Tuberculosis Diagnosis in Israel: Don't Forget Pregnant Women

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Tuberculosis (TB) remains a significant cause of morbidity and mortality, especially in developing countries. According to a World Health Organization (WHO) report [1], there were about 9 million new TB cases globally and 1.5 million TB-related deaths in 2013. It was also estimated that more than 200,000 pregnant women were diagnosed with active TB in 2011, mostly in sub-Saharan Africa, followed by the South East Asian region [2]. In Israel, on average, 388 TB cases were reported annually between 1999 and 2010, while the national TB incidence decreased from 7.5 per 100,000 in 1999 to 4.3 in 2010. About 42.0% of all cases were adult women [3]. Similar to findings from other developed countries [4], most patients with TB in Israel (87.6%) during that period were non-Israeli born, the majority having originated in high-prevalence countries.

In this issue of *IMAJ*, Bishara and colleagues [5] present their analysis of data from northern Israel, addressing the need to further increase physician awareness to possible TB infection in pregnant women. TB in pregnancy poses a diagnostic challenge, mainly because of the non-specific nature of its early symptoms. Malaise, shortness of breath, sweating and evening pyrexia, all characteristics of TB, may also overlap symptoms related to the physiological response to pregnancy and resemble other infectious and non-communicable diseases. Furthermore, physicians who suspect TB may be hesitant to use chest radiography in order to prevent harm to the fetus, thereby delaying the diagnosis. The higher proportion of extra-pulmonary TB among pregnant women is an additional factor related to the delay of diagnosis due to its non-specific clinical symptoms [6].

Diagnostic workup for active TB in pregnancy is similar to that in non-pregnant individuals, which includes chest radiography and sputum for smear microscopy for acid-fast bacilli and culture. The benefits of chest radiography in establishing the diagnosis of TB in pregnancy outweigh the potential disadvantage of fetal radiation exposure, which is negligible when using abdominal shielding [7].

There is conflicting evidence with regard to the possible effects on maternal and neonatal outcomes. While some studies have suggested that TB infection does not adversely affect pregnancy outcomes, others have reported related morbidity. These include an increased incidence of preeclampsia, vaginal bleeding, early fetal death, prematurity, suboptimal weight gain, low birth weight and Apgar score, and perinatal death, as compared with non-infected pregnant women [4,6]. The worst prognosis was recorded in women who were diagnosed with advanced disease, especially in the puerperium, as well as in women with human immunodeficiency virus (HIV) co-infection [8]. Failure to adhere to the treatment may also worsen prognosis. It was suggested that the increased incidence of postpartum TB is a result of diagnostic, immunological and administrative delays during pregnancy [8], as also found in northern Israel [5].

The management of TB in pregnancy is similar to that in non-pregnant women, which includes the use of combination anti-TB therapy through the use of directly observed therapy. The only exception is that streptomycin should be avoided as it was proven to be potentially teratogenic, causing eight-nerve paralysis, with deficits ranging from mild hearing loss to bilateral deafness. All these anti-TB drugs cross the placenta and reach low concentrations in the human fetal fluids and tissues, but there have been no reports linking the use of these drugs with congenital abnormalities (pregnancy risk factor class C). The standard regimen for drug-sensitive TB includes ethambutol, isoniazid, rifampicin and pyrazinamide for 2 months, followed by 4 months of isoniazid and rifampicin [4]. Treatment outcome is similar to that in non-pregnant women.

Mother-to-child transmission of TB may occur in utero by the hematogenous route through the umbilical vein and aspiration or swallowing of the infected amniotic fluid, and in the intarpartum period through contact with the infected amniotic fluid or genital secretion. Postpartum transmission through maternal aerosol spread is more common, and respiratory precautions should be taken until the mother is no longer infective. The risk of transmission through breast milk is minimal and breast-feeding while on anti-TB therapy is not contraindicated [4,9]. The care of the infant whose mother is diagnosed with active TB should include isoniazid prophylaxis (5 mg/kg) and should be reassessed between 6 weeks and 3 months by tuberculin skin test. If the test is positive and a diagnosis of active TB disease in the newborn is made, full multidrug therapy should be initiated. If the diagnosis of active TB in the newborn is ruled out, isoniazid treatment should be continued. In cases where the test is nega-

tive, Bacillus Calmette-Guérin (BCG) vaccination should be considered and isoniazid chemoprophylaxis discontinued. Although mycobacterial infection in infants can lead to severe morbidity, a complete medical workup was performed in only one of the newborns in the report by Bishara's group [5]. Earlier maternal diagnosis and better communication between neonatologists, obstetricians, public health professionals and TB specialists will surely improve newborn care.

The overall rate of TB in pregnant women in developed countries is generally low. In the United Kingdom it was estimated that the national incidence of TB cases per 100,000 maternities was 4.2 in 2008 [4] and 12.8 for the period 1996–2008 [8]. An earlier publication from New York reported 18–29 TB cases per 100,000 pregnancies [10].

Important operational issues emerge from the article by Bishara et al. [5], which need to be addressed by treating physicians in low TB-burden countries. Two TB cases in northern Israel were contacts of a previously diagnosed TB case and two others were detected among migrants. Contacts of known TB patients are at risk of acquiring mycobacterial infection and they should be encouraged to complete the full course of prophylactic therapy. Migrants from high-prevalence countries are at risk for TB, as published elsewhere [7]. It is likely that there are more TB cases among pregnant women in Israel since the majority of migrants live in central Israel, in the metropolitan area of Tel Aviv.

TB is a rare disease in Israel and, therefore, most physicians may not suspect this diagnosis in Israeli-born women. Yet, physicians should be aware that TB is a possible diagnosis in women who present typical symptoms. Identification of risk factors, such as origin in a high TB-prevalence country, contact with a recent active TB patient, and previous TB treatment may contribute to timely diagnosis.

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