EXTENDED REPORT

Influence of prior pregnancies on disease course and cause of death in systemic sclerosis

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Background: Microchimerism from fetal or maternal cells transferred during pregnancy has been implicated in the pathogenesis of systemic sclerosis (SSc).
Objective: To determine whether a prior pregnancy influenced disease progression and cause of death in patients with SSc.
Patients and methods: The patients comprised a retrospective study cohort of 111 women with SSc: 78 patients with prior pregnancies (PP) and 33 who were never pregnant (NP), followed up at Thomas Jefferson University. Differences in age at onset, disease subset, organ involvement, cause of death, and type of antinuclear autoantibodies were evaluated statistically, including regression analysis.
Results: The age at onset of SSc in NP patients was 32.0 years compared with 45.7 years in patients with one or two prior pregnancies (p<0.0001), 46.6 years in patients with three or four pregnancies (p<0.0001), and 51.3 years in patients with five to seven pregnancies (p<0.0005). In the 16 patients who had an elective pregnancy termination, 14/16 (87.5%) had diffuse SSc *v* 2/16 (12.5%) with limited SSc (p<0.0001; odds ratio (OR)=49.0). Of the NP women, 7/30 (23%) died from SSc related causes *v* 3/78 (4%) women who had pregnancies (p=0.0058; OR=7.6). A carbon monoxide transfer factor (TLCO) of <60% and disease duration >10 years was found in 10/13 (77%) NP patients *v* 10/23 (43%) patients who had pregnancies (p=0.05; OR=4.7), and a TLCO <50% and disease duration >10 years was identified in 7/13 (54%) NP patients *v* 6/23 (26%) of the patients who had pregnancies (p=0.09; OR=3.2).
Conclusions: There are differences in the age at onset, clinical course, severity of lung involvement, and cause of death in women who develop SSc before pregnancy compared with those who develop it after pregnancies. The NP patients with SSc had onset of disease at an earlier age, more severe lung involvement, and higher rate of death due to SSc.

Systemic sclerosis (SSc, scleroderma) is a connective tissue disease of unknown origin characterised by cutaneous and visceral fibrosis,[1] prominent microvascular changes with endothelial cell damage and proliferation of subendothelial connective tissue,[2] and production of autoantibodies.[2 3] SSc has numerous clinical features similar to those of chronic graft versus host disease[4] and, therefore, it has been postulated that SSc may be a form of chronic graft versus host disease. Skin, lung, and oesophageal involvement are prominent features of both chronic graft versus host disease and SSc.[4–6] Furthermore, lymphocytic infiltration in affected tissues,[7–9] up regulation of inflammatory cytokines,[10–12] and fibrosis in the dermis and visceral organs[1 13] characterise both diseases.

The hypothesis that fetal cells may play a part in the pathogenesis of SSc was first proposed by Pereira in a personal communication to Black.[14] Black *et al* stated that "Scleroderma has been postulated as a type of chronic graft versus host disease resulting from transplacental transfer of cells between mother and fetus"[14 15] and that "this could lead to a state of microchimerism and activation of such cells to cause a chronic graft versus host type of disease".[15] Subsequently, other investigators have proposed the involvement of fetal cells in the pathogenesis of SSc.[16] The demonstration that male fetal cells persisted in a normal woman 27 years after the birth of her infant[17] provided strong support for the hypothesis that fetal cells may participate in the pathogenesis of SSc.[18] Results of several subsequent studies support this notion.[19 20]

SSc can occur during pregnancy or in the immediate puerperal period.[21] Johnson *et al* reported that in 17% of SSc cases the onset of disease occurred during pregnancy.[22] The cytokine profile during pregnancy is generally believed to be Th2 rather than Th1, which would exacerbate fibrosis in the pregnant patient with SSc. During pregnancy SSc remains clinically stable in 40–60% of patients, deteriorates in 20%, and improves in 20%[21–24]; this variation probably relates to the heterogeneous nature of SSc.[21–24] Reduced skin fibrosis was seen in some patients during pregnancy, and the improvement lasted for up to one year post partum.[25] This is possibly because of the effects of immune suppression[26] and/or, as more recently suggested, to the effects of high levels of relaxin produced during the late stages of pregnancy which favour a Th1 profile.[27–29]

In this study we compared the disease course, clinical subset, frequency of gastrointestinal, pulmonary, cardiac, and renal involvement, cause of death, and presence and pattern of antinuclear autoantibodies in women with SSc who had pregnancies before the onset of the disease compared with women with SSc who had never been pregnant.

PATIENTS AND METHODS

Clinical records were reviewed from 111 women with SSc in whom complete pregnancy history was recorded, including sex and date of birth of offspring. This cohort comprised 78 female patients who had had all their pregnancies before the onset of SSc and 33 female patients who had never had a pregnancy. This cohort was obtained from a larger cohort of

Abbreviations: CI, confidence interval; dSSc, diffuse systemic sclerosis; lSSc, limited systemic sclerosis; MHC, major histocompatibility complex; NP, never pregnant; OR, odds ratio; PP, prior pregnancies; SSc, systemic sclerosis

Table 1 Age at onset of SSc, SSc disease subset, and pregnancy history. Results given as No (%) except where indicated otherwise

	Total	Diffuse subset	Limited subset
Never pregnant			
Number of patients	33	21 (64)*	12 (36)*
Age at onset of SSc, mean (SD)	32.0 (15.1)	30.6 (16.35)	34.3 (15.01)
Duration of SSc, mean (SD)	13.3 (11.6)	13.4 (10.7)	14.4 (10.1)
Previously pregnant			
Number of patients	78	44 (56)	34 (44)
Age at onset of SSc, (mean SD)	45.7 (12.5)	46.7 (11.09)	44.4 (14.0)
Duration of SSc, mean (SD)	8.7 (5.8)	6.9 (6.5)**	11.8 (6.6)**
Interval between first birth and SSc, mean (SD)	23.6 (11.6)	23.1 (12.1)	24.3 (12.33)
Total pregnancies	248	132 (53)	116 (47)
Mean number of pregnancies per patient	3.05	2.93	3.05
Full term births	187	97 (52)	90 (48)
Male births	101	50 (49.5)	51 (50.5)
Female births	70	43 (61)	27 (39)
Women with spontaneous abortions	22	10 (45)	12 (55)
Women with elective abortions	16	14 (87.5)***	2 (12.5)***

*p=0.048, OR=0.32; **p=0.0057; ***p<0.0001, OR=49.0.

640 female patients with SSc for whom we had no pregnancy data. All patients had been followed up at the scleroderma centre of Thomas Jefferson University for an average of five years (range 1–21). Table 1 shows the onset of SSc and gravity and parity status of the patients with SSc. All patients fulfilled the American College of Rheumatology (formerly, the American Rheumatism Association) criteria for the classification of SSc.[30] Assignment of SSc clinical subset was made according to the criteria described by LeRoy *et al* during the initial evaluation.[31] This subset assignment was not altered if the skin softened during the course of disease or after therapeutic intervention. Visceral organ involvement was defined as published by Lally *et al*,[32] with slight modifications as outlined briefly below. Gastrointestinal abnormalities were defined by manometric demonstration of characteristic motor abnormalities of the lower two thirds of the oesophagus and/or decreased lower oesophageal sphincter pressure or history of protracted dysphagia and dyspepsia requiring treatment with proton pump inhibitors. Pulmonary dysfunction was defined by a reduction of lung capacity assessed by pulmonary function testing indicating a reduction of carbon monoxide transfer factor to 70% or less of the predicted value. Cardiac abnormalities were defined by an electrocardiographic demonstration of otherwise unexplained conduction abnormalities or rhythm disturbances, clinical echocardiographic evidence of pericardial effusion, or evidence of congestive heart failure on physical examination or chest *x* ray examination. Renal dysfunction was assigned where the creatinine clearance was <60 ml/min or when pathological evidence of "scleroderma kidney" was obtained.

Statistical analyses

Analysis of the variables within the groups was carried out with GraphPad Instat Statistical Program, version 3.05. Two tailed statistical analyses were performed. Significant p values were reported with the corresponding odds ratio (OR). Linear and variance regression analyses were performed when data were stratified by age and disease duration, p values and 95% confidence intervals (CI) were reported.

RESULTS

Duration of SSc

The duration of SSc was determined from the first non-Raynaud's symptom. The mean duration of SSc in the never pregnant (NP) group was 13.3 years (range 2–36 years) and in the group who had prior pregnancies (PP) was 8.7 years (range 0.5–30 years). The differences in the duration of disease in the NP and the PP groups were not statistically significant (p=0.77). The PP group with diffuse disease (dSSc) (n=44) had a mean disease duration of 6.9 years (range 0.5–30) compared with the patients with limited disease (lSSc) (n=34) who had a mean disease duration of 11.8 years (range 1–27) (p=0.0057). In the NP group, patients with dSSc (n=21) had a mean disease duration of 13.4 years (range 2–36) compared with the patients with lSSc (n=12) who had a mean disease duration of 14.4 years (range 3–34) (p=0.67) (table 1).

Pregnancy history

Table 1 summarises the numbers of pregnancies and the age of onset of SSc in the patients studied. There were a total of 248 pregnancies with 187 live births. Of the 78 women who had completed all pregnancies before the onset of SSc, 53 women had ⩽3 pregnancies and 25 women had ⩾4 pregnancies, regardless of pregnancy outcome. Twenty two patients had 32 spontaneous abortions. Sixteen patients had undergone 24 elective terminations. Two patients had had a pregnancy and never delivered a live fetus.

Interval between last pregnancy and onset of SSc

In the PP group, 60/78 patients (77%) had completed their reproductive events 10 or more years before the onset of SSc. Furthermore, 68/78 (87%) women had their last pregnancy five or more years before the onset of SSc. Of the 10 patients who had onset of disease less than five years after delivering a child, six patients had onset of disease within one year of delivery.

Association of occurrence of SSc and sex of offspring

There was an association between the sex of the offspring and SSc; women with SSc were more likely to have given birth to a male. There were 101 live male fetuses and 70 live female fetuses delivered. Among the women with SSc who delivered live offspring (n=76), 62/76 (82%) delivered a male child and 51/76 (67%) delivered a female child, which was significant (p=0.03; OR=2.2).

Prior pregnancies and clinical SSc subsets

In the NP group (table 1) of 33 patients, dSSc was more common than lSSc (21 (64%) *v* 12 (36%)), a difference which was statistically significant (p=0.048; OR=0.32). In contrast in the PP group of 78 patients, the subset distribution was much closer (44 (56%) dSSc *v* 34 (44%) lSSc). Of the 22 patients who had a spontaneous abortion, 10 (45%) patients had dSSc and 12 (55%) patients had lSSc. Of the 16 patients who had an elective termination, 14 (87.5%) patients had dSSc, whereas two (12.5%) patients had lSSc. This difference was significant (p<0.0001; OR=49.0).

Table 2 Frequency of organ involvement, mortality, and antinuclear antibodies. Results given as No (%)

	Nulligravid (n=33)	Gravid (n=78)	p Value
Gastrointestinal involvement	25/33 (76)	55/78 (71)	0.64
Pulmonary symptoms	20/33 (61)	31/78 (40)	0.06
Cardiac symptoms	9/33 (27)	27/78 (35)	0.51
Renal crisis	4/33 (12)	8/78 (10)	0.73
Mean TLCO	64.6	73.7	0.10
TLCO<60/>10 years' duration	10/13 (77)	10/23 (43)	0.05 OR=4.7
TLCO<50/>10 years' duration	7/13 (54)	6/23 (26)	0.09 OR=3.2
Mortality	7/30 (23)	3/78 (4)	0.0058 OR=7.6
ANA+	29/30 (97)	67/73 (92)	0.67
Scl-70+	7/30 (23)	14/75 (19)	0.78
ACA+	9/30 (30)	19/75 (25)	0.81
ANA+, Scl-70– ACA–	12/30 (40)	42/75 (56)	0.13

ANA, antinuclear antibodies; Scl-70, antitopoisomerase I antibodies; ACA, anticentromere antibodies.

Prior pregnancies and age at onset of SSc

In the patient group who had all their pregnancies before the onset of SSc the mean age of disease onset was 45.7 years (range 23–77). In contrast, the onset of disease in the NP group was at 32.0 years (range 8–50) (p=0.0001). Seven NP patients had onset before the age of 18. The number of pregnancies was stratified with age of onset of SSc, regardless of pregnancy outcome. In the NP patients the mean age at SSc onset was 32.0 years, whereas in 31 patients who had one or two pregnancies the mean age at disease onset was 45.7 years (p<0.0001; 95% CI 0.90 to 1.34), in 36 patients who had three or four pregnancies the mean age at disease onset of SSc was 46.6 years (p<0.0001; 95% CI 0.96 to 1.46), and in 11 patients who had five to seven pregnancies the mean age at disease onset was 51.3 years (p<0.0005; 95% CI 0.82 to 2.09). Similarly, when parity was stratified with age at SSc onset and compared with the NP patients, it was found that in women who gave birth to one or two offspring (n=42), the mean age at onset of SSc was 44.4 years (p<0.0001; 95% CI 0.89 to 1.35), whereas in those who gave birth to three to five offspring (n=34), the mean age at onset was 51.1 years (p<0.0001; 95% CI 1.05 to 1.57).

No differences were found in the age at onset between patients with the two SSc disease subsets (table 1). In the NP group, the mean age at onset of SSc in the patients who had dSSc was 30.6 years (range 8–50) and in those who had lSSc was 34.3 years (range 14–51; p>0.1). Likewise, in the PP population, the mean age at SSc onset was 46.7 years (range 29–77) in patients with dSSc and 44.4 years (range 23–73; p>0.1) in the patients with lSSc.

Prior pregnancies and SSc related mortality

The NP patients as a group had a higher SSc related mortality rate than the patients who had had pregnancies (table 2). It was found that 7/30 (23%) of the never pregnant women studied had died, and in all cases the cause of death was related to SSc, compared with 3/78 (4%) women who had had pregnancies and had died (p=0.0058; OR=7.6). The cause of death in these patients was also SSc related and there was no discernible difference in the cause of death between the two groups (table 3).

Table 3 Cause of death in the nulligravid and gravid patients

Patient	Cause of death*
Never pregnant	
1	Pulmonary fibrosis/alveolar cell carcinoma
2	Pulmonary fibrosis
3	Pulmonary fibrosis
4	Pulmonary artery hypertension
5	Pulmonary artery hypertension
6	Pulmonary fibrosis
7	Renal failure after SSc renal crisis
Prior pregnancies	
1	Pulmonary artery hypertension
2	Renal failure after SSc renal crisis
3	Renal failure after SSc renal crisis

*p=0.0.0038; OR=7.9.

Internal organ involvement

There was a greater trend towards organ involvement with increased disease duration in the NP patients (table 2). We found that the mean duration of SSc in the NP group was 13.3 years and in the group who had pregnancies it was 8.7 years. This was analysed by linear regression and found not to be significant (p=0.7). There was a weak trend towards a higher incidence of clinically apparent gastrointestinal disease as determined by the occurrence of dysphagia and dyspepsia in the NP women (table 2). Twenty five of 33 (76%) NP women had upper gastrointestinal symptoms compared with 55/78 (71%) patients who had had pregnancies (not significant).

Documentation of TLCO was found in 90 charts. In the patients who did not have TLCO measurements there was no clinical or radiographic evidence of scleroderma lung involvement. TLCO was found to be more often decreased in the NP patients than in the patients who had had pregnancies. There was also a trend towards a greater incidence of dyspnoea and chest pain in NP women 20/33 (61%) compared with 31/78 (40%) patients who had had pregnancies, although the difference did not reach significance (p=0.06). When TLCO was stratified with duration of disease (table 2), it was observed that the NP patients had more severe lung disease than the patients who had pregnancies. In patients with >10 years of disease duration, 10/13 (77%), NP patients had a TLCO of <60% compared with 10/23 (43%) PP patients. This difference was significant (p=0.05, OR=4.7). Similarly, in patients with disease >10 years, a TLCO <50% was found in 7/13 (54%) NP women compared with 6/23 (26%) women who had had pregnancies (p=0.09, OR=3.2). There were no statistically significant differences in the incidence of cardiac or renal involvement between NP patients or the patients who had had pregnancies.

Frequency and pattern of antinuclear autoantibodies

Antinuclear antibodies were present in 67/73 (92%) women who had had pregnancies compared with 29/30 (97%) NP women (table 2). The Scl-70 antibody was observed in 7/30 (23%) NP women and in 14/75 (19%) PP women, of whom 8/53 (15%) had had one to three pregnancies and 6/22 (27%)

patients had had more than three pregnancies. Anticentromere antibodies were present in 9/30 (30%) NP women and 19/75 (25%) of PP women, of whom 14/53 (26%) patients had one to three pregnancies and 5/22 (23%) had had more than three pregnancies. Antinuclear autoantibodies that were unreactive towards either topoisomerase I (Scl-70) or to centromere proteins were seen in 12/30 (40%) NP women and in 42/75 (56%) of PP women, of whom 31/53 (58%) had had one to three pregnancies and 11/22 (50%) had had more than three pregnancies. There were no statistically significant differences in the frequency or patterns of autoantibodies in any of the groups studied.

DISCUSSION

Previous studies have reported an increased incidence of spontaneous abortions and infertility in patients with SSc before onset of disease. However, there has been no investigation of the influence of prior pregnancies on disease course and cause of death in patients with SSc. The pregnancy history, including the number of gestations and offspring of 111 patients with SSc, was analysed in relation to the disease subsets, age at onset, internal organ involvement, and presence and pattern of antinuclear autoantibodies. We found that there were several significant differences in SSc disease course between the patients who had had pregnancies compared with patients who had never been pregnant.

A previous recent study found that the average age at SSc onset in women who had been previously pregnant was 44 years, whereas, in women who had previous SSc or developed it at the time of pregnancy, the average onset of disease was at 26 years.[33] This bimodal distribution suggests that there may be differences in the pathogenesis of SSc in these two groups of women. In our study the number of gestations before the onset of SSc appeared to influence the age at which the disease manifested in the patients. The beneficial effect of pregnancy appears to relate to the age of onset of SSc and not to disease progression as a whole. We found no differences in the disease outcome in patients who had had multiple pregnancies compared with patients who had only one offspring. The mean age of the NP women was 32.0 years in contrast with a statistically significantly delayed age at onset of SSc with increasing gravity and parity. Clearly, many of the women had finished their reproductive events before the onset of SSc as 77% of women had their last pregnancy 10 or more years before onset. It was found that 10 patients with SSc had onset of disease less than five years after having a pregnancy and therefore these patients might have prematurely terminated their reproductive events owing to SSc. Although the NP group had a mean onset earlier than the group with pregnancies, 50% of patients had onset of disease after the age of 30. An alternative hypothesis for the clinical differences seen between the NP patients and those who have had pregnancies may be that those patients who develop SSc early in life, cannot or may not want to get pregnant. In some cases their disease is so severe that it shortens their life span or it produces a degree of disability that precludes pregnancy and child rearing as an option. Conversely, women who get SSc later in life are more likely to have had children at an earlier or more usual time of their life.

It is believed that pregnancy is an immunosuppressive state in which the immune regulation shifts from a Th1 to a Th2 cytokine response, which starts in the first trimester and is maintained throughout pregnancy.[34] However, a more recent study has shown a generalised down regulation of both Th1 and Th2 cytokine profiles during pregnancy.[26] Furthermore, levels of interleukin 4, a Th2 cytokine, were found to be normal in parous women, compared with normal female blood donors,[35] and the secretion of relaxin during pregnancy favours a Th1 profile.[27] Clearly, pregnancy is a complex biological state and if it is dominated by a Th2 cytokine profile then it is different from the Th2 profile of patients with SSc, that has been implicated in the development of fibrosis.

We have previously reported that there is a significant increase in the compatibility at major histocompatibility complex (MHC) class II but not at class I in SSc families.[36] These data were confirmed subsequently.[20] In the mouse, the degree of cell traffic between the mother and the fetus is dependent on the histocompatibility of the matches.[37] In the patients with SSc, owing to the class II compatibility, more fetal and maternal cells may have crossed the placenta during pregnancy. Studies investigating the numbers of fetal cells transferred during pregnancy and MHC compatibility will be required to determine whether the MHC does influence fetal cell numbers in the peripheral blood. Owing to class II compatibility, these fetal cells may react towards HLA class I or minor histocompatibility antigens. In mice, additional pregnancies have been found to expand fetal cells that already reside in the maternal blood stream from a prior pregnancy.[38] However, in humans, it is not known whether subsequent pregnancies expand fetal cells that remain from a previous pregnancy, although male cells from a previous pregnancy have been detected in the peripheral blood of pregnant women.[39]

As previously mentioned many authors believe that fetal cells play a part in the pathogenesis of SSc.[19 40] Within this hypothesis, the cause of SSc in the NP women is unclear; however, we speculate that there are maternal cells driving the disease. Recently, investigators have demonstrated the presence of maternal microchimeric cells in men with SSc[41] and we have identified maternal cells in the peripheral blood and lesions of men with juvenile myositis,[42] suggesting that these cells may have a pathogenetic role in the development of autoimmune diseases. Given the more severe clinical course and progression of SSc in NP women and in men, our results suggest that the activated maternal microchimeric cells are more aggressive or require a lower threshold of stimulation to become activated.

A recent study investigated the influence of parity on clinical and biological outcomes in women with SSc.[43] Launay *et al* found that patients with lSSc had more children than those with dSSc. Furthermore, they found that patients with pulmonary fibrosis had more offspring than patients who did not have the disease. However, this study did not investigate patients with SSc who had never been pregnant. In the patient cohort studied here we did not see a difference between the number of offspring and disease subset nor did we observe a shorter duration between first offspring and onset of SSc in patients with the lSSc subset (table 1) as reported by Launay *et al*[43]

This present study was performed to investigate disease subsets, autoantibodies, internal organ involvement, and cause of death in patients with SSc who had pregnancies in comparison with those who did not have pregnancies. We conclude that the NP patients have onset of SSc at an earlier age and the disease displays a more aggressive clinical course and leads to death from SSc related causes in a higher proportion of these patients than in patients with prior pregnancies.

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