-year delay in concep-

tion was not significantly different in the three groups (12%-15%) (35).

Sampaio-Barros *et al*. in 2000, reported a high rate of pregnancies in SSc patients before onset of the disease (23). Of their 150 patients, only 32 (21%) had never been pregnant (24 with lcSSc and eight with dcSSc) but 19 of them had no partner and 8 did not have a pregnancy desire. The fertility rate for the SSc patients was 3.4, which was higher than that observed in the Brazilian population (2.5) and in the local population of the State of São Paulo (2.2).

Kharbanda *et al*. in 2021, conducted a retrospective study in the Indian population affected by SSc, before and after disease onset, and found out that infertility was reported by 8.3% of patients. They also concluded that the overall number of pregnancies after disease onset was very low and that this data could be attributed to vasculopathy, disease activity or failure to get married at an appropriate age due to social stigma (36).

In 2023, Dai *et al*. conducted a cross-sectional study on the Chinese population affected by SSc. They collected fertility desire, fertility plan and influencing factors of all 342 enrolled participants before and after the onset of the disease. It is interesting to notice that, in their cohort, the infertility rate was not increased compared to the general population but it was found to be a decrease in reproductive intention and increase in the risk of early menopausal age (37).

According to the most recent studies, adopting more standardised and updated criteria, the infertility rate does not appear to be statistically reduced in women affected by SSc; rather, possible confounding biases should be better defined in order to obtain more representative data. In addition, it would be advisable to do careful counselling in order to better inform patients about the possible obstetrical risks related to the disease and to raise awareness and support these patients during the search for pregnancy.

*Sexual dysfunction*

In the 14 analysed articles, summarised in Table III, the primary outcome was assessing the sexual dysfunction among women affected by scleroderma using accepted and validated international questionnaires: the most relevant were FSFI (Female Sexual Function Index), BISF-W (Brief Index of Sexual Function for Women), SFQ-28 (Sexual Function Questionnaire), PISQ-12 (Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire Short Form), PFIQ-7 (Pelvic Floor Impact Questionnaire-Short Form 7), SQoL-F (Sexual Quality of Life-Female), FSFS (Female Sexual Function in Scleroderma), SF-36 (Short Form 36), IIEF-5 (International Index for the Erectile Function).

FSFI is a widely used measure of Female Sexual Dysfunction (FSD). It assesses 6 domains: desire; arousal; lubrication; orgasm; satisfaction; and pain. Validation studies in women aged 21 to 70 have demonstrated excellent internal consistency and 2-4-week test-retest reliability for each subscale (38). In particular, the mean FSFI in the general population is estimated to be 30.5 (39). On the other side, the mean FSFI of the study population in the 10 studies that used the score, was 20.04 and according to the included studies, the prevalence of sexual dysfunction in SSc females varies from 32% to 90%. Anyway, it is to point that the diagnostic criteria of sexual dysfunction were of difference among the studies, so this data must be carefully interpreted.

In particular, Heřmánková *et al*. (40) compared sexual function and pelvic floor function in women affected by SSc with healthy controls (HC) and found out that total FSFI mean score in SSc was 24 while it was 30.8 in HC, with a $p$=0.0002. The other scores, identified a significant statistical difference as well between the two groups, with a BISF-W: 30.4 ($p$=0.0005), PISQ-12: 12 ($p$=0.0002), SQoL-F: 65.6 ($p$=0.0002), PFIQ-7: 26.3 ($p$=0.0016) that means that women with SSc reported significantly worse pelvic floor function and sexual function than HC. Impaired sexual function was correlated with higher disease activity, presence of dyspnoea and interstitial lung disease, increased systemic inflammation, reduced physical activity, functional disability, more severe depression, more pronounced fatigue, and impaired quality of life. Schmalzing *et al*. (41) assessed and compared sexual dysfunction in female patients with systemic sclerosis or systemic lupus erythematosus. They found out that sexual dysfunction is a frequent problem in patients with SSc and that their FSFI value did not differ significantly compared to SLE patients. According to their work, patients who suffered from sexual dysfunctions were more likely to have at least mild depression defined by BDI. Uçar *et al*. in 2018 as well showed that total FSFI scores in SSc females was 15.27 and in the healthy control group was 25.63, with a significant statistical difference ($p$=0.0001) (42); Schouffoer *et al*. showed that total FSFI score and the subscale scores for lubrication, orgasm, arousal, and pain were significantly lower in patients with SSc ($p$<0.05) (43); Gigante *et al*. found that there was significant statistical difference in total FSFI scores between the 2 groups ($p$=0.026), too (44). They also found out that clitoral blood flow in SSc women is reduced not only for macro- and microvascular damage but also for impaired angiogenesis. Levis *et al*. indicated that patients with SSc had lower sexual activity and higher rates of sexual dysfunction than healthy women, after adjusting for age, marital status and education level ($p$=0.012 and $p$<0.001) (45); Maddali Bongi *et al*., on the other side, found out that only FSFI desire subscale score was significantly lower in patients with SSc in comparison with HC, and in SSc, the main factors independently associated with sexual functioning were vaginal dryness ($p$<0.001), PDSBE ($p$=0.001), and HADS depression scale ($p$=0.035) (46). The differences among the results of the included studies may be due to the small sample sizes and the heterogeneity in the samples and in the questionnaires used in each study.

Other 6 studies (46-48, 51-53) did not compare SSc patients with a group of controls but were just descriptive studies. They all assessed that sexual disorders in their study population were higher than in the general population. Furthermore, they analysed other com-

**Table III.** Sexual dysfunctions in SSc patients.

| Study | Year | Study design | Study population | Criteria of SD | Prevalence of SD in SSc | Results (mean score of the scales) | Conclusions |
|---|---|---|---|---|---|---|---|
| Heřmánková *et al*. (40) | 2022 | Cross-sectional study | n 90 SSc<br>n 90 HC | FSFI < 26 | 73% | **FSFI**: 24 ($p$=0.0002)<br>**BISF-W:** 30.4 ($p$=0.0005)<br>**PISQ-12:** 12 ($p$=0.0002)<br>**SQoL-F:** 65.6 ($p$=0.0002)<br>**PFIQ-7:** 26.3 ($p$=0.0016) | Significantly worse pelvic floor function and sexual function in SSc women reported. |
| Schmalzing *et al*. (41) | 2020 | Descriptive study | n 83 SSc<br>n 88 SLE | FSFI < 26.55 | 49% in SSc<br>45.8% in SLE | **FSFI in SSc:** 25.5<br>**FSFI in SLE**: 26.9 | No differences in SD between SSc and SLE. |
| Gigante *et al*. (44) | 2019 | Case-Control Study | n 15 SSc<br>n 10 HC | FSFI < 19 | 46.7% | **FSFI**: 16.9 (p=0.0026) | VEGF (pg/mL) and endostatin (ng/mL) median values significantly higher in SSc women than HC. Resistive index and systolic/diastolic ratio median values were significantly higher in SSc women than HC. |
| Uçar *et al*. (42) | 2018 | Case-Control Study | n 30 SSc<br>n 30 HC | FSFI < 22.7 | 86.6% | **FSFI:** 15.27 | Significant differences between the groups with respect to sexual desire, arousal, lubrication, orgasm, sexual satisfaction, and pain. |
| Sanchez *et al*. (47) | 2016 | Descriptive Study | n 73 SSc (60 women, 13 men) | FSFI < 26.5 | 62.5% in women 87.5% in men | **FSFI in women population:** 24.9 | LUTS more frequent in SSc patients than in the general population. The most frequent symptom is overactive bladder. |
| Frikha *et al*. (51) | 2014 | Horizontal descriptive Study | n 10 SSc | FSFI < 26 | 90% | **FSFI**: 14.2<br>**HAQ global disability score**: 1.15<br>**WHOQOL-BREF**: 60<br>**VAS**: 64 | The prevalence of SD in women with SSc is high when a specific questionnaire is used to assess it. |
| Rosato *et al*. (52) | 2014 | Descriptive Study | n 102 SSc | FSFI < 19 | 44% | **FSDS-R:** 10.2<br>**DAS:** 96<br>**FSFI:** 18.5 | Negative correlation between FSDS-R and FSFI. No correlation found between FSDS-R and DAS. FSFI showed a positive correlation with DAS. |
| Rosato *et al*. (49) | 2013 | Descriptive Study | n 22 SSc<br>n 20 HC | FSFI < 19 | 32% | **FSFI**: 23 | No differences in the PSV vs and PI between SSc women and HC. EDV significantly reduced, RI and S/D ratio significantly increased in SSc women. A negative correlation was observed between the FSFI and RI or S/D ratio. |
| Maddali Bongi *et al*. (46) | 2013 | Descriptive study | n 46 SSc<br>n 46 HC | FSFI < 26 | 67% | **FSFI**: 18.2<br>desire subscale (p=0.035) | In SSc, sexual function, is influenced by specific disease- related and psychological concerns. |
| Levis *et al*. (45) | 2012 | Descriptive study | n 730 SSc<br>n 956 HC | FSFI < 22.5 | 61% of the 296 sexually active | 181 SSc sexually active patients reported SD. | Sexual functioning is a problem for many women with scleroderma and is associated with pain and poor lubrication. |
| Levis *et al*. (53) | 2012 | Cross-sectional multicentre study | n 547 SSc | FSFI < 22.5 | 62% of the 165 sexually active | 102 SSc sexually active patients reported SD. | Future research should build upon this study and examine potential mediators of sexual activity and impairment. |
| Knafo *et al*. (48) | 2011 | Descriptive study | n 117 SSc | PAISSR scores range from 0 to 18 and higher scores reflect poorer sexual function. | - | **PAISSR**: 4.8<br>**SWAP**: 46.3<br>**VAS**: 25.3 | Pain is an important indicator of sexual function among SSc patients. Body image dissatisfaction appears to be less important than pain in determining sexual function. |
| Impens *et al*. (49) | 2009 | Descriptive study | n 101 SSc | FSFI <30.5 | - | **FSFI**: 24.9 in the sexually active population | Women with scleroderma do remain sexually active overall despite several disease-related physical and psychological difficulties. |
| Schouffoer *et al*. (43) | 2009 | Cross-sectional study | n 69 SSc<br>n 58 HC | FSFI < 26.55 | 70% | **FSFI:** 20.6<br>**FSDS:** 16.8 | In daily practice, inquiring about sexuality and screening for depressive symptoms is indicated in every patient with SSc. |

SD: sexual dysfunction; SSc: systemic sclerosis; HC: healthy controls; FSFI: Female Sexual Function Index; BISF-W: Brief Index of Sexual Function for Women; PISQ-12: Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire Short Form; SQoL-F: Sexual Quality of Life-Female; PFIQ-7: Pelvic Floor Impact Questionnaire- Short Form 7; SLE: systemic lupus Erythematosus; BDI: Beck's Depression Inventory; VEGF: vascular endothelial growth factor; LUTS: lower urinary tract symptoms; HAQ Global Disability: Health Assessment Questionnaire Global Disability; WHOQOL-BREF: World Health Organisation Quality of Life; VAS: visual analogue scale; FSDS-R: Female Sexual Distress Scale Revised; DAS: Dyadic Adjustment Scale; PSV: peak systolic velocity; PI: pulsatility index; EDV: end diastolic velocity; S/D Ratio: systolic/diastolic ratio; PDSBE: Disability Sexual and Body Esteem Scale; HADS: Hospital Anxiety and Depression Scale; PAISSR: Psychosocial Adjustment to Illness Scale Self-Report; SWAP: Satisfaction with Appearance Scale; SF-36: Short Form 36.

ponents of genito-urinary tract disorders: for example, Sanchez *et al*. (47) observed that LUTS (lower urinary tract symptoms) seemed to be more frequent in SSc patients than in the general population and the most frequent symptom was overactive bladder. Knafo *et al*. described that in his cohort of 177 women affected by SSc, reduced sexual function was associated with pain (r=0.44, $p<0.001$) and body image dissatisfaction (r=0.35, $p<0.001$) (48). Impens *et al*. instead related the rate of SD with the SF-36 (36-item Short Form Health Survey) and stated that Sexual functioning was significantly correlated with the Mental Component Score of the SF-36 (r=0.54, $p<0.001$) but surprisingly not with the Physical Component Score of the SF-36 (49).

Rosato *et al*. in 2013 conducted an interesting study relating the SD with the Doppler measurement of clitoral blood flow (50). They found out that clitoral blood flow was reduced in SSc women compared with healthy controls and in particular it was reduced in SSc women with digital ulcers and it correlated with capillaroscopic damage progression. A negative correlation exists between the RI and sexual disorders ratio. Despite the heterogeneity of the results, most of the studies examined suggest that there may be a significant impact of pathology on the quality of sexual life, on self-body image and on the relational life of couples and society. Another aspect to consider is that SSc has a great impact on physical health and that therefore, as suggested by Heřmánková *et al*. (40) the quality of personal and sexual life can correlate negatively with the degree of severity of the disease. In addition, the worsening quality of life can also be due to other aspects that may be related to the disease, such as pelvic floor dysfunction (42), urinary symptoms (47) or a greater tendency to depression (46).

All these aspects should be considered in the overall management of the disease and given attention in order to improve the quality of life of these women.

## Discussion

The existing literature regarding fertility outcome and sexual impairment in women affected by SSc is scarce. Few studies were conducted in the past years and methodology and criteria were not standardised. The aim of this review is to give a wider picture of some niche aspects of SSc, which consistently contributes to the quality of life of these particular patients but are often underestimated in the general assessment of the disease. As stated above, SSc is typically diagnosed in perimenopausal period, at a mean age of 33.5–59.8 in Europe and 46.1–49.1 years in North America (8). However, considering the increasing maternal age due to social change and the use of assisted reproductive technologies, pregnancy and pregnancy desire are no longer so rare in SSc women. In particular, SSc symptoms and its therapies can represent an obstacle to achieve a successful pregnancy, therefore prospective studies are needed in order to better assess the way of counselling and managing these patients. The current literature, in fact, is mainly composed of case reports, case series and clinical retrospective studies, that, even if not univocally, show an overall preserved fertility in SSc women, especially when the data are adjusted for social bias such as no active sexual life and no pregnancy desire. On the other hand, the available studies about sexual dysfunction agree on an impaired sexual life in almost all cases, due to organic manifestations of the disease such as vaginal dryness and dyspareunia and to the psychosocial impact of SSc on body and facial appearance. Moreover, dealing with sexual dysfunction and fertility challenges can be emotionally taxing. It appears from many of the studies that psychosocial support is essential to address the emotional and mental well-being of women with SSc. Support groups, counselling, and educational resources can help individuals and couples navigate the emotional aspects of these challenges. Open communication between patients, their partners, and healthcare providers fosters a supportive environment. Understanding the impact of the disease on intimacy and fertility is crucial for developing coping strategies and maintaining a healthy relationship. Ongoing research is essential to better understand the specific ways SSc affects sexual function and fertility. Advancements in treatment options and a deeper understanding of the disease impact on reproductive health can lead to improved outcomes for women with SSc.

## Conclusions

Sexual dysfunction and fertility assessment in females with SSc is a major health problem, impacting self-esteem, well-being and the quality of life of these women. To date, physician interest and research efforts on this topic has been limited. At present there is no definitive cure for female sexual dysfunction in SSc patients. Hence, clinical trials are necessary in order to identify a diagnostic-therapeutic procedure aimed at alleviating this disabling problem.

In conclusion, addressing sexual dysfunction and fertility issues in women with SSc requires a holistic and collaborative approach. Open communication, regular medical monitoring, and psychosocial support are essential components of comprehensive care for individuals navigating these challenges. By integrating the expertise of rheumatologists, gynaecologists, reproductive specialists, and mental health professionals, healthcare teams can better support the overall well-being of women with SSc.

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