Management of Four Pregnant Women with Multidrug-Resistant Tuberculosis

Annette Tsugie Nitta and Deborah Milligan

From the Tuberculosis Control Program, Public Health Programs and Services, Los Angeles County Department of Health Services, Los Angeles; Harbor-UCLA Medical Center, Torrance; and Saint Mary’s Medical Center, Long Beach, California

This case series describes the medical management of four pregnant women with active multidrug-resistant tuberculosis. None of the four patients were infected with human immunodeficiency virus. Three patients had disease due to multidrug-resistant Mycobacterium tuberculosis, and one had disease due to multidrug-resistant Mycobacterium bovis. Only one patient (patient 3) began retreatment during pregnancy, because her organism was susceptible to three antituberculosis drugs that were considered nontoxic to the fetus. Despite concern over teratogenicity of the second-line antituberculosis medications, careful timing of treatment initiation resulted in clinical cure for the mothers, despite some complications due to chronic tuberculosis and/or therapy. All infants were born healthy and remain free of tuberculosis. Pregnancy and multidrug-resistant tuberculosis need not be a public health disaster, as both conditions can be managed concurrently and successfully.

Tuberculosis in the United States once appeared to be headed toward elimination, since the annual number of new cases steadily declined from 1953 to the mid-1980s. However, the AIDS epidemic, immigration from countries with a high prevalence of tuberculosis, crowding and drug abuse in the inner cities, and dismantling of tuberculosis control programs because of funding cuts contributed to an increased incidence of tuberculosis between 1986 and 1992 [1–3]. This in turn prompted more funding for tuberculosis control programs, and several jurisdictions reported increasing use of directly observed therapy (DOT) [4–6]. These kinds of interventions are credited with the declining number of new cases since 1992.

Interestingly, a review of records of two public hospitals in New York City indicated an increasing case rate of tuberculosis in pregnant women, from 5/40,388 (12.4/100,000) in 1985–1990 to 11/1,595 (94.8/100,000) in 1991–1992 [7]. This increase in tuberculosis among pregnant women occurred during a time when outbreaks of multidrug-resistant (MDR) tuberculosis were occurring [8]. However, the authors could find no reports in the medical literature describing the management of pregnant women with MDR tuberculosis.

Pregnancy complicates treatment of MDR tuberculosis for the following reasons: Several antimycobacterial drugs are contraindicated during gestation, patients and physicians may fear the effects of chest radiography on the fetus, and untreated infectious MDR tuberculosis may be vertically and laterally transmitted [9–11].

This case series describes the management of four pregnant patients with MDR tuberculosis. It illustrates the need to individualize treatments according to each patient’s medical and psychosocial needs.

Methods

The MDR Tuberculosis Unit of the Tuberculosis Control Program in Los Angeles County identifies (usually via laboratory reports) all cases of MDR tuberculosis in its jurisdiction, then investigates and co-manages these cases with their respective health care providers. After its inception in August 1993, the MDR Tuberculosis Unit identified four pregnant women who had MDR tuberculosis. All medical records of the patients were reviewed, and each case was co-managed by the primary care provider in the public health clinic, the public health staff serving the patient’s district of residence, and Tuberculosis Control Program consultants. Investigation of contacts included each patient’s health care providers.

Management options were individualized according to each patient’s medical needs and personal desires. Antituberculosis medications were selected according to the susceptibility pattern and treatment history of each patient, and treatment was initiated when deemed safe for both the mother and fetus. Prenatal care of patients 1–3 was done in negative-pressure respiratory isolation rooms, because their sputa were smear-positive for acid-fast bacilli (AFB). Health care staff for all patients followed the infection-control guidelines described by the Centers for Disease Control and Prevention (CDC) during delivery and the postpartum period of all patients [11]. After delivery, the placentas were examined to investigate the possibility of vertical transmission of tuberculosis. Infants whose mothers were infectious at delivery were separated from their mothers at birth and returned when their mothers were deemed noncontagious. Immunization with bacille Calmette-Guérin (BCG) was given to infants whose mothers were at high risk for treatment failure because of extensive drug resistance, unresectable cavitary pulmonary lesions, or history of failure of...
Table 1. Demographic and susceptibility data for four pregnant women with multidrug-resistant tuberculosis.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (y)</th>
<th>Country of origin</th>
<th>Date of initial diagnosis</th>
<th>Results* of Date of testing (mo/y)¹</th>
<th>Results of susceptibility testing</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Smear/Culture</td>
<td>MIC (µg/mL)</td>
</tr>
<tr>
<td>1</td>
<td>25</td>
<td>Mexico</td>
<td>1982</td>
<td>Consistently positive</td>
<td>9/1987 Resistance: Cyse, 30.0; INH, 5.0; Rif, 10.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Susceptibility: Cpm, 10.0; Emb, 5.0; Ethi, 5.0; Km, 5.0; Stm, 2.0</td>
</tr>
<tr>
<td>2</td>
<td>29</td>
<td>Mexico</td>
<td>1986</td>
<td>Occasionally positive</td>
<td>1/1994 Resistance: Emb, 2.5; INH, 5.0; PAS, 8.0; Rif, 10.0; Stm, 4.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Positive for <em>Mycobacterium</em></td>
<td>Susceptibility: Cpm, 2.5; Cyse, 30.0; Emb, 5.0; Ethi, 2.5; Km, 2.5; Ofx, 1.25; PZA, 100.0; Stm, 10.0</td>
</tr>
<tr>
<td>3</td>
<td>24</td>
<td>United States</td>
<td>1994</td>
<td>Occasionally positive</td>
<td>8/1988 Resistance: INH, 5.0; Rif, 10.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Negative for <em>M. tuberculosis</em></td>
<td>Susceptibility: Cpm, 10.0; Emb, 5.0; Ethi, 5.0; INH, 0.2; Km, 5.0; Rif, 1.0; Stm, 2.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Susceptibility: Emb, 5.0; PZA, 25.0; Rif, 1.0; Stm, 2.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1/1995 Resistance: INH, 5.0; Rif, 10.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Susceptibility: Cpm, 2.5; Cyse, 30.0; Emb, 2.5; Ethi, 2.5; Km, 2.5; Ofx, 1.25; PAS, 8.0; PZA, 100.0; Stm, 2.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>8/1995 Resistance: Emb, 2.5; INH, 0.1; PZA, 100.0; Rif, 1.0; Stm, 2.0</td>
</tr>
</tbody>
</table>

NOTE. Cpm = capreomycin; Cyse = cycloserine; Emb = ethambutol; Ethi = ethionamide; INH = isoniazid; Km = kanamycin; Ofx = ofloxacin; PAS = para-aminosalicylic acid; PZA = pyrazinamide; Rif = rifampin; Stm = streptomycin.

* Sputum samples were obtained at time of delivery or therapeutic abortion.

² Corresponds to initial testing and just before retreatment.

Results

All four patients were HIV-negative, and all had acquired MDR tuberculosis through prior noncompliance with antituberculosis treatment (although a prescribing error may have contributed to resistance in case 3). None of the patients were known to have ever lived in New York City. Demographic data, dates of initial diagnosis of tuberculosis, results of smears and cultures of sputa at the time of delivery, and susceptibility results (initial and just before retreatment) are described in table 1. Patient 2 is remarkable for having cavitary pulmonary disease due to MDR *Mycobacterium bovis*.

All neonates who were carried to term were born healthy, and all placentas were free of microscopic tuberculous lesions. None of the three patients who elected to carry their pregnancy to term chose to breast-feed. No evidence of tuberculosis transmission was found in the patients’ health care providers. Because patients 1 and 2 were considered to be at high risk for treatment failure, their infants were immunized with BCG. Both infants received two doses of BCG vaccine, since the zone of induration on tuberculin skin testing after the first doses remained 0 mm. BCG vaccine was not given to the infant of patient 3 because the patient’s sputa were consistently culture-negative by the time of delivery; her infant’s zone of induration on tuberculin skin testing measured 0 mm at birth and 3 months later. Although the children of patients 1–3 remain healthy, those of patients 1 and 2 received preventive therapy because they both had positive results on tuberculin skin testing >1 year after their mothers became noninfectious. Patient 4 chose to have a therapeutic abortion.

All four patients completed retreatment regimens, and none demonstrated true evidence of relapse during the monitoring...
Patient 1 was a 25-year-old Hispanic woman (three pregnancies, no births, two abortions) who was first diagnosed with tuberculosis in Mexico in 1982. She immigrated to the United States in 1986, was not consistently adherent to antituberculosis treatment, and was diagnosed with cavitary MDR tuberculosis in May 1987. Despite undergoing multiple retreatment attempts over the years with regimens containing isoniazid, rifampin, pyrazinamide, ethambutol, streptomycin, ethionamide, cycloserine, para-aminosalicylic acid, capreomycin, kanamycin, ciprofloxacin, and clofazimine, testing of the patient’s sputum by smear and culture continued to yield positive results, and her organism acquired additional resistance. During multiple prior retreatment courses, the patient broke many clinic appointments, moved without notice, was transiently lost to follow-up, went to Mexico for herbal treatment, and was told she was “cured” by a physician in Mexico. She was found to be pregnant in April 1993, and although she had not completed two prior pregnancies and had contagious MDR tuberculosis, she desired to carry this gestation to term. Antituberculosis treatment was withheld during gestation because her disease was stable (although communicable), and another retreatment regimen would necessitate use of potentially teratogenic drugs. Although patient 1 remained untreated during gestation, she adopted lifestyle changes that were subsequently shown by investigation of contacts to have prevented tuberculosis transmission to her close contacts. Immediately after a normal vaginal delivery in December 1993, the neonate was separated from her mother, whose sputa were positive for MDR tuberculosis by smear and culture. Before being discharged to the care of a relative who had been screened for tuberculosis, the baby was immunized with BCG because her mother was considered to be at high risk for treatment failure. Three months after the second dose of BCG vaccine, the infant’s zone of induration on tuberculin skin testing measured 5 mm.

Patient 1 began receiving treatment with ethambutol, cycloserine, para-aminosalicylic acid, capreomycin, ofloxacin, and clofazimine, all given as DOT. Although smears and cultures of her sputum for AFB yielded negative results in April 1994, patient 1 chose to remain separated from her child until she was convinced she was noninfectious (2 years). In June 1996, patient 1 completed 24 months of retreatment after cultures began yielding negative results, and although she remains cured of MDR tuberculosis, her posttreatment course was complicated. Two months after completing MDR tuberculosis treatment, she was admitted to a hospital for hemoptysis and a new intracavitary density in her left lung. Twelve samples of sputum were collected, and all were negative for AFB by both smear and culture except for one, which demonstrated moderate AFB on smear. The patient was diagnosed with possible relapsed MDR tuberculosis and her prior treatment regimen was restarted; investigation of contacts was repeated. Testing of her immediate and extended family identified no one with tuberculosis, but the size of the zone of reaction to tuberculin skin testing of her child had increased by 10 mm. Although this test result may have been due to boosting of the BCG reaction, the child was given isoniazid preventive therapy because she lives in an area with a relatively high incidence of tuberculosis, and the increased size of the zone of induration met criteria for skin test conversion [12]. The solitary smear-positive sputum sample from patient 1 later yielded drug-susceptible Mycobacterium tuberculosis on culture, and restriction fragment length polymorphism analysis demonstrated a pattern identical to that of another patient who had been concurrently hospitalized. Patient 1 was eventually diagnosed with pulmonary aspergillosis, which responded well to itraconazole. Four months after this episode, patient 1 had spontaneous right pneumothorax, requiring placement of a chest tube. She eventually

<table>
<thead>
<tr>
<th>Patient</th>
<th>Previously used drugs</th>
<th>Treatment</th>
<th>Treatment duration (mo)*</th>
<th>Reason for discontinuing treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>INH, Rif, Emb, PZA, Stm, Clof, Cpx, Cpm, Cyse, Ethi, Km, PAS</td>
<td>Clof, Cpm, Cyse, Emb, Ofx, PAS</td>
<td>24</td>
<td>Completed recommended course of treatment</td>
</tr>
<tr>
<td>2</td>
<td>INH, Rif, Emb, PZA, Stm, Cpm, Ethi</td>
<td>Amik, Cyse, Emb, Ethi, high-dose INH, Ofx, plus right pneumonectomy</td>
<td>24</td>
<td>Completed recommended course of treatment</td>
</tr>
<tr>
<td>3</td>
<td>INH, Rif, PZA</td>
<td>Cpm, Emb, Ethi, Ofx, PZA</td>
<td>17</td>
<td>Newly pregnant near end of treatment</td>
</tr>
<tr>
<td>4</td>
<td>INH, Rif, Emb, PZA</td>
<td>Cpm, Cyse, Emb, high-dose INH, Ofx, PAS</td>
<td>24</td>
<td>Completed recommended course of treatment</td>
</tr>
</tbody>
</table>

NOTE: Amik = amikacin; Clof = clofazimine; Cpx = ciprofloxacin; Cpm = capreomycin; Cyse = cycloserine; Emb = ethambutol; Ethi = ethionamide; INH = isoniazid; Km = kanamycin; Ofx = ofloxacin; PAS = para-aminosalicylic acid; PZA = pyrazinamide; Rif = rifampin; Stm = streptomycin.

* Months after cultures began yielding negative results.
underwent surgical resection of a ruptured right apical cystic lesion, and both she and her child are now well and free of tuberculosis.

Patient 2 was a 29-year-old Hispanic woman (seven pregnancies, one birth, five abortions) who had diabetes mellitus and chronic hepatitis C virus infection and who immigrated to the United States from Mexico in 1970. She was diagnosed with pulmonary drug-susceptible tuberculosis in 1986; at that time she began the first of many self-administered antituberculosis regimens to which she was nonadherent and that were frequently interrupted by trips to Mexico and numerous pregnancies. In 1988, her organism demonstrated new resistance to isoniazid, and by 1991, new resistance to rifampin was also noted despite her receiving DOT. Her organism was later identified as M. bovis. The patient’s prior treatment regimens included isoniazid, rifampin, pyrazinamide, ethambutol, streptomycin, ethionamide, and capreomycin. Because of the frequent interruptions in and nonadherence to her therapy, results of smear and culture testing of the patient’s sputum samples remained positive for M. bovis over the years, and in July 1993 she was found to be in the first trimester of another pregnancy. Retreatment was withheld during the pregnancy to avoid exposing the fetus to potentially teratogenic medications, and the patient received a holding regimen of combination capsules containing rifampin and isoniazid (Rifamate; Marion Merrell Dow, Kansas City, MO) to keep the tuberculosis from progressing [13]. After blood was found in the amniotic fluid on amniocentesis in February 1994, she underwent emergency cesarean section (followed by elective bilateral tubal ligation) and delivered a healthy male infant, who was immediately separated from her because her sputum samples were positive for MDR M. bovis by smear and culture. Before being discharged to the care of a relative who had been screened for tuberculosis, the baby was immunized with BCG, because her mother was considered to be at high risk for treatment failure. Three months after the second BCG dose, the infant’s zone of induration on tuberculin skin testing measured 7 mm.

Patient 2 began retreatment with high-dose isoniazid, ethambutol, ethionamide, cycloserine, amikacin, and ofloxacin immediately after delivery; except for isoniazid, all medications were continued by daily DOT after discharge from the hospital. Three months later (when her sputa were consistently negative for AFB by smear and culture), she returned home to her baby. Patient 2 later underwent right pneumonectomy to remove a completely destroyed right lung that was determined to be a reservoir of drug-resistant organisms. Her postsurgical course was complicated by transient thrombocytopenia and an infected bronchopleural fistula that eventually required creation of an Eloesser flap, but she completed 2 years of retreatment after cultures began yielding negative results and remains free of disease due to relapse. Unfortunately, in 1996, her child was identified as a close contact of an uncle who acquired rifampin-resistant cavitary pulmonary M. bovis because of nonadherence to prior preventive therapy. The child’s tuberculin skin test zone (previously 7 mm) now measured 15 mm, and while the increased size may have been due to boosting of the BCG reaction, the child was given isoniazid preventive therapy, since close contact with a highly infectious case placed him at high risk for recent infection. Patient 2 and her child remain free of tuberculosis to date.

Patient 3 was a 24-year-old Hispanic woman (two pregnancies, one birth, no abortions) who was born in California but who recalled being exposed to tuberculosis in Mexico. She was first diagnosed with cavitary pulmonary tuberculosis resistant to isoniazid in early 1994, at which time she was treated with a self-administered regimen of isoniazid, rifampin, and pyrazinamide. She was found to be pregnant in November 1994 and was allowed to continue self-administered medications despite indications of nonadherence (e.g., frequently missed clinic appointments). By January 1995, her organism had acquired resistance to both isoniazid and rifampin, and her sputa were positive by both smear and culture. A new regimen of ethambutol, pyrazinamide, and ethionamide was begun, all given by daily DOT. Ethambutol was recommended because it is safe for use in pregnancy, and pyrazinamide and ethionamide were used because there are no data indicating that they are teratogenic [14]. Cultures of sputum yielded negative results in April 1995 and continue to be negative to date. However, because sputum collected in June 1995 was positive for AFB by smear (although later found to be negative by culture), she was considered infectious during delivery. Thus, immediately after being delivered by normal vaginal delivery in July 1995, the baby girl was separated from her mother and began receiving a preventive regimen of pyrazinamide and ethambutol. The baby was discharged home with her mother, because three sputum samples after delivery from patient 3 yielded negative results by smear. Preventive therapy was discontinued ~3 months later when results of repeat tuberculin skin testing of the infant were negative. Capreomycin and ofloxacin were added to the patient’s retreatment regimen in the immediate postpartum period, and she was repeatedly counseled on the importance of avoiding pregnancy while receiving the new retreatment regimen. Antituberculosis medications were discontinued in September 1996 (~17 months after cultures began yielding negative results) because the patient became pregnant again. She delivered a healthy male baby in March 1997, despite having been receiving a quinolone-containing regimen during the first trimester. She and her children remain healthy to date.

Patient 4 was a 30-year-old homeless black woman (three pregnancies, one birth, one abortion) who had a history of abusing alcohol and crack cocaine. She was diagnosed with cavitary pulmonary tuberculosis susceptible to drugs in March 1994 but was nonadherent to a self-administered regimen of isoniazid, rifampin, pyrazinamide, and ethambutol. Treatment was interrupted by her frequent moving and many broken appointments. Her organism developed resistance to isoniazid by August 1994, and although she began receiving DOT in November 1994, she was lost to follow-up soon thereafter. Her
sputa remained positive by culture despite treatment in jail from March to August 1995, and she was treated with rifampin, ethambutol, and pyrazinamide given by DOT after her release. Susceptibility testing on an organism obtained by culture of a sputum sample collected in late August 1995 demonstrated resistance to isoniazid and new resistance to rifampin, but her regimen was not changed because of a newly diagnosed pregnancy. She repeatedly stated her desire for a therapeutic abortion, which was done in November 1995, and she was thereafter treated with high-dose isoniazid, pyrazinamide, ethambutol, cycloserine, ofloxacin, and capreomycin, all given by daily DOT. She completed 24 months of retreatment after cultures began yielding negative results, and she remains disease-free. Unfortunately, she refused drug rehabilitation services.

Discussion

Even after the advent of chemotherapy for tuberculosis, the medical community disagreed on the bidirectional effects of tuberculosis and pregnancy [15]. Therapeutic abortions were once recommended for women with tuberculosis, as pregnancy was thought to be deleterious to the disease course. Studies have since indicated that the effect of pregnancy on tuberculosis is minimal, if any. However, tuberculosis has potentially negative effects on pregnancy, including possible hematogenous spread through the umbilical vein, spread to the reproductive tract, and postpartum transmission to the infant and other close contacts [16]. Thus, it is currently recommended that pregnant women be treated for tuberculosis with nonteratogenic drugs such as isoniazid, rifampin, and ethambutol [12, 17].

This case series illustrates the factors that contribute to the acquisition of MDR tuberculosis and the unique challenges presented by pregnancy and MDR tuberculosis. Factors contributing to the development of MDR tuberculosis include failure of prior health care providers to give DOT and prescription of an inadequate treatment regimen. Management issues raised by these patients and their infants include the following: the teratogenic risks of second-line tuberculosis medications, the use of holding regimens consisting of isoniazid and/or rifampin, the timing of treatment initiation, risks of vertical and lateral transmission of MDR tuberculosis, BCG immunization of the infants, and posttreatment complications due to pulmonary MDR tuberculosis.

The tuberculosis organisms of the four patients in this series apparently acquired multidrug resistance because of the patients’ prior nonadherence to self-administered antituberculosis regimens. In fact, in the majority of cases of MDR tuberculosis in Los Angeles County, the organisms have acquired multidrug resistance through the patients’ nonadherence to prior treatment regimens prescribed here or abroad [18]. Thus, DOT is vital for treatment of MDR tuberculosis and prevention of its development (especially in patients who have demonstrated prior noncompliance or whose organisms are already resistant to either isoniazid or rifampin). The role of physician error in the development of multidrug resistance is illustrated by case 3.

In 1994, the patient was diagnosed with isoniazid-resistant tuberculosis and treated with isoniazid, rifampin, and pyrazinamide. Isoniazid was probably ineffective since her organism was resistant to it, and pyrazinamide (a poor companion drug) does not prevent the emergence of resistance to the effective agent [19]. If the treating physician in 1994 had not relied on rifampin and pyrazinamide to treat isoniazid-resistant tuberculosis, patient 3 may not have developed MDR tuberculosis.

The treatment of most cases of MDR tuberculosis requires the use of second-line antituberculosis drugs that are generally less effective but more toxic than first-line drugs, and treatment regimens for MDR tuberculosis must be individualized according to the susceptibility pattern of the patient’s pathogen [20]. The potential teratogenicity of the second-line drugs complicates the treatment of pregnant patients with MDR tuberculosis, for whom the risks of no treatment (including vertical and lateral transmission of tuberculosis), timing of initiation of treatment, and treatment risks must be carefully weighed. Patients must be fully informed of their therapeutic options and must be actively involved in decision making.

The treatment of each case in this series was individualized accordingly. Patient 1 was not given any antituberculosis medications during pregnancy because her disease had not been suppressed by an isoniazid holding regimen over the 2 years preceding gestation, and most of her retreatment drugs were teratogenic. Serial susceptibility testing had shown her organism to be either resistant to ethambutol at only the lowest level tested or fully susceptible; therefore, ethambutol was included in the retreatment regimen of patient 1. During gestation, patient 2 received combination medication containing both isoniazid and rifampin because both are safe during pregnancy [17], and she had previously experienced bacteriologic suppression while receiving these drugs. Although susceptibility testing of an organism obtained by culture of sputum collected during gestation had shown isoniazid resistance at the highest level tested, prior serial susceptibility testing of isolates from patient 2 had shown either low-level isoniazid resistance or full susceptibility; therefore, high-dose isoniazid was initially used to retreat patient 2. Patient 3 was unique in that she began retreatment during gestation. She began to receive pyrazinamide, ethambutol, and ethionamide during her second trimester because ethambutol is considered safe for pregnant women [12, 17], and there are no data indicating that the other two drugs are teratogenic [14]. Her neonate is, in fact, healthy. For personal reasons, patient 4 repeatedly requested therapeutic abortion, which was done; it is important to note that the abortion was not done to manage her MDR tuberculosis. Ethambutol was used to treat patient 4 because susceptibility testing of an organism obtained by culture of sputum collected during her first trimester had shown only borderline resistance to that drug at the lowest level tested. On termination of their pregnancies, all four patients were given complete retreatment regimens by daily DOT to assure adherence to treatment and prevent development of additional drug resistance.
Patients 1–3 were considered infectious during delivery, since all had had recent sputa demonstrating AFB on smears. During the perinatal period, adherence to the infection-control guidelines described by the CDC [11] was successful in preventing perinatal aerosol transmission of MDR tuberculosis to the health care workers and neonates. It is important to note that one of the key components of preventing transmission was communication of specific infection-control procedures to all members of the patient care team, including obstetricians, anesthesiologists, pediatricians, and nurses in the labor and delivery rooms and on the ward. All housestaff and attending physicians on rotation during the patients’ confinement periods were notified of the management needs of each patient, since any one of several teams was likely to be on call on the delivery date. Ongoing tuberculosis screening of the health care workers and follow-up testing after their involvement with the patients with MDR tuberculosis were important administrative components of the infection-control plan, as it was then possible to determine whether tuberculosis transmission had occurred.

The neonates of patients 1 and 2 were immunized with BCG according to CDC guidelines because it was initially unclear whether retreatment would render their mothers noncontagious [21]. Although BCG may be effective in preventing tuberculosis infection from progressing to potentially fatal tuberculosis in neonates, its overall efficacy was estimated to be 50% [22]. BCG may result in tuberculin reactivity, making it difficult to determine whether a positive skin test result of a vaccine recipient is due to tuberculosis infection or to a booster response [21]. The benefits of BCG must therefore be balanced against the risks of compromising the utility of future tuberculin skin testing as a surveillance tool. Although there was no evidence of peripartum transmission of MDR tuberculosis to either the neonates or health care workers, the child of patient 1 had a positive tuberculin skin testing result (after previous negative results) long after the patient became noncontagious, and the child of patient 2 was subsequently exposed to another household member who, because of nonadherence to prior preventive therapy, progressed to cavitary smear-positive tuberculosis. Booster reactions could not be completely ruled out, because the infants of patients 1 and 2 had been immunized with BCG. However, the increase in the size of subsequent tuberculin skin test results indicated possible tuberculosis transmission, supported by epidemiologic evidence in the infant of patient 2. Additionally, the firstborn of patient 3 had a positive tuberculin skin test result after previous negative ones before the birth of the patient’s second child. These cases emphasize the high risk of tuberculosis transmission in certain populations and the need for education and heightened surveillance in these groups.

Posttreatment complications resulting from long-standing pulmonary MDR tuberculosis or treatment deserve comment. After completing 24 months of retreatment after cultures began yielding negative results, patient 1 had hemoptysis that was initially attributed to relapsed MDR tuberculosis, since a sputum smear was positive for AFB. The patient again began receiving her prior retreatment regimen, and she had considerable anxiety and depression because of concern that she had relapsed with MDR tuberculosis. Investigation of contacts was repeated. However, restriction fragment length polymorphism analysis proved that the single specimen collected from patient 1 during hospitalization for hemoptysis that was positive by smear and culture had a pattern identical to that of an organism from another patient. The specimen of patient 1 was probably mislabeled after collection on the ward, and this incident demonstrates the negative therapeutic impact of accepting laboratory-related data per se [23]. Four months later, patient 1 had a spontaneous right pneumothorax that eventually resolved after surgical resection of a ruptured right apical bleb. Her course demonstrates the complications of chronic cavitary tuberculosis, which include pneumothorax (possibly due to erosion of a cavitary lesion connecting the tracheobronchial tree with the pleural space), bleb formation (due to air trapping in an acinus or subsegment), empyema (due to rupture of an infected cavity or bleb into the pleural space), bronchiectasis, hemoptysis, and superinfection of the cavitary lesion [24]. Some of these complications may occur even after the tuberculosis has been successfully treated.

Medical and surgical therapies for MDR tuberculosis can also cause complications. Patient 1 developed hearing impairment after receiving streptomycin, kanamycin, and capreomycin during prior failed retreatment regimens. Although many antituberculosis medications can cause adverse effects that may be irreversible, only patient 1 had permanent treatment-related end-organ damage. Patient 2 underwent right pneumonectomy to remove a lung destroyed by chronic tuberculosis; she subsequently developed an infected bronchopleural fistula, requiring creation of an Eloesser flap. Clearly, MDR tuberculosis treatment courses are seldom uncomplicated and benign.

Finally, these cases emphasize the need for health care providers to remember that pregnancy is always a possibility for women in their reproductive years. Prior treatment courses of both patients 1 and 2 were interrupted because of intercurrent pregnancies, and patient 3 had two pregnancies while being treated for MDR tuberculosis despite repeated counseling to use contraception diligently during this time. Each of our patients acquired multidrug resistance from prior nonadherence to treatment, and this pattern of behavior may indicate a higher risk of failure to use contraception regularly. Thus, pregnant patients with acquired MDR tuberculosis must be counseled about the teratogenic risks of some antituberculosis drugs, and repeated counseling and assistance with obtaining contraception are indicated, even after a current pregnancy ends and retreatment with potentially toxic drugs begins.

In conclusion, pregnancy complicates the management of concurrent MDR tuberculosis, since the decision to treat must take into account the risks of vertical and lateral tuberculosis transmission, disease progression, and adverse drug effects. However, this case series demonstrates that MDR tuberculosis in pregnancy can be successfully and safely managed. Such
management requires individualization of therapy, careful timing of treatment initiation, thoughtful counseling of the patient so that she can make completely informed decisions, careful communication to all health care workers who will provide care to the patient and her infant, and implementation of infection-control measures.

Acknowledgments

The authors are indebted to Paul T. Davidson, M.D., for reviewing this manuscript, and to Muriel de Koning, R.N., Patricia Kuykendall, R.N., Carol Salminen, R.N., and Harriet Pitt, R.N., for their assistance in collecting data for this report.

References