Review

Pregnancy issues in scleroderma

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Abstract

Systemic sclerosis is a systemic, inflammatory, autoimmune disease affecting the skin and viscera, manifesting pathologically with microvascular lesions, perivascular infiltration by mononuclear cells and increased deposition of extracellular collagen. The rarity of the disease as well as its propensity to appear in the early 1940s, explain the low frequency of concurrent scleroderma and pregnancy. However, the marked female excess, as well as the trend for increasing maternal age due to social change and assisted reproductive technologies, renders heightened significance to issues of fertility, pregnancy course and pregnancy outcomes.

In the past, scleroderma patients were thought to be at high risk for poor fetal and maternal outcome, but more current retrospective studies show that despite an increased frequency of prematurity and small for gestational age infants, overall maternal and neonatal survival is good. Hence, at present, with close monitoring and appropriate therapy most scleroderma patients can sustain a successful pregnancy. Therapy with hydroxychloroquine and low dose steroids as well as judicious use of intravenous immunoglobulins is permitted. Renal crisis remains the most dreaded complication of a scleroderma pregnancy and necessitates prompt institution of ACE inhibitor therapy despite its potential teratogenicity. In order minimize the risk for renal crisis, pregnancies should be avoided in rapidly progressive diffuse disease as such patients are at a greater risk for developing serious cardiopulmonary and renal problems early in the disease. This review shall focus on the bi-directional effects of scleroderma on fertility and pregnancy as well as on the management of pregnancy and delivery in the scleroderma patient.

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Scleroderma is a connective tissue disease of unknown etiology that affects the lungs, heart, gastrointestinal tract and kidneys. It is a relatively rare disease with an estimated incidence rate ranging from 2 to 10 cases per million, typically presenting in the 5th or 6th decade. Scleroderma is 3 times more frequent in women than men [1] and this gender difference is heightened during the reproductive years (ages 15–50), during which females are afflicted 15-fold more [2]. The etiopathogenesis of scleroderma includes vascular dysfunction, mononuclear mediated inflammation and connective tissue fibrosis. The composite effects of the ischemic changes, the excessive fibrosis and the inflammation on conception, pregnancy and delivery, shall be discussed herewith.

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1. Fertility

1.1. Psychosocial morbidity

The deleterious effects of SSc on fertility begin long before conception as the progressive connective tissue disease is associated with significant changes in appearance including skin discoloration and/or hardening, skin tightening around the mouth, finger lesions, and in some cases digit amputation [3]. These facial and bodily changes bring afflicted women to report an elevated body image dissatisfaction, even compared to severe burn patients [4]. The reduced self-esteem and altered body image may adversely affect the ability of scleroderma patients to form social and sexual relationships. Indeed, an earlier report by Steen et al., who surveyed 214 scleroderma patients found that a significantly higher portion of them were never pregnant compared with rheumatoid arthritis patients and normal controls [5]. Adjustment for the number of women who had never been married, were sexually inactive or who chose not to have children, obliterated the differences between the groups and inadvertently highlighted these factors as major psychosocial obstacles in scleroderma. The disease poses further difficulties to inter-personal relationships due to vaginal dryness and dyspareunia which afflicts up to 37% of patients [6] as well as arthritic involvement and joint contractures with may prevent sexual intercourse.

1.2. Infertility before disease onset

As scleroderma typically manifests towards the end of the reproductive period, one might presume that its effects on fertility would be negligible. However, several reports have unraveled that an adverse reproductive history antedates the diagnosis of scleroderma by many years [7,8]. Silman et al. [9] performed a case control study encompassing 155 patients with scleroderma using a postal questionnaire in England. Women with scleroderma had twice the rate of spontaneous abortion and three times the rate of fertility problems (no successful pregnancy by the age of 35) of the control women. Taking into account the unexplained, marked female excess in the incidence of the reproductive and the age of onset, which peaks shortly after the reproductive period, it may be postulated that the adverse reproductive history is a contributing factor in the initiation of scleroderma. The proposed mechanism linking fertility to scleroderma suggests that trans-placental transfer of fetal cells during prior pregnancies and abortions initiates a chronic graft versus host disease, the latter leading to sclerodermatous changes. Putatively, recurrent abortions enhance the HLA-mismatched cell trafficking, increasing the load of potential cells.

1.3. Fertility and pregnancy outcome in established disease

In contrast to decreased fertility rates reported in women prior to the onset of scleroderma [9], a large survey performed by Steen et al. [10] which compared 214 scleroderma patients to 167 rheumatoid arthritis (RA) patients and 105 normal controls, found similar rates of conception and pregnancy among the three groups. The results showed that while only 2–5% of patients who had attempted to become pregnant were unsuccessful, 12–15% of the women had at least a 1 year delay in conception. The overall rate of a successful pregnancy following a period of infertility was 37% in the scleroderma patients, similar to the 40% rate in RA patients and 43% in normal controls.

Notwithstanding, the rate of miscarriages is increased, to variable degrees, in scleroderma, more so in women with established disease than in the pre-scleroderma phase (15% vs. 8%) [5]. Moreover, the rate of miscarriage in patients with diffuse disease is double the rate experienced by patients with limited skin involvement (24% vs. 12%) [11].

Early case reports of pregnancy outcomes in SSc, published before 1990, informed of maternal and/or fetal death in 50% of 42 pregnancies [12] whereas case-control series stated vastly reduced risks of 1–2% [5] and 2.4–4% [5,13], respectively, in addition to a 9% risk of premature delivery [5].

A 10 year prospective study, summarizing the outcome of 91 pregnancies in fifty-nine scleroderma patients, between 1987 and 1996, corroborated these rather optimistic findings [11]. Increased rate of miscarriage was found only in women with long-standing diffuse scleroderma while preterm births, with generally good neonatal outcomes, were common, occurring in 26% of pregnancies. Here again, patients with diffuse skin involvement suffered more significant morbidity, with premature delivery culminating 40% of pregnancies [14]. Despite excess prematurity, the overall rate of a successful live birth was 84% in limited and 77% in diffuse scleroderma.

These findings were, by and large, resonated in a comprehensive study assessing the outcomes of patients with scleroderma and mixed connective tissue disease (MCTD) from the West coast of the United States [15]. Here, the summation of 20 pregnancies yielded a preterm delivery rate of 39% and small for gestational age infants in 50% and 63% of pregnancies associated with SSc and MCTD, respectively. Fetal loss complicated two pregnancies in women with severe diffuse SSc and the antiphospholipid antibody syndrome. The two most recent studies focusing on this subject matter, showed higher rates for miscarriage but a lower incidence of premature deliveries and small term babies [16,17]. A summary of these studies is provided in Table 1. Overall, maternal flares of disease during pregnancy were generally mild.

1.4. Scleroderma and anti-phospholipid antibody syndrome

Secondary anti-phospholipid anti-body syndrome (APAS) may co-exist in scleroderma patients and should be sought in cases of recurrent pregnancy loss as well as in the presence of additional relevant manifestations. Although earlier reports have questioned the contribution of anti-phospholipid antibodies (APA) to the clinical manifestations in scleroderma patients, more recent studies suggest that their presence is independently associated with pulmonary hypertension [18], macrovascular disease and an overall increased mortality [19]. More explicitly, Steen and colleagues have recently shown that anti-phospholipid antibodies were present in 50% of scleroderma patients

### Table 1

<table>
<thead>
<tr>
<th>Source (ref. no.)</th>
<th>n</th>
<th>Miscarriage, %</th>
<th>Premature birth, %</th>
<th>Small full term baby, %</th>
<th>Neonatal death, %</th>
<th>Maternal death, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silman et al. [9]</td>
<td>155</td>
<td>28.7</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Steen et al. [5]</td>
<td>48</td>
<td>15</td>
<td>11</td>
<td>ND</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Steen et al. [10]</td>
<td>214</td>
<td>12</td>
<td>9</td>
<td>16</td>
<td>3.5</td>
<td>1</td>
</tr>
<tr>
<td>Steen [11]</td>
<td>91</td>
<td>14.3</td>
<td>25.3</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Sampaio-Barros et al. [6]</td>
<td>150</td>
<td>13.5</td>
<td>ND</td>
<td>ND</td>
<td>0.7</td>
<td>0</td>
</tr>
<tr>
<td>Chung et al. [15]</td>
<td>20</td>
<td>10</td>
<td>39</td>
<td>50</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Chakravarty et al. [17]</td>
<td>149</td>
<td>ND</td>
<td>1.16</td>
<td>5.3</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Van Wyk et al. [16]</td>
<td>103</td>
<td>32.7</td>
<td>ND</td>
<td>13.7</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

ND—not defined.
with lower extremity ulcers [20] proving that the occurrence of these anti-bodies in scleroderma patients is far higher than appreciated. Indeed, we had previously described a small case-series of 5 patients which displayed both full-blown APAS on top of manifestations of systemic sclerosis [21]. Taken together, it may be prudent to assess the status of APA of a scleroderma patient prior to conception, and most certainly, in cases of infertility or recurrent pregnancy loss.

2. Effects of pregnancy on scleroderma

2.1. Persistent fetal microchimerism and the initiation of scleroderma

The short term effects of pregnancy on the maternal immune system are well known, leading to clinical improvement in some autoimmune diseases, notably RA, while exacerbating or having a neutral effect on others, such as systemic lupus erythematosus. Less well appreciated is the long-term effect or “legacy” that pregnancy imprints in the mother and offspring as a result of acquisition of genetically disparate cells [22]. Studies have shown that fetal progenitor cells persist in maternal blood or bone marrow for more than 30 years after delivery. The long-term persistence of low levels of cells harboring DNA from a genetically disparate individual is referred to as microchimerism (MC). While MC is common in healthy individuals, it is not yet understood how it is tolerated by the immune system. In fact, iatrogenic chimerism after transplantation [23] is the underlying mechanism of chronic graft-versus-host disease (GVHD), which, shares many clinical similarities with autoimmune diseases such as systemic sclerosis, primary biliary cirrhosis, Sjögren’s syndrome, myositis and systemic lupus erythematosus. Based on these similarities and recognizing the importance of donor-recipient HLA relationship to chronic GVHD, it was hypothesized that MC induces autoimmunity via HLA mismatch between donor (fetal) and host (maternal) cells. This hypothesis is strengthened by the observation that autoimmune diseases are more common in women, especially in post-childbearing years.

The role of MC in the initiation of SSc is of particular interest due to the striking clinical resemblance to chronic GVHD. Indeed, a prospective study compared women with scleroderma to healthy women who had given birth to at least one son found significantly higher levels of male DNA in the former [24]. Extraordinarily, although some of these women had given birth to their sons decades previously, they retained high levels of male DNA corresponding to the highest quartile of fetal MC measured in healthy women who were pregnant with a normal male fetus. Particular HLA genes and HLA-relationships between host and microchimeric cell populations are likely key determinants of the effect of MC on the host. Maternal HLA is another factor that determines that ability of persistent MC to initiate autoimmunity. The latter is enhanced when the mother and the previously born son share HLA-DR (class II) genes [24]. The notion that persistent MC contributes to the development of scleroderma has been strengthened by a case control study published recently [16]. The authors took note that preeclampsia and other pregnancy complications such as miscarriage and intra-uterine growth restriction (IUGR) could be associated with increased levels of fetal cell trafficking and suggested that women with these pregnancy complications would be at greater risk of later development of scleroderma. As expected, they found a statistically significantly increased incidence of having had a pregnancy history of hypertension or a fetus with IUGR in 103 women who subsequently developed SSc compared to healthy controls. Further studies are indicated to examine this putative relationship.

2.2. Effects of pregnancy on established scleroderma

Overall, pregnancy does appear to exacerbate organ involvement or adversely affect 10 year survival of scleroderma patients [10]. In a prospective series, maternal disease was stable in 60% of pregnancies, improved in 20% and worsened in another 20% [11].

Albeit, the enlarging gravid uterus may worsen symptoms of gastro-esophageal reflux which are prevalent in scleroderma, regardless of pregnancy. Likewise, limitation of diaphragmatic breathing may exacerbate pre-pregnancy symptoms of dyspnea. On the other hand, Raynaud’s phenomenon tends to improve in pregnancy due to generalized peripheral vasodilation.

Whereas pregnancy is not considered to worsen skin disease per se, worsening of skin thickening has been observed in the post-partum in patients with diffuse disease [11].

On the whole, as women with diffuse scleroderma are at a greater risk for developing cardiopulmonary and renal problems early in the disease course, they should be encouraged to delay pregnancy up to a time point at which organ function is stable.

2.3. Scleroderma renal crisis in pregnancy

Scleroderma renal crisis (SRC) is an acutely developing syndrome of malignant hypertension, proteinuria and renal failure associated with microangiopathic changes on renal biopsy with “onion skin” appearance of renal arteries due to endothelial proliferation [25]. SRC afflicts 5%–10% of SSc patients overall yet more at risk are patients with recent onset disease and diffuse, rapidly progressive skin involvement. Moreover, pregnancy itself has been hypothesized to be a precipitant of SRC [26]. Angiotensin-converting enzyme (ACE) inhibitors have brought about a dramatic change in the management and prognosis of SRC. Whereas renal crisis was almost uniformly fatal and accounted for 32% of scleroderma-related deaths, prior to the advent of ACE inhibitors, their routine use has reduced death rates from SRC to less than 10% [27]. Notwithstanding, SRC may still culminate in perinatal death. Steen et al. reported two cases of SRC in a retrospective study of 86 pregnancies occurring after the diagnosis of SSc [5]. Both developed SRC abruptly in the third trimester of pregnancy; one developed end-stage renal disease, and the other died from status epilepticus. In a prospective study of 91 pregnancies, two additional cases of renal crisis were reported [11]. Both women required hemodialysis after delivery, yet their long term renal outcome is unknown. On the premise that ACE inhibitors lead to persistent improvement in renal function, it is recommended that therapy be continued even after onset of dialysis [28]. Again, it should be emphasized that these cases occurred in women with early, rapidly progressive, diffuse disease, a subgroup which should probably postpone or refrain from pregnancy. Yet, it has not been established that rates of renal crisis are increased in pregnant women compared to nonpregnant women with severe diffuse disease [14]. Routine use of ACE inhibitors is not recommended at this time for fear of masking promontoory manifestations of SRC without reducing its incidence. This controversial issue has an additional perspective in pregnancy, as first trimester use of ACE inhibitors has been associated with congenital malformations [29]. Therefore, the use of these drugs should be restricted to instances of suspected or frank SRC in which their profound benefit definitely outweighs the possible risk of fetal toxicity. During the second half of pregnancy, differentiation between renal scleroderma and pre-eclampsia may be difficult. Seizures, elevated transaminases or urate may assist in the diagnosis although, if the situation remains unclear, measurement of plasma renin may prove useful. In pre-eclampsia, the serum renin is low to normal while, in the renal crisis of systemic sclerosis, plasma renin is elevated as a result of renocortical ischaemia. At times when SRC is indistinguishable from preeclampsia, an immediate trial of ACE inhibitors may be instituted, or, in cases of profound maternal or fetal distress, emergent delivery, which curtails the eclampsia, should be performed, followed by ACE inhibitor therapy.
1–2 weeks, starting at 16 weeks of gestation, for early detection of fetal abnormalities that might be a target for preventive therapy [31]. There are no data regarding the preferred mode of delivery in scleroderma patients and the decision should be based on a joint consultation of the inter-disciplinary team. When no fetal distress is present and the patient has no pulmonary, cardiac or renal involvement and range of motion of hip joints is satisfactory, vaginal delivery would be the optimal choice. One should also keep in mind that severe restrictive lung disease may be present in patients without current alveolitis due to established lung fibrosis as well as underappreciated chest-wall involvement. On this premise, performing pulmonary function tests during the first trimester, and if needed, repeating them in later stages of pregnancy, is advisable. The presence of major organ involvement or severe musculoskeletal restriction may tip the balance toward delivery by cesarean section.

As in other aspects of treatment, the clinical effects of excess fibrosis and vascular damage in the scleroderma patient create a great challenge to the anesthesiologist [32]. Thickened skin and chronic vasococonstriction impair venous access while flexion contractures and vasoconstriction may hinder blood pressure measurement. Skin contractures and microstomia make tracheal intubation difficult, nasal and oral telangiectasia may bleed if traumatized, while esophageal dysmotility and sphincter incompetence can lead to aspiration. The presence of pulmonary fibrosis, pulmonary hypertension and cardiac involvement manifesting as myocardial fibrosis, pericarditis, arrhythmias and conduction defects should be assessed. Disturbed renal function due to “sclerodermatous” intimal thickening of interlobar arteries should be ruled out or aggressively treated with ACEI, if present.

Both pregnancy and systemic sclerosis are associated with risks of difficult intubation and aspiration of gastric contents. On occasions when regional anesthesia is contraindicated and general anesthesia is the only option for Caesarean section, awake tracheal intubation should be considered for the patient with systemic sclerosis. This is especially true when mouth opening is limited, as spontaneous respiration will be maintained should difficulties arise and the cough reflex is preserved if regurgitation occurs. Even better, when possible, regional anesthesia which avoids the risks of aspiration and failed intubation. This should, of course, be performed cautiously to avoid total spinal or inadequate anesthesia requiring emergency tracheal intubation. It has also been suggested that scleroderma patients require smaller doses of local anesthetic as they exhibit prolonged sensitivity to the effects of nitrous oxide. Failure to achieve effective anesthesia when the patient is fully awake points to the need for intubation, which is indicated in severe cases of diffuse and limited skin involvement.

### 3. Management of pregnancy and labor

Pregnant scleroderma patients should be managed in high risk obstetric clinics in view of the increased risk of premature delivery and potential for maternal complication, most notably, SSc.

Initial risk assessment should include disease categorization, as women with diffuse disease are at higher risk for miscarriage, pre-term delivery and SSc, as noted above (Table 2). Autoantibody profile should include anti-topoisomerase and anti-centromere antibodies as well as anti-Ro/SSA and anti-La/SSB antibody titers (Table 3). The latter, which have been found in 12–37% [30,31] and 4% of scleroderma patients, respectively, have been associated with the development of fetal or post-partum heart block. Although the prevalence of complete heart block (CHB), diagnosed in utero or within the neonatal period, in the offspring of anti-Ro/SSA-positive women is only 1–2% it may be up to 10 times higher in recurrent pregnancies. Serial echo-cardiograms and obstetric sonograms are recommended every 1–2 weeks, starting at 16 weeks of gestation, for early detection of fetal abnormalities that might be a target for preventive therapy [31].

<table>
<thead>
<tr>
<th>Organ involvement in scleroderma</th>
<th>Mode of assessment</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lungs Pulmonary hypertension</td>
<td>Cardiac echo and right heart catheterization if further indicated</td>
<td>Avoid pregnancy if severe, allow with caution in milder cases</td>
</tr>
<tr>
<td>Intestinal lung disease</td>
<td>Pulmonary function tests including carbon monoxide diffusion capacity and high resolution CT if required</td>
<td>Avoid pregnancy if severe, allow with caution in milder cases</td>
</tr>
<tr>
<td>Heart Congestive heart failure</td>
<td>Cardiac echo</td>
<td>Avoid pregnancy if severe, allow with caution in milder cases</td>
</tr>
<tr>
<td>Kidney Renal crisis</td>
<td>Serum creatinine, evidence of microangiopathic hemolytic anemia, systemic blood pressure, proteinuria</td>
<td>Avoid pregnancy presently and treat aggressively with ACEI. Reconsider when stabilized.</td>
</tr>
<tr>
<td>Skin Diffuse vs. limited involvement</td>
<td>Modified Rodnan skin score (mRSS)</td>
<td>Consider delaying pregnancy if rapidly progressive, diffuse involvement</td>
</tr>
<tr>
<td>Esophagus Gastro-esophageal reflux</td>
<td>Clinical symptoms, gastroscopy in cases of refractory iron deficient anemia</td>
<td>Optimize anti-acid therapy</td>
</tr>
<tr>
<td>Digits Ulcers</td>
<td>Clinical features</td>
<td>A marker for decreased survival – reconsider pregnancy plans. Notwithstanding, ulcers tend to improve during pregnancy</td>
</tr>
<tr>
<td>Conduction blocks</td>
<td>ECG</td>
<td>Rarely require intervention</td>
</tr>
</tbody>
</table>

### Table 2: Autoantibody profiles and pregnancy risk assessment.

<table>
<thead>
<tr>
<th>Autoantibody</th>
<th>Possible risk</th>
<th>Suggested action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-topoisomerase (Scl-70)</td>
<td>Diffuse, rapidly progressive disease with excessive risk of renal crisis</td>
<td>Avoid pregnancy in early disease. Allow pregnancy in established cases if major organ involvement permits</td>
</tr>
<tr>
<td>Anti-centromere</td>
<td>PHT</td>
<td>Cardiac echo and right heart catheterization if required. Avoid pregnancy in moderate to severe cases</td>
</tr>
<tr>
<td>Anti-RNA polymerase III</td>
<td>Renal crisis</td>
<td>Approach pregnancy judiciously, especially in early disease</td>
</tr>
<tr>
<td>Anti-Ro/SSA, anti-La/SSB</td>
<td>Fetal heart block</td>
<td>Monitor fetal heart rate biweekly from 16 weeks of gestation onwards</td>
</tr>
<tr>
<td>Anti-phospholipid antibodies</td>
<td>Macrovascular complications, PHT, possibly recurrent abortions</td>
<td>Assess for PHT, digital ulcers, advise low molecular weight heparin in cases of prior fetal loss</td>
</tr>
</tbody>
</table>

PHT—pulmonary hypertension.
while prolonged application of a pulse oximeter probe to one digit should be avoided.

4. Concluding remarks

Just over two decades ago scleroderma was considered a strict contraindication for procreation as incurring risks for the mother and the baby were thought to be major. However, these concepts have evolved and currently, maternal and perinatal mortality is probably no higher in scleroderma without severe organ involvement, i.e. without pulmonary hypertension, cardiac or respiratory insufficiency and in those without recent onset, diffuse disease. Notwithstanding, there is a significantly higher frequency of prematurity and small full-term infants as a result of placental vascular abnormalities. Although the effects of pregnancy on scleroderma are generally mild, specific potential problems should be recognized by physicians. Renal crisis, in particular, when occurring in the course of pregnancy, may be life threatening for both mother and child. Also, the pregnant scleroderma patient is a potential anesthetic challenge because of abnormalities and in those without recent onset, diffuse disease. Notwithstanding, there is a significantly higher frequency of prematurity and small full-term infants as a result of placental vascular abnormalities. Although the effects of pregnancy on scleroderma are generally mild, specific potential problems should be recognized by physicians. Renal crisis, in particular, when occurring in the course of pregnancy, may be life threatening for both mother and child. Also, the pregnant scleroderma patient is a potential anesthetic challenge because of physical difficulties and visceral involvement highlighting the importance of follow-up and treatment by a multidisciplinary team, experienced in high risk pregnancies. Finally, recent clinical data corroborate previous studies noting that pregnancies could be involved in the pathogenesis of scleroderma through persisting MC of fetal origin.

References