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SHORT COMMUNICATION

Standardised second-line treatment of multidrug-resistant tuberculosis during pregnancy

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SUMMARY

We describe the efficacy and outcome of standardised second-line anti-tuberculosis (TB) medications during pregnancy. Treatment outcomes of five pregnant women with documented multidrug-resistant TB (MDR-TB) referred to the National Research Institute of Tuberculosis and Lung Diseases from 2003 to 2009 were analysed in two categories, maternal and neonatal. Patients became pregnant during treatment for MDR-TB without any changes in their anti-tuberculosis regimen. None of them had any adverse effects during pregnancy and delivery. No adverse effects were observed in mothers or neonates. The treatment of MDR-TB during pregnancy with a standardised second-line regimen in this study population was safe, with an acceptable rate of treatment success.

KEY WORDS: MDR-TB; standardised second-line anti-tuberculosis medications; pregnancy

MULTIDRUG-RESISTANT tuberculosis (MDR-TB, defined as resistance at least to both isoniazid [INH] and rifampicin [RMP]) imposes a serious burden on health systems and is considered a major threat to global health.[1] Treatment of MDR-TB requires up to 2 years of therapy with alternative second-line anti-tuberculosis drugs that are less potent, 100-fold more expensive and cause more side effects than the first-line drugs used for non-resistant TB.[2,3]

An efficient TB control strategy needs a thorough approach to all subgroups of TB patients, including pregnant women with MDR-TB. Although several drugs are used to treat MDR-TB during pregnancy, little is known about the safety of these drugs for mothers and infants.[4–10]

The objective of this study was to describe the maternal and neonatal outcomes of a standardised second-line anti-tuberculosis regimen during pregnancy.

METHODS

The present study was carried out at the National Research Institute of Tuberculosis and Lung Diseases (NRITLD), a tertiary level centre collaborating with the World Health Organization (WHO), in Tehran, Iran. The NRITLD provides special care for both Iranian TB patients and those from neighbouring countries. Based on the national TB treatment protocol, patients with documented MDR-TB are treated with a second-line anti-tuberculosis drug regimen consisting of amikacin (AMK 15 mg/kg), cycloserine (CS 750–1000 mg/day), ofloxacin (OFX 400–800 mg/day), prothionamide (PTH 750–1000 mg/day), supplemented by pyridoxine (80 mg daily). All patients receive AMK for a period of at least 6 months. If major side effects are diagnosed, the offending agent is replaced by amoxicillin/clavulanate (2–4 g/day). Treatment lasts for at least 24 months, and patients are hospitalised until their sputum becomes negative.[11,12]

Drug susceptibility testing (DST) is performed for all first- and second-line anti-tuberculosis drugs in the regimen using the proportion method on Löwenstein-Jensen medium. The above-mentioned methods are discussed elsewhere in greater detail.[12]

In this case study, we describe five women with documented MDR-TB who became pregnant while on second-line anti-tuberculosis treatment and who chose not to terminate their pregnancy. Treatment was suspended until the patient, her partner and care-givers could reach an agreement about initiating treatment. After explaining the potential teratogenicity of the drugs and the possibility of pregnancy termination to the

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Table 1 Characteristics of pregnant women with documented MDR-TB who received standardised second-line anti-tuberculosis treatment during pregnancy. Data refer to the time pregnancy was diagnosed

Patient	Age years	Nationality	DST results showing resistance to	Weight kg	Gestational age weeks	Time to culture conversion months	Severe CXR findings	General condition
1	18	Afghan	INH, RMP, EMB, SM	42	8	5	Yes	Ill*
2	25	Iraqi	INH, RMP, EMB, SM, CS, PTH	53	12	2	Yes	Good
3	20	Afghan	INH, RMP, EMB, SM	35	8	2	Yes	Ill
4	36	Afghan	INH, RMP, EMB, SM	36	20	16	Yes	Ill
5	22	Afghan	INH, RMP, EMB, SM	45	13	16	Yes	Ill

*Febrile and had dyspnoea.
MDR-TB = multidrug-resistant tuberculosis; DST = drug susceptibility testing; CXR = chest radiography; INH = isoniazid; RMP = rifampicin; EMB = ethambutol; SM = streptomycin; CS = cycloserine; PTH = prothionamide.

mothers, informed consent was obtained from all patients according to the NRITLD human ethics committee protocol.

Directly observed treatment (DOT) was implemented for patients during the periods of non-hospitalisation. Following delivery, the paediatrician made bi-monthly follow-up visits for the infants up to month 6, followed by 6-monthly visits, to detect possible anomalies or abnormalities. In these evaluation sessions, the paediatrician actively looked for known anomalies related to exposure to second-line anti-tuberculosis drugs, including comprehensive hearing tests (mother and infant), growth assessment (evaluation of height and weight according to national protocol) and thyroid function tests. None of these reviews have revealed abnormal findings to date. Breastfeeding began within the initial hours after birth in mothers with negative smear.

Infants were also tested for TB infection. Three gastric washes were negative and a chest X-ray appeared normal. As no sign of active TB was found in the infants, they were given prophylaxis consisting of ethambutol (EMB) and pyrazinamide for 2 months after birth (other drugs available in Iran are not felt to be safe for infants).[5,11,12] Following treatment, a purified protein derivative test was performed, which was negative in all infants. In accordance with national guidelines, the infants were vaccinated with bacille Calmette-Guérin,[5] and as per the Iranian national protocol, we followed the children for at least 3 years.

RESULTS

Among patients with documented MDR-TB who were admitted to the NRITLD, five women became pregnant while on second-line anti-tuberculosis regimens; however, the course of treatment was not altered. All patients (median age 22 years) were resistant to the same four first-line anti-tuberculosis medications (INH, RMP, EMB and streptomycin). Pregnancy was diagnosed at a median of 12 weeks gestation (mean 12.2 ± 4.91; Table 1).

Patients generally had advanced chronic disease. All patients had severe radiographic findings (cavitary lesions and/or bilateral infiltration), and four had advanced clinical disease (i.e., constitutional symptoms and/or initial weight <50 kg). All patients except one had negative cultures at the time pregnancy was diagnosed. The woman who was smear-positive at the time pregnancy was diagnosed remained smear-positive post-partum. Although one of the patients had had negative mycobacteriological tests at the time pregnancy was diagnosed, she became sputum smear-positive during the second trimester of pregnancy (Table 2).

All patients had received second-line anti-tuberculosis drugs for at least 5 months prior to the diagnosis of pregnancy (mean 10.6 ± 6.34 months). All patients continued their regimens up to the time of delivery and after (Table 3). Excluding loss of appetite, no other serious adverse effects attributable to the anti-tuberculosis medications were observed.

Table 2 Duration and type of medications used to manage MDR-TB in pregnant patients

Patient	Duration of first-line anti-tuberculosis regimen months	Second-line anti-tuberculosis drugs before diagnosis of pregnancy		Current age of baby months*	Changes in second-line anti-tuberculosis drugs	
		Duration months	Regimen		Pre-partum	Post-partum
1	24	12	AMK, CFZ, OFX, PTH, PZA, pyridoxine	75	None	None
2	5	8	AMK, CS, OFX, PTH, PZA, pyridoxine	22	None	None
3	5	7	AMK, CS, OFX, PTH, PZA, pyridoxine	16	None	None
4	36	5	AMK, CS, OFX, PTH, PZA, pyridoxine	31	None	None
5	15	21	AMK, CS, OFX, PTH, PZA, pyridoxine	25	None	None

*As of December 2009.
MDR-TB = multidrug-resistant tuberculosis; AMK = amikacin; CFZ = clofazimine; OFX = ofloxacin; PTH = prothionamide; PZA = pyrazinamide; CS = cycloserine.

Table 3 Dosing schedule of medications used to manage MDR-TB during pregnancy and post-partum

	Patient 1				Patient 2				Patient 3				Patient 4				Patient 5			
	1st	2nd	3rd	PP	1st	2nd	3rd	PP	1st	2nd	3rd	PP	1st	2nd	3rd	PP	1st	2nd	3rd	PP
Sputum smear	−	+	−	−	−	−	−	−	−	−	−	−	+	+	+	+	−	−	−	−
Sputum culture	−	+	−	−	−	−	−	−	−	−	−	−	+	+	+	+	−	−	−	−
AMK 15 mg/kg	+	+	+	+	+	+	+	+	*	−	−	−	+	+	+	+	−	−	−	−
CFZ 200 mg/day	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
CS 750 mg/day	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
OFX 400–800 mg/day	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PTH 750–1000 mg/day	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PZA 1000 mg/day	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pyridoxine 80 mg/day	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

*Received AMK only up to week 4 of pregnancy.
MDR-TB = multidrug-resistant tuberculosis; 1st, 2nd, 3rd = respective pregnancy trimester; PP = 3 months post-partum; AMK = amikacin; CFZ = clofazimine; CS = cycloserine; OFX = ofloxacin; PTH = prothionamide; PZA = pyrazinamide.

All women had an uncomplicated normal vaginal delivery (NVD). No obstetrical, congenital or neonatal complications or perinatal transmission of TB was observed, and the treatment regimen was not changed post-partum. Following completion of treatment by all mothers, based on negative culture and radiographic improvement on chest X-ray, their treatment outcome was categorised as 'cured'.[13]

Paediatric reviews of the neonates revealed no abnormal findings. As of December 2009, the healthy children were on average 33.8 ± 23.65 months old (range 16–75 months). All were physically healthy, with normal growth.

DISCUSSION

Treatment of MDR-TB during pregnancy is a controversial issue, and there is no consensus regarding treatment. Little information exists about the outcome of treatment in MDR-TB cases during pregnancy worldwide.[4–7] Although recommendations for the treatment of pregnant women with pulmonary TB are available, there are no specific guidelines for the treatment of MDR-TB during pregnancy. The response to treatment is not clear, and it has not yet been elucidated which drugs are safe during pregnancy in these patients.

The paucity of evidence in this area results from both the small number of patients reported to date and insufficient studies about the safety of second-line drugs during pregnancy for the mother and the foetus.[8–10] Nonetheless, several articles have recently been published on the use of fluoroquinolones during pregnancy for infections other than TB. Bar-Oz et al., in a meta-analysis, concluded that 'the use of quinolones during the first trimester of pregnancy does not appear to represent an increased risk for major malformations recognised after birth, stillbirths, preterm births or low birth weight'.[14] Shin et al. concluded that under certain circumstances MDR-TB can be successfully treated during pregnancy.[7] Klaus-Dieter et al. described a positive outcome for neonates with the use of second-line medications.[8]

Palacios et al. recently analysed the treatment outcomes of 38 cases in Lima.[4] As all patients did not receive the same anti-tuberculosis regimen in that study, making decisions about the side effects of second-line anti-tuberculosis medications during pregnancy was too complicated. Drobac et al. suggested that aggressive management of gestational MDR-TB may benefit both mother and child.[6]

In the present study, all patients received the same regimen. Accordingly, paediatric and maternal treatment outcomes and treatment side effects could be readily evaluated and compared in a uniform format. All mothers achieved cure, and we found no major anomaly or abnormality in the babies.

This study suggests that a positive outcome for neonates is possible with the use of second-line anti-tuberculosis medications during pregnancy. The small number of cases is a limitation of this study. A larger number of similar cases needs to be studied in the future to evaluate responses and side effects and to perform higher powered statistical analyses.

In conclusion, treatment of MDR-TB with a standardised second-line regimen during pregnancy was safe in this study population, with an acceptable rate of success.

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RÉSUMÉ

Dans une étude de cas, nous avons décrit l'efficacité et les résultats des traitements standardisés par médicaments antituberculeux de deuxième ligne au cours de la grossesse. Les résultats du traitement chez cinq femmes enceintes dont la tuberculose multirésistante (TB-MDR) avait été documentée et qui avaient été adressées au National Research Institute of Tuberculosis and Lung Diseases entre 2003 et 2009 ont été analysés dans deux domaines, maternel et néonatal. Les grossesses étaient survenues chez les patientes pendant le décours de traitement de la TB-MDR, sans qu'aucune modification ne soit apportée au régime antituberculeux. Chez aucune d'entre elles on n'a observé un effet indésirable au cours de la grossesse ou au moment de l'accouchement. On n'a observé non plus aucun effet indésirable, que ce soit pour les mères ou pour les nouveau-nés. Au cours de la grossesse, le traitement de la TB-MDR par un régime standardisé de deuxième ligne s'est avéré sûr au sein de la population étudiée, et le taux de résultats couronnés de succès a été acceptable.

RESUMEN

En el presente estudio de casos se describe la eficacia y el desenlace del tratamiento estándar antituberculoso con medicamentos de segunda línea durante el embarazo. Se analizó el desenlace clínico de cinco mujeres embarazadas con tuberculosis multidrogorresistente (TB-MDR) documentada y tratados en el National Research Institute of Tuberculosis and Lung Diseases entre 2003 y 2009 en dos categorías: la madre y el recién nacido. El comienzo del embarazo tuvo lugar durante el tratamiento de la TB-MDR y no se modificaron las pautas terapéuticas. Ninguna paciente comunicó efectos indeseables durante el embarazo ni el parto. No se presentaron reacciones adversas en las mujeres ni en los recién nacidos. El tratamiento de la TB-MDR con una pauta normalizada de segunda línea en la población estudiada fue seguro y ofreció una tasa aceptable de desenlaces favorables.