NCT
Neumología y Cirugía de Tórax
Vol. 81 - No. 2 / April-June 2022

Clinical case
doi: 10.35366/108501

Use of bedaquiline during pregnancy in a patient with MDR-TB. First case reported in Mexico

Uso de bedaquilina durante el embarazo en una paciente con TB-MDR. Primer reporte de caso en México

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ABSTRACT. Treatment of rifampin-resistant and multidrug-resistant tuberculosis in pregnant women is more complicated since little is known about the safety of second-line antituberculosis drugs during pregnancy and lactation. Drug-resistant tuberculosis, not having many options in the past, has been treated with regimens that include drugs with teratogenic potentials, such as thioamides and second-line injectables. Currently, there are new oral drugs, including bedaquiline, for the treatment of drug-resistant disease; however, the safety of bedaquiline during pregnancy and lactation has not been satisfactorily demonstrated so far. We report the first case in Mexico treated with a regimen that includes bedaquiline for multidrug-resistant tuberculosis during pregnancy, with favorable results, and without maternal-fetal complications.

Keywords: tuberculosis, rifampin-resistant, multidrug-resistant, pregnancy, bedaquiline.

RESUMEN. El tratamiento de la tuberculosis resistente a la rifampicina y multirresistente en mujeres embarazadas es complicado ya que se sabe poco sobre la seguridad de los fármacos antituberculosis de segunda línea durante el embarazo y la lactancia. La tuberculosis farmacorresistente, no tenía muchas opciones en el pasado, se ha tratado con regímenes que incluyen medicamentos con potencial teratogénico, como tioamidas e inyectables de segunda línea. Actualmente, hay nuevos medicamentos orales, incluida la bedaquilina, para el tratamiento de enfermedades resistentes a los medicamentos de primera línea; sin embargo, la seguridad de la bedaquilina durante el embarazo y la lactancia no se ha demostrado satisfactoriamente hasta el momento. Reportamos el primer caso en México tratado con un régimen que incluye bedaquilina para la tuberculosis multirresistente durante el embarazo, con resultados favorables, y sin complicaciones materno-fetales.

Palabras clave: tuberculosis, resistencia a la rifampicina, multidrogo-resistencia, embarazo, bedaquilina.

INTRODUCTION

The World Health Organization (WHO) estimates that in 2020 there were 31,000 cases of tuberculosis (TB) in Mexico[1] which represents 10.3% of all patients in America and the third-highest prevalence of TB in the continent. Also, Mexico has the third-highest number of rifampin-resistant or multidrug-resistant TB (RR-TB and MDR-TB) cases in America.[2]

The prevalence of tuberculosis during pregnancy in low-burden countries (< 20 cases per 100,000 h), such as Mexico, ranges between 0.06 and 1%.[3] Tuberculosis during pregnancy has been associated with maternal-fetal complications; in a study of pregnant women with tuberculosis in Mexico,[4] the neonatal outcome was compared with pregnant women without TB. There was a significantly higher neonatal morbidity rate, a significantly lower birth weight (including weight < 2,500 g), and a significantly higher risk of prematurity in the group of women with TB. In this study, TB treatment included exclusively first-line drugs (isoniazid, rifampicin, ethambutol, or pyrazinamide), currently considered as safe during pregnancy.[4]

Treatment of RR-TB and MDR-TB in pregnant women is more complicated since little is known about the safety of

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Received: 03-II-2022; accepted: 04-V-2022.

How to cite: López-de la Cruz PL, Ruiz-Pérez S, Laniado-Laborín R. Use of bedaquiline during pregnancy in a patient with MDR-TB. First case reported in Mexico. Neumol Cir Torax. 2022; 81 (2): 138-140. https://dx.doi.org/10.35366/108501

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second-line anti-TB drugs during pregnancy and lactation.[5] Treatment of drug-resistant TB has traditionally required drugs with teratogenic potential, including thioamides (ethionamide and prothionamide) and second-line injectables (amikacin, kanamycin, and capreomycin).[6] Since 2019, based on new evidence, the WHO recommends an exclusively oral treatment regimen for drug-resistant TB, including new drugs (bedaquiline, delamanid and pretomanid) and repurposed drugs (linezolid, clofazimine and fluoroquinolones).[7] However, all of these drugs are currently classified as category C during pregnancy, that is, those for which animal reproduction studies have shown an adverse effect on the fetus and for which there are no adequate and well-controlled studies in humans, but whose potential benefits may justify the use of the drug during pregnancy despite the potential risks.

We report the first case in Mexico of MDR-TB during pregnancy, treated with a regimen that included bedaquiline (BDQ).

PRESENTATION OF THE CASE

A 21-year-old female was referred for evaluation to the Tuberculosis Clinic of the Tijuana General Hospital with TB and pregnancy; primiparous, with 16 weeks of gestation (WOG) at the time of reference; seronegative for HIV. Her main complaints are productive cough, occasionally hemoptoic, unquantified fever, and diaphoresis for the previous three months. She denies drug addiction or comorbidities. The chest radiograph shows bilateral airspace opacities and a cavitation in the lingula. The Xpert® MTB/RIF (Cepheid, Sunnyvale, CA) assay detects *Mycobacterium tuberculosis* complex (MTBC) with a high load of mycobacterial DNA, and resistance to rifampicin; subsequently, the line probe assay (LPA; GenoType®MTBDRplus VER 2.0, Hain Life Sciences, Nehren Germany) for the analysis of the *rpoB* and *katG* genes and the *inhA* promoter reported resistance to isoniazid (detected) and rifampicin (inferred); second-line LPA (GenoType®MTBDR sl VER 2.0) did not detect mutations associated to fluoroquinolones or second-line injectable antibiotics. Despite the lack of evidence on the safety of their use in pregnancy and lactation, the need for second-line is explained to the patient, for which she is requested and gives her informed consent to initiation of outpatient treatment with home video supervision (videoDOT).

Treatment included Bdq 400 mg for two weeks and 200 mg three times a week for 22 weeks, linezolid 600 mg/day, levofloxacin 750 mg/day, clofazimine 100 mg/day, and pyridoxine 100 mg/day. After a few days of treatment, she complained of nausea and vomiting; thus, sucralfate (2 g) and ondansetron (8 mg) are prescribed every 24 hours. After two months of treatment, serum magnesium was reported at 1.5 mg/dL, and the regimen was supplemented with 250 mg of magnesium every 24 hours.

Spontaneous labor begins at 39 WOG, obtaining a single, live female product. APGAR was graded 8/9 and CAPURRO at 39 weeks. Birth weight 3,090 g, height 49 cm, head circumference 33.5 cm, thoracic perimeter 32 cm, abdominal perimeter 30 cm, lower segment 20 cm, and foot length 8 cm.

After completing six months of treatment with BDQ, the patient continues with the rest of the initial regimen without any other complications; converted sputum smears by the second month and the culture by the third month of treatment. BCG vaccination was recommended for the child, and she was referred to the HGT Pediatric TB Clinic for follow-up. It was decided not to recommend breastfeeding, given the little information on the safety of these drugs during lactation.

DISCUSSION

This is the first case in Mexico treated with a regimen that includes BDQ for MDR-TB during pregnancy, with favorable results, and without maternal-fetal complications. Our case adds to the growing body of evidence on the effectiveness and safety of BDQ during pregnancy.

Biological changes during pregnancy double the risk of pregnant women developing tuberculosis compared to non-pregnant women. Pregnancy itself complicates the treatment of tuberculosis, and untreated tuberculosis may be associated with mortality up to up to 40%.[3] Treatment of RR/MDR-TB, not having many options, traditionally required including drugs with teratogenic potential, including thioamides (ethionamide and prothionamide) and second-line injectables.

The WHO currently recommends a long-term treatment regimen for patients with MDR/RR-TB and pregnancy, with at least four effective drugs, which must include all group A drugs (levofloxacin or moxifloxacin, BDQ and linezolid) for which there is no resistance or contraindication and at least one group B drug (clofazimine or cycloserine).[7]

However, the safety of BDQ during pregnancy and lactation has not been satisfactorily demonstrated so far. In the largest cohort of pregnant women with RR/MDR-TB reported to date with 108 South African women, 81% of which were HIV-positive and 83% were on antiretroviral treatment. At the start of treatment, the median gestational age was 22 weeks (IQR 14-28); 45% of fetuses were exposed to BDQ with a median fetal exposure of 118 days (IQR 70-208). When the group of newborns exposed to BDQ (49) was compared with those not exposed to this drug (60, there was a twin birth), no significant differences were found in the percentage of live births, gestational age at delivery, and fetal/neonatal deaths. Forty-five percent of the products exposed to BDQ had a birth weight under 2,500 g vs 26% of the unexposed products ($p = 0.03$).

However, at the end of twelve months of follow-up, both groups had already reached the expected weight for their age.[8] Even though no significant congenital malformations were reported, the number of fetuses exposed to BDQ during the critical period of the first trimester was too low (17%) for this study to provide a reliable assessment of safety in this regard.[9]

Our case did not have low birth weight as reported in the South African study, where 45% of the products had low birth weight, even though BDQ exposure in our case was higher (154 days vs 118 days in the South African study).

Although it would be essential to have more information, there is no justification for denying pregnant women with drug-resistant TB (DR-TB) access to innovative therapeutic regimens containing new drugs such as bedaquiline or delamanid and repurposed drugs such as linezolid and clofazimine. The development of clinical trials to include pregnant women with DR-TB would undoubtedly provide high-quality information; however, since pregnant women are routinely excluded from such clinical trials, it would likely take decades for information on the safety of these drugs to be obtained. This evidence gap could also be supplemented by developing and using registries of pregnant women with DR-TB treated with these drugs.[10]

CONCLUSIONS

Pregnant and postpartum women have traditionally been underrepresented in clinical trials. We have minimal evidence on the use of new drugs against drug-resistant TB in pregnant women, which constitutes a critical knowledge gap. The exclusion of pregnant women from drug-resistant TB treatment trials constitutes a significant research challenge.

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Conflict of interest: the authors declare that they have no conflict of interest regarding this publication.