Reumatol Clin. 2015;**11(2)**:99–107

Reumatología Clínica

www.reumatologiaclinica.org

Review Article

Comprehensive Approach to Systemic Sclerosis Patients During Pregnancy☆

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ARTICLE INFO

Article history:
Received 3 March 2014
Accepted 3 June 2014
Available online 6 October 2014

Keywords:
Systemic sclerosis
Pregnancy
Obstetric complications

ABSTRACT

Systemic sclerosis (SSc) is a connective tissue disease that usually affects women, with a male:female ratio of 1:4–10.

It was thought that there was a prohibitive risk of fatal complications in the pregnancies of patients with SSc. It is now known that the majority of these women undergo a normal progression of pregnancy if the right time is chosen and a close obstetric care is delivered. The obstetric risk will depend on the subtype and clinical stage of the disease, and the presence and severity of the internal organ involvement during the pregnancy.

The management of these pregnancies should be provided in a specialized center, with a multidisciplinary team capable of identifying and promptly treating complications.

Treatment should be limited to drugs with no teratogenic potential, except when renal crises or severe cardiovascular complications develop.

Manejo integral de las pacientes con esclerosis sistémica durante el embarazo

Palabras clave:
Esclerosis sistémica
Embarazo
Complicaciones obstétricas

RESUMEN

La esclerosis sistémica (ES) es una enfermedad del tejido conectivo poco común que afecta principalmente a mujeres (relación mujer:hombre de 4–10:1).

En el pasado se pensaba que existía gran riesgo de complicaciones fatales en los embarazos de pacientes con ES. Actualmente, se sabe que muchas de estas mujeres pueden llevar a buen término un embarazo si se elige el momento adecuado y se lleva monitorización obstétrica estrecha. El riesgo obstétrico dependerá del subtipo y la fase clínica de la enfermedad y de la presencia y la gravedad de la afección de órganos internos durante el embarazo.

El manejo del embarazo de las pacientes con ES debe realizarse en un centro de atención especializada, con un equipo multidisciplinario capaz de detectar y tratar las complicaciones tempranamente.

El tratamiento debe limitarse a fármacos sin potencial teratogénico, excepto en crisis renales y en complicaciones cardiopulmonares que pongan en peligro la vida de la madre.

Introduction

Systemic sclerosis (SSc) or generalized scleroderma is a relatively rare connective tissue disease of unknown etiology affecting skin, joints, blood vessels, heart, lungs, gastrointestinal tract and kidneys. It has an incidence of 2–10 cases per million and prevalence of 150–300 cases per million worldwide. It mainly affects women, with a peak incidence between the fifth and sixth decades of life with a female to male ratio of 4–10:1; this ratio increases

☆ Please cite this article as: Rueda de León Aguirre A, Ramírez Calvo JA, Rodríguez Reyna TS. Manejo integral de las pacientes con esclerosis sistémica durante el embarazo. Reumatol Clin. 2015;11:99–107.

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2173-5743/

during reproductive age (15–50 years), in which the relationship can reach 15:1.[1,2]

Survival in SS has improved in recent years, mainly thanks to the introduction of angiotensin-converting enzyme inhibitors (ACEI) in the 1980s, which decreased complications and mortality due to renal crisis. Interstitial lung disease and pulmonary hypertension have replaced renal failure as the most common causes of morbidity and mortality from scleroderma.[2–9] The improvement in the prognosis of the patients due to the greater knowledge of the disease as well as increased access to health services and treatment of SS complications has been accompanied by an increase in the number of women with this condition who seek and achieve pregnancy.

This article will discuss the effects of SS on pregnancy, the influence of vascular disease, inflammation and fibrosis on the health of the mother and fetus, and the effects of pregnancy on SS.

Pregnancy and Systemic Sclerosis

In the past there were few reports of pregnancies in patients with SS due, in part, to the fact that the peak age of onset is between 45 and 55 years, and the fact that reports of early cases showed disappointing outcomes for both mothers and babies.[10–14] 25–30 years ago it was relatively common for doctors to recommend their patients with SS not to conceive and even consider abortion because of the supposed high risk of fatal complications for mother and children. This initial information, based on isolated case reports, was replaced by a series of retrospective and prospective case series which showed large proportion of women with SS who led successful pregnancy with little risk of serious complications when the patient and physician discussed the issue and chose an appropriate time for pregnancy, performing[15–18] close obstetric monitoring.

Pregnancy in women with SS should be considered from the onset as a high risk pregnancy due to the increased risk of premature delivery and low birth weight for gestational age. In early pregnancy, each patient should be carefully assessed to establish the subtype of disease (diffuse or limited), the (early or late) phase and the extent and severity of damage to internal organs. Those patients with a duration of symptoms of less than 4 years (scleroderma in early stage), diffuse subtype, or anti-topoisomerase I or anti-RNA polymerase III antibodies have a higher associated obstetric risk and, if possible, should delay pregnancy until the patient is in a late stage and hence has a less active disease.[15]

The third trimester of pregnancy is considered the one with the highest risk, since the patient may develop complications secondary to hypertension, renal failure, pulmonary hypertension, interstitial lung disease or heart failure.[19,20]

Fertility in Systemic Sclerosis

It has been difficult to establish whether fertility is affected in patients with SS, as studies have shown conflicting results. An Italian report made several decades ago suggested that there was no direct association of the disease with decreased fertility and conception problems and concluded that these issues should not be attributed to the SS.[21] On the other hand, in two English studies, the authors postulate that fertility may be impaired in patients even years before the onset of the disease, with a twice greater risk of repeated spontaneous abortion and three times more fertility problems, defined by them as an unsuccessful pregnancy before 35 years of age.[22,23]

Steen et al. have examined this controversy in two retrospective studies in which they compared patients with SSc patients with rheumatoid arthritis (RA) and healthy women, and later performed a prospective study.

The first study demonstrated that patients who already had SS and who become pregnant have similar frequencies of spontaneous abortions (15%) than RA patients (16%) and healthy controls (13%), and conclude that the disease per se does not directly affect total fertility by increasing the proportion of abortions.[16]

In the second study, the pregnancy outcomes of women whose SS onset occurs during the childbearing years were compared with RA and healthy women. As for fertility, it showed that the percentage of women who had never been pregnant is higher in groups of patients with SS and RA than in healthy controls ($P<0.05$). However, this does not necessarily mean that patients have fertility problems, as there are additional factors that contribute to these differences. Among the study patients, 8%–10% had no sexual activity; women with SS or RA in this had developed the disease at a younger age compared to those sexually active; A questionnaire study showed that most women with SS (5%) and RA (11%) had chosen not to have children compared with the control group (3%), some of them motivated by the advice of doctors or family. Only 2%–5% of patients with SS had sought unsuccessfully to become pregnant; in most of them, the age of onset of SS was after 40, so they were already probably infertile.[17]

The study found no significant differences between groups in the number of women who reported a period of at least one year during which they failed to conceive (15% of patients with SS, 12% of patients with RA and 13% of controls). There were 27 women with SSc who were evaluated for infertility, and in that 63% of them already had the disease at the time of the evaluation; the rate of successful pregnancies in patients evaluated for infertility, regardless of the treatment they received for it, was similar in the three groups: 37% for patients with SS, 40% for patients with RA and 43% for healthy women. The analysis found no significant differences in the frequency of infertility or the rate of successful pregnancies in women with RA and SS before or after disease onset.[17]

Besides the above, this topic is especially related to the sexuality of patients, since vascular lung disease, skin and physical limitations, as well as changes in the appearance and the emotional effects of the disease, have the ability of impact relationships of some of the patients, thus affecting the possibility of conception. The main symptoms that patients reported as affecting their sex life were fatigue, muscle/joint pain, vaginal dryness and dyspareunia. They also associated Raynaud's phenomenon, sore hands, digital ulcers, dyspnea and chest pain.[24–26]

Patients may also have coexisting secondary antiphospholipid antibody syndrome (APS), so it would be appropriate to identify lupus anticardiolipin antibodies, β2 glycoprotein 1 and lupus anticoagulant in all patients with SS and recurrent fetal loss. In a study by Steen et al. antiphospholipid antibodies were found in 50% of patients with SS and ulcers of the lower limbs, indicating that the association of SS and APS cannot be that uncommon.[27] There are other studies indicating that the antiphospholipid antibodies may be independently associated with pulmonary arterial hypertension, macrovascular disease and increased total mortality in patients with systemic sclerosis.[28,29]

Effects of Pregnancy on Systemic Sclerosis

It is difficult to determine the effects of pregnancy on the disease, as some symptoms are very similar and, therefore, it is not easy to distinguish which of the causes are attributable. Such is the case of GERD, joint pain and swelling, to name a few. The consensus of several studies on this is that there are no significant changes in