Mixed connective tissue disease is a rheumatic disease that resembles systemic lupus erythematosus and scleroderma. It occurs in women of all age groups and is usually not associated with major organ involvement. As with any chronic maternal illness, mixed connective tissue disease can predispose to intrauterine growth retardation. Good neonatal outcome is directly related to early diagnosis and aggressive management. Mixed connective tissue disease has not been previously described in association with pregnancy.

Incidence and characteristics
The collagen diseases and their interrelations with pregnancy long have been an enigma. In 1938, Hench described the beneficial effect of pregnancy on rheumatoid arthritis. This was corroborated by Persellin. But there are many connective tissue diseases on which the effects of pregnancy vary. One disorder which has not been described previously in pregnancy is mixed connective tissue disease (MCTD). This paper will describe a case in which MCTD was associated with fever of undetermined origin during pregnancy and was followed by intrauterine growth retardation.

The disease primarily affects women in all age groups. The clinical picture includes many features of both SLE and scleroderma, although renal involvement and neuropsychiatric disease are absent, and alopecia, photosensitivity, mucosal lesions, pleurisy, pericarditis, and myocarditis are not prominent. The most common characteristics of patients with this disease are polynarthralgia or polyarthritis, Raynaud's phenomenon, diminished esophageal motility, swollen hands, hypergammaglobulinemia, myositis, lymphadenopathy, positive reactions for rheumatoid agglutinins and fluorescent antinuclear antibody, and lymphadenopathy. Pulmonary involvement recently has been shown to be common. Diffusion capacity is decreased, and x-ray films of the chest show diffuse interstitial infiltrates, with occasional volume loss or pleural disease. Unlike SLE, MCTD is associated with severe renal disease in only about 10 percent of patients. Renal biopsy may reveal only mesangial hypercellularity, focal glomerulonephritis, and diffuse membranous glomerulonephritis, diffuse membranoproliferative glomerulonephritis, vascular changes consistent with hypertension, and focal thickening of the basement membrane with marked intimal proliferation, and obliteration of arteries. The glomerular basement membrane also has shown deposits of immunoglobulin G and complement components 3 and 4. The most common neurosensory dysfunction is a trigeminal sensory neuropathy. Anemia and leukopenia are frequent hematologic abnormalities. Lymphadenopathy and fever occur in only about one-third of patients. Hashimoto's thyroiditis and Sjögren's syndrome have been associated with MCTD occasionally. Proximal muscle weakness and increases in transaminase, creatinine phosphokinase, and aldolase in the serum are common.

Sharp said that patients with MCTD characteristically have high levels of antinuclear antibody, and these appear to be specific for a nuclear antigen extractable in isotonic buffers (ENA). Low titers of ENA also are detected in about 50 percent of patients with SLE. ENA consists of two distinct antigens, one sensitive to ribonuclease and trypsin (a nuclear ribonucleoprotein [RNP])—the other resistant to these. This is identical to Sm antigen. It
has been shown\(^a\) that serum containing RNP antibodies in high titer and no Sm antibodies usually is present with MCTD and is uncommon with SLE, progressive systemic sclerosis (PSS), polymyositis, or rheumatoid arthritis. The most common characteristics of patients with RNP antibody only are the same as those of patients with MCTD. Patients also characteristically have high titers of fluorescent antinuclear antibody in a speckled pattern. Serum that reacts with either RNP or Sm antigens yields a speckled ANA pattern, but this is eliminated by ribonuclease if it is due to RNP antibody. Rheumatoid agglutinins are present in many patients. Antibodies to deoxyribonucleic acid and LE cells are seen occasionally. Levels of complement in the serum usually are normal. The erythrocyte sedimentation rate may be elevated. Hypergammaglobulinemia occurs in 3 of 4 patients.\(^8\)

**Report of case**

A 23-year-old white woman was seen early in her second pregnancy in January 1981. She reported that her last menstrual period had occurred in the last 2 weeks of November 1980, and that there had been brief spotting on December 24. She had suffered spontaneous abortion at 8 weeks of her first pregnancy in July 1976. She had had two intrauterine contraceptive devices, and the second had been removed because of menorrhagia in the spring of 1978.

Her past medical history included measles, mumps, varicella, herpes type II, and serum hepatitis 7 years prior to the current presentation. She was allergic to soap. She said that she had experienced occasional nausea and vomiting, headache, constipation for 2 months, Raynaud’s disease, and arthritis in both wrists.

On physical examination, the patient’s pulse rate was 76 beats per minute and her respiratory rate 18 per minute; her blood pressure was 104/70 mm. Hg. The heart was regular, without murmurs, rubs, thrills, or gallops. The abdomen was nonpregnant, and the cervix was closed. Her past medical history included measles, mumps, varicella, herpes type II, and serum hepatitis 7 years prior to the current presentation. She was allergic to soap. She said that she had experienced occasional nausea and vomiting, headache, constipation for 2 months, Raynaud’s disease, and arthritis in both wrists.

At 28 weeks’ gestation, the patient was hospitalized through the emergency department with a complaint of severe pain in the right flank. She said that the pain had begun 48 hours prior to admission and that she had come to the emergency department, where she had been treated with oral penicillin and released. The pain worsened and she again came to the emergency department, this time with shaking chills and an oral temperature of 105.6 F. Examination in the emergency department showed red inflammation of the throat, submandibular adenopathy, and harsh lung sounds bilaterally. She said that she had been seen in the clinic and had had no problems with her pregnancy until that time. She denied any further occurrence of hepatitis in the past several years. The patient had tenderness in the right flank. The liver was of normal size, with no tenderness. There was no jaundice or scleral icterus. The fundal height was consistent with 27 weeks’ gestation, and the fetal heart beat was normal. The leukocyte count was 7,100/cu. mm., with a differential count of 90 percent segmented forms and 10 percent lymphocytes. Hemoglobin and hematocrit values were normal. Urinalysis revealed both leukocytes and erythrocytes, occult blood, and many varied casts.

At admission, a septic work-up was begun, and ampicillin was administered intravenously. X-ray examination of the chest on two occasions showed no abnormality. Ultrasonographic study of the kidneys showed dilatation of the right renal collecting system consistent with the gestational stage, but no other evidence of renal abnormality. The urine was consistently normal. The leukocyte count dropped to 3,000/cu. mm., and there was a persistent left shift in the differential count. Australian antigen evoked no reaction. Serum laboratory studies revealed the following values: glutamic oxalacetic transaminase, 84 units/ml.; glutamic pyruvic transaminase, 55 units/ml.; total protein, 5.7 gm./100 ml.; albumin, 2.6 gm./100 ml.; direct bilirubin, 0.3 mg./100 ml.; and lactic dehydrogenase, 261 units/ml. The titer for ANA was positive at 1:640, and the RA latex test was negative.

The patient had a spiking fever throughout her hospital course. Because of the absence of leukocytosis and normal urinalysis, the possibility of an antibiotic-related fever was entertained. Antibiotics were discontinued and she became afebrile. After 30 hours without fever the patient was discharged, to be followed as an outpatient in the clinic.

At the time of discharge the uterus measured 26 cm., and she was at 34 weeks’ gestation by date. This repeat ultrasonogram gave results consistent with developing intrauterine growth retardation. During a search for an etiology of the intrauterine growth retardation, questioning elicited the admission that she had taken a friend’s diet pills during the first trimester of pregnancy. A diagnosis of intrauterine growth retardation was made.

The patient was followed closely and was admitted 3 days prior to the expected date of confinement, and 24-hour collection of urine for determination of estriols, creatinine, and protein was started. At this stage the uterus measured approximately 31 cm., and fetal heart tones were 130 per minute. The patient’s temperature was 98 F., the pulse rate 80 per minute, the respiratory rate 16 per minute, and the blood pressure 120/70 mm. Hg. A nonstress test was reactive, and an oxytocin challenge test was negative.

On the second hospital day, the patient had irregular
uterine contractions throughout the night. There was good fetal movement. Later that day contractions increased to 1 every 4 minutes. Ultrasonographic examination showed the biparietal diameter to be 90 mm., which was consistent with a head-sparing type of intrauterine growth retardation. The neonate was in cephalic presentation. There was oligohydramnios; the placenta was anterior, and fetal kidneys were not identified. The cervix was 4 cm. dilated. Membranes were ruptured artificially. Old meconium was noted. A scalp clip was applied and monitoring at first showed a normal pattern. The patient was placed in the left lateral recumbent position and given oxygen to increase fetal oxygenation. Approximately 20 minutes after rupture of membranes, one deceleration was noted. Baseline variability increased over the next 45 minutes, but there were frequent nonsevere variable decelerations. Contractions occurred every 2½ or 3 minutes.

Two hours later, there was a period in which the fetal heart rate was between 50 and 60 beats per minute for 7 or 8 minutes. There was no improvement with change of position or administration of fluids and oxygen. It was decided to do an emergency cesarean section. The neonate was delivered from the left occipitotransverse position. There was one loose loop of cord around the neck. The neonate was male, with Apgar scores of 8 and 9 at 1 and 5 minutes, respectively. The birth weight was 5 pounds, 2 ounces, which is below the tenth percentile on the intrauterine growth charts of Lubchenco and associates.

The patient’s uterus was small for the gestational stage. Her tubes and ovaries appeared normal. The neonate was grossly dysmature. He was sent to the nursery in stable condition. The night after cesarean section the patient’s temperature was 102.8 F. Fever persisted, and intravenous administration of cefoxitin was begun. The patient responded well. Cultures of lochia showed moderate amounts of Citrobacter and rare enterococci. Other cultures gave negative results. Anemia developed, with a drop in the hemoglobin level within 24 hours, from 11.8 gm./100 ml. postoperatively to 8.8 gm./100 ml. A transfusion of 2 units of blood cells was given. A torch screen revealed a RPR nonreactive rubella titer of 1:128. A toxoplasma titer was negative at 1:16. The patient was discharged on the fifth postoperative day.

At the 6-week postpartum check-up, the patient requested and received a copper 7 intrauterine contraceptive device (IUD). Four months later she complained of pain from the IUD only when she used a tampon. Physical examination showed the IUD string to be in place at the cervical os. There was questionable tenderness at the left costovertebral angle. The abdomen was soft and nontender, and the incision was well healed. The uterus was mobile, nontender, and of normal size, and the adnexa was nontender and without masses. The bladder was tender to palpation. The patient neglected to carry out the order for a urinalysis.

The patient’s history, including pregnancy, were reviewed, and the finding of an ANA titer at 1:640 had not been explained. She was sent for consultation with a rheumatologist, who elicited a history of vague arthralgias in the wrists and in the right knee at times. There had been some hair loss at the time of delivery, but this was not progressive. The patient reported fatigue consistent with the postpartum period. She denied any photosensitivity, although she said that the sun made her sick. She had no family history of rheumatoid disease or SLE. Physical, rheumatologic, and neurologic examination gave relatively normal results. Follow-up serologic studies were ordered.

At the second examination, the rheumatologist noted small synovial effusions bilaterally in the knees, with no joint heat. Serologic studies showed a positive reaction for ANA at 1:640 in a speckled pattern. Antibody to ENA showed all RNP antibody, with a titer of 1:524,288. Single-stranded DNA was elevated at 18.8 percent; the double-stranded DNA level was not reported. There were only 2,800 leukocytes per cu. mm.; the differential count revealed 50 percent segmented forms, 48 percent lymphocytes, and 2 percent monocytes. The sedimentation rate was 23 mm./hr. The platelet count was 221,000/cu. mm. Urinalysis showed from 15 to 30 erythrocytes, although the patient said that she was menstruating at the time. She reported some menometrorrhagia. Multiplas chemical study (SMA-12) was normal. It was decided to forego corticosteroid therapy because the patient’s symptoms were mild.

After discussion with the patient’s obstetrician and rheumatologist, it was decided to try a different means of contraception. The IUD was removed. There was no cervical tenderness, and the uterus was of normal size. It was thought that the abnormal uterine bleeding could be due to the IUD. The patient was fitted for a diaphragm. Menses subsequently became regular. One month later, however, the patient continued to have vague polyarthralgias. She also reported pain in the lower part of her back in the vicinity of the left costovertebral angle. There was also discomfort during urination and urinary frequency. The temperature was 99.2 F., and the blood pressure was 110/80 mm. Hg. The heart was regular, with no murmurs or rubs. The lungs were clear. There were no objective joint abnormalities. Anti-DNA testing elicited a normal response, less than 10 units/ml. The fourth complement component was on the borderline, at 15 mg./dl. The CH50 value was normal at 44 units/ml. A 24-hour urine specimen showed 78 mg. protein, with a clearance of 150 ml. per minute, although the total volume was only 1,000 ml. The patient was given a prescription for Disalcid for her arthralgias and was treated for infection of the urinary tract with antibiotics. Because there was no evidence of major organic involvement, steroids were not prescribed.

The following month the patient was doing well, with only occasional vague arthralgias. The menstrual irregularity and urinary symptoms had subsided. Rheumatologic evaluation showed nothing remarkable. The sedimentation rate was 12 mm./hr. Urinalysis showed a 1+ reaction for bacteria but was otherwise unremarkable. The patient discontinued the salicylate voluntarily because she could not tolerate it. Because the symptoms had subsided, all medication was discontinued. On the most recent examination, the patient had only mild arthralgias and a sedimentation rate of 28 mm./hr.
Pathogenesis, treatment, and prognosis

The collagen diseases, said White,\textsuperscript{11} share the trait of "widespread inflammatory damage to connective tissue and blood vessels, often in conjunction with deposition of fibrinoid material." The specific cause and pathogenesis of MCTD are unknown. The immune complex deposition may play a role in end-organ involvement. There is also evidence that 7-S immunoglobulin G antibodies can cross the placenta freely and cause disease in the fetus if the fetus carries the appropriate antigen. There is a possible etiologic path for a passive IgG antibody effect.

There is recent evidence\textsuperscript{12} of congenital heart block in babies of mothers with tissue diseases. The mechanism for this also may be immune complex deposition affecting only the fetus, because of possible "blocking" antibodies present in the mother to protect her. Congenital heart block might have been the cause of the fetal distress in the present case, although it seems more likely that a cord accident was the cause, because of the antecedent variable deceleration.

Immune complex deposition has been noted\textsuperscript{13} in the trophoblast basement membrane of SLE mothers, and was similar to that found in glomeruli. This could help explain the intrauterine growth retardation and the pathologic changes noted in the placenta (focal infarct and calcification).

The observation that some of the rheumatoid diseases improved during pregnancy\textsuperscript{1} led to the introduction of corticosteroid therapy for these diseases. MCTD is definitely not associated with major organ involvement and as a rule has a good prognosis. Mild disease often is controlled with nonsteroidal, anti-inflammatory drugs. Occasionally steroids must be used, and low doses usually suffice. With severe pulmonary or esophageal involvement, occasionally cytotoxic drugs must be used along with corticosteroids. The disease appears to be highly responsive to corticosteroids in its early stages. Causes of death include renal failure, pulmonary failure, colonic perforation, cerebral hemorrhage, myocardial infarction, disseminated infection, and suicide.\textsuperscript{8}

Steroids are indicated for labor, delivery, and the puerperium for patients with SLE.\textsuperscript{12} Although there are no similar recommendations for MCTD, it would seem prudent to continue steroids for any patient who needs them during her pregnancy and to be willing to treat any possible exacerbation of the disease aggressively in pregnancy.

Conclusion

Chronic maternal illness can predispose to intrauterine growth retardation.\textsuperscript{14} MCTD is a chronic disorder, the incidence of which is unknown. It is found predominantly in women of childbearing age and can be associated with significant maternal and fetal morbidity. The case presented illustrates an exacerbation during pregnancy of MCTD, which manifested itself as a prolonged febrile episode with vague arthralgias. The neonatal outcome was good only because the associated intrauterine growth retardation was identified early and followed closely and the patient had aggressive obstetric management.

Appreciation is expressed to Raymond A. Adelizzi, D.O., for his help, tutelage, and interest in managing this case.


Accepted for publication in June 1984. Updating, as necessary, has been done by the authors.