Treatment of Multidrug-Resistant Tuberculosis during Pregnancy: A Report of 7 Cases

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Multidrug-resistant tuberculosis (MDR-TB) is a global public health problem affecting women of childbearing age. Little is known, however, about the safety of the drugs used to treat MDR-TB during pregnancy. We describe 7 patients who were treated for MDR-TB during pregnancy. These patients had chronic tuberculosis that had caused extensive parenchymal damage and had high-grade resistance to antituberculous drugs. All patients received individualized antituberculous therapy prior to delivery of healthy term infants. Neither obstetrical complications nor perinatal transmission of MDR-TB was observed. One patient experienced treatment failure, and another abandoned therapy. The other 5 patients are currently cured or in treatment and have culture-negative status. In each of these 7 cases, excellent treatment outcomes were obtained for the women and their children. Under certain circumstances, MDR-TB can be successfully treated during pregnancy.

Multidrug-resistant tuberculosis (MDR-TB)—defined as disease due to strains of Mycobacterium tuberculosis with resistance to isoniazid and rifampin—is a global health crisis that affects women in their reproductive years [1]. MDR-TB requires more-aggressive treatment than does its pan-susceptible counterpart, with multidrug therapy that includes second-line agents. Compared with first-line drugs (isoniazid, rifampin, ethambutol, pyrazinamide, and streptomycin), the second-line agents are considered less effective and more toxic [2]. Little is known about the safety of second-line drugs during pregnancy. Untreated tuberculosis, however, has been associated with higher morbidity and mortality among pregnant women [3]. Given the risks of disease progression and transmission to the newborn, treatment of tuberculosis is often pursued during pregnancy [4]. Here we report 7 cases of MDR-TB that were treated with second-line drugs during pregnancy.

METHODS

A retrospective review of all 905 patients with confirmed or suspected MDR-TB was done. All patients began receiving individualized treatment regimens (ITRs) based on drug-resistance patterns between August 1996 and July 2003. Inclusion criteria for this case series were patients who had documented MDR-TB (i.e., an infecting strain resistant to at least isoniazid and rifampin), were pregnant at any time while receiving an ITR, and chose not to terminate the pregnancy. Two patients who still were pregnant at the time of review (August 2002) were excluded because the outcome of the pregnancy could not be assessed. In addition, routine inquiry was not conducted regarding therapeutic or spontaneous abortions, thus possibly contributing to an underestimate of adverse pregnancy outcomes.

Patient treatment protocol, principles for individ-
ualized regimen design, and the methods used for sputum smear analysis, identification of *M. tuberculosis*, culture, and drug susceptibility testing are described elsewhere [5, 6]. Of note, initially we did not routinely screen for the presence of β-human chorionic gonadotropin for all women of childbearing age; however, within the first year, we incorporated this test into our baseline laboratory tests. Informed consent was obtained from all patients, according to the institutional review board guidelines approved by the Harvard Medical School (Boston, MA).

**RESULTS**

Among the 905 cases reviewed, 356 (39%) were in females; of these, 285 (80%) were of childbearing age, that is, between 15 and 44 years old. We identified 7 cases of MDR-TB during pregnancy (table 1). The median age of these patients was 21 years. The median time of tuberculosis illness was 4 years prior to initiation of the ITR. Five (71%) of 7 were infected with isolates resistant to >4 drugs; all were resistant to at least 4 first-line drugs. Patients generally had advanced, chronic disease. Four of the patients had severe radiographic findings (i.e., both cavitary and bilateral disease), and 4 of the patients had advanced clinical disease (i.e., constitutional symptoms, massive hemoptysis, and/or initial weight of <50 kg). With the exception of 1 patient who experienced treatment failure and became pregnant during year 3 of her ITR, all other patients promptly achieved smear and culture conversion (median time to culture conversion, 2 months). Three patients reported gastrointestinal intolerance related to the ITR, and 1 patient experienced hypokalemia; however, no serious adverse reactions to antituberculous therapy were observed in this group.

Although 2 patients were determined to be pregnant before initiation of an ITR, 5 others were found to be pregnant during treatment (having received a median of 10 months of ITR at the time pregnancy was identified). Pregnancy was diagnosed at a median of 14 weeks' gestation. Of the 5 patients who were receiving ITR when they were found to be pregnant, 4 were receiving parenteral therapy and 3 were receiving prothionamide or ethionamide. In 3 cases, the ITR was suspended until discussions among the patient, caregivers, and family led to a decision regarding further treatment. Aside from the woman who was undergoing treatment failure at the time of her pregnancy, modifications were made for all other patients once pregnancy was diagnosed. For 2 patients, ethionamide-prothionamide was stopped. For 2 patients who had already received therapy for >8 months, the parenteral agent was discontinued.

For the 2 patients who were known to be pregnant before initiation of their ITR, both were in their first trimester at the time of referral, and both were clinically stable. Therefore, initiation of treatment for MDR-TB was deferred until drug susceptibility testing results were available and the pregnancy was safely into the second trimester. One patient initiated treatment with streptomycin and para-aminosalicylic acid (PAS), whereas the other patient received rifampin (on the basis of discrepant drug susceptibility testing data), pyrazinamide, ofloxacin, PAS, and amoxicillin-clavulanic acid (table 2).

All patients received prenatal care. All babies were delivered at term. All mothers, with the exception of patient 1, were culture-negative at the time of delivery. There were no obstet-

<table>
<thead>
<tr>
<th>Characteristics at ITR initiation</th>
<th>Drugs to which isolate was resistant</th>
<th>Severe CXR findings</th>
<th>Severe symptoms</th>
<th>Time to culture conversion, months</th>
<th>Gestational age at time pregnancy diagnosed, weeks</th>
<th>Adverse reactions due to ITR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>INH, Rif, Eth, PZA, Stm, Km, Tha, Cm</td>
<td>No</td>
<td>Yes</td>
<td>—</td>
<td>19</td>
<td>GI</td>
</tr>
<tr>
<td>Patient 2</td>
<td>INH, Rif, Eth, PZA, Tha</td>
<td>No</td>
<td>Yes</td>
<td>2</td>
<td>&lt;12</td>
<td>None</td>
</tr>
<tr>
<td>Patient 3</td>
<td>INH, Rif, Eth, PZA, Stm</td>
<td>Yes</td>
<td>No</td>
<td>1</td>
<td>14</td>
<td>None</td>
</tr>
<tr>
<td>Patient 4</td>
<td>INH, Rif, Eth, PZA, Stm</td>
<td>No</td>
<td>No</td>
<td>3</td>
<td>20</td>
<td>GI</td>
</tr>
<tr>
<td>Patient 5</td>
<td>INH, Rif, Eth, Stm</td>
<td>Yes</td>
<td>Yes</td>
<td>2</td>
<td>8</td>
<td>None</td>
</tr>
<tr>
<td>Patient 6</td>
<td>INH, Rif, Eth, PZA, Stm, Tha</td>
<td>Yes</td>
<td>Yes</td>
<td>2</td>
<td>12</td>
<td>None</td>
</tr>
<tr>
<td>Patient 7</td>
<td>INH, Rif, Eth, Stm</td>
<td>Yes</td>
<td>No</td>
<td>1</td>
<td>14</td>
<td>GI, hypokalemia</td>
</tr>
</tbody>
</table>

**NOTE.** Cm, capreomycin; CXR, chest radiograph; Eth, ethambutol; INH, isoniazid; Km, kanamycin; PZA, pyrazinamide; Rif, rifampin; Stm, streptomycin; Tha, ethionamide; GI, gastrointestinal.

a Isolates were tested for resistance to Eth, INH, Rif, PZA, Stm, Km, Cm, and Tha, as well as ciprofloxacin and cycloserine. All isolates were resistant to >4 drugs.

b Cavitary and bilateral lesions.

c Fever, weight loss, night sweats, massive hemoptysis, and/or initial weight of <50 kg.

d Treatment failed for this patient.
Table 2. Summary of individualized treatment regimens (ITRs) used to manage multidrug-resistant tuberculosis in pregnant patients.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Duration, months</th>
<th>Regimen</th>
<th>Prepartum Changes in ITR</th>
<th>Postpartum Changes in ITR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>36</td>
<td>Amik, Eth, Spfx, Cs, PAS, Cfz, Amox-CA</td>
<td>None</td>
<td>Failure of ITR</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>INH, Rif, Eth, PZA</td>
<td>Sm and PAS added at month 8 of pregnancy</td>
<td>Failure of first-line therapy</td>
</tr>
<tr>
<td>3</td>
<td>16</td>
<td>INH, Rif, Cpfx, Tha, Cs, Amox-CA</td>
<td>Decreased Cs dosage and stopped Tha</td>
<td>Clinically doing well</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>Cm, Ofx, Tha, Cs, PAS, Cfz, Amox-CA</td>
<td>Suspended treatment for 1 week at diagnosis, then administered Cm, INH, Eth, Ofx, Tha, Cs, and PAS</td>
<td>Drug susceptibility test results</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>INH, Rif, Eth, PZA</td>
<td>Rif, PZA, Ofx, PAS, Amox-CA initiated at month 4 of pregnancy</td>
<td>Failure of first-line therapy; progression of symptoms</td>
</tr>
<tr>
<td>6</td>
<td>10</td>
<td>Km, Cpfx, Cs, PAS, Cfz, Amox-CA</td>
<td>Suspended treatment for 1 week at diagnosis, then administered Cpfx, Cs, PAS, and Amox-CA</td>
<td>Clinically doing well</td>
</tr>
<tr>
<td>7</td>
<td>9</td>
<td>Cm, PZA, Cpfx, PTH, Cs, Amox-CA</td>
<td>Suspended treatment for 3 weeks at diagnosis, then administered PZA, Cpfx, Cs, and Amox-CA</td>
<td>Clinically doing well</td>
</tr>
</tbody>
</table>

NOTE. Amik, amikacin; Amox-CA, amoxicillin-clavulanic acid; Cfz, clofazimine; Cm, capreomycin; Cpfx, ciprofloxacin; Cs, cycloserine; Eth, ethambutol; Km, kanamycin; Ofx, ofloxacin; PAS, para-aminosalicylic acid; PTH, prothionamide; PZA, pyrazinamide; Rif, rifampin; Spfx, sparfloxacin; Strm, streptomycin; Tha, ethionamide.

rival, congenital, or neonatal complications in this group, nor were any spontaneous abortions observed in this group. As of January 2003, the children are now, on average, 2.7 years old, ranging from 1.2 months to 5.4 years old. No developmental or physical defects have been observed in these children. None of these infants has ever had evidence of *M. tuberculosis* infection or active disease (table 3).

Postpartum, regimens were adjusted in 3 cases (parenteral drugs were added in 2 cases, ethionamide in 2). One patient abandoned therapy after her delivery but continues to be asymptomatic and culture-negative. Another patient had treatment failure (persisting culture-positive despite treatment for >3 years); she died postoperatively because of respiratory failure following a right upper lobectomy.

**DISCUSSION**

Although much literature exists regarding the teratogenicity of first-line antituberculous drugs, experience with second-line drugs during pregnancy is poorly described. Yet a historical review of the literature regarding first-line antituberculous drugs reveals many of the same concerns currently held regarding the use of second-line drugs during pregnancy [7]. Although therapeutic abortions were previously recommended for pregnant patients with tuberculosis, this practice fell out of favor once there was greater familiarity with the use of first-line tuberculosis drugs during pregnancy [3]. Currently, pregnant women with MDR-TB are often counseled to consider pregnancy termination [8]. In large part, this practice is motivated by concern for potential toxicities of second-line antituberculous drugs.

Similarly, the stance toward the safety of first-line drugs during pregnancy has shifted over the years. Because reassuring experience has been gained, most experts now advocate the use of isoniazid, rifampin, ethambutol, and pyrazinamide in pregnancy, [3, 4, 9–11], even though some authors continue to caution against the use of pyrazinamide and/or ethambutol because insufficient information is available [12–15]. However, overall, almost all authors recommend some form of aggressive treatment of active tuberculosis, given that the benefit of treatment likely outweighs the risk of fetal damage, even in the case of drugs that may have some toxicity associated with in utero exposure [13].

In the case of MDR-TB, the same considerations must be made. It is not known if rates of teratogenicity associated with second-line drugs are greater than those associated with first-line drugs. In fact, large-scale experience with second-line drugs is still absent. Thus, insufficiency of data rather than compelling evidence of toxicity causes physicians to err on the side of caution and, at times, to undertreat pregnant patients who have MDR-TB [16].

Yet the reasons to treat these patients are equally, if not more, compelling. Adequate treatment decreases morbidity in both mothers and infants in cases of tuberculosis associated with gestation. In a cohort of 25 patients in Mexico City, women who initiated treatment late during pregnancy (i.e., during or after the second trimester) had higher rates of obstetrical complications, preterm labor, and neonatal complications than did...
Table 3. Summary of pregnancy and treatment outcome for patients with multidrug-resistant tuberculosis.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Received prenatal care</th>
<th>Complications during pregnancy</th>
<th>Current age of baby, years&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Outcome&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Yes</td>
<td>None</td>
<td>2.5</td>
<td>Healthy; Treatment failure; died postoperatively after right upper lobectomy</td>
</tr>
<tr>
<td>2</td>
<td>Yes</td>
<td>None</td>
<td>5.4</td>
<td>Healthy; Cured in 1999; culture-negative to date</td>
</tr>
<tr>
<td>3</td>
<td>Yes</td>
<td>None</td>
<td>2.9</td>
<td>Healthy; Cured in 1999; culture-negative to date</td>
</tr>
<tr>
<td>4</td>
<td>Yes</td>
<td>None</td>
<td>3.5</td>
<td>Healthy; Cured in 2000; culture-negative to date</td>
</tr>
<tr>
<td>5</td>
<td>Yes</td>
<td>None</td>
<td>3.6</td>
<td>Healthy; Abandoned therapy in month 8, in 1999; culture-negative to date</td>
</tr>
<tr>
<td>6</td>
<td>Yes</td>
<td>None</td>
<td>0.5</td>
<td>Healthy; Receiving treatment, culture-negative in month 22</td>
</tr>
<tr>
<td>7</td>
<td>Yes</td>
<td>None</td>
<td>0.1</td>
<td>Healthy; Receiving treatment, culture-negative in month 16</td>
</tr>
</tbody>
</table>

<sup>a</sup> As of January 2003.

either women who received treatment early or noninfected pregnant control subjects [17]. Thus, in this cohort, withholding treatment during the first trimester, although minimizing toxic exposure to the fetus, nonetheless resulted in higher rates of complications for both the fetus and mother.

Among patients with drug-resistant tuberculosis, pregnancy is associated with even worse outcomes for both the mother and infant [8]. In a cohort from National Jewish Hospital (Denver, CO) of 27 patients who received treatment for tuberculosis during pregnancy, 16 patients had drug-resistant disease. There were more adverse outcomes among children born to patients infected with drug-resistant strains than there were among children born to patients infected with drug-susceptible strains (6 of 16 cases vs. 2 of 11). Complications among the neonates included 3 cases of active disease, 2 instances of positive TB skin test results, and a spontaneous abortion in the drug-resistant group versus 1 spontaneous abortion and 1 case of active tuberculosis among those born to drug-susceptible cases.

Therefore, the risk of postpartum transmission of tuberculosis to the baby may be higher among those born to patients with drug-resistant tuberculosis, mainly because culture conversion is slower to achieve in cases of MDR-TB. Given the high mortality associated with congenital and perinatal tuberculosis, as well as challenges in treating pediatric cases of MDR-TB, aggressive treatment of pregnant women is an important preventative measure for vertical transmission [13, 18–20].

In one of the few publications describing cases of pregnancy and MDR-TB, Nitta and Milligan [21] report on 3 pregnant patients with MDR <i>M. tuberculosis</i> infection (and 1 patient with <i>Mycobacterium bovis</i> infection). Although the management of each patient was individualized, the general approach was to avoid second-line drugs until after delivery whenever possible. One patient remained separated from her child for 2 years after delivery until completion of MDR-TB therapy; she had sequelae of chronic tuberculosis with hemoptysis and pulmonary aspergillosis. The second patient received treatment during her pregnancy, with transient culture conversion, but had positive results of smear testing at the time of delivery, necessitating chemoprophylaxis with ethambutol and pyrazinamide for the child. The mother subsequently received a second course of treatment with second-line drugs but became pregnant again during this course of treatment. The second child was healthy and the mother had shown no evidence of relapse at the time when Nitta and Milligan wrote their report [21]. The third patient received MDR-TB treatment and opted for a therapeutic abortion. For 1 of the children, the size of the tuberculin skin test induration increased by 10 mm at ~2 years of age. Although none of these women experienced seriously adverse outcomes, 1 patient experienced a sequela of chronic cavitary tuberculosis, and another patient continued to have active disease, ultimately exposing her subsequent child to second-line antituberculous therapy in the first trimester. In all 3 cases of MDR-TB, serial drug susceptibility testing revealed an increase in the level of resistance. In addition, it is possible that 1 child may have become infected with his mother’s strain of <i>M. tuberculosis</i>, despite precautions to minimize transmission.

Greater risks of obstetrical and tuberculosis-related complications for the mother and the risk of vertical and postpartum transmission are the strongest incentives for prompt and appropriate treatment of pregnant patients who have MDR-TB. Many authors recognize the need to weigh these risks and benefits individually and advocate treatment with careful selection of drugs according to drug susceptibility profiles [4, 12, 21, 22]. As Good et al. [8] state, “it is mandatory to administer appropriate chemotherapy to a pregnant woman with tuberculosis in order to prevent progressive tissue injury, to prevent disseminated disease in the mother, and to reduce the possibility of infecting the neonate” (p. 496).
In terms of individual second-line drugs, a variable degree of information is available on their use during pregnancy. In addition to first- and second-line agents, several drugs that are observed to have in vitro efficacy against *M. tuberculosis*—clofazimine, clarithromycin, and amoxicillin-clavulanic acid—are included in this review.

The association of streptomycin with ototoxicity from in utero exposure has been extrapolated to apply to all aminoglycosides, as well as capreomycin. Kanamycin has not been associated with teratogenic effects in animal studies, although dose-related nephrotoxicity in rat fetuses exposed to kanamycin has been observed [23]. In human studies, no toxic effects have been reported aside from hearing loss. Although there are no reports of amikacin-associated fetal damage, the potential for ototoxicity must be assumed [23]. Notably, amikacin is reportedly less ototoxic among adults than is kanamycin [24].

Capreomycin shares a similar toxicity profile with the aminoglycosides. However, aside from reports of “wavy ribs” in rats and increased birth defects in amphibian embryos [25, 26], no other studies are available. In adults, rates of ototoxicity with capreomycin are lower than those observed with kanamycin and no greater than rates observed with streptomycin [27, 28].

Use of ethionamide and prothionamide during pregnancy remains controversial. In rodents, high doses of ethionamide have been associated with growth retardation, abortions, and malformations, including CNS defects [29–32]. In human studies, 2 reports reviewing 47 cases failed to observe deleterious effects of ethionamide [33, 34]. On the other hand, Potworowski et al. [35] encountered congenital malformations in 7 of 23 children exposed to ethionamide. Of note, 2 of these infants had Down syndrome; in addition, there was no consistency in the defects observed (which included congenital heart defects, spina bifida, and gastrointestinal atresia). Schardein [36], citing ~70 case reports, found no other reported teratogenic effects. Many authors still recommend withholding its use [37, 38], although some recognize the need to use this drug if the risk of active disease outweighs potential risks to the fetus [39].

PAS has not been convincingly associated with congenital defects [40–42]. Varpela [43] observed congenital anomalies in 9.8% of infants of 123 mothers receiving multidrug therapy (isoniazid, streptomycin, and PAS), compared with 3.6% of infants born to mothers patients not receiving treatment; whether these defects (including limb and ear abnormalities) were associated with PAS is unclear. In addition, the Collaborative Perinatal Project described 43 women who were exposed to PAS during the first trimester [44]. Five congenital defects were observed among exposed infants. This incidence of 11.6% was noted to be twice the baseline incidence of anomalies, although no specific class of defects was observed. Nonetheless, Good et al. [8] believe that PAS is one of the safer antituberculous drugs for use during pregnancy.

As for cycloserine, little experience is available to exonerate it of having teratogenic effects. Although cycloserine does cross the placenta, anecdotal data are reassuring [45, 46].

The safety of short-term fluoroquinolone use during pregnancy appears to be established. Although results of animal studies are conflicting [47, 48], human experience with fluoroquinolones during pregnancy is reassuring. Several studies have found no evidence of congenital defects, spontaneous abortions, fetal deaths, prematurity, or intrauterine growth retardation associated with the use of fluoroquinolones during pregnancy, although exposure duration is often short (5–10 days) [49–52]. Of note, in no study was there an association with fluoroquinolone use and musculoskeletal defects. Although such experience is reassuring, the safety of long-term quinolone use during pregnancy, as in the case of tuberculosis, has not been established. In addition, data about newer-generation fluoroquinolones, such as moxifloxacin and gatifloxacin, are still scarce [23].

There are almost no animal or human data regarding the safety of thiacetazone during pregnancy. The cohort described by Marcus [41] included several patients who received thiacetazone during pregnancy without apparent harm.

Clofazimine, although known to cross the placenta, has not been associated with teratogenic effects in animal studies [53]. A case report by Farb et al. [54] describes 2 leprosy patients successfully treated during pregnancy without harm to the fetus. In a review of the available literature, Holdiness [55] finds no teratogenic effects associated with clofazimine, although he does describe 3 neonatal deaths reported among 13 pregnancies involving clofazimine exposure. Whether the deaths were associated with clofazimine use is unclear. Of note, infants may acquire a bronze skin color from exposure to clofazimine either in utero or through maternal milk [23].

Both animal and human studies suggest that clarithromycin may be associated with adverse fetal outcome from in utero exposure. Congenital abnormalities and fetal loss have been observed in high-dose exposure in animal studies [56]. The largest human experience observed significantly higher rates of spontaneous abortions (14% vs. 7%) among 157 pregnant patients who received clarithromycin compared with a matched control group [57]. On the other hand, Drinkard et al. [58] found no significant difference in major congenital anomalies among 149 children born to 143 women receiving clarithromycin during their first trimester.

Amoxicillin and clavulanic acid are safe during pregnancy [59, 60]. Experience with long-term exposure is less extensive, but the well-established use of β-lactams and β-lactamase inhibitors during pregnancy is highly reassuring.

In terms of breast-feeding, most authors recommend breast-
<table>
<thead>
<tr>
<th>Drug</th>
<th>Teratogenic effects in humans</th>
<th>Comments</th>
<th>Safe during pregnancy</th>
<th>Compatible with breastfeeding</th>
<th>Concentration in breast milk, % range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>Not likely [42, 65]</td>
<td>Crosses placenta; few reports of myelomeningocele and encephalopathy; pyridoxine should be used with isoniazid during pregnancy [67]; Yes; nursing infants reported to have seizures that responded to pyridoxine [68]; neonates with glucose-6-phosphate dehydrogenase deficiency may have sensitivity (hemolysis) to isoniazid [69]; recommend vitamin B&lt;sub&gt;6&lt;/sub&gt; to prevent peripheral neuropathy in infant</td>
<td>Yes</td>
<td>Yes</td>
<td>6.4–25</td>
</tr>
<tr>
<td>Rifampin</td>
<td>No [65]</td>
<td>Crosses placenta; interferes with oral contraceptives; in rodents at high doses, observed spina bifida and cleft palates; in humans no increase in rates of birth defects [70]; Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>0.57–7.3</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>No</td>
<td>Crosses placenta; some teratogenic effects in rodents [8]; no congenital complications in humans (including ophthalmologic) [71, 72]; Few animal or controlled human studies; however, large experience with use during pregnancy; most investigators believe it safe to use</td>
<td>Yes</td>
<td>Yes</td>
<td>2.8–6.9</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>No</td>
<td>Crosses placenta; hearing loss observed in 8%–11% of children [36, 65]; Clinically significant defects very rare [77]; Yes; poorly absorbed by GI tract</td>
<td>Likely yes</td>
<td>Not known</td>
<td>0.75–1.5</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>Ortoxicity; no congenital defects; risk of ototoxicity greater during period of inner ear development (week 7–20), although ototoxicity observed even when administered late during pregnancy [65, 78]; Yes; cross placenta; hearing loss observed in 8%–11% of children [36, 65]; children may have hearing loss 2.3%, congenital deafness rare [79, 80]; Yes; poorly absorbed by GI tract</td>
<td>No</td>
<td>Yes</td>
<td>0.95–22.5</td>
<td></td>
</tr>
<tr>
<td>Amikacin</td>
<td>Likely ototoxicity; no congenital defects</td>
<td>Crosses placenta;-no teratogenic effects associated with short-term exposure; less experience with newer-generation fluoroquinolones and pregnancy</td>
<td>No</td>
<td>Yes</td>
<td>Not known</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>Ortoxicity; no congenital defects; incidence of hearing loss 2.3%, congenital deafness rare [79, 80]; Wavy ribs in rodents; speculated to have effects similar to aminoglycoside; Wavy ribs in rodents; speculated to have effects similar to aminoglycoside</td>
<td>No</td>
<td>Yes</td>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td>Capreomycin</td>
<td>Unknown</td>
<td>Crosses placenta; vitamin B&lt;sub&gt;6&lt;/sub&gt; should be coadministered; Unknown; concentrations in breast milk unknown; minimal GI absorption</td>
<td>Likely yes</td>
<td>Yes</td>
<td>Not known</td>
</tr>
<tr>
<td>Cycloserine</td>
<td>No evidence</td>
<td>Crosses placenta; vitamin B&lt;sub&gt;6&lt;/sub&gt; should be coadministered</td>
<td>Yes</td>
<td>Yes</td>
<td>11–28</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>No</td>
<td>Crosses placenta; no teratogenic effects associated with short-term exposure; less experience with newer-generation fluoroquinolones and pregnancy</td>
<td>Yes</td>
<td>No data on breast milk concentrations</td>
<td>Not known</td>
</tr>
<tr>
<td>Para-aminosalicylic acid</td>
<td>No</td>
<td>Not known if it crosses placenta</td>
<td>Yes</td>
<td>Present in breast milk</td>
<td>0.05–0.95</td>
</tr>
<tr>
<td>Ethionamide-prothionamide</td>
<td>Possibly</td>
<td>Teratogenic effects observed in rodents; vitamin B&lt;sub&gt;6&lt;/sub&gt; should be coadministered</td>
<td>Unknown</td>
<td>No data on breast milk concentrations</td>
<td>Not known</td>
</tr>
<tr>
<td>Thiacetazone</td>
<td>Unknown</td>
<td>No data available</td>
<td>Unknown</td>
<td>No data on breast milk concentrations</td>
<td>Not known</td>
</tr>
<tr>
<td>Amoxicillin-clavulanic acid</td>
<td>No</td>
<td>Yes Amoxicillin excreted in breast milk in low concentrations; clavulanate excreted in breast milk unknown</td>
<td>Unknown</td>
<td>No data on breast milk concentrations</td>
<td>Not known</td>
</tr>
<tr>
<td>Glistazine</td>
<td>Not likely</td>
<td>Crosses placenta; newborns may be bronzed</td>
<td>Unknown</td>
<td>Present in breast milk</td>
<td>Not known</td>
</tr>
<tr>
<td>Gaithrymycin</td>
<td>Possibly</td>
<td>Limited conflicting data in human studies</td>
<td>Unknown</td>
<td>Likely excreted in breast milk; safe experience with other macrolides</td>
<td>Not known</td>
</tr>
</tbody>
</table>

**NOTE.** GI, gastrointestinal.  
* Based on [22, 23, 64].  
† According to the American Association of Pediatrics [23, 63].  
‡ Compared with therapeutic doses for infants [81, 63].
MDR-TB continues to pose challenges to the effective control of tuberculosis worldwide. To our knowledge, this is the largest published case series of MDR-TB patients treated during gestation. Although this experience is limited by the small number of patients in our series, the success of these patients demonstrates that successful and aggressive management of such cases is possible. Although data are limited regarding the safety of second-line antituberculous drugs, the individual and public health threat of untreated MDR-TB has been well-described. Our experience has shown that patients with MDR-TB who are pregnant need not be deprived of appropriate treatment nor the choice to continue their pregnancy.

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References