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Review Article

Tuberculosis and Pregnancy: Present Status

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Abstract

Tuberculosis (TB) remains a significant global health concern, particularly in pregnant women, where it poses serious risks to both maternal and fetal health. The physiological and immunological changes during pregnancy can alter TB presentation, leading to delayed diagnosis and increased complications. This review explores the epidemiology, pathophysiology, clinical manifestations, and diagnostic challenges of TB in pregnancy. Special emphasis is placed on the safety and efficacy of anti-tubercular therapy (ATT), drug interactions, and potential teratogenic effects. We also discuss the impact of TB on pregnancy outcomes, including preterm birth, low birth weight, and perinatal transmission. Management strategies, including screening protocols, and treatment modifications, are reviewed in light of current guidelines. Given the rising burden of TB in endemic regions, a multidisciplinary approach involving obstetricians, pulmonologists, and infectious disease specialists is essential to ensure optimal maternal and fetal outcomes.

Keywords: Tuberculosis in pregnancy, Maternal TB, Extrapulmonary TB in pregnancy, Perinatal tuberculosis, TB and HIV in pregnancy, The impact of pregnancy on TB, Anti-tubercular therapy (ATT), Drug-resistant TB, TB and fetal outcomes, TB screening in pregnancy, Maternal-fetal complications, TB treatment guidelines India.

Introduction

Tuberculosis (TB) remains a formidable global health challenge and a significant contributor to maternal morbidity and mortality.[1] A study from Nigeria revealed that human immunodeficiency virus (HIV) coinfected tuberculosis women of reproductive age face the highest risk of death due to non-obstetric causes, accounting for 17.74% of cases.[2] The burden of TB is disproportionately distributed, with the highest prevalence seen in the World Health Organization (WHO) South-East Asia regions (44%).[3] Alarmingly, just eight nations account for two-thirds of the global TB cases including 27% in India, 9% in China, 8% in Indonesia, 6% in the Philippines and Pakistan, 4% in Nigeria and Bangladesh, and 3% in South Africa. Even though TB predominantly affects mostly men, still women represent 32% of all reported cases. The true rate of TB with pregnancy is still uncertain in a majority of regions, though it's presumed to mirror that of the community. The review aims to lay out a thorough update on TB during pregnancy, examining the impact on maternal and neonatal health while integrating the latest advancements in pathogenesis, cutting-edge diagnostic innovations, novel therapeutic strategies, and evolving national treatment protocols.

Pathogenesis

Tuberculosis (TB) is caused by "*Mycobacterium tuberculosis (Mtb)*", an aerobic acid-fast bacillus that was first come upon by Robert Koch in the year 1882. Lungs are the most commonly affected organs by TB, accounting for over 80% of cases, although it can infect any organ of the human body. In individuals with HIV, the disease often follows a different course, with an increased tendency for extrapulmonary involvement.

Transmission occurs primarily through inhalation of aerosolized *M. tuberculosis* bacilli, which are expelled during acts of cough, sneeze, or talking, and can be during the

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handling of tissues infected by TB. The bacteria can remain dormant in the body and is referred to as latent tuberculosis infection (LTBI), which in many cases does not advance to active disease. However, the lifetime risk of TB activation in a healthy adult is approximately 5 to 10%, whereas immunocompromised individuals have an annual risk of reactivation up to 10%, particularly in HIV-co-infected individuals.

Following primary infection, three possible disease outcomes exist:

- LTBI: A non-infectious as well as asymptomatic condition.
- Primary TB: Active disease occurrence within the first two years post-infection.
- Secondary Tuberculosis**:** Reactivation of previously healed TB or again infected with a new strain, leading to active disease.

Impact of Pregnancy on Tuberculosis

Research suggests that pregnancy itself does not significantly alter the course of TB. However, repeated pregnancies may contribute to the reactivation of latent TB due to physiological changes in the immune system. Given that TB primarily affects young adults, many females are either detected with the disease during pregnancy or conceive when on anti-tuberculosis therapy.[4]

A significant concern is the underdiagnosis of TB in pregnancy, leading to severe maternal and perinatal complications. However, pregnancy does not appear to affect key disease parameters such as sputum conversion rates, disease stabilization, or relapse risk.

Several factors influence TB progression and prognosis during pregnancy:

- Extent of the disease.
- Drug sensitivity patterns.
- Radiographic findings and individual susceptibility to TB[5]

While LTBI itself does not have a risk of vertical transmission, its progression to active TB during pregnancy can have significant implications. In India, with the incidence of TB up to 100 cases per 100,000 women of reproductive age and approximately 26 million annual births, it is projected that 20,000 to 40,000 pregnant women develop active TB each year.[6,7] The postpartum period also presents an increased vulnerability due to immune system shifts.

Although the exact global prevalence of active TB during pregnancy is not well documented, estimates range from 0.06 to 0.25% in the general population**.** Among HIV-negative pregnant women, the rate varies from 0.07 to 0.5%**,** whereas in HIV-positive women, the incidence can be as high a**s** 0.7 to 11%**.**

Impact of Tuberculosis on Pregnancy

Tuberculosis is the reason for many adverse outcomes in pregnancy. The severity of these outcomes depends on several key factors:

- Extent of the disease.
- Drug resistance patterns.
- Gestational age at the time of diagnosis.
- Association of extrapulmonary TB.
- HIV co-infection with HIV along with treatment response.

Poor prognostic factors include late-stage TB diagnosed in the third trimester or postpartum period, HIV co-infection, diabetes, and poor adherence to treatment regimens.[8]

Obstetric complications of TB in pregnancy include

- Increased risk of spontaneous miscarriage.
- Fetal growth restriction leading to small-for-gestational-age infants.
- Insufficient maternal weight gain.
- Higher incidence of pre-eclampsia, preterm labor, and postpartum hemorrhage.
- Increased neonatal mortality or low birth weight.[9-11]

A systematic review by Sobhy *et al.*[11] emphasized that the risk of perinatal and maternal complications is higher in pregnant women having TB than those without it. The odds of maternal morbidity 2.8, maternal anemia 3.9, cesarean delivery 2.1, preterm birth 1.7, low birth weight 1.7, birth asphyxia 4.6, and perinatal death 4.2 were the key findings of the analysis.

Furthermore, there is a 300% more risk of infant and maternal mortality in TB-HIV co-infection**.** In high-burden regions, 15 to 34% of indirect maternal deaths are attributed to TB-HIV co-infection as well as doubling the risk of HIV vertical transmission**.**

Although the COVID-19 pandemic has significantly impacted pregnancy outcomes, data on pregnant women with concurrent TB and COVID-19 remain scarce.

Maternal and Perinatal Outcomes in Extrapulmonary Tuberculosis (EPTB)

When diagnosed early and appropriately treated, outcomes in extrapulmonary TB (EPTB) can be favorable. However, studies suggest that certain forms of EPTB—such as vertebral, renal, abdominal, and meningeal TB—are linked to higher rates of antenatal hospitalization and pregnancy complications.

- Jana *et al.* (1999): EPTB contributed to 20% of cases of TB in pregnancy**.**
- Chopra *et al.* (2016): Revealed a 62% prevalence of EPTB in pregnant TB patients.
- Yadav *et al.* (2019): Found that 66.6% of TB in pregnancy cases were extrapulmonary[15-17]

The impact of EPTB on pregnancy depends on:

- Location of infection (lymph node TB has the best prognosis).
- The severity of disease (disseminated, military, and meningeal TB have poorer outcomes).
- HIV co-infection.
- Gestational age at diagnosis.
- Adherence to anti-TB therapy (due to potential adverse drug reactions).

Siza *et al.*[18] noted that pregnant women affected with TB face an elevated risk of preterm birth and fetal growth restriction. Chopra *et al.*[17], in their study of comparing pulmonary and extrapulmonary TB in pregnancy, found that:

- Anemia prevalence was significantly higher in TB pregnancies (41%) compared to non- TB pregnancies (23%).
- Fetal growth restriction was three times more common in TB pregnancies.
- Increased incidence of oligohydramnios.

Similarly, Yadav *et al.*[16] reported that EPTB pregnancies had a higher prevalence of oligohydramnios and premature rupture of membranes (PROM). However, they found no significant difference between EPTB and normal pregnancies regarding gestational diabetes, pre-eclampsia, intrahepatic cholestasis, antepartum hemorrhage, mode of delivery, or postpartum complications.

Nevertheless, adverse fetal outcomes were evident. The mean birth weight in EPTB pregnancies was significantly lower (2324 g) compared to normal pregnancies (2712 g).

Clinical Manifestations

A long cough is the most commonly reported symptom which is initially dry and nonproductive and often progresses to a productive cough over time. Additional symptoms may include hemoptysis, breathlessness, chest pain, and localized wheezing or crackles. Weight loss, fever, and night sweats are also frequent presentations. However, in pregnant females, the typical weight gain associated with pregnancy can temporarily mask the weight loss caused by tuberculosis.

The WHO has advised a four-symptom screening method, which includes cough, weight loss, fever and night sweats, to help in diagnosis of TB early in "people living with HIV (PLHIV)". However, meta-analyses and studies conducted in India, Kenya, and South Africa have indicated that while this screening has a high negative predictive value, its sensitivity and specificity remain suboptimal, limiting its effectiveness in accurately identifying TB cases.[12-14] This highlights the need for additional diagnostic tests to enhance case detection in pregnant females.

A pregnant female is classified as a case of presumptive TB if there is persistent documented and unexplained fever (>38°C) associated with or without cough for two weeks accompanied by loss of weight or failure to gain weight appropriately.

Extrapulmonary tuberculosis (EPTB) can affect almost any organ system in the body, with lymph node tuberculosis being the most prevalent form. Other commonly affected sites include the pleura, abdomen, skeletal system, central nervous system and genital tract. The most severe and disseminated form of the disease is miliary tuberculosis, which can lead to widespread systemic complications.

Laboratory Investigations

The approach to laboratory investigations for TB in pregnant females is similar to a state without pregnancy. "The tuberculin skin test (TST)" is often advised as an initial screening tool. While older studies suggested that pregnancy might reduce the sensitivity of this test, recent research indicates no significant difference in results due to pregnancy. Interferon-gamma release assays (IGRA) offer higher sensitivity than TST; however, they have not yet been fully validated for use in pregnancy.

Microbiological Tests

Diagnostic testing in pregnancy includes sputum smear analysis, culture testing, and molecular assays. Rapid molecular including the cartridge-based nucleic acid amplification test (CBNAAT) and line probe assay (LPA) provides more exact results in a shorter time frame. For culture-based detection, radiometric BACTEC 460 was previously used but has been discontinued due to radiation concerns. The BACTEC MGIT 960 system, a fully automated and non-radiometric mycobacterial growth indicator, is now the preferred method, though its availability is limited to specialized centers.

The WHO recommends "universal drug sensitivity testing (UDST)" in all suspected TB cases—whether pulmonary or extrapulmonary—before initiating treatment. This is especially crucial for detecting rifampicin resistance and, in the future, should extend to all anti-TB drugs for both new and retreatment cases.

Radiological Evaluation Chest X-Ray

On radiographic imaging, TB typically presents as patchy or nodular opacities in the upper lung zones, often accompanied by volume loss, fibrosis, and possible cavitation. In latent TB infection (LTBI), a primary focus may be observed. Concerns about fetal radiation exposure have historically limited the use of chest radiography in pregnancy. However, the risk of complications to a fetus is negligible with modern shielding techniques and lower radiation doses (< 0.01 mGy).[19] Chest X-rays remain a critical tool in diagnosing smear-negative TB, although normal radiographic findings can be seen in 14% of TB cases confirmed on culture.[20] Additionally, residual lung opacities may persist after bacteriological control, representing healed old lesions of TB.

Other Imaging Modalities

Ultrasonography (USG) and CT scans are not routinely required for TB diagnosis in pregnancy but can be used in specific cases where additional diagnostic clarity is needed.

Diagnostic Approach in Pregnancy

The diagnostic workup for both pulmonary and extrapulmonary TB during pregnancy follows the same principles as in the general population. A thorough history and risk assessment should be performed, including contact tracing and travel history to high-prevalence regions. A comprehensive clinical examination should be followed by necessary radiological and laboratory investigations, including a chest X-ray with proper abdominal shielding.

It is important to have microbiological confirmation and drug sensitivity testing using rapid molecular tests such as NAAT, and LPA along with liquid culture (MGIT). The diagnosis of LTBI includes IGRA and TST. However, a positive test result alone does not confirm the active disease, similarly, negative results do not rule TB out. Therefore, the clinical and epidemiological background of an individual must be considered before making a diagnosis.

Similarly, a diagnosed case of TB must be evaluated for HIV and glycemic control status due to the strong association of TB with HIV and diabetes.

Infection Control Measures

TB is contagious primarily when it affects the lungs or larynx. Effective infection control strategies are essential to prevent transmission, particularly in healthcare settings and among close contacts of infected pregnant women. Proper education about TB transmission and screening should be provided to healthcare workers, caregivers, and family members dealing with TB-positive pregnant individuals.

Management of Tuberculosis in Pregnancy

Tuberculosis (TB) during pregnancy presents unique challenges, requiring a delicate balance between achieving a complete maternal cure and ensuring fetal safety. The primary goals of treatment include preventing disease progression, minimizing transmission risk to newborns, along avoiding the emergence of resistant TB. Given the difficulties in managing TB in pregnancy, a multidisciplinary approach is essential, involving obstetricians, pulmonologists, neonatologists, microbiologists, TB specialists, counselors, and public health officials.

Standard Anti-TB Treatment (ATT) in Pregnancy

The management of drug-susceptible TB in pregnant females largely follows similar guidelines as in non-pregnant individuals, with minor modifications. The preferred regimen begins with an intensive phase of a duration of two months with "isoniazid, rifampicin, pyrazinamide, and ethambutol" and is followed by a continuation phase of a duration of four months with "isoniazid, rifampicin, and ethambutol". When adhered to properly, this regimen has a cure rate of over 90%.

The Second-line injectable drugs (SLIs), like streptomycin and amikacin, in pregnancy are contraindicated due to their potential to cause complications such as fetal ototoxicity. Treatment is typically administered on an outpatient basis unless complications necessitate hospitalization.

Managing Multidrug-Resistant TB (MDR-TB) in Pregnancy

Multidrug-resistant TB (MDR-TB) poses a significant challenge in pregnancy due to the limited availability of safe treatment options and the increased risks to both the mother and fetus. According to the National Tuberculosis Elimination Programme (NTEP) and WHO guidelines, several key considerations must be taken into account (Figure 1).

Injectable second-line aminoglycosides such as amikacin and streptomycin are strictly avoided due to their risk of fetal ototoxicity, while ethionamide, known for its teratogenic effects, should be avoided before 32 weeks of gestation. Recent guidelines have replaced injectable regimens with all-oral treatment options, improving both safety and patient adherence.

For pregnant women diagnosed with MDR-TB, comprehensive counseling is crucial. The potential risks of treatment delay, the possible effects of second-line drugs on fetal development, and the likelihood of congenital abnormalities should all be carefully discussed. In severe cases, where fetal malformations are expected, medical termination of pregnancy (MTP) may be considered. Close monitoring through electronic health records, such as the Nikshay system, ensures proper tracking of drug safety and treatment outcomes. Nutritional supplementation with locally available, nutrient-rich foods is also recommended to improve maternal health and fetal development.

Latent Tuberculosis Infection (LTBI) in Pregnancy

While it is asymptomatic, LTBI carries a significant risk of reactivation, particularly in PLHIV or immunosuppression, and diagnosis mostly relies on the TST or IGRA.

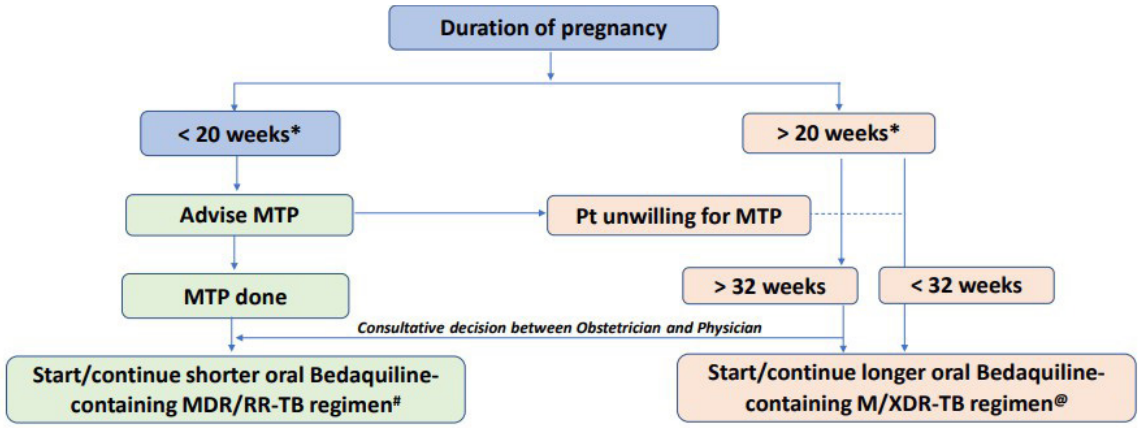
The recommended treatment here includes six months of "isoniazid preventive therapy (IPT)" with pyridoxine supplementation or a three-month regimen of rifampicin and isoniazid, both of which have been shown to be safe and effective in pregnant women. However, the treatment of LTBI during pregnancy remains controversial. Guidelines from the CDC and the American College of Obstetricians and Gynecologists (ACOG) recommend deferring treatment until the postpartum period unless there is a high risk of progression to active TB, such as in cases of latest contact with an infective TB case or high prevalence of TB in the community.[21] In situations where immediate treatment is necessary, the benefits of prevention of active TB outweigh the associated risks with isoniazid toxicity.

Perinatal Tuberculosis: Congenital and Postnatal Transmission

Tuberculosis in neonates can be acquired either in utero (congenital TB) or postnatally through exposure to an infectious caregiver. Congenital TB occurs when the fetus is infected via transplacental transmission or by ingesting infected amniotic fluid. In contrast, postnatal transmission is more common and typically results from close contact with an infected mother, family member, or healthcare worker.

Several factors influence the risk of perinatal TB transmission:

- Active TB in a mother with a high bacillary load: The risk is significantly higher when the mother has smear-



* 24 weeks will apply wherever the bill is passed.
# Regimen: 4-6 Bdq (6m) Lfx, Cfz, Eto, Hh, Z, E / 5 Lfx, Cfz, Z, E. No modifications allowed.
@ Regimen:18-20 Lfx, Bdq(6m or longer) Lzd#, Cfz, Cs. Lzd dose to be tapered to half after 6-8 months based on bacteriological response. Modify regimen if one or more drug cannot be used due to reasons of resistance, tolerability, contraindication, availability etc.

- in the order of Z E PAS.
- Eto may be considered after 32 weeks' gestation.
- Am may be considered in post-partum period only. Am will not be started in the final 12 months of treatment.

Figure 1: Showing programmatic approach in patients of MDR with pregnancy

positive pulmonary tuberculosis or has miliary TB, meningeal TB. However, in cases of pleural effusion or TB lymphadenitis, the risk of transmission is low.

- Coexisting maternal conditions: Co-infection with HIV, severe malnutrition, diabetes mellitus smoking and alcohol consumption can increase the likelihood of transmission.
- Status of Treatment: Significant reduction in transmission after two effective weeks of treatment with ATT and is nearly eliminated once treatment is completed.
- Degree and duration of neonatal exposure: Closer and prolonged contact with an infected individual raises the risk.
- Cough etiquette and barrier nursing: Proper infection control practices can significantly reduce the risk of neonatal infection.

Clinical Presentation of Perinatal TB

Diagnosing perinatal TB is particularly challenging, as its symptoms often overlap with other congenital infections. Clinical signs typically appear between the second and third week and may include:

- Irritability and poor feeding
- Failure to thrive and weight loss
- Fever and respiratory distress
- Lymphadenopathy and hepatosplenomegaly
- Abdominal distension, maculopapular skin lesions, and ear discharge.

A lack of response to antibiotics and ruling out other congenital infections should raise the likelihood of perinatal tuberculosis.

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