

Tuberculosis during Pregnancy in Northern Israel, 2002–2012: Epidemiology and Clinical Practices

Hashem Bishara MD MPH^{1,2}, Noam Goldstein MD^{2,3}, Marwan Hakim MD^{2,4}, Olga Vinitsky MD MPH⁵, Danit Shechter-Amram RN⁶ and Daniel Weiler-Ravell MD^{1,2}

¹Tuberculosis Center and ⁴Department of Obstetrics and Gynecology, Nazareth Hospital, Nazareth, Israel

²Faculty of Medicine in the Galilee, Bar-Ilan University, Safed, Israel

³Tuberculosis Center, Galilee Medical Center, Nahariya, Israel

⁵Public Health Department, Northern District, Ministry of Health, Israel

⁶Public Health Department, Acre Subdistrict, Ministry of Health, Israel

ABSTRACT: **Background:** Atypical presentation of tuberculosis (TB) during pregnancy may cause diagnostic delay and adversely influence pregnancy outcome.

Objectives: To examine the incidence and clinical and epidemiological features of TB during pregnancy and investigate infection control measures at delivery and during the postpartum period.

Methods: We retrospectively evaluated all reported cases of TB diagnosed during pregnancy to 6 months postpartum in Israel's Northern Health District (2002–2012).

Results: Active TB was detected in six patients; all were negative for human immunodeficiency virus (HIV). Two patients were diagnosed in the postpartum period, and four had pulmonary involvement. The average incidence during this period (3.9 per 100,000 pregnancies) was similar to that in the general population. Five patients were at high risk of contracting TB due to either recent immigration from a high-burden country or being in contact with another individual with active TB. Patients with pleuropulmonary involvement had prolonged cough and abnormal chest X-rays, without fever. Diagnosis was delayed for 3 to 7 months from symptom onset. Investigation of the newborn to rule out intrauterine infection was conducted in only one of four relevant cases. All patients were infected with organisms susceptible to all first-line drugs, and all were cured with standard therapy.

Conclusions: There was a considerable delay in the diagnosis of TB among pregnant women, and investigation of the newborn upon delivery to rule out TB infection was routinely omitted. Effective management of TB during pregnancy and the postpartum period requires a multidisciplinary approach including an obstetrician, pediatrician, TB specialist, and public health physician.

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For Editorial see page 383

Tuberculosis (TB) is a leading cause of morbidity and mortality among women of child-bearing age in developing countries. TB during pregnancy has been found to be associated with a sixfold increase in perinatal deaths and a twofold higher risk of premature birth and low birth weight for age [1].

Since the incidence of TB in Israel is low, physicians rarely encounter patients with the disease [2]. Furthermore, the clinical presentation of TB in pregnant women is often atypical, and physicians tend to be unjustifiably reluctant to perform chest X-rays on pregnant women [3–5]. Therefore, the diagnosis of active TB may frequently be delayed, especially if the patient is not considered to be at risk for TB. However, a delay in the diagnosis and treatment of TB during pregnancy, especially during advanced pregnancy, increases the risk of TB infection in the fetus in utero and in the newborn [3–6].

The aims of the present study were to examine the incidence and clinical and epidemiological characteristics of TB during pregnancy in Israel's Northern Health District, evaluate the occurrence of diagnostic delay, and investigate infection control practices.

PATIENTS AND METHODS

All patients with TB in the Northern District (population 1.32 million) are investigated and managed at one of two TB clinics: one located in Nazareth Hospital, Nazareth and the other in the Galilee Medical Center, Nahariya.

The list of women registered in the childbirth surveillance system (Ministry of Interior registry, which includes personal details and date of delivery for all women residing in the Northern District who gave birth during 2002–2012) was cross-tabulated with the TB surveillance system (includes all patients diagnosed with TB in the Northern District since 1996 who had resided in the Northern District at the time of their diagnosis or treatment).

To ensure that no cases of TB occurring during pregnancy were missed, we included patients diagnosed with TB until 6 months after delivery, a criterion used in previous reports. This was necessary because the diagnosis of TB during pregnancy is frequently delayed.

In addition to utilizing the TB and childbirth registry for case identification, the records at both TB clinics were also checked to identify women diagnosed with TB during pregnancy and thus ensure that all cases were included. The medical files of all pregnant women with TB and their newborns were reviewed to identify the clinical and epidemiological characteristics of the patients and evaluate management practices that were used to rule out TB infection in the newborn.

A patient was considered positive for TB if *Mycobacterium tuberculosis* complex (*M. tuberculosis*) was cultured from sputum, body fluid, or body tissue. A diagnosis of TB was considered to be probable if a full course of anti-TB drugs was prescribed to a culture-negative patient by the TB clinic physician [7].

Pulmonary TB was defined as *M. tuberculosis* infection of the lung parenchyma, while extrapulmonary TB was defined as the presence of *M. tuberculosis* disease in any other site without lung involvement (including the pleura and larynx) in accordance with the World Health Organization (WHO) definitions [7].

A diagnostic delay was defined as the time that elapsed from onset of symptoms recorded in the patients' medical charts to the decision to initiate a full course of anti-TB treatment. Thus, diagnostic delay included both patient- and system-related delays. Treatment success was defined as a TB cure as classified by the WHO guidelines [7].

This study was approved by the Ethics Review Committee of Nazareth Hospital, and all patients' confidentiality was preserved.

RESULTS

In total, from 2002 to 2012 there were 152,531 deliveries in the Northern District. Of all women who gave birth during that period, six fulfilled the inclusion criteria for TB diagnosed during pregnancy and up to 6 months postpartum. The average cumulative incidence of TB during pregnancy and the postpartum period was 3.9 cases per 100,000 pregnancies.

Of the six pregnant women with TB [Table 1], four had pulmonary TB and two had extrapulmonary disease (one pleural and the other spinal TB). Two patients were diagnosed 18 and 6 weeks after delivery, respectively; however, both were symptomatic while pregnant. All patients with pleuropulmonary TB presented because of a persistent cough, and only one presented with fever. The patient with spinal TB sought medical care because of back pain during pregnancy that became increasingly more severe during the postpartum period. The

Table 1. Epidemiological and clinical features of pregnant women diagnosed with tuberculosis, Northern Israel Health District, 2002–2012

	Patient 1* (2010)	Patient 2** (2007)	Patient 3 (2006)	Patient 4 (2006)	Patient 5 (2004)	Patient 6 (2002)
Age (years)	21	28	23	18	31	20
Ethnicity	Jewish	Ethiopian	Arab	Arab	Arab	Jewish
Country of birth	Israel	Ethiopia	Israel	Israel	Israel	Chechnya
Gestational age at diagnosis	38 weeks	35 weeks	4 months postpartum	21 weeks	6 weeks postpartum	35 weeks
Delivery time	39 weeks	36 weeks	35 weeks	41 weeks	36 weeks	37 weeks
Risk factors	Travel	Immigrant	Contact	Contact	Unknown	Immigrant
Diagnosis delay	3 months	3 months	5 months	1 week	7 months	6 months
Organ involved	Lung	Lung	Lung	Pleura	Spine	Lung
TST (mm)	–	25	–	15	19	20
Main symptoms	Cough	Cough	Cough	Cough/Fever	Back pain	Cough
X-ray findings	Lung cavity	Lung infiltrate	Lung cavity	Pleural effusion	Vertebral lesion	Lung cavity
Specimen culture/smear	Sputum +/+	Sputum +/-	Sputum +/+	Pleural +/-	Vertebral biopsy +/	Sputum +/

Newborn investigation upon delivery to rule out TB infection and delivery outcome

Investigation	Conducted	None	NR	None	NR	None
Outcome	Normal	IUGR	Normal	Pneumonia	Pneumonia	Normal

*Ref 8

**Ref 9

TST = tuberculin skin test, NR = not relevant, IUGR = intrauterine growth retardation

time delay from symptom onset to diagnosis ranged from 1 week to 7 months.

Five of the six pregnant patients with TB had risk factors for TB infection; two were recent immigrants from high-burden countries, one contracted the disease following a 1 year stay in a high-prevalence country, and two native Israeli patients (sisters) had been repeatedly exposed to other individuals with active TB in their extended family.

Patient 1 [Table 1] presented to the Emergency Department (ED) with a complaint of sharp stabbing pain in the right chest exacerbated by cough and deep breathing. During the preceding 3 months she had had a scanty productive cough without hemoptysis, fever or wheezing. A day earlier she had presented with the same complaints to the ED but had signed out because she refused a chest X-ray, recommended among other reasons because at the time an influenza epidemic was considered imminent. Her chest X-ray showed two large cavities in the right upper lobe. Further questioning revealed that she had spent the previous year in Georgia with her future husband's family. Her sputum smear showed numerous acid-fast bacilli (AFB). A week later she gave birth to a healthy 2614 g male

infant delivered by cesarean section at her request. During labor and postpartum a thorough investigation to rule out TB infection in the newborn was conducted, as were infection control measures. The infant received directly observed prophylactic treatment (DOPT) with isoniazid for possible latent TB infection (LTBI) and 6 months later the treatment was stopped following a negative second tuberculin skin test (TST).

Patient 2 was a recent immigrant from Ethiopia, para 2 in her 26th week of pregnancy. She was evaluated for possible LTBI because of a positive routine TST measuring 25 mm. She complained of a dry cough of 3 weeks duration with no fever or sputum production. Her chest X-ray showed a paracardial infiltrate in the left mid-lung field. She was referred to the ED for an urgent workup for possible active TB. She was hospitalized for a week with a diagnosis of pneumonia and received antibiotic therapy. A week after discharge she coughed up blood and was evaluated again in the ED. There was no change in the X-ray finding. A workup for possible pulmonary infarction revealed a high D-dimer level and a lung scan was performed, showing low probability for pulmonary embolism. She refused admission and was discharged for ambulatory follow-up in the regional TB clinic and treatment for suspected pulmonary TB was started. Her sputum cultures were eventually positive, with an organism susceptible to all first-line drugs. Her two daughters aged 4 and 7, when assessed as part of the routine contact investigation, were found to have active TB (culture-positive pulmonary and culture-negative pleural, respectively) and were treated and cured by standard therapy. At 36 weeks gestation, the woman delivered at home. The newborn was examined later at the TB clinic and LTBI treatment was started.

Patient 3 had persistent cough without fever during the third trimester of pregnancy. She was treated with antibiotics without improvement. She delivered spontaneously at 35 weeks gestation. Three months later she had a chest X-ray and chest computed tomography (CT) because of her worsening persistent cough. She was found to have a right upper lobe cavitary lesion with diffuse bilateral upper lobe infiltration and was referred to the ED and hospitalized. Her sputum was smear and culture positive, with *M. tuberculosis* susceptible to all first-line drugs. This patient had been a close contact of active TB cases in her family during two different time periods, 1995 and 2001. She was examined and treated for LTBI in 1995. However, she was not retreated following her second exposure in 2001. Contact investigation of this patient revealed that her 18 year old pregnant sister (patient 4) had pleural TB.

Patient 6, a recent immigrant from Chechnya, in the 35th week of her pregnancy was referred to the pulmonary clinic because of a worsening cough during the previous month, without fever and a 20 mm TST. She had been examined 6 months earlier because of cough and low-grade fever of one month duration which partially responded at the time to anti-

biotic treatment. At the time her chest X-ray showed a faint infiltrate in the right lower lobe without an adjacent pleural effusion. She was advised to have a follow-up chest X-ray in 2 weeks time. She subsequently realized that she was pregnant and did not have a second X-ray or return for follow-up despite her persistent cough. Six months later, her chest X-ray revealed a dense infiltrate in the right lower lobe. Treatment with four first-line drugs – isoniazid, rifampin, ethambutol and pyrazinamide – was begun pending results of sputum samples. The smears showed numerous AFB. Cultures grew *M. tuberculosis* susceptible to all first-line drugs. Two weeks after treatment was begun, in the 37th week of pregnancy, the patient presented in early stages of labor and a healthy infant weighing 2420 g was delivered by cesarean section at her request. On delivery no investigation of the newborn was conducted to rule out TB other than a routine examination. Later, at the TB clinic, treatment for LTBI was started for 6 months, at which point his TST was negative and the treatment was stopped.

All women were available for follow-up, all were treated and cured with a standard regimen (isoniazid, rifampin, and ethambutol with or without pyrazinamide), and none had resistant forms of TB or human immunodeficiency virus (HIV) co-infection.

A thorough investigation to rule out TB infection in the newborn and infection-control measures during labor were carried out in only one case (Patient 1). This investigation was facilitated by effective coordination and communication among the attending pediatrician, pediatric infectious disease specialist, obstetrician, and TB clinic staff members [8]. The investigation included histological inspection of the placenta for granulomas; culture of the amniotic fluid for TB; and examination of the newborn for signs of respiratory distress, elevated body temperature, lymphadenopathy, hepatosplenomegaly; as well as performance of a chest X-ray and routine blood tests.

Three of five newborns were preterm; one had intrauterine growth retardation, and one had pneumonia. None of the newborns developed TB. All had negative tuberculin skin test results at the age of 6 months. Until they tested negative, four infants received LTBI treatment with twice-weekly isoniazid under direct observation.

DISCUSSION

Our results showed that the average cumulative incidence of TB during pregnancy and the postpartum period was 3.9 cases per 100,000 pregnancies. This rate is somewhat lower than the 4–8 cases per 100,000 pregnancies in the general population of Israel from 2002 to 2012. This finding conforms to the current dictum that pregnancy is not a risk factor for TB as was once thought. We also found a considerable delay in the diagnosis of TB among pregnant women and inconsistent methods of investigating the newborn upon delivery to rule out TB infection.

Only two of the six pregnant women had extra-pulmonary TB, which is somewhat lower than the rate of 50% reported in the literature [5,11,12]. This is probably due to the small number of cases evaluated, the fact that four women in our report were Israeli-born (among whom the rates of extra-pulmonary TB are relatively low), and the absence of co-infection with HIV.

Similar findings were reported by Knight et al. [10], who examined all cases of TB diagnosed in pregnant women in the United Kingdom from August 2005 through July 2006. They reported 33 cases among an estimated 792,193 pregnancies (incidence of 4.2 per 100,000 pregnancies). All but one of these women were foreign-born, and all came from immigrant families. However, about half of these patients had extra-pulmonary disease and five had co-infection with HIV.

Zenner et al. [11] examined the rates of TB diagnosis at pregnancy and up to 6 months postpartum from 1996 to 2008 in 460 general practices in England. There were 177 women with TB in this cohort, and 43 of the 68 patients in whom organ involvement was known to be present exhibited extra-pulmonary involvement. After adjusting for age, place of residence and socioeconomic status, the authors found that the risk-ratio rate for TB was significantly higher (incidence rate ratio 1.95, confidence interval 3.07–1.24) than in non-pregnant women.

Because a persistent cough without fever was the cardinal presenting symptom of TB with pleura-pulmonary involvement in this series, it transpires that this non-specific finding might be very significant in similar groups. An abnormal chest X-ray was found in all women with pleura-pulmonary TB described here, as in other reports. [12]. Thus, a simple chest X-ray is essential to establish a diagnosis of TB during pregnancy. Reluctance to perform a chest X-ray because of the pregnancy was a main reason for diagnosis delay in all four pulmonary cases in this series. Physicians should not hesitate to perform chest radiography in pregnant patients, as long as an abdominal lead shield is used to minimize radiation exposure to the fetus [13].

Our cohort of pregnant women had a long diagnostic delay. However, this diagnostic delay in our cohort was similar to that in previous reports on TB in pregnancy (4–26 weeks) [4,5,10].

As demonstrated in this study, TB during pregnancy may be associated with a number of adverse effects. These adverse effects include an increased rate of premature birth and intrauterine fetal growth retardation [13–15]. Congenital TB is a rare complication of TB during pregnancy and is the result of hematogenous dissemination of TB through the placenta or aspiration of amniotic fluid in utero. Peng et al. [16] described 6 cases of congenital TB and reviewed 164 from the literature (1946–2009). Symptoms appeared from 2 to 3 weeks after birth and mainly comprised fever, respiratory distress and hepatosplenomegaly in about 68% of the cases. The mortality rate

among treated and untreated infants was 21.7% and 100.0%, respectively.

Because the incidence of TB is generally very low in Israel, general practitioners and obstetricians do not often suspect the presence of active TB on clinical grounds. TB in pregnant women is often an indolent disease with non-specific symptoms at presentation, as demonstrated above. However, if the epidemiology of TB in Israel is considered, the chances of a timely diagnosis should increase significantly. Currently, about 80% of all new cases of TB in Israel occur in foreign-born individuals, especially within 5 years of arrival in the country [2]. Thus, a key factor to consider when evaluating a patient for possible TB is the country of origin and TB exposure history. A history of travel to high-burden areas of TB is often a tip-off for diagnosis when the patient does not belong to a high risk group. This was the case in patient 1; her history of living with her spouse's family in Eastern Europe, where the rate of TB is high, led to an otherwise unsuspected diagnosis of active TB [8].

Timely diagnosis of TB in pregnant women is essential to prevent congenital TB and other adverse outcome during pregnancy to ensure diagnosis of intrauterine fetal infection upon delivery and to prevent TB infection of the newborn [17]. Symptoms of neonatal TB are non-specific; many viral and bacterial infections have similar presentations. Therefore, diagnosis of neonatal TB may be perplexing, and the diagnostic delay may have irreversible consequences for the infant [15–17]. It is thus crucial to rule out TB infection in newborns whose mothers have been diagnosed with TB, and this investigation should be performed at the time of delivery [18]. The initial assessment should include a careful medical evaluation and chest X-rays (the tuberculin skin test is usually negative in newborn infants). Microscopic examination of the placenta to identify any granulomas and taking a TB culture are strongly recommended [18]. Gastric aspiration and cerebrospinal fluid should be microscopically examined and cultured for TB if there is a high clinical suspicion of active TB in the newborn [18]. When there is no clinical evidence of active TB, prophylactic treatment with isoniazid should be considered.

All women in the present study were cured with a standard regimen comprising three or four anti-TB drugs. The WHO and the British Thoracic Society recommend treating TB during pregnancy with all four first-line drugs (isoniazid, rifampicin, ethambutol, pyrazinamide) [19,20]. In the USA, the Centers for Disease Control prefers to abstain from the use of pyrazinamide during pregnancy because of the lack of adequate information regarding adverse effects on the fetus [21]. Its use is recommended in cases of resistance to other first-line drugs. For drug-resistant strains of *M. tuberculosis*, the use of second-line drugs during pregnancy (e.g., aminoglycosides and quinolones) is associated with significant risks to the fetus. Additionally, there is a lack of information regarding the safety of other second-line drugs [18–21].

LIMITATIONS

The main limitation of this study was the small number of cases reported. A nation-wide study would enable a better assessment of the clinical and epidemiologic profile of TB during pregnancy in Israel, and of infection control practices. The fact that we relied on the 'Childbirth registry' implies the exclusion of pregnant women with abortions or stillbirths as well as women who moved out of the Northern District while pregnant or gave birth in a foreign country. Therefore, denominators based on the number of live births may not accurately determine TB rates. However, we tried to minimize the magnitude of this limitation by examining the patient registries in each TB clinic.

CONCLUSIONS

TB among pregnant women in Israel's Northern Health District was associated with many risk factors causing infection and eventual active disease. The diagnosis of TB in pregnant women is often delayed, and the methods used to investigate the newborn for TB infection at the time of delivery are inconsistent and often inadequate. Physicians should be aware of the possibility of active TB among pregnant women with risk factors and of the need to rule out TB infection of the newborn at delivery.

Correspondence

Dr. H. Bishara

Tuberculosis Center, Nazareth Hospital, P.O. Box 422, Nazareth 16100, Israel

Phone: (972-4) 602-8888

Fax: (972-4) 602-8857

email: hbishara@bezeqint.net

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