Tuberculosis and Pregnancy—Maternal, Fetal, and Neonatal Considerations

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ABSTRACT The issue of tuberculosis during pregnancy is not simply a historical inquiry but rather an increasingly familiar clinical problem facing industrial nations as well as the developing countries of the world. This review focuses on the maternal aspects of tuberculous infection, as well as transmission to the fetus and newborn.

EPIDEMIOLOGY
The epidemiology of tuberculosis in pregnancy reflects that of tuberculosis at large. Worldwide, the number of cases of tuberculosis appears to have peaked in 2004, with declining rates in Western and Central Europe, Latin America, the Eastern Mediterranean, Southeast Asia, and the Western Pacific. High prevalence rates have yet to decline substantially in Africa and Eastern Europe (1). According to the WHO, in 2013 tuberculosis caused half a million deaths among women worldwide, most of whom were human immunodeficiency virus (HIV) negative (2). For the United States, the rising incidence of tuberculosis seen during the late 1980s and early 1990s appears to have ended. The U.S. case rate (per 100,000 persons) of 10.4 in 1992 declined to 2.96 in 2014, with 66% of reported TB cases occurring among foreign-born persons. Different ethnic groups have widely different rates, however, with Asians having the highest case rate of 17.8 per 100,000 persons, followed by Native Hawaiians and other Pacific Islanders, with a case rate of 16.9 per 100,000 persons (2). The 2014 tuberculosis case rates for women of childbearing age from various ethnic groups (3) are shown in Table 1. A recent systematic review of latent tuberculosis in pregnancy revealed a prevalence of 14 to 48% in the United States, with skin test positivity varying with ethnicity, representing a significant opportunity to potentially impact upon the development of tuberculosis disease in both the mother and the infant (4). For women of childbearing age, infection with HIV represents a significant risk factor for tuberculosis infection. Of 16 pregnant women with tuberculosis in New York City reported by Margono and coworkers, 7 of 11 (64%) tested were HIV positive (5). Another study of a cohort of HIV-infected women in the United States found that 5 out of 46 (11%) of the pregnant women were coinfected with the tuberculosis agent (6). In sub-Saharan Africa, where the burden of HIV and tuberculosis is among the largest worldwide, HIV infection has been correlated with a 10-fold-higher incidence of tuberculosis infection (7).

EFFECT OF PREGNANCY ON TUBERCULOSIS
Hippocrates believed that pregnancy had a salutary effect on tuberculosis. This belief persisted until the middle of the 19th century, when case reports of accelerated progression of disease during pregnancy surfaced (8).
Osler recommended that physicians veto the marriage of any girl “whose family history is bad, whose chest expansion is slight, and whose physique is below the standard” (9). By the early 20th century, physicians began to advocate sterilization for women suffering from a variety of health problems, including tuberculosis. J. Edgar Clifton, a physician writing in 1918, stated, “A candidate for tuberculosis runs very great risk of becoming consumptive through childbirth” (10).

A number of reports from the 1950s, however, showed that pregnancy did not predispose women to progressive disease (11, 12). In a report of 250 women with active tuberculosis in the pretreatment era, 83.9% remained stable during pregnancy and 9.1% improved. Although only 7% had evidence of progressive disease during pregnancy, an additional 8.2% experienced progression in the year following pregnancy (11). A study from New York published two decades later, in the era of chemotherapy, had similar results, with a progression rate of only 2% in the cohort of pregnant and postpar- tum women who had received antitubercular chemother- apy. As with the earlier study, most of the relapses occurred in the postpartum period (13). These findings were similar to those in other studies of nonpregnant women, thus showing that pregnancy does not adversely impact the course of tuberculosis infection. Pregnancy does not alter the site of disease; most studies report 5 to 10% of patients with extrapulmonary disease, similar to the rate in nonpregnant patients (14, 15). A recent study performed in the United Kingdom demonstrated that after adjustment for age, socioeconomic status, region of residence, and Mycobacterium bovis BCG vaccination status, tuberculosis incidence was significantly higher during the 180 days postpartum but not during pregnancy (16).

Pregnancy itself, however, may mimic and thus mask the symptoms of early tuberculosis, such as tachypnea and fatigue; this, in turn, may delay diagnosis and treatment. Of pregnant women screened for and diagnosed with tuberculosis, the majority have been shown to be asymptomatic and unaware of their disease (14, 15). Failure to recognize and treat the infection in the pregn- ant woman may lead to congenital infection in the in- fant. As evidence of this, in some series of congenital tuberculosis, the mother was evaluated and tuberculosis was diagnosed only after the disease was diagnosed in the infant.

EFFECT OF TUBERCULOSIS ON PREGNANCY

Tuberculosis can impact all phases of female reproduc- tion, including fertility and birth outcomes. Infection of the reproductive organs may result in infertility as well as abdominal or tubal pregnancy (17). Several studies have shown genital tuberculosis to be the cause of 1 to 17% of infertility cases (18, 19). Genital tuberculosis can cause tubal obstruction, impairment of implantation due to endometrial involvement, ovulatory failure from ovarian involvement, and synechiae of the uterine cavity. Successful pregnancy even after tuberculosis treat- ment is unusual and often requires in vitro fertilization and embryo transfer (20). In the prechemotherapy era, prematurity rates in tuberculous women ranged from 23 to 44%, with the higher rates in the most severely affected mothers (21). Studies from Mexico, India, and Taiwan have shown that infants born to mothers with tuberculosis have a 2- to 3-fold increase in rates of prematurity and low birth weight and an increase in perinatal death as high as 6-fold (22–25). Adverse peri- natal outcome was associated with late diagnosis, in- adequate treatment, and advanced disease (23). With early recognition and effective chemotherapy, however, there is no evidence of an adverse effect on pregnancy (13, 26).

PATHOGENESIS AND CONGENITAL INFECTION

The pathogenesis of tuberculosis in the pregnant woman begins as in all other patients. After exposure, usually by inhalation, and local replication, there is dissemination of the organism by lymphatic spread, hematogenous spread, or both. If the organism affects the placenta or genital tract, the child may be congenitally infected. Congenital tuberculosis is a rare disease with a high mortality rate. The mycobacterium may be delivered to the infant directly via the umbilical vein, forming a primary complex in the liver of the infant with secondary

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**TABLE 1** Tuberculosis case rates per 100,000 population for women of childbearing age, United States, 2014*

<table>
<thead>
<tr>
<th>Ethnic group</th>
<th>15- to 24-yr-olds</th>
<th>25- to 44-yr-olds</th>
</tr>
</thead>
<tbody>
<tr>
<td>White, non-Hispanic</td>
<td>0.0</td>
<td>0.2</td>
</tr>
<tr>
<td>Black, non-Hispanic</td>
<td>3.1</td>
<td>5.5</td>
</tr>
<tr>
<td>Hispanic</td>
<td>2.2</td>
<td>4.0</td>
</tr>
<tr>
<td>Asian</td>
<td>13.2</td>
<td>14.1</td>
</tr>
<tr>
<td>Native Hawaiian/Pacific Islander</td>
<td>17.8</td>
<td>11.7</td>
</tr>
<tr>
<td>American Indian/Alaskan Native</td>
<td>3.7</td>
<td>2.5</td>
</tr>
</tbody>
</table>

*Source: reference 1.

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1. Gould and Aronoff
2. ASMscience.org/MicrobiolSpectrum
hematogenous spread, or through aspiration or ingestion of infected amniotic fluid, leading to a primary focus in the lungs or gastrointestinal tract (27, 28). The placenta should be examined histologically for granulomas, and acid-fast bacillus smear with mycobacterial culture should be obtained from a placental specimen when suspecting congenital tuberculosis in the infant.

Congenital infection, or infection of the fetus, must be distinguished from disease in the newborn acquired postnatally. The original standardized criteria for distinguishing between the two were proposed by Beitzke (29) in 1935 and were as follows:

Infant has proven tuberculous lesions, and one of the following:

- Lesions in the first few days of life
- A primary hepatic complex
- Exclusion of postnatal transmission by separation at birth of the infant from the mother and other potential sources

Cantwell et al. (30) reviewed congenital tuberculosis in 1994, including all case reports published since 1980. They concluded that the original diagnostic criteria had limited use, based, in part, on overreliance on autopsy or liver biopsy data as well as the now uncommon practice of isolating the newborn. Therefore, they proposed modified diagnostic criteria, more compatible with modern practice. These consist of the following:

Infant has proven tuberculous lesions and one of the following:

- Lesions in the first week of life
- A primary hepatic complex or caseating hepatic granulomas
- Tuberculous infection of the placenta or maternal genital tract
- Exclusion of postnatal transmission by a thorough investigation of contacts and adherence to current infection control guidelines

The authors showed these criteria to have increased diagnostic sensitivity when applied to the cases reported in the literature. A 2011 case series of congenital tuberculosis using these criteria (n = 6 cases) performed in China with review of the world’s literature from 1946 to 2009 (n = 164 cases) revealed that the average age of onset was 20 days; nonspecific signs and symptoms were found in 170 cases, and abnormal chest radiographs were found for 133 infants, with miliary and nodular disease in 83 cases. Mortality was high (52.6% before 1994 and 33.9% after 1994). Normal or decreased blood leukocyte count, earlier age of symptom onset, and presence of intracranial lesions negatively impacted the prognosis (31).

**CLINICAL MANIFESTATIONS**

The clinical manifestations of tuberculosis in pregnancy are similar to those in nonpregnant women. Good and associates (32) reported that among 27 pregnant women with active disease, cough (71%), weight loss (41%), fever (30%), and malaise and fatigue (30%) were the most common symptoms. However, 20% of the women in their cohort were asymptomatic.

The lungs are the most common site affected and account for approximately 90% of all cases (15, 33). Lymph node, bone, and kidney diseases affect most of the remaining patients. A study of 22 cases of breast tuberculosis in Iran revealed that most affected persons were young (mean age of 32.4 years), lactating, multiparous women presenting with a breast mass and pain (34).

HIV infection modifies the type of tuberculosis disease to more serious forms. In a study of 16 patients with tuberculosis in an area of high HIV prevalence, there were 10 cases of pulmonary disease (5 cavitary), 2 meningeal, 1 mediastinal, 1 renal, 1 gastrointestinal, and 1 pleural (5).

**DIAGNOSIS**

The tuberculin skin test (Mantoux) is the test of choice for diagnosing tuberculosis infection in pregnant women. In recent years, blood tests have been developed which measure T-cell gamma interferon release in response to specific tuberculin antigens. These tests have potential advantages in terms of logistics (only one visit needed) and accuracy (not subjectively interpreted and not affected by previous *Mycobacterium bovis* BCG vaccination). However, there are currently insufficient data on the use of these tests in pregnant women to recommend them as the method of choice.

Although pregnant women have suppressed cell-mediated immunity to tuberculin in *in vitro* studies (35, 36), this does not appear to be clinically relevant (37). While pregnancy does not alter the response to a tuberculin skin test, 10 to 25% of immunocompetent persons with active tuberculosis, pregnant or not, have a negative test result (38). Because the nonspecific symptoms of tuberculosis (increased respiratory rate, poor appetite, and fatigue) mimic the physiologic changes in pregnancy and therefore may be missed, tuberculosis skin testing
should be pursued in high-risk populations. These include members of minority urban communities, recent immigrants from countries with a high prevalence of tuberculosis, intravenous drug users, populations at high risk for HIV infection, and persons already infected with HIV (39). A simple clinical algorithm recommended by the WHO based upon the absence of cough, fever, weight loss, and night sweats has been shown to reliably exclude active tuberculosis disease among persons living with HIV. When this algorithm was applied to 800 pregnant women in India, the negative predictive value was 99.3%. Tuberculin skin test and targeted chest radiography provided little improvement (40).

HIV-infected persons with active tuberculosis have a negative skin test result in 40 to 60% of cases (5, 39). Skin test negativity is highly correlated with CD4 count and not with pregnancy. A study of pregnant and non-pregnant women infected with HIV showed that the rates of anergy to tetanus toxin and mumps were 14 of 46 (30%) in pregnant women and 38 of 78 (49%) in nonpregnant women. Anergy was associated with lower CD4 counts in both groups in this study, and although the nonpregnant women were more likely to be anergic, the CD4 counts were similar in both groups (6).

A thorough investigation to detect tuberculosis should be pursued for all persons with clinical features compatible with tuberculosis. To rule out active disease, routine chest radiographs (with proper shielding of the abdomen after the 12th week of gestation) should be performed in women with a positive tuberculin skin test result. Chest radiographs should be performed sooner if symptoms suggest pulmonary tuberculosis, even if the skin test result is negative. In addition, examination of specimens for mycobacteria should be performed for all patients with HIV infection and pulmonary symptoms. A complete review of systems and physical examination should be conducted to exclude extrapulmonary tuberculosis (39, 41).

**TREATMENT**

**Preventive Therapy**

Isoniazid (INH) effectively prevents the progression of latent infection to active disease in individuals infected with susceptible strains. There is no evidence of teratogenic effects on the fetus. The major side effect of INH is hepatitis, which occurs most frequently in persons over 35 years of age. Pregnancy and the postpartum period, however, are also considered independent risk factors for INH toxicity. In a report of 20 deaths due to INH toxicity, four were of women who began taking INH in pregnancy and continued after delivery. The incidence of death was estimated to be 1 in 2,000 postpartum women taking INH (42).

The American Thoracic Society states that for most pregnant women, preventive therapy should generally be delayed until after delivery. The exception is for women who are HIV positive or who have had recent contact with a contagious person. In this case, preventive therapy should begin when tuberculosis is documented, but not until after the first trimester. The recommendation to begin therapy after delivery is based on the increased risk of active tuberculosis during the postpartum period, notwithstanding the increased toxicity of INH during this period (43). Because of the high risk of development of active disease in the tuberculosis agent-infected, HIV-positive woman, preventive therapy should be given to all patients who demonstrate purified protein derivative conversion. Preventive therapy should also be considered for HIV-positive women who have negative test results but are anergic and live in high-incidence areas.

In all cases, preventive therapy should consist of 300 mg of INH in a single daily dose. Pyridoxine supplementation (25 mg/day) should be given to all pregnant and breast-feeding women taking INH (44). In addition, because nursing infants receive approximately 20% of a therapeutic dosage of INH through breast milk, these infants should also receive pyridoxine supplementation (45, 46). Although neurotoxicity, including seizures, has been reported for nursing children of mothers taking INH (47), treatment with first-line agents should not be considered a contraindication to nursing (48). Breast-feeding mothers may take their medication immediately after breast-feeding and consider substituting a bottle for the next feeding if feasible. The amount of INH in breast milk is inadequate for treatment of latent tuberculosis in the infant (46).

**Active Disease**

Pregnant women with active tuberculosis should begin therapy as soon as the diagnosis is established. The risk of transmission of the organism to the infant outweighs the risks of the drugs to the mother’s own health. The preferred initial treatment for pregnant women is the combination of INH, rifampin, and ethambutol. Rifampin and INH freely cross the placenta. Pyrazinamide is recommended for routine use in pregnant women by the WHO but has not received such approval in the United States due to a paucity of safety data. At least 6 months of therapy is recommended for drug-susceptible disease if pyrazinamide is used, and at least 9 months of therapy is
recommended if pyrazinamide is excluded. Streptomycin should not be used because there is a risk of sensorineural hearing loss in the infant (44). All first-line drugs are compatible with breast-feeding.

If resistance to the first-line drugs is encountered, the risks and benefits of second-line drugs should be weighed and their use considered. Unfortunately, most second-line medications may have deleterious effects on the fetus. Ethionamide and cycloserine have been associated with teratogenic effects in animals. Aminoglycosides, including kanamycin, capreomycin, and amikacin, presumably share streptomycin’s ototoxic potential. The fluoroquinolones have been shown to damage growing cartilage and thus should be avoided in pregnancy if at all possible (44). There are limited safety data on the use of delamanid and bedaquiline in pregnancy for the treatment of drug-resistant tuberculosis (49). Treatment duration is generally extended to 18 to 24 months.

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REFERENCES