Pregnancy and progressive systemic sclerosis

Case report and review of the literature[1]

Leonard Scarpinato, D.O.
Allen H. Mackenzie, M.D.

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

Cleve Clin Q 52:207–211, Summer 1985

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 cyanosis) 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. Roentogenograms 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-

[1] Departments of Internal Medicine (L.S.) and Rheumatic and Immunologic Disease (A.H.M.), The Cleveland Clinic Foundation. Submitted for publication Jan 1985; accepted Mar 1985. lp

0009-8787/85/02/0207/05/$2.25/0

Copyright © 1985, The Cleveland Clinic Foundation

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 pulmonary 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 pencillamine 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 nontoxemic 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 death[5–7] 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[23]	1937	1	Etterich and Mall[40]	1955
1	Eno[23]	1937	1	Leinwand et al[25]	1954	1	Casten and Boucek[41]	1957
1	Guttmacher[24]	1943	1	Hayes et al[38]	1962	1	Slate and Graham[31]	1967
1	Leinwand et al[25]	1954	1	Spellacy[39]	1964	1	Donaldson[32]	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[31]	1967	1	Sood and Kohler[9]	1970
1	Winkleman[28]	1962	1	Donaldson[32]	1967	1	Karlen and Cook[12]	1973
36	Johnson et al[29]	1964	1	Watson et al[8]	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[31]	1967				1	Palma et al[7]*	1981
3	Donaldson[32]	1967				1	Smith and Pinals[5]	1982
1	Knupp and O'Leary[11]	1971				1	Mor-Yosef et al[36]	1984
2	Spiera[33]	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.

Allen H. Mackenzie, M.D.
Department of Rheumatic and Immunologic Disease
The Cleveland Clinic Foundation
9500 Euclid Ave.
Cleveland OH 44106

References

1. Masi AT, Rodnan GP, Medsger TA Jr, et al. Clinical criteria for early diagnosed systemic sclerosis: preliminary results of the ARA Multicenter Cooperative Study (abst). Arthritis Rheum 1978; **21**:576–577.
2. Stein ZA. A woman's age: childbearing and child rearing. Am J Epidemiol 1985; **121**:327–342.
3. Fear RE. Eclampsia superimposed on renal scleroderma: a rare cause of maternal and fetal mortality. Obstet Gynecol 1968; **31**:69–74.
4. Cannon PJ, Hassar M, Case DM, Casarella WJ, Sommers SC, LeRoy EC. The relationship of hypertension and renal failure in scleroderma (progressive systemic sclerosis) to structural and functional abnormalities of the renal cortical circulation. Medicine 1974; **53**:1–46.
5. Smith CA, Pinals RS. Progressive systemic sclerosis and postpartum renal failure complicated by peripheral gangrene. J Rheumatol 1982; **9**:455–458.
6. Ehrenfeld M, Licht A, Stressman J, Yanko L. Rosenmann E. *Post partum* renal failure due to progressive systemic sclerosis treated with chronic hemodialysis. Nephron 1977; **18**:175–181.
7. Palma A, Sanchez-Palencia A, Armas JR, Milan JA, Fernandez-Sanz J, Llach F. Progressive systemic sclerosis and nephrotic syndrome: an unusual association resulting in postpartum acute renal failure. Arch Intern Med 1981; **141**:521–522.
8. Watson MA, Radford NJ, McGrath BP, Swinton GW, Agar JW. Captopril-induced agranulocytosis in systemic sclerosis. Aust NZ J Med 1981; **11**:79–81.
9. Sood SV, Kohler HG. Maternal death from systemic sclerosis: report of a case of renal scleroderma masquerading as preeclampsia. J Obstet Gynaecol Br Commonw 1970; **77**:1109–1112.
10. Giordano M, Valentini G, Lupoli S, Giordano A. Pregnancy and systemic sclerosis. Arthritis Rheum 1985; **28**:237–238.
11. Knupp MZ, O'Leary JA. Pregnancy and scleroderma: systemic sclerosis. J Fla Med Assoc 1971; **58**:28–30.
12. Karlen JR, Cook WA. Renal scleroderma and pregnancy. Obstet Gynecol 1974; **44**:349–354.
13. White CA. Collagen diseases in pregnancy. [In] Sciarra JJ, ed. Gynecology & Obstetrics. Philadelphia, Harper & Row, vol 3, 1984, pp 1–13.
14. Burnakis TG, Mioduch HJ. Combined therapy with captopril and potassium supplementation: a potential for hyperkalemia. Arch Intern Med 1984; **144**:2371–2372.
15. Chadelaud M, Moore N, Berland C, et al. The effects of chronic treatment with captopril in spontaneously hypertensive rats (SHR) and their offspring. Clin Exp Hypertens [A] 1984; **6**:1179–1186.
16. Thompson J, Conklin KA. Anesthetic management of a pregnant patient with scleroderma. Anesthesiology 1983; **59**:69–71.
17. Jablonska S, Chorzelski TP, Blaszczyk M. Pathogenesis of scleroderma. [In] Jablonska S, ed. Scleroderma and Pseudoscleroderma. 2nd ed. Warsaw, Polish Medical Publishers; Stroudsburg, Pa, Dowden, Hutchinson & Ross, Distributors, 1975, pp 15–35.
18. Cathcart MK, Krakauer RS. Immunologic enhancement of collagen accumulation in progressive systemic sclerosis (PSS). Clin Immunol Immunopathol 1981; **21**:128–133.
19. Sridama V, Pacini F, Yang S-L, Moawad A, Reilly M, DeGroot LJ. Decreased levels of helper T cells: a possible cause of immunodeficiency in pregnancy. N Engl J Med 1982; **307**:352–356.
20. Siegel I, Gleicher N. Peripheral white blood cell alterations in early labor. Diagn Gynecol Obstet 1981; **3**:123–126.
21. Gleicher N, Siegel I, Toder V. Decreased levels of helper T cells in pregnancy. N Engl J Med 1982; **307**:1582.
22. Anselmino KJ, Hoffmann F. Über Sklerodermi und Schwangerschaft Ztschr f Geburtsh u Gynäk 1932; **103**:60–66.
23. Eno E. Pregnancy in a patient suffering with scleroderma. Am J Obstet Gynecol 1937; **33**:514–515.
24. Guttmacher AF. A case of severe scleroderma with successful delivery. Urol Cutan Rev 1943; **47**:107–108.
25. Leinwand I, Duryee AW, Richter MN. Scleroderma (based on a study of over 150 cases). Ann Intern Med 1954; **41**:1003–1041.
26. Tischler S, Zarowitz H, Daichman I. Scleroderma and pregnancy. Obstet Gynecol 1957; **10**:457–459.
27. Hoffman JB, Diamond B. Scleroderma treated with steroids through pregnancy, cesarean section and puerperium. Postgrad Med 1961; **30**:498–501.
28. Winkleman E. Pregnancy in advanced systemic scleroderma. J Am Med Wom Assoc 1962; **17**:557–561.
29. Johnson TR, Banner EA, Winkelmann RK. Scleroderma and pregnancy. Obstet Gynecol 1964; **23**:467–469.
30. Gunther RE, Harer WB Jr. Systemic scleroderma in pregnancy: report of a case. Obstet Gynecol 1964; **24**:98–100.
31. Slate WG, Graham AR. Scleroderma and pregnancy. Am J Obstet Gynecol 1968; **101**:335–341.
32. Donaldson LB in discussion, Slate WG, Graham AR. Scleroderma and pregnancy. Am J Obstet Gynecol 1968; **101**:335–341.
33. Spiera H. The clinical picture of connective tissue diseases in pregnancy. Prog Clin Biol Res 1981; **70**:303–307.
34. Sivanesaratnam V, Chong HL. Scleroderma and pregnancy. Aust NZ J Obstet Gynaecol 1982; **22**:123–124.

35. Goplerud CP. Scleroderma. Clin Obstet Gynecol 1983; **26**:587–591.
36. Mor-Yosef S, Navot D, Rabinowitz R, Schenker JG. Collagen diseases in pregnancy. Obstet Gynecol Surv 1984; **39**:67–84.
37. Ballou SP, Morley JJ, Kushner I. Pregnancy and systemic sclerosis. Arthritis Rheum 1984; **27**:295.
38. Hayes GW, Walsh CR, D'Alessandro EE. Scleroderma in pregnancy: report of a case. Obstet Gynecol 1962; **19**:273–274.
39. Spellacy WN. Scleroderma and pregnancy: report of a case. Obstet Gynecol 1964; **23**:297–300.
40. Etterich M, Mall M. Sklerodermie und Schwangerschaft. Gynaecologia 1955; **139**:236.
41. Casten GG, Boucek RJ. Use of relaxin in the treatment of systemic scleroderma. JAMA 1958; **166**:319–329.
42. Garcez D de M, Costa C, Prompt CA. Gestation and rapidly progressive form of scleroderma. Rev Ass Med Brasil 1979; **25**:445–446.