

Pregnancy and progressive systemic sclerosis

Case report and review of the literature¹

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A case of progressive systemic sclerosis and successful pregnancy is reported. The 82 other reported cases are reviewed with emphasis on the potentially lethal sequela seen 15% of the time (primarily, accelerated renal hypertension, sometimes heralded by proteinuria with renal failure). Accelerated renal hypertension is noted to be present only in primigravid or multigravid patients who manifested sclerodermatous changes prior to the pregnancy. Close blood pressure monitoring and weekly urine tests for protein are recommended as a way to possibly warn the clinician of the onset of this condition. The use of captopril is considered as a possible treatment as there is one reported case of maternal salvage with its use.

Index terms: Case reports • Hypertension, renal
• Pregnancy, complications • Scleroderma, systemic

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A 21-year-old nulliparous black woman presented to The Cleveland Clinic Foundation in 1979 with chief complaints of two-phase discoloration of her fingers (pallor and cy-

anosis) related to cold, small distal phalangeal ulcerations, thickening of the skin especially around the nail folds, slight dysphagia to solid foods, and mild dyspnea on exertion. The remainder of her review of systems and previous medical history were unremarkable at that time. The physical examination was unrevealing with the exception of loss of skin creases (folds) over the interphalangeal joints (distal phalanges) and evidence of healed ulcerations on the fingertips (pads). Cutaneous sclerosis involved hands and fingers. No telangiectases were observed. A diagnosis of scleroderma was made in accord with published criteria.¹ Laboratory tests revealed an antinuclear antibody positive at a titer of 1:320. Results of SMA-17 chemistry profile (including electrolytes), complete blood count, and urinalysis were normal. Roentgenograms of the hands revealed tapering of the soft tissues with erosions of the distal phalangeal osseous tufts of the thumb and index fingers bilaterally. No soft tissue calcification was noted. Upper gastrointestinal roentgenographic study by barium swallow, chest roentgenogram, and echocardiogram were within normal limits. Pulmonary function studies revealed a moderate restrictive defect with normal diffusion capacity. It was suspected that she suffered from a systemic sclerosis form of scleroderma disease because restrictive defect was present. At this point, she was given colchicine (0.6 mg, twice a day).

She did reasonably well without significant changes in symptoms until May 1981, when she had increased hand pain and dysphagia. The colchicine was discontinued and penicillamine (250 mg daily) was started. Repeat roentgenograms with barium swallow were within normal limits, and one month later the penicillamine was increased to 500 mg daily as planned. Over the course of the next six months, she had recurrent bouts of pleuritic chest pain. Penicillamine was stopped, and prednisone, along with a nonsteroidal anti-

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inflammatory drug, was initiated with some relief. The steroids were tapered and eventually discontinued. She remained stable until June 1982, when she had a recurrence of the pleuritic chest pain, and the penicillamine was once again added to her regimen. Repeat pulmonary function studies were essentially unchanged. The echocardiogram was normal with no evidence of pericardial effusion. Subsequently, the penicillamine was increased to 1,000 mg/day. In July 1982, her pleuritic pain and dysphagia progressed and she was treated with three courses of lymphopheresis (2 L every other day). She obtained moderate relief of symptoms, and results of laboratory studies remained within normal limits. She was maintained on penicillamine (500 mg daily).

In August 1982, a beta human chorionic gonadotropin test was positive, and it was estimated that she was approximately 12 weeks pregnant. At that time, the penicillamine was discontinued. Three weeks later, she had another bout of pleuritic chest discomfort, and prednisone (5 mg daily) was begun. The echocardiogram and chest roentgenogram were again normal at this time.

The risks of pregnancy and scleroderma (miscarriage, spontaneous abortion, maternal mortality) were discussed at length with the patient, as well as possible deleterious effects the early weeks of penicillamine might have caused. She was referred to a high-risk perinatologist. Blood pressure was taken daily. She was seen every week either by her rheumatologist or perinatologist, alternately. Substernal chest pain continued, and prednisone was increased to 15 mg/day. At no point did proteinuria or hypertension develop. At 36 weeks, she was admitted to the hospital in labor and was delivered of a normal, full-term child via spontaneous vaginal delivery. Episiotomy was performed and healed normally. She and the child did well for two years postpartum except for gastrointestinal symptoms relieved by metoclopramide (Reglan). Chest discomfort persisted despite trials of sulindac (Clinoril) (200 mg, twice a day), trigger point injection, and imipramine (Tofranil).

Discussion

Scleroderma and progressive systemic sclerosis had been interchangeable terms, but at present, the latter is favored, often prefaced by the word *progressive*. For the purposes of this paper, *scleroderma* and *systemic sclerosis* are defined in accord with published criteria.¹ It is a disease primarily of women (2:1 ratio) with peak age of onset between 30 and 50 years. This late age of onset and the trend of early second-decade pregnancies had combined to keep the coincidence of scleroderma or systemic sclerosis and pregnancy low, with only 82 cases in the literature. With the recent trend of pregnancies later in life,² the incidence should increase.

As reported herein, a case of concurrent systemic sclerosis and pregnancy was seen. A major concern was the risk of pregnancy in this patient who had systemic sclerosis with diminished pul-

monary function. She had been advised not to become pregnant. When she became pregnant, the risks were explained to her, but abortion was not suggested because of our uncertainty about the numbers of unreported cases with normal outcome. We monitored blood pressure daily and performed weekly edema checks and urinalyses. Close monitoring should probably be performed in all cases of systemic sclerosis, even though there is no proof that early detection is protective. It is less clear still that CREST variant (calcinosis, Raynaud's disease, esophageal dysmotility, sclerodactyly, telangiectasias) requires close monitoring. Had she become hypertensive, proteinuric, or edematous, she would have been hospitalized. She did not, and went on to deliver a normal child. It is of note that she was receiving 500 mg of penicillamine during her first trimester.

When she was found to be pregnant, a literature search was performed and revealed a lack of consensus on management of systemic sclerosis during pregnancy (*Table*).

Of the 82 cases of systemic sclerosis and pregnancy in the literature, 12 (15%) resulted in maternal death secondary most often to accelerated hypertension of the nontoxic variety, refractory to all modes of therapy. The immediate concern of a physician caring for a pregnant systemic sclerosis or scleroderma patient should be the prevention or detection and management of complications such as accelerated hypertension distinct from preeclampsia.^{3,4} Characteristically, this occurred during third trimester with proteinuria and without edema (although occasionally with both). The sequela of accelerated hypertension was postpartum renal failure and then death⁵⁻⁷ in all but one case despite trials of all known antihypertensive drugs and bilateral nephrectomy.⁸ To the unknowing physician, it may masquerade as preeclamptic toxemia.⁹ Because they are not often published, normal-outcome pregnancies were probably reported less frequently than those resulting in either maternal or fetal death. This skews results to look worse; however, it is probable that maternal death and fetal wastage in scleroderma are significantly higher than in the general population.

The previous pregnancy history of 5 patients with accelerated hypertension was unknown, but 4 of the 12 were primiparous. Another 2 of the 12 were multiparous, but the complicated preg-

Table. Pregnancy outcome in progressive systemic sclerosis

Mother and Child (Normal)			Fetal Death (Maternal Condition Stable)			Maternal Death (Usually Also Fetal Loss)		
No. of Patients		Year	No. of Patients		Year	No. of Patients		Year
1	Anselmino and Hoffmann ²²	1932	1	Eno ²⁵	1937	1	Etterich and Mall ⁴⁰	1955
1	Eno ²⁵	1937	1	Leinwand et al ²⁵	1954	1	Casten and Boucek ⁴¹	1957
1	Guttmacher ²⁴	1943	1	Hayes et al ⁵⁸	1962	1	Slate and Graham ⁵¹	1967
1	Leinwand et al ²⁵	1954	1	Spellacy ³⁹	1964	1	Donaldson ⁵²	1967
1	Tischler et al ²⁶	1957	1	Johnson et al ²⁹	1964	1	Fear ⁵	1968
1	Hoffman and Diamond ²⁷	1961	2	Slate and Graham ⁵¹	1967	1	Sood and Kohler ⁹	1970
1	Winkleman ²⁸	1962	1	Donaldson ⁵²	1967	1	Karlen and Cook ¹²	1973
36	Johnson et al ²⁹	1964	1	Watson et al ⁶	1981	1	Ehrenfeld et al ⁶	1977
1	Gunther and Harer ³⁰	1964	1	Thompson and Conklin ¹⁶	1983	1	Garcez ^{42*}	1979
3	Slate and Graham ⁵¹	1967				1	Palma et al ^{7*}	1981
3	Donaldson ⁵²	1967				1	Smith and Pinals ⁵	1982
1	Knupp and O'Leary ¹¹	1971				1	Mor-Yosef et al ³⁶	1984
2	Spiera ³⁵	1981						
1	Sivanesaratnam and Chong ³⁴	1982						
1	Goplerud ³⁵	1983						
1	Mor-Yosef et al ³⁶	1984						
3	Ballou et al ³⁷	1984						
1	(Scarpinato and Mackenzie)	1985						

* No fetal death.

Fetal wastage = fetal death + (maternal death - no fetal death)/total.

nancy was in each case the first to occur following the onset of scleroderma. Of the case histories known, accelerated renal hypertension seems to affect primigravid patients with established disease, as well as multiparous women whose disease became evident just before this pregnancy.

There was also a high amount of fetal wastage near term—23% for all reported cases. Not included were the frequent previous spontaneous abortions in the reported cases. More data has recently become available that support this higher incidence of spontaneous abortion.¹⁰ Both maternal and fetal enhanced risk has led some physicians to discourage systemic sclerosis patients from getting pregnant. Some have even suggested sterilization.¹¹⁻¹³

The reports of the 12 cases of maternal death recount various attempts at controlling the accelerated hypertension with the use of medications and even bilateral nephrectomy, all to no avail. There is one 18-month survival with the use of captopril, but the patient eventually died despite bilateral nephrectomy and hemodialysis.⁶ The only case report of a pregnant systemic sclerosis patient who survived a postpartum accelerated hypertension episode with eclampsia is entitled "Captopril-induced Agranulocytosis in Systemic Sclerosis."⁸ Unfortunately, the title makes no mention of her successful postpartum status. Accelerated hypertension had developed during her

pregnancy and she was given captopril. She survived despite the resulting agranulocytosis. In pregnant patients with systemic sclerosis in whom accelerated hypertension develops, a reasonable therapy might be captopril, although only one successful outcome has been reported. Hyperkalemia, especially in situations of some degree of renal failure, may also be seen as a complication of captopril therapy.¹⁴ Anecdotal reports in humans have not suggested that captopril is harmful to the fetus. Studies in which captopril has been used in spontaneously hypertensive rats during pregnancy have demonstrated no difference for any gestational parameters between treated and untreated animals.¹⁵ Length of pregnancy, birth rate, weight at birth, and cannibalism were unchanged by captopril therapy.

An excellent review of anesthetic precautions to be taken with pregnant systemic sclerosis patients was recently published.¹⁶

The association with antinuclear antibody and/or hypergammaglobulinemia, as well as other recent data, supports the hypothesis that scleroderma is an immune-mediated disease.^{17,18} Changes in the immune system also occur during pregnancy.¹⁹⁻²¹ When accelerated hypertension is induced by concurrent scleroderma and pregnancy, this may indeed be the result of combined alterations. Further research via case study is necessary to discern exactly why accelerated hy-

pertension develops in some patients and not in others.

Conclusion

A case of scleroderma and pregnancy with successful maternal and fetal outcome has been presented. A search of the literature revealed 82 such cases, which were reviewed. Progressive systemic sclerosis was found to be a high-risk situation for both mother and fetus. Close antepartum blood pressure and proteinuria monitoring is recommended. Finally, the use of captopril to treat accelerated hypertension in scleroderma with pregnancy should be considered because of the successful result reported in one similar case.

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