Scleroderma pregnancy: can the price be too high to pay?

M. Østensen

Monika Østensen, Department of Rheumatology, University Hospital of Berne, Switzerland.

Please address correspondence to: Professor Monika Østensen MD, PhD, Department of Rheumatology and Clinical Immunology/Allergology, University Hospital, CH-3010 Bern, Switzerland.
E-mail: monika.oestensen@insel.ch

Received on November 18, 2008; accepted on November 26, 2008.

Competing interests: none declared.

Introduction

Systemic sclerosis (SSc) is a rare connective tissue disease characterized by a vasculopathy and progressive fibrosis in the skin and internal organs. Typical clinical manifestations are Raynaud's phenomenon, tight skin and manifestations from the lung, heart, kidney and gastrointestinal tract. The disease can manifest as a limited or systemic condition, and varies regarding the extent of skin and organ involvement and progress of the disease.

SSc has a female preponderance of about 8-10:1 in reproductive years (1). Onset of symptoms occurs predominantly in the early 40s. The prognosis of the disease has improved during the last two decades with an increase in the 10-year survival rate (2). Diffuse visceral scleroderma and particularly renal and lung involvement carry a serious prognosis. At present there is no satisfactory or uniequivocal successful therapy for the disease. As modern women often choose to postpone pregnancy, patients with SSc have the potential to become pregnant.

In the 1960s and 70s published reports on the concurrence of pregnancy and SSc was rare and consisted mostly of case reports or small series with often unfavourable maternal and fetal outcome (3. 4). This resulted in the view held by many doctors that patients with systemic sclerosis should not become pregnant. In 1976 a letter in JAMA stated: "The interaction of pregnancy and scleroderma may therefore be so inimical as to produce the worst possible outcome: fetal and maternal death, … It would seem incontestable that pregnancy in a patient with scleroderma must be considered a serious and, at least potentially lethal situation – rather than an association of little concern" (5). The picture changed when retrospective and prospective studies of a substantial number of patients showed much better pregnancy outcomes. In 2007 Dr. V. Steen wrote: "Pregnancy in systemic sclerosis may be uneventful with good maternal and fetal outcomes. Careful planning, close monitoring, and aggressive management should allow women who have scleroderma to have a high likelihood of a successful pregnancy"(6).

The effect of pregnancy on systemic sclerosis

Early case reports described deterioration of systemic sclerosis in more than 50% with a high proportion of maternal death due to renal failure, pulmonary hypertension and other complications (3, 4, 7). Obviously these case reports were biased towards patients with severe systemic disease and negative outcomes. Retrospective, uncontrolled series including more patients with the limited form of systemic sclerosis showed a much better prognosis (8). Recently 2 retrospective and 1 prospective study described successful pregnancies for the majority of patients (9, 10). In a review of the 27 case reports no change of disease was found in 33%, deterioration in 44% and improvement in 11% during pregnancy (11). In the uncontrolled retrospective series the disease was unchanged in 34%, deteriorated in 30% and improved in 11% (11). In the retrospective controlled study of 86 pregnancies performed by Steen no change of symptoms during pregnancy was found in 88%, improvement in 5% and worsening in 7% (8). Similar findings were made in the prospective study of 67 pregnancies in 50 women with SSc (12). The prospective studies have shown favourable maternal and fetal outcomes of pregnancy in the majority of patients with SSc. Doctors will therefore no longer advise against pregnancy, less progressive disease or severe organ damage are present in a patient.

Serious complications of SSc

During the course of SSc, serious organ manifestations can develop. Some of these can severely jeopardize the outcome of pregnancy. Renal disease and the risk of developing renal crisis is one of the most threatening complications of systemic sclerosis. In the early case reports, renal failure was the most common cause of maternal death (3, 4). Renal involvement may present as sudden onset malignant hypertension or as rapidly progressing renal failure. Risk factors for renal crisis are: early diffuse systemic sclerosis and rapidly progressing skin disease. Treatment with high dose prednisolone may be an additional risk factor (13). In the early

case reports 33% of mothers developed renal crisis, most of them postpartum (11). In the retrospective, case-control study of Steen, renal crisis occured in 2 % of pregnancies, and in her prospective study 11% of patients with diffus scleroderma developed renal crisis during the second trimester (8, 12). However, the frequency of renal crisis was not increased during pregnancy compared to nonpregnant patients with systemic sclerosis. The complication occurred only in patients with early diffuse scleroderma. In the majority of cases, renal crisis developed in normotensive patients without a previous history of renal disease (8). Successful pregnancy after the occurrence of renal crisis has been described (6). Among ten patients with an episode of renal crisis, five healthy children were born to four mothers who continued treatment with ACE inhibitors throughout pregnancy. Among those who discontinued ACE inhibitors before pregnancy, major problems occurred requiring restart of captopril in two women (6).

Another serious complication is pulmonary hypertension (PHT), which at present is the predominant cause of death in SSc (2). Pregnancy in patients with PHT may carry a lethal risk as has been shown in case reports (14). Pulmonary hypertension has still the poorest survival rate of about 2.8 years (15) with a 30-50% risk of maternal mortality in case of pregnancy. A recent study on pregnancy outcomes in 85 pregnancies of women with PHT found a fivefold increase of hypertensive disorders during pregnancy and a nearly double risk for intrauterine growth restriction (16). Fortunately, a multidisciplinary team approach has now improved pregnancy outcome also in these high-risk pregnancies (17).

Management of SSc

Improvements made in diagnosis and management have allowed more women with SSc to consider pregnancy. Management of scleroderma has changed and has improved the outcome of several organ manifestations. Renal disease and renal crisis can be successfully treated with ACE inhibitors. However, ACE inhibitors can induce serious side effects in the fetus, and are therefore contraindicated during pregnancy. The vascular changes of Raynaud's phenomenon can be successfully treated with prostaglandin analogues. Endothelin receptor antagonists can prevent deterioration of exercise capacity in patients with pulmonary hypertension secondary to SSc, and may improve survival (18). Likewise, the number of new digital ulcers in patients can be reduced (19) by therapy with bosentan. Unfortunately, none of the new therapies are compatible with pregnancy either because of proven risk for the fetus or because of insufficient data regarding pregnancy. Therefore important risks remain in pregnant patients with renal disease, severe restrictive lung disease, pulmonary hypertension or severe gastrointestinal involvement.

Autologous haematopoetic stem cell transplantation (HSCT) has shown promising results in selected patients with severe SSc (20, 21). After a median follow-up of 5.3 (1-7.5) years, 81% of 26 European patients demonstrated a clinically beneficial response with event-free survival in 57.1% at seven years follow-up. There were three deaths: 2 related to SSCc and one to cancer. An American study of 34 SSc patients found sustained positive responses at a median follow-up of 4 years in 17 of 27 (63%) evaluable patients. There were 12 deaths during the study, thereof four related to SSc and eight transplantation-related. The estimated progression-free survival was 64% at 5 years in this study.

Autologous HSCT conditioning protocols include a high dose of cyclophosphamide with a risk of infertility as a consequence of treatment. Therefore pregnancies after HSCT are rare.

A retrospective study evaluated the outcome of pregnancy after autologous and allogeneic SCTD including 65 women with malignant disease. The study found that 85% of pregnancies resulted in live births (22). However, no follow-up of the mothers was performed. Another study of women with non-Hodgkin lymphoma assessed pregnancy outcome in 14 women who had received autologous HSCT (23). The 14 women had 15 children, one miscarriage and one fetal death. One mother died during follow-up. Four other women treated with allogeneic or autologous SCT recovered ovarian function after hormonal replacement therapy and had uncomplicated pregnancies (24).

In this issue of *Clinical and Experimental Rheumatology*, Tyndall and colleagues (page xxx-xxx) present a case of pregnancy and childbirth after autologous haematopoetic stem cell transplantation in a patient with severe systemic sclerosis. The patient had extensive cutaneous involvement, pulmonary fibrosis and severe gastrointestinal involvement. After successful autologous HSCT the patient's condition improved. In spite of advise against pregnancy, the patient became pregnant three years after autologous HSCT. The first pregnancy ended in miscarriage, the second pregnancy ended with the premature delivery of a healthy child. Ten years after the autologous HSCT, the patient died during a new aggravation of SSc from gastrointestinal obstruction with pericarditis. The case shows that successful pregnancy is possible in severe SSc and also after autologous HSCT. However, the further course of events raises the question whether the price for having a child may sometimes be too high. Severe SSc still carries a risk of mortality, which, as in this woman, may strike after an initially successful therapy.

Ethical considerations

The tragic event of maternal death early in a child's life raises several complex issues.

The question is how to deal with the patient who desires children and has potentially life-threatening organ manifestations or considers a therapy with a potential risk of mortality. The first requirement is time to discuss all aspects involved: maternal health, fetal health, and prognosis for mother and child. Is the wish for a child a strong one or is it just a desirable option for the patient? The doctor needs to find out how important childbearing is for the patient, and what risk she is willing to take on its behalf. The second task of the doctor is to assess the clinical

manifestations of SSc which constitute possible risks for becoming pregnant or for long-term prognosis. The doctor needs to discuss risks inherent to SSc and possibly enhanced by pregnancy with the patient. Any decision for or against pregnancy has to be based on medical facts. However, few studies exist in pregnant SSc women with severe organ manifestations or in women pregnant after autologous HSCT.

The patient will have her own perspective of quality of life and personal well-being. These are based on personal values and beliefs, and should be respected by the doctor. Improving management and prognosis of a serious disease means to enable the patient to lead a more normal life. This includes also childbearing for a female patient in her fertile years. For many women having a family is of utmost importance and allows them to fulfil their role as a mother. Women may consider pregnancy in spite of their doctors discouraging them because of a serious risk for their health. Even when a substantial risk is explained, the patient may feel that there may be unreported cases with a good outcome, and hence she will try.

Religious and cultural reasons may play a role in a woman's decision, either by preventing birth control or by demanding the generation of offspring in matrimony. These reasons may in the view of the woman have priority over concerns regarding her health, and they are most often not changed by logical arguments. However, there is no guarantee for any parent that she or he will stay healthy and will live long enough to see their children being able to care for themselves. A parent may fall seriously ill or have an accident with a fatal outcome. At the end of the day, no doctor can make a decision for the patient: she has to decide herself whether or not she wants to have children. The task of the doctor is to give the best possible information, and to assist the patient throughout pregnancy and the time thereafter with careful monitoring and management.

References

1. SILMAN AJ, JANNINI S SYMMONS DPM, BACON P: An epidemiological study of scleroderma in the West Midlands. *Br J Rheumatol* 1988; 27: 286-90.
2. AL-DHAHER FF, POPE JE, OUIMET JM: Determinants of Morbidity and Mortality of Systemic Sclerosis in Canada. *Semin Arthritis Rheum* 2008; published online.
3. KARLEN JR, COOK WA: Renal scleroderma and pregnancy. *Obstet Gynecol* 1974; 44: 349-54.
4. SOOD SV, KOHLER HG: Maternal death from systemic sclerosis. *J Obstet Gynaecol Br Commonwealth* 1970; 77: 1109-12.
5. COOK WA: Raynaud phenomenon in pregnancy. *JAMA* 1976; 235: 145-6.
6. STEEN VD: Pregnancy in scleroderma. *Rheum Dis Clin N Am* 2007; 33: 345-58.
7. YOUNKER D, HARRISON B: Scleroderma and pregnancy. *Br J Anaesth* 1985; 57: 1136-39.
8. STEEN VD, CONTE C, DAY N, RAMSEY-GOLDMAN R, MEDSGER TA: Pregnancy in women with systemic sclerosis. *Arthritis Rheum* 1989; 32: 151-7.
9. CHUNG L, FLYCKT RLR, COLON I, SHAH AA, DRUZIN M, CHAKRAVARTY EF: Outcome of pregnancies complicated by systemic sclerosis and mixed connective tissue disease. *Lupus* 2006; 15: 595-9.
10. STEEN VD: Pregnancy in women with systemic sclerosis. *Obstet Gynecol* 1999; 94: 15-20.
11. BLACK CM, LUPOLI S: *Scleroderma and pregnancy. Progress in Obstetrics and Gynaecology.* Churchill Livingstone, Edinburgh, 1990; 8: 49-69.
12. STEEN VD, BRODEUR M, CONTE C: Prospective pregnancy study in women with systemic sclerosis (SSc) (Abstract). *Arthritis Rheum* 1996; 39 (Suppl.): S151.
13. STEEN VD, CONTE C, MEDSGER TA Jr: Case-control study of corticosteroid use prior to scleroderma renal crisis. *Arthritis Rheum* 1994; 37: S360.
14. ROBERTS NV, KEAST PJ: Pulmonary hypertension and pregnancy - a lethal combination. *Anaesth Intensive Care* 1990; 18: 366-74.
15. MCLAUGHLIN VV: Classification and epidemiology of pulmonary hypertension. *Cardiol Clin* 2004; 22: 327-41.
16. CHAKRAVARTY EF, KHANNA D, CHUNG L: Pregnancy outcomes in systemic sclerosis, primary pulmonary hypertension, and sickle cell disease. *Obstet Gynecol* 2008; 111: 927-34.
17. SMEDSTAD KG, CRAMB R, MORRISON DH: Pulmonary hypertension and pregnancy: a series of eight cases. *Can J Anaesth* 1994; 41: 502-12.
18. OLDFIELD V, LYSENG-WILLIAMSON KA: Bosentan: a review of its use in pulmonary arterial hypertension and systemic sclerosis. *Am J Cardiovasc Drugs* 2006; 6: 189-208.
19. KORN JH, MAYES M, MATUCCI-CERINIC M *et al.*: Digital ulcers in systemic sclerosis: prevention by treatment with bosentan, an oral endothelin receptor antagonist. *Arthritis Rheum* 2004; 50: 3985-93.
20. VONK MC, MARJANOVIC Z, VAN DEN HOOGEN FHJ *et al.*: Long-term follow-up results after autologous haematopoietic stem cell transplantation for severe systemic sclerosis. *Ann Rheum Dis* 2008: 67: 98-104.
21. NASH RA, MCSWEENEY PA, CROFFORD LJ *et al.*: High-dose immunosuppressive therapy and autologous hematopoietic cell transplantation for severe systemic sclerosis: long-term follow-up of the US multicenter pilot study. *Blood* 2007; 110: 1388-96.
22. SALOOJA N, SZYDLO RM, SOCIE G *et al.*: Pregnancy outcomes after peripheral blood or bone marrow transplantation: a retrospective survey. *Lancet* 2001; 358: 271-6.
23. BRICE P, HAIOUN C, ANDRÉ M, GISSELBRECHT C: Pregnancies after high-dose chemotherapy and autologous stem cell transplantation in aggressive lymphomas (letter). *Blood* 2002; 100: 736.
24. LIU J, MALHOTRA R, VOLTARELLI J *et al.*: Ovarian recovery after stem cell transplantation. *Bone Marr Trans* 2008; 41: 275-8.