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Pregnancy and Scleroderma

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1. Introduction

More than 30 years ago, pregnancy was not recommended for patients with systemic sclerosis (SSc) because of the overrepresentation in the literature of pregnancies with poor outcome. Thus, women with SSc had been strongly advised against pregnancy and often counseled to terminate ongoing pregnancies.
Retrospective studies found an increased frequency of pre-term births and small full-term infants in cohorts of patients with SSc. However, it turned out that finally the frequency of miscarriage and neonatal survival rate did not differ from that observed in the general population. Thus, in recent retrospective studies, maternal prognosis has improved as compared to historical series, possibly as a consequence of a better knowledge of the natural history of SSc and complications that may occur during pregnancy and a better multidisciplinary management of pregnancies occurring in patients with SSc.

2. Epidemiology

SSc is a rare disease with a prevalence of 50 to 250 cases per million inhabitants [1]. SSc predominantly affects women (3-8 for women one man) with a peak incidence between 45 and 64 years. However, women tend to develop SSc earlier than men and 1 out of 2 women have early symptoms of the disease while of childbearing age. As a consequence, pregnancies in patients with SSc are infrequent. In the past, this connective-tissue disease ordinarily affected patients in the late reproductive and post-reproductive age [2]. In the more recent decades, many women have postponed childbearing into their 30s and 40s year. For this reason, the number of women who develop SSc and may become pregnant is likely to increase. Interestingly, Johnson et al reported in 1988 that in 17% of women with SSc, the onset of disease occur during pregnancy [3].
The number of gestations before the onset of SSc might influence the age at which the disease starts [4], since nulliparous women are younger at SSc onset and present with a more aggressive clinical course. Thus, the average age at SSc onset in women with a past history of pregnancy is 44 years, whereas, in women in whom SSc started before or occurred at the time of pregnancy, the average age at disease onset is 26 years [5]. This result, in favor of a bimodal distribution, suggests that there may be differences in the pathogenesis of SSc in these two groups of women.

The type of SSc is associated with marked differences in term of number of pregnancies. Thus, patients with limited SSc experience more pregnancies and get more children than those with diffuse SSc, most probably because of the severity of the disease. In addition, an association between the sex of the offspring and SSc has been suggested, women with SSc being more likely to give birth to male children [6]. However, the underlying explanation for this observation is not known and these data remain to be confirmed.

3. Pathogenesis

SSc is characterized by vascular hyperreactivity and collagen deposition. Endothelial cells, fibroblasts and lymphocytes abnormalities have been reported in SSc. Endothelial cells produce an excess of endothelin 1 and inducible NO synthase and undergo increased apoptosis. Oxydative stress seems to play a major role in disease progression.

Fibroblasts dysfunction is characterized by an uncontrolled activation of the transforming growth factor-β (TGF-β) pathway, an excess in synthesis of connective tissue growth factor (CTGF) and free radicals, favoring the accumulation of extra-cellular matrix. Increased levels of interleukine 4, a pro-fibrosing cytokine, have been detected in plasma and skin of SSc patients. Autoantibodies are detectable in the serum of more than 90% of SSc patients, which are directed against well identified ubiquitous nuclear proteins without evidence of a pathogenic role. Other autoantibodies bind to endothelial cells and/or fibroblasts and may exert a pathogenic role.

It has been proposed, by analogy to chronic graft versus host disease, that fetal cells might play a role in the pathogenesis of SSc [7]. Thus, although histologic and immunologic parameters differ between chronic graft versus host disease and SSc [8], it has been postulated that SSc might be understood as a type of chronic graft versus host disease resulting from transplacental transfer of cells between mother and fetus [9]. This hypothesis was further supported by the identification of fetal Y DNA and cells in skin lesions from women with SSc and a past history of delivery of male children [7]. Although a higher incidence of Y microchimerism (the persistence of foetal cells in the mother after delivery) has been reported in females with scleroderma who gave birth of child of male sex, than in healthy control females [10], these data remain controversial since not confirmed in other studies, particularly because of a higher incidence of detection of Y microchimerism in healthy control females than in the initial publications. Thus, if microchimerism has been suspected to play a role in the pathogenesis of SSc [11, 12], this postulate is actually controversial.

4. Influence of SSc on pregnancy

4.1 Fertility

Infertility is defined by difficulty in conception and the failure to achieve a successful pregnancy by the age of 35. Reports are contradictory in females with SSc. Silman and Black [13] reported a significantly higher spontaneous abortion rate in cases than in controls, with 33 (28.7%) vs 20 (17.4%), corresponding to a relative risk of 2.1 (p=0.05). In addition, multiple abortions were more frequently reported in women with SSc. In a Swedish national population-based registry [14], nulliparity was associated with increased risk of SSc (odds ratio = 1.37, 95% confidence interval: 1.22-1.55). Another study reported that both delay in conception and infertility were more common in patients who subsequently developed SSc. Women with SSc were more likely than women in the whole population to have had a delay

in conception (> or = 12 months): OR 2.6 (1.1, 5.7) or be infertile: OR 2.3 (0.7, 7.2). These differences were not apparent when the group of patients with SSc was compared to the group of women with Raynaud's phenomenon, with OR's of 0.7 and 1.1, respectively [15]. In an Italian case-control study, the risk of SSc was found to be 70 percent lower for women with a past history of pregnancy (odds ratio = 0.3, 95% confidence interval: 0.1, 0.8) and the risk decreased with increasing parity [16]. It has been also reported that infertility was 3 times higher than in healthy controls in SSc patients before the diagnosis was made [6]. Similar findings were reported by Englert et al [15]. An alternative explanation might be that women, who develop SSc early in life, cannot or may not want to get pregnant.
In recent studies, the frequency of miscarriage and neonatal survival rate did not differ in patients with SSc as compared to healthy controls. Thus, Giordano et al did not find significant level of infertility among a series of 86 women with SSc when compared with matched healthy controls [17], although they observed a significantly increased frequency of miscarriages per pregnancy (50 of 299 pregnancies in patients with SSc versus 32 of 322 pregnancies in controls; $p<0.05$). Steen and Medsger reported that fertility in SSc patients did not differ significantly from that observed in either of the control groups [18]. In addition, the proportion of nulliparous women did not differ significantly between SSc and control patients.

4.2 Spontaneous abortion

Rates of early pregnancy loss of 14%-15% are somewhat increased from the estimated 10% in the general population. Late pregnancy losses occurred scarcely, generally in women with severe diffuse SSc [18]. The anti-Ro/SSA antibody might be associated with spontaneous abortion [19]. A retrospective study of Silman did not find increased risk of fetal loss in SSc patients [13].

4.3 Preterm delivery and fetal outcomes

Reported preterm delivery rates ranged from 8% to 40% in patients with SSc [18, 20, 21], most of them being observed on or after gestational age 34.
The frequency of small full-term babies was slightly increased among SSc patients [18]. Low birth weight infants (<10th% tile for gestational age) ranged from 0% to 50%.

4.4 Delivery

The optimal mode of delivery in patients with SSc remains controversial. Vaginal delivery is associated with fewer shifts in blood volume but has a prolonged second stage of labor and issues regarding increased pressure with contractions. Cesarean delivery reduces the second stage of labor and may be necessary in cases of extreme maternal or fetal distress but increases risks of infection and thrombosis [22]. Among women who had an elective termination, 87.5% had diffuse SSc whereas 12.5% had limited SSc ($p<0.0001$) [6]. Cases of preeclampsia were isolated [18]. Labor and delivery represent a very vulnerable period in this setting, and extended observation in the hospital following delivery may be required, particularly in patients with PAH, although PAH is a contra-indication to pregnancy [23].

4.5 Placenta

The placenta, which embodies the maternal-fetal interface, may be involved in women with SSc, with vascular abnormalities inducing placental ischemia [22, 23]. The higher rates of

prematurity and low birth weight infants encountered in SSc may be the direct consequence of placental vascular insufficiency [23]. In a large study, 13 placentas from women with SSc were examined and correlations were made with perinatal outcomes. In 5/13 placentas, marked decidual vasculopathy was noted, in association with intrauterine fetal demise between week 16 and 30 in 4 cases [24]. These findings are similar to those observed in eclampsia. In 1986, Labarrere and colleagues investigated 18 placentas of 15 mothers with various autoimmune diseases including idiopathic thrombocytopenic purpura, autoimmune thyroid diseases, and multiple sclerosis. Interestingly, the group of patients with autoimmune diseases had significantly more maternal vascular lesions and chronic villitis of unknown etiology than the control group. Investigators failed to identify lesions that could be attributed to any of the diseases in particular. Placental vascular damage with deposits of IgM, C3, and C1q was more prominent in a patient with SSc. In both of these diseases, these lesions were related to poor fetal outcome. Placental vascular damage with deposits of IgM, C3, and C1q was more prominent in a patient with SSc and these lesions were related to poor fetal outcome [25]. Thus, we are convinced that systematic placental examination might help to identify the role of placental vasculopathy in pregnancy outcome [23].

5. Influence of pregnancy on the course of SSc

For years, SSc has been considered as a strict contraindication for pregnancy because of physiologic changes observed during gestation, including blood volume, vascular resistance, cardiac output and oxygen consumption, with a peak at the end of the second trimester of pregnancy. Recent studies demonstrated that women with SSc have acceptable pregnancy outcomes. More provocatively, it has been proposed that pregnancy might be protective against SSc [2, 12, 20]. Artlett at al suggested in a retrospective study that pregnancy was protective, since diffuse disease and worsening interstitial lung disease were more common in nulliparous women with SSc. Alternatively, it has been reported that pregnancy-related phenomena may contribute to SSc development [26, 27], and Cockrill at al. [28] proposed in a large cohort of women with SSc and sibling controls that immune responses associated with early childhood infections might predispose to the occurrence of SSc. In this study, it was observed that the risk of SSc increased with increasing birth order, and that a history of one or more pregnancy losses without any live births had the strongest association with SSc development.

Visceral involvement represents the major hurdle to pregnancy outcome in women with SSc, particularly in patients with pulmonary arterial hypertension (PAH), advanced pulmonary fibrosis and/or scleroderma renal crisis (SRC). Thus, a past history and/or de novo severe visceral involvement in a woman with SSc during pregnancy represent major risk factors for the occurrence of complications and/or materno-foetal mortality. Overall, during pregnancy, SSc remains clinically stable in 40-60% of patients, deteriorates in 20%, and improves in 20%. The variation probably relates to the heterogeneous nature of SSc [2, 29].

5.1 Vasculopathy

Vasculopathy is a prominent feature of SSc which may influence pregnancy outcome in women with preexisting SSc [23]. Thus, 22.9% of pregnant women with SSc develop hypertensive disorders including preeclampsia, corresponding to a four-fold increased as compared to the general population (85% CI, 2.4-6.6) [29]. Similarly, a nearly four-fold increased rate of intrauterine growth restriction was observed in the same study.

5.2 Scleroderma renal crisis

Scleroderma renal crisis (SRC) represent the worst complication that may occur in pregnant SSc patients. SRC is characterized by malignant hypertension, proteinuria, acute renal failure and in more than half of the cases thrombotic microangiopathy. SRC occur in patients with rapidly progressing diffuse skin disease of less than four years evolution. The frequency of maternal complications in SSc women with either diffuse or limited disease is not increased as compared with healthy controls, except for SRC [30]. This risk of SRC is lower if pregnancy is planned within 3-5 years from onset of symptoms [31]. Many of the perinatal deaths reported among SSc women are reported in those who develop SRC [32, 33]. Steen reported two cases of SRC in retrospective study of 86 pregnancies occurring after the diagnosis of SSc [34]. One woman developed end-stage renal disease, and the other died from status epilepticus. In a prospective study of 91 pregnancies, two cases of renal crisis were reported [20]. Both women required hemodialysis after delivery. Overall, it remains unclear if rates of SRC are increased in pregnant women compared to non pregnant women with severe diffuse disease [23]. Finally, SRC may be difficult to distinguish from preeclampsia in the pregnant SSc patient and renal biopsy may be indicated in case of difficulties to distinguish both disorders [35].

5.3 Pulmonary arterial hypertension

Pulmonary arterial hypertension is a major cause of morbidity and mortality in patients with SSc. In contrast to SRC, PAH can occur both in patients with limited or diffuse disease. Women with PAH identified by right heart catheterism are at extremely high risk of severe hemodynamic complications during pregnancy. Thus, the reserve in the pulmonary arterioles is markedly reduced and as a consequence vascular resistance cannot be reduced to accommodate the increased blood volume and cardiac output that occurs during pregnancy [23]. Reports estimated a 30%-56% maternal mortality rate in women with PAH . This maternal mortality rate is relevantly higher (56%) in women with secondary vascular pulmonary hypertension included connective tissues diseases, than in primary PAH and Eisenmenger's syndrome (30% and 36% respectively). The most vulnerable period occurring with delivery and the first two weeks postpartum [36]. Women with PAH should be strongly discouraged from becoming pregnant. All complaints of dyspnea in pregnant SSc women should prompt an immediate evaluation for the occurrence or worsening of PAH. Despite currently available treatments, a pregnancy is a principle-cons in pregnant women with PAH and a contraception is recommended for women of childbearing age.

5.4 Other complications

Gastro-oesophageal reflux increases during third trimester of pregnancy. Skin thickening has been reported to increase during post-partum in women with diffuse SSc.

Raynaud's phenomenon is characterized by vascular hyperactivity and vasospasm. Among all vascular complications of SSc, Raynaud's phenomenon and digital ulcers are the most likely to improve during pregnancy and worsen in postpartum [37]. Raynaud's phenomenon should not be considered a contraindication to pregnancy, even in patients with recurrent digital ulcers [23]. Reduction in skin fibrosis has been reported in SSc patients during pregnancy, with improvement lasting for up to one year post partum [38].

6. Management of pregnancy in patients with SSc

Women with SSc who become pregnant should be considered at high risk for complication related to the pregnancy. Multidisciplinary approach and aggressive prenatal monitoring are necessary for the management of women presenting with complications. PAH requires careful hemodynamic monitoring and specific management in collaboration with pneumologists. Women with SSc require extended observation in hospitalisation following delivery. Pregnancy must be planned when the disease is stable. Pregnancies should be avoided in women with SSc with significant cardio-pulmonary or renal disease because of the increased risk of maternal death. If women with SSc carefully consider the timing of pregnancy recomanded by their physician and are closely monitored, successful outcome can be obtained without excessive risk for the mother or the foetus [18].

7. Medications during pregnancy

At the time of diagnosis of pregnancy, drugs associated with an increased risk of fetal toxicity must be stopped. The treatment of severe hypertension during pregnancy in patients with SSc is difficult despite the use of multiple antihypertensive agents [39]. The routine use of ACE inhibitors is not recommended during pregnancy. An increased risk of fetal waste, teratogenic effects, fetal distress, and severe postpartum neonatal renal failure has been reported in the literature in this setting [40]. However, if the women has a history of SRC or is at high risk for developing SRC, an immediate initiation of Angiotensin conversing enzyme (ACE) inhibitors may be indicated. In cases of profound maternal or fetal distress, emergent delivery may be the most appropriate option followed by initiation of ACE inhibitor therapy. The severity of SRC during pregnancy and the benefits of ACE inhibitor treatment are highly likely to outweigh the risks of fetotoxicity [23].

Hydroxychloroquine in the setting of polyarthritis, intravenous immunoglobulin in the setting of documented myositis and low doses of steroids may be safely used during pregnancy. In case of pulmonary hypertension, successful use of epoprostenol and sildenafil has been reported in patients with PAH during pregnancy. Anticoagulation with low-molecular-weigth heparin is recommended to reduce risk of thromboembolism, since anti-vitamine K agents are teratogenic [41].

Calcium channel blockers are classically contra-indicated during pregnancy. However, Wilson and Kirby reported the successful conception and pregnancy in a woman with SSc while receiving continuous treatment with nifedipine 30 mg/day, after a previously poor obstetric record and involuntary secondary infertility. They speculated that nifedipine might have had a beneficial effect on conceiving and maintaining the pregnancy in this patient [42]. In addition, calcium channel blockers might prevent hypertension and premature labour. Thus, nifedipine is regularly prescribed in women with SSc during pregnancy. Finally, Basso and Ghio reported the first case of successful pregnancy in a woman with SSc treated with cyclosporine [43].

A Japan team reported the case of a woman with SSc who experienced two spontaneous abortions before delivering a healthy baby after administration of vitamin E. Vitamin E is known to have properties of antioxidants and anti-platelet aggregation agents and may prevent placental ischemia induced by decidual vasculopathy [19].

Among immunosuppressive treatments prescribed in patients with SSc, azathioprine is the only one which can be prescribed during pregnancy. Thus, the drug does not seem to be teratogenic in humans [44], whereas cyclophosphamide, methotrexate and mycophenolate mofetyl are teratogenic. Because of the potential for carcinogenesis and the unknown long-term effects of fetal immunosuppression, the use of azathioprine should be reserved for pregnant women whose diseases are severe or life-threatening. Reduction of the azathioprine dose at 32 weeks' gestation may prevent serious neonatal leukopenia and thrombocytopenia. Close prenatal monitoring for growth and long-term evaluation of the offspring are essential [45].

8. Conclusion

Pregnancies in patients with SSc are infrequent. There is no increase in the frequency of miscarriages but an increased premature births and small full-term babies in patients with SSc. Vascular manifestations including SRC and PAH should be considered as contraindications for pregnancy due to the increased risk of both maternal and fetal morbidity and mortality. The use of ACE inhibitors is recommended in pregnant women with SRC despite the risk of teratogenicity. In order to minimize risks, a multidisciplinary approach is necessary to suggest the best timing for pregnancy and provide adequate supportive treatment to patients with SSc during pregnancy.

SSc : Systemic sclerosis
SRC : Scleroderma renal crisis
PAH : Pulmonary arterial hypertension
ACE : Angiotensin conversing enzyme

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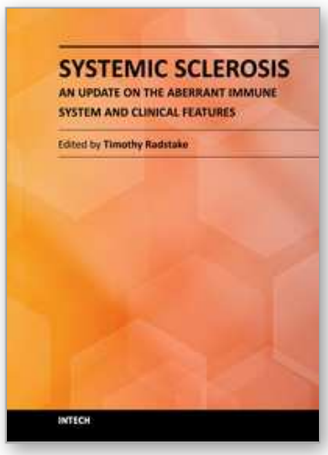
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Systemic sclerosis (SSc), or often referred to as Scleroderma (tight skin), is characterized by an exaggerated formation of collagen fibers in the skin, which leads to fibrosis. Accumulating evidence now points toward three pathological hallmarks that are implicated in Ssc, the order of which has yet to be determined: endothelial dysfunction, autoantibody formation, and activation of fibroblasts. This current book provides up-to-date information on the pathogenesis and clinical features of this severe syndrome. It is our hope that this book will aid both clinicians and researchers in dealing with patients with this clinical syndrome. In addition, we hope to shed more light on this rare and severely disabling syndrome, ultimately leading to better research and successful therapeutic targeting.

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