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Tuberculosis in pregnancy

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BASIC EPIDEMIOLOGY OF TUBERCULOSIS

According to World Health Organization data, 9.2 million incident cases and 1.7 million deaths were attributed to tuberculosis in 2006, the overwhelming majority of which affected individuals residing in developing nations[1]. A staggering one-third of the world's population is estimated to be infected with tuberculosis. Of those infected, 5–10% progress to active tuberculosis (TB) in their lifetime, with HIV-positive individuals carrying an even higher risk of progression to active disease[2]. Worldwide, approximately 3 million women become afflicted with TB each year and 750,000 die, rendering tuberculosis one of the leading infectious disease causes of death in women[3].

In the UK, the number of tuberculosis cases declined until the mid-1980s, but began rising again in the early 1990s. In 2006, there were 8497 cases of TB reported (14 per 100,000). The London metropolitan area accounted for 40% of these cases (44.8/100,000)[4]. This represents a rise from 2002, when 6638 cases were identified. Approximately 350 people die annually from TB in the UK[5]. In terms of demographics, 2003 data reveal that the TB incidence in London was 11 times higher for foreign-born individuals (83% of reported cases) than for UK-born individuals[6]. Of equal importance, between 1998 and 2005 rates of TB cases resistant to isoniazid increased from 5% to 7%, those resistant to rifampicin from 1% to 1.2% and those with multidrug resistance from 0.8% to 0.9%[7].

These data mirror similar figures from the USA, where the years 1985–1992 witnessed a rise in TB rates, which has been variably ascribed to the coincident HIV epidemic, degradation of public health support for TB eradication, homelessness, alcohol and drug use, and increased immigration from countries with endemic tuberculosis[8] (Figure 1). Foreign-born cases represented 58% of total reported TB cases in the US in 2006[9,10]. From the general cohort of infected individuals, 116 multidrug-resistant TB (MDRTB) and four extensively drug-resistant TB (XDR) individuals were reported to health authorities in 2006[9,10]. The current incidence of TB infection in pregnant women in the US ranges from 0.1 to 1.9%, but this percentage is predicted to rise, given the general increase of TB incidence. The rate of new cases in women attains its zenith between the ages of 25 and 34[11].

DEFINITIONS OF TUBERCULOSIS TERMS AND ACRONYMS, BASIC MICROBIOLOGY AND PATHOPHYSIOLOGY

Mycobacterium tuberculosis (MTB) is a small, aerobic bacillus within the family *Mycobacteriaceae*, which also includes *Mycobacterium bovis*, *Mycobacterium africanum* and *Mycobacterium microti*. All species possess cell walls laden with lipids and waxy substances, which enable

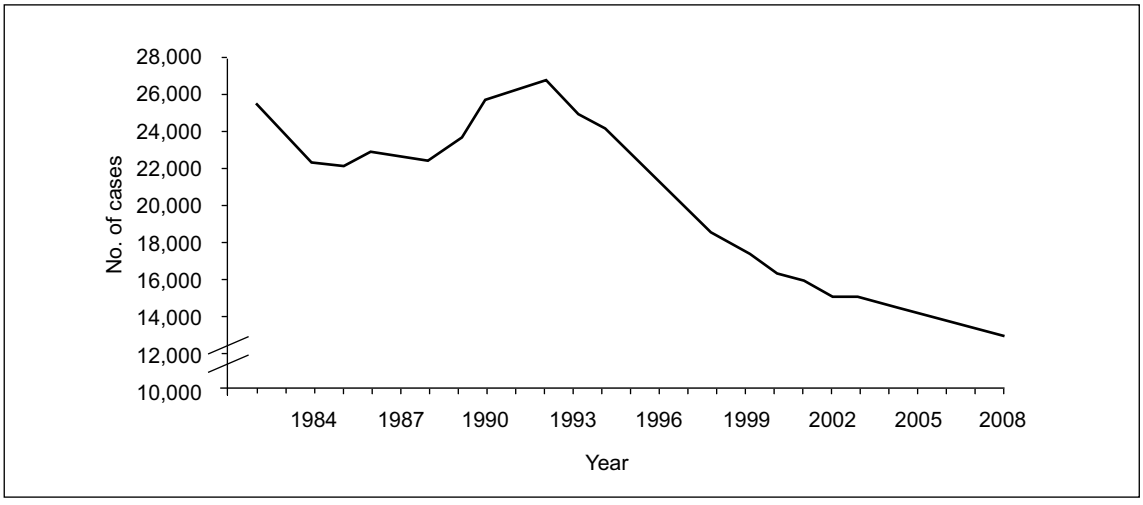

Figure 1 Reported TB cases in the USA for 1982–2008[9]

them to elude typical Gram stain. The term acid-fast arises from observations pertaining to two different commonly utilized staining mechanisms: carbol fuchsin (Ziehl-Neelsen and Kinyoun) and a fluorochrome method which uses auramine-O or auramine-rhodamine. Once stained, bacilli retain their color even after an acid-alcohol wash, and are thus referred to as 'acid-fast'[12,13].

Transmission occurs when infected individuals aerosolize organisms during coughing, sneezing, singing, or speaking; respiratory droplets persist in the air for hours. Infectious aerosolized particles lodge in the host's alveoli, where alveolar macrophages encounter them and they undergo phagocytosis. After initial infection, the lifetime risk of progression to active disease is 10%, with a 5% risk of progression within the first 2 years. Host factors such as age, comorbid conditions, especially those affecting the immune system, and nutritional status all influence the probability of progression. Mycobacteria somehow evade death within macrophages, replicate within these cells, and spread throughout the lymphatic system to other parts of the body. In individuals with normally functioning cell-mediated immunity, macrophages attract T lymphocytes, which then work in concert to form granulomas to contain further spread. This response typically occurs over 2–8 weeks, and is the basis of the tuberculin skin test (TST). Antibodies are also formed to MTB, but do not appear to confer protection[13]. Activated T lymphocytes secrete interferon γ, which serves as the immunologic rationale for the interferon γ release assay (IGRA); QuantiFERON (Cellestis Ltd, Australia) and ELISpot (Oxford Immunotec Ltd, UK) being two common blood tests which help detect latent tuberculosis infection[14]. The Mantoux skin test is the oldest test in continual use, whereas the blood tests are relative newcomers (Table 1).

Primary infection occurs when MTB enters a susceptible host, a process resulting in three potential outcomes:

1. Latent tuberculosis infection (LTBI), which refers to an asymptomatic and non-infectious state after the host has mounted an effective granulomatous response, successfully sequestering the organism, and one that satisfies the conditions of having either a positive TST or QuantiFERON test, a negative chest X-ray and no evidence for

Table 1 Tuberculosis tests

	Specificity (%)	*Sensitivity* (%)	*Affected by BCG vaccine*	*Mechanism*
Tuberculin skin test	97*	77**	Yes	Measures amount of skin induration based on cutaneous delayed-type hypersensitivity response to purified protein derivative
ELISpot	93†	90†	No†	Measures the number of IFNγ-producing T cells in reaction to the antigens ESAT-6 and CFP-10 produced by MTB, and not in the BCG vaccine
ELISA	96†	70†	No†	Measures the serum concentration of IFN-γ produced by T cells in reaction to the antigens ESAT-6 and CFP-10 produced by MTB, and not in the BCG vaccine

BCG, Bacille Calmette-Guerin; ESAT-6, early secretory antigen target-6; CFP-10, culture filtrate protein 10; MTB, *Mycobacterium tuberculosis*; IFN, interferon

*In non-BCG vaccinated individuals. **From Pai *et al*.[15] †From Lalvani *et al*.[16]

active TB disease either symptomatically (i.e. night sweats, weight loss, prolonged cough, hemoptysis) or by laboratory evaluation (i.e. positive sputum cultures)[17];

2. Primary tuberculosis, which refers to active disease within the first 2 years of infection;
3. Reactivation disease, which signifies active disease after a period of latency beyond 2 years.

MDRTB denotes TB which is resistant to the two first-line drugs, isoniazid and rifampicin, while XDR refers to MDRTB which is also resistant to any one of the fluoroquinolones as well as one of the intravenous second-line medications which include amikacin, kanamycin or capreomycin[18].

Compared to the general public, signs and symptoms are no different for pregnant women, but diagnosis is often delayed. Manifestations of active TB depend on the site, which for most people is pulmonary, although the bacterium may attack any part of the body, including the lymphatic, genitourinary (especially damaging in females), musculoskeletal, central nervous, gastrointestinal and cardiac systems. Manifestations of pulmonary TB include cough, weight loss, fever, fatigue and malaise, hemoptysis, night sweats and chest pain. The non-specific nature of these symptoms, as well as the often ill-informed reluctance to perform radiographic testing in pregnancy, presents a diagnostic challenge to physicians. For these reasons, health care providers must be vigilant to consider this diagnosis in pregnant patients[19].

TUBERCULOSIS AND PREGNANCY

Opinions regarding the effects of tuberculosis on pregnancy, and conversely, of pregnancy on the course of tuberculosis, have varied greatly throughout history. In the era of Hippocrates,

pregnancy was thought to have a salutary effect on tuberculosis, this perspective being in diametric opposition to that of the early 20th century when professionals actually recommended therapeutic abortions if pregnancy and tuberculosis diagnoses coincided. Current medical opinion holds that pregnancy and TB do not affect each other's course, but that active tuberculosis has adverse obstetrical and neonatal outcomes[19]. One prospective cohort study compared pregnant women with TB (subdivided into those treated early or before pregnancy and those treated in the second or third trimester) to pregnant, non-tuberculosis infected women, and found that pulmonary TB was the most common manifestation in pregnancy. Furthermore, the relative risk of obstetrical morbidity (defined by the authors as 'the presence of any complication during pregnancy attributed directly or not to the infectious disease') in TB-infected patients was three times the risk of uninfected individuals; this risk increased when treatment commenced later in the pregnancy[20]. Major complications experienced by women in this study included preterm labor, pre-eclampsia, premature rupture of membranes and fetal growth retardation. Average birth weight was 200 g lower for infants whose mothers had TB versus controls[18]. Other studies corroborate these findings. In one series, active pulmonary TB was associated with prematurity, fetal growth retardation, low birth weight and increased perinatal mortality among infants of mothers with TB as compared to infants of healthy women[21]. Another prospective cohort study that examined the effects of extrapulmonary TB (representing about 10–27% of TB cases), found that tuberculous lymphadenitis had no effect on pregnancy or perinatal outcome, but women with other-site extrapulmonary disease suffered more antenatal hospitalizations, and had babies with lower Apgar scores and lower birth weights compared to non-infected controls[22]. Other studies have also documented adverse neonatal outcomes. One series demonstrated a 23% morbidity rate among children born to TB-infected mothers versus 3.8% in the control group, including higher incidences of prematurity, perinatal mortality and low birth weight among the TB group. Risk factors included maternal pulmonary disease and late start of treatment[23]. Other considerations include the fact that congenital tuberculosis is a rare but serious complication of maternal TB, and the presence of genitourinary TB remains an important cause of female infertility, especially in developing countries. In summary, active tuberculosis produces deleterious effects on the mother as well as on the newborn, and merits prompt diagnosis and treatment.

TUBERCULOSIS SCREENING

The Health Protection Agency in the UK recommends targeted screening of pregnant women for TB; for instance, for those who have recently been exposed to tuberculosis (occupational or household contacts), or for those who are HIV positive. Screening should then proceed with determination of Bacille Calmette-Guerin (BCG) vaccination status, tuberculin testing, interferon γ blood tests and/or chest radiography if indicated[24]. Chemoprophylaxis should commence if a pregnant woman is a close contact of a known active TB case and has reactive skin or blood tests, with a negative chest X-ray. A Mantoux TST is considered positive with induration of 6 mm or more[25]. The recommended treatment regimen is 6 months of isoniazid plus pyridoxine.

Another question to be considered is provision of the BCG vaccine as a preventive measure. Because BCG is a live attenuated vaccine, it should not be administered during pregnancy. The 2005 UK Department of Health guidelines recommend that all infants (0–12 months) receive the BCG vaccine as soon as possible (preferably prior to hospital discharge) if they reside in areas where TB

incidence is 40/100,000 or higher, or they have a parent or grandparent whose country of origin carries a TB incidence of 40/100,000 or higher[26].

Because most cases of active TB in the US arise from LTBI patients, the joint Centers for Disease Control and Prevention (CDC) and American Thoracic Society (ATS) guidelines recommend targeted testing for tuberculosis among high-risk individuals as a strategic method to reduce prevalence[27]. The CDC notes cut-offs of >5 mm induration, >10 mm induration and >15 mm induration in the interpretations of the TST, depending on the risk factors of the tested individual (Table 2)[28].

According to the National Institute for Clinical Excellence (NICE), the probability of evolution to active tuberculosis in a latently infected individual is enhanced by HIV positivity, injection drug use, solid organ transplantation, jejuno-ileal bypass or gastrectomy, presence of a hematological malignancy, chronic renal failure or on hemodialysis, receiving antitumor necrosis factor (TNF)-α treatment or history of silicosis[25]. The US guidelines have similar criteria for assessing risk of progression to active TB and, in addition, include age under 20 years, abnormal or fibrotic lung lesions, underweight by 10% or more of ideal body weight, diabetes mellitus, prolonged corticosteroid therapy, and head and neck cancers[27,28].

Table 2 Recommendations for targeted tuberculin testing

High risk (+PPD = 5 mm)
HIV positive
Contacts of TB patients
Fibrotic changes on chest radiograph
Organ transplantation patients
Persons on prolonged corticosteroid therapy
Moderate risk (+PPD = 10 mm)
Recent immigrants from high prevalence countries
Injection drug users
Homeless persons
Resident or employee of high-risk congregate setting
Mycobacteriology laboratory employee
People with certain clinical conditions (silicosis, diabetes mellitus, renal failure, underweight, gastrectomy, certain cancers)
Children younger than 4 years of age
Infants, children or adolescents exposed to high-risk adult
Low risk (+PPD = 15 mm)
Testing not recommended

PPD, purified protein derivative. Adapted from Bergeron *et al*.[28]

Treatment of LTBI represents one of the chief means of TB control in low-TB incidence nations. Although the BCG vaccine, a live attenuated strain of *M. bovis*, is available in many nations around the world, it is not an approved method of TB control in the US. It is, however, used with varying degrees of success for primary prevention and to mitigate against disseminated or devastating disease in many other parts of the world, particularly in children, including in the UK[12]. As previously mentioned, the BCG vaccination is not given to pregnant women, but may be considered in (1) neonates born in an area with TB incidence of >40/100,000 or with a parent or grandparent born in a high-incidence country or with a family history of TB within the past 5 years; (2) infants and children (older than 4 weeks and younger than 16 years) who are at increased risk (would qualify for neonatal vaccine) and are Mantoux negative; (3) selected new entrants to the UK (from high-incidence nations and without previous vaccination as noted by history and/or scar); (4) health care workers (without prior history of BCG vaccination, and who are Mantoux or interferon γ negative); (5) contacts of people with active TB, and others at increased risk of contracting TB (e.g. working with prisoners or in nursing homes)[25].

Recommended screening for TB begins with the TST, 0.1 ml of 5 units of purified protein derivative (PPD) injected intradermally on the

volar aspect of the forearm and read 48–72 hours later[28]. If used, this test should be performed as early in the pregnancy as possible or, in high-risk populations, preconceptionally. The biological basis of the TST is a delayed-type hypersensitivity reaction to antigenic moieties derived from the mycobacterium. Previous exposure to the BCG vaccine may confound visual test interpretation, however, by producing a potentially false-positive reaction. Fortunately, the newer IGRAs do not cross-react with previous inoculation with the BCG vaccine; on the other hand, their use has not been extensively evaluated in pregnant populations[29,30]. The joint 2008 CDC/ATS statement on diagnostic evaluation also underscores the exigency of evaluating for active TB if a positive reaction is obtained. A recent prospective study to evaluate a newer T cell-based IGRA called ELISpot-PLUS, found the ELISpot-PLUS assay to be more sensitive than the standard ELISpot test, and was particularly effective in helping to rule out latent or active TB if used in conjunction with the TST when a moderate to high pretest probability exists[31]. In general, the IGRAs have excellent specificity, and results are not confounded by previous BCG vaccination; sensitivity is not quite as high, but the T-SPOT appears to have greater sensitivity than either the TST or the QuantiFERON tests[31,32].

DIAGNOSIS AND TREATMENT

Health care professionals caring for pregnant women with TB ideally should consult with a knowledgeable pulmonary or infectious disease colleague for advice and guidance, especially if comorbid diseases and conditions exist or are suspected to exist, such as HIV infection or MDR or XDRTB. Tripathy and Tripathy[33] concluded in a prospective study that no statistical differences existed between pregnant women divided into TB-positive women who received antituberculosis chemotherapy throughout pregnancy and non-TB infected same sex controls in terms of outcomes of gestational duration, occurrence of preterm labor, or congenital anomalies of their babies[33]. The CDC concurs that most first-line agents for tuberculosis are safe to use during pregnancy, even though they do cross the placenta.

Directly observed therapy (DOT) is an important component of treatment regimens in the US and India; however, in the UK, DOT is not usually required for most standard cases of active TB unless the risk assessment for treatment adherence reveals homelessness, or history of previous non-adherence to therapy[25]. DOT is a widely recognized strategy of TB management whereby health workers directly observe patients as they take their medication. This strategy increases adherence and reduces the likelihood of emergence of drug-resistant forms of *Mycobacterium tuberculosis*. If the TST or IGRA is positive, a meticulous history should be performed, specifically assessing for BCG vaccination history, symptoms of active TB, past or present contacts of infectious TB patients, previous PPD history (especially if negative within the last 2 years), and indicators of immune dysfunction. If suspicious symptoms or comorbid immunosuppressing conditions exist, a shielded chest X-ray should be performed; otherwise, shielded radiographic evaluation can be deferred until the second trimester. A positive chest X-ray prompts the need to examine three sputum samples collected at separate times for acid-fast bacilli smear, culture and susceptibility testing[28].

LATENT TUBERCULOSIS INFECTION

Pregnant women diagnosed with LTBI are at high risk of developing active TB, especially if they are HIV positive, have had contact with active TB cases, or reveal new PPD positivity within the past 2 years. Such women should begin treatment in the first trimester in any of the aforementioned circumstances[28].

Otherwise healthy women may wait until the postpartum period to commence their treatment of LTBI. Some experts advocate treating LTBI during pregnancy for all patients regardless of risk of progression to active TB, asserting that for some higher-risk women (homeless, immigrants from endemic areas, low socioeconomic status, etc.) pregnancy represents the only encounter with and opportunity for medical care. This statement is true both in resource poor and in developed countries. Treatment should be viewed as a critical means of preventing active TB in vulnerable populations and as a means to contain further spread in the communities wherein these women and their babies reside[28,34]. A cost–benefit analysis conducted by Boggess *et al*. described favorable economics for antenatal treatment of LTBI even with the increased need for hepatotoxicity monitoring related to isoniazid[35]. Regardless of these considerations, presently both the CDC and the American College of Obstetricians and Gynecologists (ACOG) recommend targeted testing for TB only in high-risk populations, and, unless compelling reasons exist (HIV infection, recent TB infection), delaying LTBI treatment until 2–3 months postpartum. This position is mostly in deference to fears of exposure to any medications during pregnancy.

In the UK, isoniazid is considered safe for treatment of latent TB during pregnancy, although the general reluctance to prescribe medications during gestation is acknowledged; treatment may be delayed until the postpartum period unless the woman is HIV positive or has had recent contact with active TB cases. Bothamley cites the East European Prevention Trial, whereby isoniazid was used for chemoprophylaxis, and determined that the risk attributed to isoniazid was two orders of magnitude less than the risk of TB on the pregnancy[36]. A common regimen for treatment of LTBI consists of isoniazid plus pyridoxine for 6 months[36]. Bothamley recommends that baseline liver function testing be performed before initiating isoniazid therapy, repeated every 2 weeks for the first 8 weeks of therapy (or weekly if chronic liver disease is present), and continued monthly for the remainder of pregnancy and certainly if symptoms such as fever, malaise, anorexia, or jaundice occur. Isoniazid and other hepatotoxic medications such as rifampicin and pyrazinamide should be discontinued if liver function tests exceed 3–5 times the upper limits of normal[36]. The CDC recommends isoniazid daily or twice a week for 9 months for women at high risk of developing active disease. Pregnant women on isoniazid should receive pyridoxine supplementation to diminish the risk of peripheral neuropathy[27]. Baseline liver function testing is recommended in pregnant women receiving isoniazid, and routine clinical and laboratory monitoring during therapy should be considered. It is recommended to discontinue isoniazid if liver function enzymes exceed three times the upper limits of normal in symptomatic patients, or five times the upper limits of normal in asymptomatic patients[11].

ACTIVE TUBERCULOSIS

The CDC states that untreated active TB imperils a pregnant woman and her baby more than the treatment itself[29]. Medications contraindicated in pregnancy include streptomycin (concerns of fetal hearing loss); kanamycin and amikacin (risks of nephrotoxicity and congenital hearing loss); capreomycin (risks of nephrotoxicity and congenital hearing loss); and, finally, the fluoroquinolones (due to teratogenic effects). In the US, relative contraindications to PZA (pyrazinamide) exist mostly due to a dearth of evidence regarding its use[30].

Treatment is divided into an initial or intensive phase followed by a continuation phase. The initial phase is intended to kill actively replicating and semidormant bacteria. Three or more drugs are used to help guard against the emergence of resistant organisms. In

non-pregnant individuals, the initial phase typically is 2 months in duration, and consists of a four-drug plan consisting of isoniazid, rifampicin, pyrazinamide and ethambutol. The continuation phase, on the other hand, consists of isoniazid and a rifamycin product daily or intermittently for the remaining 4–7 months. The choice of drugs and length of administration depend on organism susceptibility, site and severity of disease[37]. In the UK, standard treatment for TB, consisting of isoniazid and rifampicin for 6 months, with pyrazinamide and ethambutol for the first 2 months, may be given throughout pregnancy. Whereas daily or intermittent (three times a week) treatment is acceptable, intermittent treatment is cheaper and also allows for supervised therapy. Twice weekly regimens are not recommended because adverse effects from rifampicin may become more evident[36]. The UK regimen is a departure from therapy in the US, where pyrazinamide is relatively contraindicated. The CDC guidelines state:

> 'The initial treatment regimen should consist of INH [isoniazid], RIF [rifampicin], and EMB [ethambutol]. SM [streptomycin] should not be substituted for EMB. Although PZA [pyrazinamide] is recommended for routine use in pregnant women by the WHO[37] and the IUATLD[38], the drug has not been recommended for general use in pregnant women in the United States because of insufficient data to determine safety…If PZA is not included in the initial treatment regimen, the minimum duration of therapy is 9 months. Pyridoxine, 25 mg/day, should be given to pregnant women who are receiving INH…INH, RIF, and EMB cross the placenta, but none has been shown to have teratogenic effects[39]. SM (streptomycin), the only antituberculosis drug documented to have harmful effects on the human fetus, interferes with development of the ear and may cause congenital deafness…The fluoroquinolones have been associated with arthropathies in young animals; therefore, they should be avoided if possible in pregnant women…In general, administration of antituberculosis drugs is not an indication for termination of pregnancy...'[30].

BREASTFEEDING

Breastfeeding may continue in women being treated for LTBI. First-line agents do enter breast milk, but have not been found to produce toxicity in the newborn[30]. Mothers with active TB who may still communicate the disease should not remain in direct contact with their infants to reduce the risk of spread. MTB bacilli do not enter breast milk, and such women may pump their milk to be fed to their infants, unless the mother possesses a tuberculous breast lesion. If a tuberculous breast lesion does exist, however, the mother may pump and discard the milk to maintain her supply until the lesion heals. When the mother is no longer considered infectious (amelioration of signs or symptoms of active disease, has been on effective therapy for at least 2 weeks, and repeat sputum smear is negative), she may resume direct breastfeeding of her child[41].

MULTIDRUG RESISTANT TUBERCULOSIS AND HIV INFECTION

MDRTB necessitates treatment using second-line drugs for which there is limited clinical experience. One study found no significant evidence of toxicity in children either congenitally or at long-term follow-up (average age 3.7 years) with use of second-line drugs[42]; another revealed no obstetrical complications or congenital TB transmission in a series of pregnant women treated for MDRTB[43]. This suggests that MDRTB may be successfully treated during pregnancy without significant harm

to mother or child, and without requiring recommendation of a therapeutic abortion[43].

Any tuberculosis-positive patient should be tested for concurrent HIV infection. HIV greatly increases the risk of progression to active TB. HIV is believed to complicate tuberculosis treatment during pregnancy primarily by drug interactions between HIV and tuberculosis medications, especially rifampicin, which induces hepatic drug metabolism[35].

In conclusion, TB remains an increasingly common infectious disease and a major cause of mortality and morbidity among pregnant women worldwide. Diagnosis of TB in pregnancy is frequently delayed, and a high index of suspicion is often required to detect it. Nevertheless, pregnancy can be an important opportunity for identification and treatment of TB. The authors wish to emphasize that any health care provider who undertakes treatment of pregnant women with MDR or XDRTB and/or HIV should do so in close collaboration with experts in pulmonary and infectious diseases.

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