Treatment of Multidrug-Resistant Tuberculosis during Pregnancy: Long-Term Follow-Up of 6 Children with Intrauterine Exposure to Second-Line Agents

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Treatment of gestational multidrug-resistant tuberculosis (MDR-TB) is controversial. We describe follow-up of 6 children exposed to second-line antituberculous agents in utero. Each child (average age, 3.7 years) underwent comprehensive clinical evaluation. One child had MDR-TB diagnosed. There was no evidence of significant late-presentation toxicity among the children. The results suggest that aggressive management of gestational MDR-TB may benefit both mother and child.

Multidrug-resistant tuberculosis (MDR-TB), defined as infection with strains of *Mycobacterium tuberculosis* with resistance to both isoniazid and rifampin, has emerged as a global health crisis [1]. The incidence of tuberculosis (TB) among pregnant women is increasing [2, 3]. It is likely that pregnancies complicated by MDR-TB will become increasingly common.

To date, experience with the management of MDR-TB in pregnant women has been limited. MDR-TB requires aggressive treatment with second-line agents, which are generally considered more toxic than first-line agents [4, 5]. Although there are limited animal data in the literature on teratogenicity, large-scale clinical experience with the use of second-line agents during pregnancy is absent. Small case series involving the treatment of gestational MDR-TB have reported reassuring outcomes for neonates whose mothers were treated with second-line drugs [6, 7]. However, the literature lacks data regarding teratogenicity that may be diagnosed later in life. Potential concerns include ototoxicity resulting from exposure to aminoglycosides and other injectable agents, neuropsychiatric deficits from exposure to cycloserine or thiamide agents, ethionamide-induced ophthalmologic complications, and long-term bronzing of skin from clofazimine exposure [8–13].

We previously reported the outcomes for 7 women who received treatment for MDR-TB during pregnancy, all of whom carried their pregnancies successfully to term [6]. Here, we report data from long-term clinical follow-up of the children, each born after intrauterine exposure to second-line agents.

Patients and methods. The 7 patients with gestational MDR-TB generally had advanced disease, and all were infected with *M. tuberculosis* strains resistant to at least 4 first-line drugs. Each of the women delivered a successful singleton birth at term between March 1997 and September 2002. Of the 7 children, 1 was lost to follow-up after her mother died of postsurgical complications. For the 6 surviving children identified, maternal treatment records were reviewed to ascertain the timing of exposures to antituberculous agents throughout pregnancy and, when applicable, during the period of breastfeeding. Maternal use of an antituberculous agent for any duration during pregnancy or the postpartum period was recorded as an exposure. The birth history and neonatal course of each child was reviewed, along with any subsequent medical records available from the children's respective health care centers.

Between September 2003 and February 2004, each child underwent a standardized evaluation at the Instituto de Salud del Niño (Lima, Peru). Evaluation was done by a pediatric pulmonologist, who performed a physical examination and obtained a medical history, including a history of bacille Calmette-Guérin (BCG) vaccination and TB contacts. Weight and height were recorded as age percentiles based on parameters developed by the US National Center for Health Statistics and approved by the World Health Organization [14]. Each child also underwent clinical evaluation by pediatric specialists in the Departments of Neurology, Ophthalmology, and Otorhinolaryngology. These evaluations included visual examination, hearing screening, and assessment of language and psychomotor development. Further diagnostic studies were performed at the recommendation of the evaluating physicians. These diagnostic studies included audiometry and tympanometry for one child and electroencephalography for another child. Mantoux skin testing was performed for all children at the time of initial evaluation. A positive reaction, defined as a purified protein derivative (PPD) induration of >10 mm at 48–72 h, prompted

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the performance of a chest radiography. Informed consent was obtained from all mothers, in accordance with the institutional review board guidelines approved by the Harvard Medical School (Boston, MA).

Results. Intrauterine and postpartum drug exposures for each child are summarized in table 1. Of 6 children, 4 (67%) were exposed to second-line antituberculous agents during the first trimester of pregnancy. Two (33%) of the children are female. There were no reports of low birth weight, physical malformations, or perinatal complications. Both of the children exposed to clofazimine were noted to exhibit bronzing of the skin, which disappeared over time. All 6 mothers had a sputum smear and a blood culture negative for *M. tuberculosis* at the time of delivery, and they have remained smear- and culture-negative to date. None of the children exhibited evidence of *M. tuberculosis* infection during the neonatal period. Five (83%) of the children received BCG vaccination at birth.

The average age of the children at the time of evaluation was 3.7 years (range, 15 months to 6.5 years). One child had a history of poor weight gain and failure to thrive. Medical histories and examinations of the children were otherwise unremarkable, including normal findings of musculoskeletal examinations. All children had received scheduled vaccinations. Growth parameters were normal, with the exception of the above-mentioned child, who exhibited a weight and height well below the third percentile for age. Although otherwise asymptomatic, this child had a reactive PPD skin test and a chest radiograph finding of unilateral hilar adenopathy. Although her mother remained smear-negative, a maternal uncle suffered from active pulmonary TB and was experiencing the failure of a standardized retreatment regimen. On the basis of clinical presentation and MDR-TB contact history, the child had primary MDR-TB diagnosed, and individualized therapy was initiated on the basis of the resistance pattern of the infecting strain from her mother, since results of drug-susceptibility testing for the strain from her uncle were pending. Of note, both the child and her uncle had a recent negative culture result, and their conditions clinically improved after 7 months of individualized treatment. The other 5 children had nonreactive PPD tests and showed no clinical signs of TB infection. Results of clinical evaluations are summarized in table 2.

The findings of visual examinations for all children were normal. One child demonstrated mildly increased thresholds on auditory brainstem response testing. His mother chose to defer formal audiometric testing. His language development has been normal, as were the findings of an otorhinolaryngological assessment. This child was exposed to capreomycin until pregnancy was diagnosed at the 14th week of gestation, at which time the intravenous treatment with the drug was stopped. None of the 4 children exposed to an injectable agent exhibited any evidence of clinically significant hearing loss.

Neurologic and developmental examinations were normal for all children. One child underwent cranial radiography for mild cranial asymmetry and underwent electroencephalography for hyperactive behavior; results from both studies were unremarkable, and he is currently undergoing behavioral therapy. Another child is receiving speech therapy for a mild expressive-language delay.

Table 1. In utero and postpartum exposures to antituberculous drugs among children born to mothers with multidrug-resistant tuberculosis.

Patient[a]	Gestation at pregnancy diagnosis, weeks	Treatment withheld, weeks	Drug exposures			Breastfed
			First trimester	Second and third trimester	Postpartum	
2	<12	0	INH, Rif, Eth, Pza	INH, Rif, Eth, Pza, **Stm**, PAS[b]	INH, Rif, Eth, Pza, **Stm**, PAS	No
3	14	0	INH, Rif, Cpfx, Tha, Cyse, Amox-CA	INH, Rif, Cpfx, Cyse, Amox-CA	INH, Rif, Cpfx, Cyse, Amox-CA	Yes
4	20	0	**Cpm**, Ofx, Tha, Cyse, PAS, Amox-CA, Clof	INH, Eth, **Cpm**, Ofx, Tha, Cyse, PAS	INH, Eth, **Cpm**, Ofx, Tha, Cyse, PAS	Yes
5	8	0	INH, Rif, Eth, Pza	Rif, Pza, Ofx, PAS, Amox-CA	Rif, Pza, **Cpm**, Ofx, PAS, Tha, Cyse, Amox-CA	Yes
6	12	1	**Km**, Cpfx, Cyse, PAS, Amox-CA, Clof	Cpfx, Cyse, PAS, Amox-CA	**Km**, Cpfx, Cyse, PAS, Amox-CA, Clof	Yes
7	14	3	Pza, **Cpm**, Cpfx, Pth, Cyse, Amox-CA	Pza, Cpfx, Cyse, Amox-CA	Pza, Cpfx, Cyse, Amox-CA	Yes

NOTE. Amox-CA, amoxicillin–clavulanic acid; Clof, clofazimine; Cpfx, ciprofloxacin; Cpm, capreomycin; Cyse, cycloserine; Eth, ethambutol; INH, isoniazid; Km, kanamycin; Ofx, ofloxacin; PAS, para-aminosalicylic acid; Pth, prothionamide; Pza, pyrazinamide; Rif, rifampin; Stm, streptomycin; Tha, ethionamide. Intravenously administered agents are shown in boldface.

[a] Patient numbers correspond to those used for their mothers in the previous report [6]. As noted above, patient 1 (the child of patient 1 in the previous report [6]) was lost to follow-up.

[b] Stm and PAS treatments were initiated during month 8 of pregnancy, reflecting 2 months of exposure.

Table 2. Clinical evaluation of children born to mothers with gestatational multidrug-resistant tuberculosis (MDR-TB) and exposed to antituberculous drugs in utero.

Patient[a]	Age, years	Sex	Weight, percentile for age[b]	Height, percentile for age[b]	BCG vaccination status	PPD test reaction, mm	Chest radiograph performed; finding	Evidence of hearing loss	IV drug exposure	Vision	Neurologic analysis	Other diagnosed conditions
2	6.5	M	50	75	Yes	2	No	No	Yes	Normal	Normal	None
3	3.9	F	10	10	Yes	4	No	No	No	Normal	Normal	None
4	4.6	M	75	70	Yes	8	Yes; normal	No	Yes	Normal	Normal	Mild speech delay
5	5.1	M	90	85	No	4	No	No	No	Normal	Normal	Hyperactivity
6	1.8	F	<3	<3	Yes	18	Yes; hilar adenopathy	No	Yes	Normal	Normal	MDR-TB[c]
7	1.25	M	60	75	Yes	0	No	No	Yes	Normal	Normal	None

NOTE. BCG, bacille Calmette-Guérin; IV, intravenous; PPD, purified protein derivative.

[a] Patient numbers correspond to those used for their mothers in the previous report [6]. As noted above, patient 1 (the child of patient 1 in the previous report) was lost to follow-up.

[b] Percentiles from the National Center for Health Statistics, Centers for Disease Control and Prevention, 2000 [14].

[c] The mother of patient 6 had a sputum smear and blood culture negative for *M. tuberculosis* at delivery, and she has remained smear- and culture-negative to date. A maternal uncle, also receiving therapy for MDR-TB, is the presumed source case.

Discussion. For decades after the advent of effective chemotherapy, the management of TB during pregnancy remained controversial [15]. However, by the 1990s, an international consensus strongly favored treatment of drug-susceptible TB during pregnancy and mentioned reports of reassuring experiences with treatment that used the oral first-line agents isoniazid, rifampin, ethambutol, and, in most cases, pyrazinamide [5, 16–20].

The emergence of MDR-TB has brought about a remarkably similar debate. Concern regarding the safety of second-line agents has led some physicians to recommend termination of pregnancies complicated by MDR-TB [21] and has led others to undertreat the patient's condition [22, 23]. This concern results not from known fetotoxicity of second-line agents but rather from a lack of evidence regarding their safety. Thus, in the consideration of MDR-TB during pregnancy, the substantial risks of nontreatment must be weighed against the possible toxicities of second-line agents.

Comprehensive reviews of the human and animal data in the teratogenicity literature have been published elsewhere [6, 8]. These include reports of potential ototoxicity, neurotoxicity, and cartilage defects. In the small cohort in the present study, we have no evidence of long-term or late-presentation toxicities associated with in utero exposure to second-line drugs, with the possible exception, in one child, of mild ototoxicity due to exposure to capreomycin during the first trimester. The child in this series with elevated auditory thresholds on auditory brainstem response testing had no clinical evidence of hearing loss, but the situation certainly merits continued monitoring.

Risks of toxicity must be weighed against the risks of untreated maternal TB. Increased rates of maternal morbidity, prematurity, and small-for-gestational-age births, as well as up to 6-fold increases in perinatal mortality, are documented risks of maternal TB infection [24–26]. As a result, any benefit gained from delaying exposure to antituberculous agents beyond the first trimester may be outweighed by the risk of both perinatal complications and maternal progression of disease. Perhaps more significant is the risk of vertical and early postnatal transmission of *M. tuberculosis* infection. Congenital TB, with a reported mortality rate of up to 38%, is becoming more common with the resurgence of TB worldwide [27, 28]. Similarly, young infants with postnatal infection are at high risk for the development of rapidly disseminated and fatal disease [23, 29].

The only adverse outcome in this small case series illustrates a central challenge in the control of MDR-TB: the disease runs in households. Patient 6 was born healthy, and her mother's condition was cured. However, the mother's brother had latent primary MDR-TB, likely caught from his sister, which reactivated and infected the child. Large-scale observational studies in the prechemotherapy era demonstrated that 60%–80% of children with prolonged household contact with a family member who was smear-positive for *M. tuberculosis* became infected. Notably, the risk of progression to disease was highest among infants and children aged <2 years, 60%–80% of whom developed active disease [30]. Such data emphasize the need to continue with active case finding in such families and to consider multidrug resistance whenever a family member presents with TB infection.

Conclusions. The current case series reports data from long-term follow-up of children exposed during gestation to second-line antituberculous agents for the treatment of maternal MDR-TB. The absence of perinatal morbidity, mortality, or congenital malformations, coupled with reassuring long-term developmental outcomes, is highly encouraging. In fact, the only serious adverse outcome observed in this series resulted from ongoing household transmission, rather than toxicity of second-line agents. Although limited by the small number of patients in the series, the finding of excellent outcomes for these children demonstrates that aggressive management of ges-

tational MDR-TB may benefit the child as well as the mother. Children born to these women benefit from close monitoring by experienced clinicians, not only for potential manifestations of toxicity, but also for signs and symptoms of active TB.

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