Diagnosis of Maternal Cystic Fibrosis During Pregnancy

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The third and fourth cases of maternal cystic fibrosis diagnosed during pregnancy are presented. Quantitative pilocarpine iontophoresis (sweat chlorides) must be performed to establish the diagnosis. Other important findings include recurrent or persistent respiratory symptoms, chest x-ray abnormalities, abnormal pulmonary function studies, and abnormal arterial blood gases. Gastrointestinal tract dysfunction and a positive family history for respiratory disease also suggest the diagnosis. Pregnant patients with cystic fibrosis require careful and frequent cardiopulmonary and gastrointestinal surveillance. A higher incidence of premature labor is noted and all patients are best managed in tertiary referral centers. Patients should also be monitored carefully during the puerperium because maternal pulmonary decompensation may occur during this time. *(Obstet Gynecol 61:2S, 1983)*

Because of improved diagnosis and treatment, an increasing number of children suffering from cystic fibrosis are surviving to adulthood.[1] More pregnancies complicated by maternal cystic fibrosis are also being reported,[2-11] although the initial diagnosis of cystic fibrosis has only rarely been made in pregnancy.[2,4] The authors wish to report the third and fourth cases of maternal cystic fibrosis diagnosed during pregnancy.

The first previously reported case, reported in 1960, was in a 20-year-old primigravida with a history of persistent cough and recurrent pneumonia since age 12, previously diagnosed as bronchiectasis.[2] Her brother was being treated for cystic fibrosis. A sweat chloride study during pregnancy showed an elevated chloride value of 79.8 mEq/liter (normal, less than 60 mEq/liter). The patient was treated for the remainder of her pregnancy with nutritional supplements and antibiotics. She delivered spontaneously at 34 weeks' gestation but died 1 month post partum of respiratory failure.

The second woman was seen at a regional care center at 31 weeks' gestation with an exacerbation of life-long unexplained respiratory symptoms.[4] Results of sweat chloride testing locally had been normal. Results of repeat testing were abnormal, and the diagnosis of cystic fibrosis was made. The remainder of labor, delivery, and postpartum course were unremarkable.

The authors present 2 additional cases, discuss the criteria for diagnosis of cystic fibrosis in adults, and present updated information related to management of the pregnant patient.

Case Reports

Patient 1

SW, a 24-year-old primigravid white woman, was first seen at University of Iowa Hospitals on January 23, 1978, at 22 weeks' gestation. She was referred for evaluation of productive cough and shortness of breath that began in the first trimester. She had been admitted to her local hospital for presumed asthma attacks, but did not respond to antibiotics or bronchodilators. She had no fever, chills, or steatorrhea, but had lost 2.25 kg over the preceding month.

Before the pregnancy she had never been hospitalized and had taken no medications. She had had nonspecific respiratory allergies since childhood. Her brother died at age 17 of cystic fibrosis; she had never undergone a sweat chloride test.

On admission she was noted to be a thin woman in moderate respiratory distress. Examination revealed poor chest wall expansion and use of accessory muscles, diffuse inspiratory rhonchi, diffuse expiratory wheezing, and hyperresonance with dullness to percussion. Uterine size was consistent with a 22-week gestation. Laboratory studies included forced vital capacity in 1 second (FEV_1), 200 to 250 ml (normal, 2.7 liters); and vital capacity, 500 ml (normal, 3120 ml). Arterial blood gases on 8 liters of oxygen were Po_2, 64 torr; Pco_2, 40 torr; and pH, 7.39. Sputum cultures grew *Pseudomonas aeruginosa*. The chest x-ray showed bronchial wall thickening and dilatation, particularly in the basal segments. On the basis of these findings, sweat chloride testing

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was performed by the quantitative pilocarpine iontophoresis method with 65 mEq/liter chloride in a volume of 117.3 mg sweat initially and 57 mEq/liter in a volume of 127.3 mg sweat on a repeat study.

The patient was treated with aminophyllin, gentamicin, carbenicillin, oxygen, intravenous hydration, and vigorous pulmonary toilet. She did well for 10 days until intermittent lower abdominal pain developed. Premature labor was suspected, but the cervix was undilated and no contractions were palpable. Serum amylase was 1320 U/dl (normal, 45 to 200 U/dl), prompting the diagnosis of pancreatitis. The patient was treated with peripheral venous nutrition and cimetidine. She gradually improved and was sent home 4 weeks later on a regimen of ampicillin, general diet, and supplemental oxygen.

The patient was readmitted at 33 weeks' gestation with increasing respiratory symptoms and deterioration of pulmonary function. Sputum cultures again grew *P aeruginosa*. The patient was treated with intravenous tobramycin, carbenicillin, and aminophyllin. The membranes ruptured spontaneously 5 days after admission. After an unremarkable spontaneous labor an 1800-g female infant was delivered by low forceps with Apgar scores of 8 and 9 at 1 and 5 minutes, respectively. The infant did well and was discharged in good condition. Sweat chloride studies were performed on the infant at 2 months of age, with chloride values of 5.9 and 6.1 mEq/liter in 141.6 and 93.9 mg sweat, respectively. The child has followed normal developmental milestones to 43 months of age.

The patient remained stable post partum and resumed oral diet. Ampicillin therapy was begun 2 days after delivery and the other antibiotics were discontinued. She gradually improved, but on the eleventh postpartum day she had acute pulmonary decompensation. Vital capacity, maximum mid-expiratory flow rate, and FEV_1 all decreased dramatically and CO_2 retention requiring mechanical ventilation developed. Intravenous antibiotic therapy was resumed. The condition was stabilized but the patient could not be weaned from the ventilator. After 12 days a tracheostomy was performed in an attempt to improve control of secretions. Despite these measures, there was a progressive decline in pulmonary compliance and the patient died of respiratory failure on the 26th postpartum day.

Autopsy findings consistent with cystic fibrosis were found in the lung, pancreas, and intestine.

Patient 2

DC, a 17-year-old white primigravid woman, was referred to Iowa Methodist Medical Center at 28 weeks' gestation for treatment of premature labor as well as progressive cough and shortness of breath. She had a 5-year history of productive cough and shortness of breath, but had not had a previous chest x-ray or hospitalization. A sister had died of pneumonia at age 9; cystic fibrosis had been suspected, but sweat chloride testing of the sister had been negative.

On admission, regular uterine contractions were noted, and the patient appeared chronically ill. Circumoral and conjunctival cyanosis were present. Diffuse rales and coarse breath sounds throughout both lung fields were noted, as was a decreased expiratory rate. The cardiac examination was normal. The estimated fetal weight was 1000 g. The cervix was 3 cm dilated and 100% effaced.

Laboratory studies included hematocrit, 34.2%, and white blood cell count, 10,000/mm^3. Arterial blood gases on room air showed Po_2, 50 torr; Pco_2, 29 torr; and pH, 7.46. These improved on 70% oxygen to Po_2, 83 torr; Pco_2, 26 torr; and pH, 7.50. Chest x-ray showed diffuse involvement with fluffy interstitial infiltrate predominantly in the upper lobes. Sputum cultures subsequently grew *Staphylococcus aureus*. The impression was of premature labor with probable cystic fibrosis and superimposed pneumonia.

The patient was treated with intravenous hydration and isoxsuprine, which promptly stopped the contractions. She was also given betamethasone 12 mg orally for 2 doses at 24-hour intervals. The pneumonia was treated initially with intravenous cephalothin and aminophyllin plus 70% oxygen and chest physical therapy. A sweat chloride test done by quantitative pilocarpine iontophoresis revealed a chloride of 70 mEq/liter (volume not specified). On the sixth hospital day contractions resumed and continued despite attempted tocolysis. Spontaneous rupture of the membranes occurred, and labor progressed rapidly to the spontaneous vertex delivery of a 1070-g female infant with Apgar scores of 8 and 9 at 1 and 5 minutes, respectively. The infant was 29 weeks by gestational age assessment, and examination was otherwise unremarkable. The infant, who did not have respiratory distress, had an uncomplicated course and was discharged in good condition. A sweat chloride study performed on the infant at 1 month of age was within the normal range. A subsequent study at 33 months of age on the child revealed a sweat chloride content of 16 mEq/liter.

Post partum there was gradual improvement in the patient's pulmonary status. Repeat sweat chloride studies on the fifth postpartum day showed a chloride of 63 mEq/liter. Sputum cultures revealed no pathogenic organisms. She was discharged on the ninth postpartum day on a regimen of oral contraceptives, night oxygen supplementation, and dicloxacillin sodium for 2 weeks. She has done well for more than 40 months post partum with only mild exacerbations of lung disease and return of blood gases to the normal range.

Discussion

Cystic fibrosis is the most common lethal genetic disease in white people, with a gene frequency estimated as high as 1:20 and an occurrence that may approach 1 in 1600 live births. The cause is unknown, but appears to be related to an abnormality of exocrine gland secretions. Pathophysiologic features include immotile cilia, excessively thick mucus, pancreatic enzyme deficiency, and elevated sodium and chloride in sweat. Pulmonary disease is the most serious clinical problem, and respiratory failure is the usual cause of death, although cirrhosis from progressive hepatic disease accounts for a small number of deaths in adolescents and adults.

Although the number of adults with cystic fibrosis

increases each year, most diagnoses have been in children. However, an estimated 2 to 3% of this group is not initially diagnosed until late adolescence or early adulthood. Although female fertility may be impaired, an increasing number of pregnancies in women with cystic fibrosis has been noted.[6,11] The authors' experience suggests that there are women in whom cystic fibrosis is not suspected or diagnosed until pregnancy.

Diagnosis

The presentation of cystic fibrosis in the older adolescent or young adult differs from that in the infant or child, so the diagnosis is often not considered. The older patient may appear healthy and well nourished, instead of chronically ill and emaciated. Pancreatic function is usually deficient, but is often not symptomatic. Recurrent unexplained respiratory symptoms such as chronic cough and sputum production, although sometimes mild, may be the only abnormality and should arouse suspicion. Other pulmonary symptoms and signs include hemoptysis, pneumothorax, bronchiectasis, and cor pulmonale. Initial diagnostic studies should include proper sweat chloride determinations and a chest x-ray. A positive family history is helpful, but is not always present.

The interpretation of sweat chloride testing has been said to be difficult in adults, because normal values up to 60 mEq/liter occur.[12] However, most authorities believe that the test is a good discriminator in adults.[13,14]

To obtain accurate and reproducible results, it is important that quantitative pilocarpine iontophoresis be done by an experienced technician. Because of the implications of either a false-positive or a false-negative diagnosis, patients should be referred to a center at which the test is performed frequently. The amount of sweat must be quantitated, and the test should always be done in duplicate. The currently accepted technique for this procedure has been described by Gibson and Cooke.[15] Many laboratories currently use "quick" methods (the Orion test and Med therm test), which do not involve quantitation of sweat. These methods result in both false-positive and false-negative results, as most recently documented by Denning et al,[16] and should not be used. It must be emphasized that the diagnosis of cystic fibrosis is not made on the basis of sweat chloride testing alone. It is essential to consider the patient's entire clinical picture in the diagnostic process.

A few rare disorders are known to raise chloride values: hyperhydrotic ectodermal dysplasia, untreated adrenal insufficiency, and renal diabetes insipidus. None of these should present diagnostic difficulty. The effect of pregnancy on sweat chloride values is not known. It is interesting that all 4 patients diagnosed during pregnancy had chloride values less than 100, and 2 were in the borderline range. Some information is available about the effects of hormones on sweat chlorides. Chloride values in adult women are the same as in adult men and have not been found to vary with the menstrual cycle. In adults, administration of glucocorticoids and mineralocorticoids has not been found to alter sweat chloride values. Cervical mucus composition is altered in girls with cystic fibrosis.[17]

Pulmonary function tests are usually abnormal and reflect a primarily obstructive process affecting the small airways. FEV_1 and maximum midexpiratory flow rates are decreased. The prognosis is related to the severity of the obstructive abnormality.[18] There may also be a restrictive component to the pulmonary function abnormality.

The chest x-ray is usually abnormal. The upper lobes are usually involved and show varying degrees of fibrosis, cystic change, atelectasis, and mucus plugging. Prominent interstitial markings are common. Hyperinflation is less common in adults than in children. Acute infiltrates represent superimposed pneumonitis.[13,19] Although the findings are not pathognomonic, patchy diffuse upper lobe changes, irregular aeration, or air trapping in a young patient with a history of respiratory symptoms is highly suggestive.

Arterial blood gases are usually abnormal. Typical initial changes are hypoxia with a normal CO_2. Hypercarbia is seen in more advanced cases.

Pancreatic insufficiency may be present. It is probably not necessary to test the duodenal secretions for pancreatic enzymes, although this was done routinely in the past. Fecal fat determination can be used to determine the need for pancreatic enzyme replacement, but clinical evaluation is usually satisfactory. Other evidence of gastrointestinal tract dysfunction includes cirrhosis, portal hypertension, carbohydrate intolerance, volvulus, obstruction, or intussusception.

Salt depletion may be seen (and may also occur in breast-fed infants of mothers with cystic fibrosis). Other abnormalities that may be encountered include an increased susceptibility to heat stroke, skeletal demineralization, and nasal polyposis.

Management

Once the diagnosis of cystic fibrosis is established, management must be aggressive. Since Larsen's[6] discussion in 1972, new information about this disease in adults has become available.[13,14] Based on these new facts as well as the reported cases, the authors would like to present what seems to be a logical approach. For all these women, pregnancy should be considered

high risk, and the regional specialists most familiar with cystic fibrosis should be consulted.

A careful history should be taken, emphasizing pulmonary and gastrointestinal symptoms. Exercise tolerance should be estimated. Studies should include a chest x-ray, pulmonary function studies, arterial blood gases, and sputum culture to evaluate the respiratory function. The patient should be evaluated for malabsorption. Liver function studies and a glucose tolerance test complete the evaluation of the gastrointestinal system. Additional studies should include serum electrolytes, hemoglobin and hematocrit, urinalysis, and in appropriate patients an electrocardiogram and echocardiogram to assess right ventricular function.

A functional classification with prognostic value was developed in 1972 and should be done at one of the initial visits.[18] Although this may not predict pregnancy outcome, it can be helpful in counseling the patient about her future.

Follow-up visits should occur at least every 2 weeks until approximately 26 weeks' gestation and weekly thereafter. Pulmonary function studies, arterial blood gases, sputum culture, weight, and blood count should be assessed monthly and systems should be carefully reviewed. Ultrasound may be useful for dating purposes as well as assessment of the fetus for appropriate growth. Fetal heart rate testing should be done in the third trimester.

Pulmonary Management

The major therapeutic goal is maintenance of open airways and control of pulmonary infection. The former is achieved by adequate hydration and chest physiotherapy that includes percussion and postural drainage 3 to 4 times daily. There is increasing clinical evidence that a vigorous aerobic exercise program is important for bronchial toilet. Prolonged bed rest should be avoided, and the patient's ability to tolerate exercise should be considered in both prenatal and early pregnancy counseling.

Pulmonary infection should be suspected if pulmonary function studies deteriorate. Proper collection of sputum specimens is essential. Cultures accurately representing the lower respiratory tract can be obtained by having the patient rinse her mouth with saline before coughing, and then transporting the sputum to the laboratory within 20 minutes for plating. The most common organisms are *P aeruginosa*, *Hemophilus influenzae*, and *S aureus*.

P aeruginosa is the most common respiratory pathogen in cystic fibrosis. Substantial investigational effort has been directed toward the frequent association of maternal cystic fibrosis and pulmonary colonization and/or infection with this organism. diSant' Agnese and Davis,[13] in a major review article of cystic fibrosis in adults, note that 90% of such patients have had chronic obstructive bronchitis associated with *P aeruginosa*. The majority of *Pseudomonas* isolates recovered from patients with cystic fibrosis produce an unusual and relatively specific polysaccharide slime-like material. This material has been characterized as a polymer of uronic acid[20] and is widely thought to enhance the persistence of pseudomonads in such patients.[21,22] These mucoid strains of pseudomonads are seldom seen except in cystic fibrosis. Some authors recommend the diagnosis of cystic fibrosis be seriously considered whenever such organisms are isolated from patients with bronchitis.[23] Most patients with cystic fibrosis are initially colonized with nonmucoid *Pseudomonas* strains that subsequently evolve into mucoid forms of the same strain.[24] After such a transformation, the organism is very seldom eradicated and is usually associated with progressive deterioration in the patient's condition.[25] There is evidence to suggest that the increased virulence is the result of impaired phagocyte clearance and decreased effectiveness of opsonic antibodies.[26,27] Similar mucoid strains of *Escherichia coli* have also been recently identified in the respiratory tracts of patients with cystic fibrosis.[28]

Treatment with an appropriate antibiotic should continue for at least 2 weeks, and some patients may need continuous antibiotic therapy. Organism-specific therapy is critical. *Staphylococcus* should be treated with a penicillinase-resistant penicillin or cephalosporin. Ampicillin, amoxicillin, or intravenous carbenicillin can be used for *H influenzae*. *Pseudomonas* is the most difficult to eradicate.

Parenteral therapy is mandatory for *Pseudomonas* pneumonia. In patients with normal renal function, divided doses of gentamicin or tobramycin totally 5 mg/kg/day inhibit most strains of *Pseudomonas*. However, amikacin in doses of 15 mg/kg/day is also effective and may be particularly useful against strains that have developed resistance to gentamicin or tobramycin. Ticarcillin (16 to 20 g/day) and carbenicillin (24 to 30 g/day) are also frequently effective. Enhanced anti-*Pseudomonas* activity can be achieved by combination therapy with an aminoglycoside and either ticarcillin or carbenicillin.

Pulmonary function tests can be used to monitor clinical progress. Fortunately, all these antibiotics can be used with relative safety in pregnancy. Although tetracycline is commonly used in the nonpregnant patient, it should not be used during pregnancy.

If the patient is hypoxic, supplemental oxygen is necessary. Theophylline or adrenergic bronchodilator agents are often used, as bronchospasm is frequently present. Intermittent positive-pressure breathing, al-

though recommended in the past, is now believed ineffective except to deliver medication. The risk of pneumothorax is a contraindication to its use.[12] Because the major cause of deterioration and eventual death is related to pulmonary dysfunction and infection, it is especially important that the patient be impressed at the start with the importance of meticulous pulmonary care, including aerobic exercise.

Patients who complain of increased shortness of breath or sputum production or in whom respiratory function deteriorates usually have infection, but the possibility of spontaneous pneumothorax or the development of cor pulmonale should be considered. Hemoptysis secondary to bronchiectasis is common and should be treated with antibiotics. Rarely, massive or life-threatening hemoptysis unresponsive to antibiotics requires surgical therapy.

The prognosis for a patient with cor pulmonale as a result of long-standing hypoxia and respiratory insufficiency is poor. Every patient should be screened with arterial blood gas determination, electrocardiogram, and spirometry. If the results of these studies point to cor pulmonale, diagnostic echocardiography should be considered for corroborative evidence,[29,30] because the disease is a potentially serious problem in pregnancy.

Pancreatic Insufficiency

If there is evidence of pancreatic insufficiency, pancreatic extracts should be considered. Even though the patient may not have marked malabsorption, these supplements are believed to decrease the risks of cholelithiasis and may facilitate nutrition during pregnancy. A low-fat diet is helpful. Also, adult patients with pancreatic insufficiency are at increased risk for meconium ileus equivalent, and there may be value in pancreatic extract to prevent this complication.

Meconium ileus equivalent is characterized by the triad of intermittent recurrent right lower quadrant pain, right lower quadrant mass, and radiographic evidence of mechanical obstruction.[31] The pathogenesis of this problem is thick stool in the ascending colon and terminal ileum. Complications include complete obstruction, intussusception, and volvulus. The patient may have acute abdominal pain, and this diagnosis needs to be considered along with appendicitis and adnexal problems. The diagnosis can only be made radiographically, and the treatment consists of meglucamine diatrizoate (Gastrografin) enemas. Surgery is only rarely required.

Glucose intolerance is common among adult patients; it may occur in more than 50%. Insulin is only occasionally required, so dietary management should suffice for the pregnant patient.

Other gastrointestinal complications include biliary cirrhosis and focal hepatic lesions that may cause elevation of liver function studies. Portal hypertension can occur. Acute pancreatitis is not uncommon and should be managed conservatively with intravenous fluids and nasogastric intubation; the benefit of cimetidine is unproved, despite its use in the first patient reported here.

The patient with cystic fibrosis who has abdominal pain should be evaluated for pancreatitis, meconium ileus equivalent with either obstruction or intussusception, and cholecystitis in addition to the usual causes of abdominal pain in the pregnant woman.

Labor and Delivery

There appears to be a higher incidence of premature labor in women with cystic fibrosis.[6,11] The use of tocolytic agents does not appear to be contraindicated for pulmonary reasons unless severe cor pulmonale is present, although the wisdom of suppressing labor when hypoxia may be the cause requires careful consideration. The use of steroids to induce fetal pulmonary maturation is controversial under any circumstance. When maternal infection is present, steroid induction of labor should be undertaken with caution, although the short regimens used may not present a problem. The management of labor and delivery is similar to that used with high-risk women with cardiac and pulmonary problems. Respiratory depressants should be avoided. Adequate hydration is essential. The second stage may be shortened with outlet forceps. Epidural anesthesia would be preferable to general anesthesia for either labor or delivery. Cesarean section should be done only for obstetric reasons.

Based on the reported cases, maternal pulmonary decompensation can take place in the puerperium (up to several months), and the patient should be monitored closely during this time.

Prognosis

Until recently, the maternal mortality in reported cases was high.[6] A survy of 119 cystic fibrosis centers reported by Cohen et al[11] adds perspective. One hundred twenty-nine pregnancies were identified; of the 97 completed pregnancies, 86 infants were viable. There were no maternal deaths during pregnancy; however, 15 of 84 women died within the first 6 months post partum. This rate was similar to the expected mortality of nonpregnant patients. The rates of stillbirth (6.2%), neonatal death (5.2%), and prematurity (16.5%) were higher than the control data. One infant had cystic fibrosis (1.2%).

Although this report is encouraging in that the majority of pregnancies resulted in a living infant and

mother, the incidence of pregnancy wastage was high. Also, many of the women who died had exacerbation of infection during pregnancy. This was also true of the present authors' first patient.

The literature suggests that maternal mortality is related to prepregnancy pulmonary status, and it has been suggested that a vital capacity of less than 1 liter places the mother at serious risk. Other ominous signs are extensive emphysema, atelectasis or bronchiectasis, significant cor pumonale, progressive pulmonary hypertension, progressive hypoxia, pulmonary hemorrhage, and pneumothorax. Pregnancy termination should be considered when any of these is present.[6,11]

Summary

It is probable that an increasing number of women with an established diagnosis of cystic fibrosis will become pregnant. In addition, pregnant women with unexplained recurrent respiratory symptoms, including infections, hemoptysis, and asthma-like symptoms, deserve evaluation for this disease. If the chest x-ray is abnormal, sweat chloride testing should be considered, even if the prepregnancy history is not suggestive of cystic fibrosis. Certainly any patient with a family history of cystic fibrosis should be tested. Patients with significant pulmonary compromise or complications should be counseled regarding the risks and offered the option of abortion and/or sterilization.

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