Systemic Sclerosis: Exploring the Potential Interplay Between Thyroid Disorders and Pregnancy Outcome in an Italian Cohort

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ABSTRACT: **Background:** Evidence has shown that pregnancy failure (PF) in women with systemic sclerosis (SSc) consists mainly of preterm delivery (PD) and intrauterine growth restriction (IUGR). Thyroid dysfunction (TD) and Hashimoto's thyroiditis (HT) represent a common feature of SSc. Since TD has been associated with PF, its presence in SSc women may potentially affect pregnancy outcome.

Objectives: To analyze the interplay between TD and PF in a cohort of SSc women.

Methods: SSc women (n=77) and age-matched controls from the general obstetric population (n=50) were included. Clinical/biochemical/instrumental data exploring TD and the visceral involvement were collected in the context of a clinical practice setting. Pregnancy outcome was assessed by registering the history of primary infertility, recurrent spontaneous abortion, PD (≤ 37 gestational week), IUGR, and intrauterine fetal death.

Results: A higher prevalence of PD/IUGR was recorded in the SSc cohort than the controls (P = 0.04). SSc women with PF showed a higher prevalence of diffuse SSc than women without PF (P = 0.03). Scl-70 positive SSc women had a higher prevalence of PF than women with anti-centromere positivity (P = 0.01). A higher prevalence of HT was recorded in SSc women with PF than in patients without (P = 0.04).

Conclusions: Our findings support the evidence that women with SSc can have successful pregnancies despite a higher prevalence of PD/IUGR. Diffuse SSc and Scl-70 positivity may predispose SSc women to PF. Routine thyroid workup may be included in the multi-specialist monitoring of SSc women for the early detection of thyroid dysfunctions.

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KEY WORDS: autoimmunity, pregnancy, systemic sclerosis, thyroid

Systemic sclerosis (SSc) is an autoimmune disorder that affects organs via inflammation, vascular damage, and fibrosis with a variable multi-organ system involvement [1]. SSc is most prevalent in females and can be divided into three categories: (a) scleroderma and morphea; (b) scleroderma-like skin diseases; and (c) SSc including limited cutaneous SSc (lcSSc), diffuse cutaneous SSc (dcSSc), sine scleroderma, and overlap syndrome [2]. Predictors of a rapidly progressive SSc have been identified concerning diffuse skin and/or internal organ involvement such as the scleroderma renal crisis (SRC) and cardiopulmonary involvement, either due to interstitial lung disease or pulmonary hypertension [3,4]. It was previously thought that pregnancy in SSc was associated with poor outcome for both the mother and the child. Recent evidence has revealed that women with SSc can have a good pregnancy outcome [5,6]. However, it has been reported that women who have early disease, dcSSc, anti-Scl-70 antibody, and/or anti-RNA polymerase III antibody are at particularly increased risk of pregnancy syndromes [5,7]. In particular, studies showed that pregnancy failure in SSc women consists mainly of preterm delivery, intrauterine growth restriction (IUGR), and very low birth weight [5]. Thyroid dysfunctions and autoimmune thyroid disease, such as Hashimoto's thyroiditis, represent a common feature of SSc [8,9]. Since thyroid dysfunctions have been associated with pregnancy failure [10-13], in particular with recurrent spontaneous abortion (RSA), their presence in SSc women may potentially affect the pregnancy outcome.

There are no studies to date exploring the potential relationship between thyroid dysfunctions and pregnancy outcome in women with SSc. This study was thus conducted to analyze the interplay between thyroid dysfunctions and pregnancy failure in a cohort of SSc women.

PATIENTS AND METHODS

As this was a cohort pilot study, we restricted the enrollment to women attending the Rheumatology Clinic (University of Rome Tor Vergata, Rome, Italy) and the Polymedical

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Center for Prevention of Recurrent Spontaneous Abortion (San Giovanni Addolorata Hospital in Rome, Italy), during a 10 year period (January 2005 to December 2015). Women were eligible for the study if they received a diagnosis of SSc according to American College of Rheumatology criteria [4]. Data from 77 women with SSc and in stable clinical condition at the time of the medical evaluation were analyzed [Table 1]. Complete thyroid workup was conducted in the context of clinical practice setting, including serum levels of thyroid hormones and specific autoantibodies (antithyroid peroxidase [TPO] and antithyreoglobulin [ATG]) and with thyroid ultrasound to explore the presence of Hashimoto's thyroiditis, non-toxic multinodular goiter, hypothyroidism, and thyroid cancer [14]. Laboratory data included circulating autoantibodies (antinuclear antibody [ANA], anti-double-stranded DNA, anti-extractable nuclear antigen [ENA], antiphospholipid antibodies [aPL]), according to standardized methods.

Data of clinical evaluation, along with nailfold capillaroscopy findings, pulmonary function testing [diffusing capacity for carbon monoxide (DLCO)], echocardiography (with eco-doppler systolic pulmonary artery pressure estimation), and evaluation of gastroesophageal reflux/dismotility (manometry/endoscopy) that explored visceral involvement were recorded from SSc patients. Clinical complications, such as sicca syndrome and digital ulcers, and treatments at the time of the enrollment were reported [Table 1]. Pregnancy outcome was assessed by registering the history of primary infertility (defined as the inability to conceive a child after 12 months of regular sexual intercourse without contraception in couples who have never had a child), recurrent spontaneous abortion (RSA) (≥ 2 spontaneous abortions within 20 weeks of gestation), preterm delivery (≤ 37 gestation weeks), IUGR, and intrauterine fetal death (IFD) [15]. Age-matched women (n=50) extracted from a random sample of the general obstetric population served as controls. All subjects gave their verbal permission to use the data for research.

Table 1. Demographic and clinical data from the cohort of women with systemic sclerosis

	SSc (N=77)
Age at diagnosis (years, mean ± SD)	49.7 ± 16
Limited SSc (n/%) Diffuse SSc (n/%)	46/59.7 31/40.3
Sicca syndrome (n/%)	15/19.5
ANA positivity (n/%)	61/79.2
Anti-dsDNA positivity (n/%)	0/0
aPL positivity (n/%)	3/3.9
ENA positivity (n/%) Scl-70 (%) Anti-centromere (%) Others (%)	54/70.1 31.5 48.2 27.3
Raynaud's phenomenon (n/%)	74/96.1
Digital ulcers (n/%)	18/23.3
Heart: elevated US-PAPs (n/%)	22/28.6
Lung: reduced DLCO (n/%)	32/41.6
Esophageal reflux, dysphagia (n/%)	33/42.9
Kidney (n/%)	0/0
Treatments: Prednisone (%) Hydroxycloroquine (%) DMARDs (%) Other treatments* (%)	 34/44.2 30/38.9 13/16.9 52/67.5

SD = standard deviation, SSc = systemic sclerosis, ANA = anti-nuclear antibodies, dsDNA = double stranded DNA, aPL = antiphospholipid antibodies, ENA = anti-extractable nuclear antigen, US-PAPs = systolic pulmonary arterial pressure on heart ultrasound (≥ 25 mmHg), DLCO = diffusing capacity for carbon monoxide (DLCO ≤ 70%), DMARDs = disease modifying anti-rheumatic drugs

*Other treatments included endothelin receptor antagonists, synthetic prostacyclin analogue, calcium channel blockers

STATISTICS

Continuous variables were expressed as mean ± standard deviation. Normally distributed and non-normally distributed continuous variables were compared using an independent *t*-test and Mann–Whitney U test, respectively. Chi-square or Fisher's exact test was utilized for proportion comparisons. *P* values < 0.05 were considered statistically significant. All data were stored on a server and statistical analyses were performed using GraphPad Prism 6.0 (GraphPad Software, California).

RESULTS

Demographic and clinical data from the SSc cohort are reported in Table 1. The control group included 50 age-matched women (mean age at enrollment 39.6 ± 4.9 years).

PREGNANCY OUTCOME

In the SSc cohort we registered 23 women with pregnancy failure (29.9%), including 9 with RSA (39.1%), 5 with preterm delivery (21.8%), 4 with IUGR (17.4%), 3 with primary infertility (13%), and 2 with IFD (8.7%). All of the SSc women reported no disease progression during pregnancy. SSc women revealed overall the same prevalence of pregnancy failure with respect to controls (8/50, 16%) that included six cases of RSA and two cases of primary infertility. Nevertheless, a higher cumulative prevalence of preterm delivery and IUGR was recorded in SSc cohort than in controls ($P = 0.04$) while infertility and RSA were more prevalent in controls than in SSc women ($P = 0.003$) [Figure 1A].

Characteristics of SSc women with pregnancy failure are reported in Table 2 together with data from SSc women without pregnancy failure. SSc women with pregnancy failure had Scl-70/anti-centromere positivity in 52.2% of cases and 47.8% were positive for RNP, Jo1 or SSA. SSc women with pregnancy failure showed a higher prevalence of diffuse SSc ($P = 0.03$) and ANA positivity ($P = 0.03$) while women without pregnancy

Table 2. Clinical data from the cohort of women with systemic sclerosis in accordance with the presence of pregnancy failure

	Women with pregnancy failure (N=23)	Women without pregnancy failure (N=54)
Limited SSc (n/%) Diffuse SSc (n/%)	12/52.2* 11/47.8*	42/77.8 12/22.2
Sicca syndrome (n/%)	4/17.4	11/20.4
ANA positivity (n/%)	22/95.7*	39/72.3
aPL positivity (n/%)	1/4.3	2/3.7
ENA positivity (n/%) Scl-70 Anti-centromere Others	17/73.9 47 23.5* 29.5	37/68.5 21.6 62.2 16.2
Digital ulcers (n/%)	4/17.4	14/26
Heart: elevated US-PAPs (n/%)	4/17.4	14/26
Lung: reduced DLCO (n/%)	7/30.4	29/53.7
Esophageal reflux, dysphagia (n/%)	8/34.8	25/46.3
Thyroid disorders (n/%) Hashimoto's thyroiditis Non-toxic multinodular goiter Hypothyroidism Thyroid cancer	13/56.5 9/69.2* 2/15.4* 2/15.4 0/0	28/51.8 10/35.7 14/50 3/10.7 1/3.6

SSc = systemic sclerosis, ANA = anti-nuclear antibodies, ENA = anti-extractable nuclear antigen, US-PAPs = systolic pulmonary arterial pressure on heart ultrasound (≥ 25 mmHg), DLCO = diffusing capacity for carbon monoxide (DLCO ≤ 70%), chi-square or Fisher's exact test was utilized for proportion comparisons
*P < 0.05 between the groups

failure had a higher prevalence of limited SSc (P = 0.03) and anti-centromere positivity (P = 0.03) [Table 2]. A higher prevalence of pregnancy failure was recorded in SSc women with Scl-70 positivity (53%) than in SSc women with anti-centromere positivity (4.8%, P = 0.01) [Figure 1B].

No difference in the prevalence of sicca syndrome, digital ulcers or cardiopulmonary and esophageal involvement were seen between women with pregnancy failure and those without [Table 2].

THYROID DISORDERS

Of a total of 77 SSc women, we identified 41 women with thyroid dysfunctions (53.2%), including 19 with Hashimoto's thyroiditis (46.3%), 16 with non-toxic multinodular goiter (39%), 5 with hypothyroidism (12.2%) and one case of thyroid cancer (2.5%). Characteristics of SSc women with thyroid dysfunctions are reported in Table 3 together with data from SSc women without thyroid dysfunctions.

SSc women revealed the same prevalence of thyroid dysfunctions with respect to controls (23/50, 46%) including, in particular, non-toxic multinodular goiter (47.8%), Hashimoto's thyroiditis (26%), and hypothyroidism (13%).

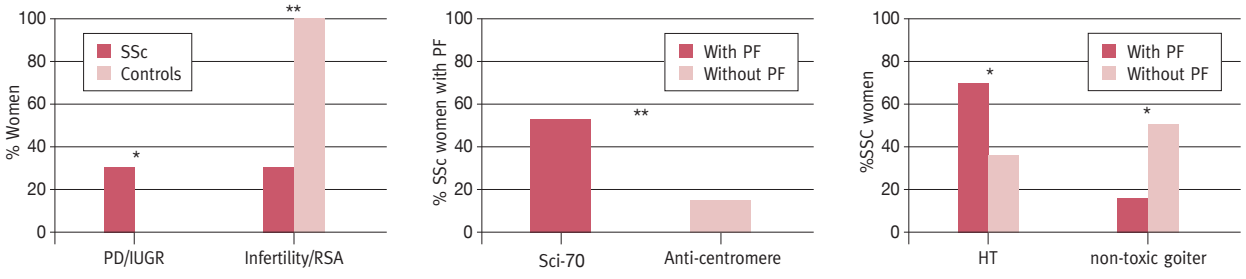
In 26.8% of cases, SSc women with thyroid dysfunctions were anti-centromere antibody positive and 31.6% of them had Hashimoto's thyroiditis.

Women with Scl-70 antibody positivity and women with anti-centromere antibodies showed a similar prevalence of thyroid dysfunctions (53% vs. 40.7%). SSc women with thyroid dysfunctions showed a higher prevalence of limited SSc (P = 0.04) and ENA positivity [other than anti-centromere/Scl-70] (P = 0.04) than SSc women without thyroid dysfunctions [Table 3].

Prevalence of digital ulcers and esophageal involvement were higher in SSc women without thyroid dysfunctions than in women with thyroid dysfunctions (P = 0.01, for both) [Table 3]. The complications of sicca syndrome were not more prevalent in SSc patients with thyroid dysfunctions than in patients without [Table 3]. However, when women with sicca syndrome also showed a thyroid dysfunction, Hashimoto's thyroiditis occurred in 62.5% of cases.

When stratifying SSc women according to pregnancy failure, a higher prevalence of Hashimoto's thyroiditis resulted in women

Figure 1. [A] Women with systemic sclerosis showed a higher cumulative prevalence of preterm delivery and intrauterine growth restriction than controls (P = 0.04), while controls had a higher prevalence of primary infertility and recurrent spontaneous abortion than women with SSc (P = 0.003). **[B]** Scl-70 positive SSc women showed a higher prevalence of pregnancy failure than SSc women with anti-centromere positivity (P = 0.01). **[C]** SSc women with pregnancy failure showed a higher prevalence of Hashimoto's thyroiditis than women without pregnancy failure (P = 0.04) while women without pregnancy failure had a higher prevalence of non-toxic multinodular goiter (P = 0.03)



HT = Hashimoto's thyroiditis, IUGR = intrauterine growth restriction, PF = pregnancy failure, RSA = recurrent spontaneous abortion, SSc = systemic sclerosis chi-square or Fisher's exact test was utilized for proportion comparisons
*P < 0.05, **P < 0.01

Table 3. Clinical data from the cohort of women with systemic sclerosis in accordance with the presence of thyroid disorders

	Women with thyroid disorders (n=41)	Women without thyroid disorders (n=36)
Limited SSc (n/%) Diffuse SSc (n/%)	33/80* 8/20*	21/58.4 15/41.6
Sicca syndrome (n/%)	8/19.5	7/19.5
ANA positivity (n/%)	31/75.6	30/83.4
ENA positivity (n/%) Scl-70 Anti-centromere Others	28/68.3 28.6 39.3 32.1*	26/72.3 34.6 57.7 7.7
Digital ulcers (n/%)	5/12.2*	13/36.2
Heart: elevated US-PAPs (n/%)	9/22	13/36.2
Lung: reduced DLCO (n/%)	17/41.5	15/41.7
Esophageal reflux, dysphagia (n/%)	12/29.3*	21/58.4
Women with PF (n/%): RSA (n/%) Primary infertility (n/%) PD (n/%) IUGR (n/%) IFD (n/%)	13/31.7 6/46.2 2/15.4 2/15.4 3/23 0/0	10/27.8 3/30 1/10 3/30 1/10 2/20

SSc = systemic sclerosis, ANA = anti-nuclear antibodies, ENA = anti-extractable nuclear antigen, US-PAPs = systolic pulmonary arterial pressure on heart ultrasound (≥ 25 mmHg), DLCO = diffusing capacity for carbon monoxide (DLCO ≤ 70%), PF = pregnancy failure, RSA = recurrent spontaneous abortion, PD = preterm delivery, IUGR = intrauterine growth restriction, IFD = intrauterine-fetal-death, chi-square or Fisher's exact test was utilized for proportion comparisons

*$P < 0.05$ between the groups

with pregnancy failure than in women without ($P = 0.04$), while women without pregnancy failure had a higher prevalence of non-toxic multinodular goiter ($P = 0.03$) [Figure 1C].

DISCUSSION

In support of results found in the literature, our data showed that SSc women can have successful pregnancies [5,7,16]. However, evidence shows that although the rate of RSA does not appear to increase in SSc, women with SSc are exposed to a higher risk of preterm delivery and IUGR compared to the general population [6,17]. Indeed, in our cohort of SSc, we observed an increased risk of IUGR and preterm delivery, as has been described in patients with other autoimmune diseases [5]. However, while the majority of women with autoimmune diseases delivered healthy infants, they remain at increased risk of having both maternal and neonatal complications [17]. Evidence has shown that high rates of pregnancy failure occur before the clinical occurrence or the diagnosis of autoimmune disorders suggesting a potential role of undiagnosed and/or early diseases in the occurrence of pregnancy complications [18-20]. Few previous studies have addressed a prevalence of IUGR in patients with SSc that was similar to what we observed in our study [5,21]. It is reported that both preterm delivery and IUGR can be associated with adverse outcomes in children, such as cognitive deficits and lower lung function [22]. Consequently, newborn infants of mothers with SSc may have an increased risk of such complications.

In our SSc cohort we found that SSc women with Scl-70 positivity showed a higher prevalence of pregnancy failure than SSc women with anti-centromere positivity. Accordingly, authors reported a progression of disease in SSc women during pregnancy in anti-Scl-70 antibody-positive women suggesting a potential association between anti-Scl-70 positivity and adverse outcome [5]. In our cohort, no disease progression during pregnancy was registered from SSc women but the retrospective design of our study may have limited the interpretation of these data. Moreover, we described that SSc women with pregnancy failure more frequently showed a diffuse SSc. It has been reported that patients with diffuse skin involvement suffered more significant morbidity, with preterm delivery in almost half of the pregnancies [2,23]. Moreover, women who have diffuse SSc are at a greater risk for developing serious complications such as cardio-pulmonary and renal disorders early in the disease, suggesting a delay in pregnancy until the disease stabilizes [23].

In accordance with the idea that thyroid dysfunctions may affect pregnancy outcome in SSc women, we analyzed prevalence of thyroid dysfunctions in our SSc cohort. First, we found that SSc women did not show a significantly different prevalence of thyroid dysfunctions with respect to controls. In addition, we observed that Hashimoto's thyroiditis was more prevalent in SSc women with pregnancy syndromes than in women without. Accordingly, evidence supports that thyroid antibodies could add to the risks of moderate to severe complications in pregnancy (miscarriage, IUGR, preeclampsia, preterm delivery) associated with connective tissue diseases [24]. Indeed, it is well known that the presence of autoantibodies may represent a risk factor for poor prognosis in autoimmune diseases [25]. However, the presence of thyroid dysfunctions in SSc women does not seem to be associated with a poor disease outcome or with Scl-70 positivity. Our findings found high rates of ANA positivity and Hashimoto's thyroiditis in SSc women with a history of pregnancy failure, which is in accordance with data from the literature showing that thyroid autoimmunity and ANA positivity increase the risk of adverse pregnancy outcomes [24]. Secondary aPL syndrome may coexist in SSc women and should be sought in cases of RSA. In our SSc cohort only one case of RSA was associated with the presence of aPL. However, it may be prudent to assess the status of aPL in SSc women prior to conception and primarily in cases of infertility or RSA [7].

We analyzed the pregnancy outcome on the basis of data collected from clinical records. Previous studies have been mainly based on self-administered questionnaires [21] or on the analysis of prospectively recorded data [5,24]. Our results reached the same conclusion but have certain limitations. The retrospective design, the number of women enrolled and the

collected data that were not registered during pregnancies are the main limitations of the study.

CONCLUSIONS

In conclusion, our findings support the idea that women with SSc can have successful pregnancies despite a higher prevalence of preterm delivery and IUGR than in the general population. Hence, at present, with close and multi-specialist monitoring most women with SSc can experience a successful pregnancy [7,16]. Routine thyroid examinations may be included in the workup of SSc women for the early detection of hypothyroidism or thyroid autoimmunity since a percentage of women may developed thyroid dysfunctions before, during and after the pregnancy [9,14,24].

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Capsule

Hematopoietic stem and progenitor cells from human pluripotent stem cells

A variety of tissue lineages can be differentiated from pluripotent stem cells by mimicking embryonic development through stepwise exposure to morphogens, or by conversion of one differentiated cell type into another by enforced expression of master transcription factors. To yield functional human hematopoietic stem cells, Sugimura and colleagues performed morphogen-directed differentiation of human pluripotent stem cells into hemogenic endothelium followed by screening of 26 candidate hematopoietic stem-cell-specifying transcription factors for their capacity to promote multi-lineage hematopoietic engraftment in mouse hosts. They recovered seven transcription factors (*ERG*, *HOXA5*, *HOXA9*, *HOXA10*, *LCOR*, *RUNX1*, and *SPI1*) that are sufficient to convert hemogenic endothelium into hematopoietic stem and progenitor cells that engraft myeloid, as well as B and T cells in primary and secondary mouse recipients. These combined approaches of morphogen-driven differentiation and transcription-factor-mediated cell fate conversion produce hematopoietic stem and progenitor cells from pluripotent stem cells, which holds promise for modeling hematopoietic diseases in humanized mice and for therapeutic strategies in genetic blood disorders.

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