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Tuberculosis in Pregnancy

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Abstract

Tuberculosis (TB) during pregnancy presents significant risks to both the mother and fetus, including complications such as abortion, preterm birth, low birth weight, and postpartum hemorrhage. The immune changes in pregnancy, particularly the shift in TH1/TH2 balance, increase the risk of latent TB reactivation. Diagnosing TB in pregnant women is challenging due to overlapping symptoms with normal pregnancy changes. However, early diagnosis is crucial for effective management, with molecular tests offering assistance, although bacterial culture remains the gold standard. High-risk pregnant women include those with close contact with active TB patients, HIV, immunosuppressive conditions, or severe immunocompromised states such as lymphoma, leukemia, or organ transplant recipients. These women should undergo sputum testing for acid-fast bacilli smear, mycobacterial culture, and nucleic acid amplification testing if TB is suspected. Immunosuppressed patients may require further testing, even if interferon-gamma release assays or tuberculin skin tests are negative. Retesting is recommended eight weeks after exposure to infectious TB. The management of TB in pregnancy involves a multidisciplinary approach, including obstetricians, infectious disease specialists, and neonatologists. First-line anti-TB medications are safe during pregnancy and help prevent maternal and perinatal complications. Treatment for latent TB infection (LTBI) is generally delayed until after delivery. Breastfeeding is safe for mothers on first-line anti-TB medications, as drug levels in breast milk are too low to harm the infant. Early diagnosis, prompt treatment, and proper care are essential to reduce TB-related risks during pregnancy.

Introduction

Tuberculosis continues to be the leading cause of mortality from infectious agents in women of childbearing age globally (Elkady et al., 2019). According to the World Health Organization, approximately 54 million tuberculosis-related deaths could have been avoided from 2000 to 2017 through enhanced prevention and better disease management (Elkady et al., 2019; Mehta & Grover, 2022). On a global level, an estimated 216,500 cases of active tuberculosis were reported in pregnant women in 2011, with the risk increasing 2.56 times for those with human immunodeficiency virus infection (Hui & Lao, 2022). Physiological changes occurring during pregnancy complicate the diagnosis of tuberculosis (Elkady et al., 2019). However, pregnancy also creates an opportunity to incorporate tuberculosis and human immunodeficiency virus screening into prenatal care. For this reason, updated information on tuberculosis status during pregnancy and the postpartum period is essential (Elkady et al., 2019; Hui & Lao, 2022).

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Active tuberculosis during pregnancy is linked to a higher risk of adverse maternal and fetal outcomes, including a threefold rise in maternal morbidity such as anemia, elevated cesarean delivery rates, increased chances of miscarriage, preterm birth, low birth weight, and perinatal mortality. Screening individuals at risk of tuberculosis infection or its progression to active disease, along with ensuring appropriate treatment, is essential for minimizing complications and supporting tuberculosis control efforts (Miele et al., 2020). This article will provide a comprehensive discussion on the pathophysiology, methods of diagnosis, treatment strategies, and potential complications associated with tuberculosis during pregnancy, highlighting its impact on maternal and fetal health.

Definition

Tuberculosis infection refers to what was previously called latent tuberculosis, while tuberculosis disease is the updated term for active tuberculosis (Friedman & Tanoue, 2024). Mycobacterium tuberculosis infection is typically latent in most cases, but it has the potential to progress to active disease at any moment. Detecting and treating latent TB infection can lower the risk of progression by up to 90%. Individuals with latent tuberculosis infection (LTBI) remain asymptomatic, are not infectious, and do not present a risk of transmitting LTBI vertically (Elkady et al., 2019).

Epidemiology

Tuberculosis ranks as a major global cause of mortality, accounting for 1.4 million deaths. It is also one of the three primary causes of death among women aged 15 to 45 (Elkady et al., 2019; Mehta & Grover, 2022). Active TB prevalence in pregnant women ranges from 0.06-0.25% in low tuberculosis-burden countries and approximately 0.07-0.5% in high-burden countries. TB during pregnancy, however, is recognized to be linked to significant obstetric morbidity outcomes (Mehta & Grover, 2022). The risk of mortality rises during pregnancy and the postpartum period, particularly in women with HIV co-infection. Research in Africa found that TB contributed to 12.9% of total deaths and 27.7% of deaths in women living with HIV. Without treatment, TB during pregnancy can lead to a mortality rate as high as 40% (Elkady et al., 2019).

Numerous studies have highlighted that ensuring sufficient, high-quality, and accessible public health services (PHS) for tuberculosis (TB) can significantly contribute to controlling the TB epidemic. For instance, implementing rapid molecular testing has the potential to decrease regional disparities in TB prevalence substantially. Moreover, raising public awareness through health education initiatives can minimize delays in TB diagnosis. Enhancing the effective use of PHS for TB may lower both the incidence and mortality rates among vulnerable populations. The World Health Organization has also emphasized the need for countries to adopt systematic and comprehensive measures to improve access to TB prevention services and related initiatives (Chen et al., 2022; Li et al., 2021; O'Hara et al., 2017; Xiao et al., 2021).

Improving public health requires collaboration across multiple sectors beyond health administration and institutions. Socioeconomic development significantly contributes to reducing TB prevalence, while the increasing specialization within society highlights the need for involvement from policy-making bodies, construction agencies, and public security organizations in TB prevention and control efforts. Coordinated participation across these sectors, focusing on service quality and effectiveness, ensures the proper implementation of public health services. This underscores the importance for policymakers to measure and prioritize the quality and impact of public health services when designing strategies for preventing and managing TB and other diseases (Chakaya et al., 2020; Chen et al., 2022).

Tuberculosis remains one of the leading causes of death from infectious diseases, making effective screening and diagnosis essential for controlling its spread. Despite advancements, significant diagnostic gaps persist, particularly in rural and remote areas, due to limited access

to testing and diagnostic tools (Nooy et al., 2024). Early detection and timely treatment initiation are critical, yet the lack of decentralized laboratory services at health centers presents a major obstacle. Many facilities are not equipped with essential diagnostic equipment, requiring samples to be sent to district hospitals for testing. If sputum test results are negative, patients must travel to district hospitals for further examinations, such as x-rays or additional tests, causing further delays. Strengthening the healthcare system by equipping all levels of community, facility, district, and national with reliable TB diagnostic capabilities is crucial in reducing transmission and improving disease control efforts (Andom et al., 2023).

The tuberculosis infection prevention and control strategies introduced by the World Health Organization and the US Centers for Disease Control and Prevention in 1999 have been widely adopted in healthcare facilities to reduce TB transmission. Administrative measures, such as prioritizing individuals with TB symptoms, implementing respiratory separation, and isolating those suspected of being infectious, have been particularly effective in countries with a high TB burden (Nazneen et al., 2021). However, the successful implementation of environmental control practices has been hindered by inadequate isolation facilities and physical infrastructure constraints in many healthcare settings (Marme et al., 2023).

The shortage of isolation areas in hospitals with specialized tuberculosis services is a common issue, with high patient turnover further complicating the proper allocation of space for both triage and isolation (Paleckyte et al., 2021). Healthcare guidelines stress the importance of triage and isolation for suspected tuberculosis cases, but the lack of adequate infrastructure, especially in terms of space, is often overlooked. Many healthcare facilities face difficulties in isolating these patients due to overcrowding and limited space. When dedicated isolation rooms are unavailable, alternative solutions such as using verandas or corridors with open windows may be considered (Islam et al., 2021).

Etiology and Risk Factors

Tuberculosis is caused by the *Mycobacterium tuberculosis* complex, which includes *M. tuberculosis*, *M. africanum*, *M. bovis*, *M. caprae*, *M. microti*, and *M. canettii*. The primary cause of this infection is the *Mycobacterium tuberculosis (Mtb)* bacillus, which belongs to the MTB complex (Furin et al., 2019). *Mycobacterium tuberculosis* is a strictly intracellular pathogen that is aerobic, non-spore-forming, and immobile (Elkady et al., 2019; Mehta & Grover, 2022). When inhaled, Mtb encounters the initial immune defense made up of airway epithelial cells (AEC) and phagocytic cells, including neutrophils, monocytes, and dendritic cells. If this first line of defense effectively eliminates the bacteria quickly, infection is prevented. However, if the defense fails, the phagocytic cells become infected, allowing Mtb to multiply within them, typically resulting in minimal or no clinical symptoms during the early stages (Carabalí-Isajar et al., 2023). Tuberculosis can impact almost all organs in the human body, with the lungs being the primary site of infection. Transmission happens via inhalation of infectious droplets expelled during coughing, sneezing, or speaking. The aerosolized bacilli reach the terminal airspaces, where tubercle formation and multiplication begin. Pulmonary macrophages engulf the bacilli, leading to granuloma formation, within which the bacilli remain dormant (Mehta & Grover, 2022).

Factors that increase the risk of tuberculosis include close contact with individuals infected with the disease, residing in or visiting high-burden tuberculosis countries, having HIV or being immunocompromised, chronic malnutrition, overcrowding, alcohol abuse, drug addiction, and living in poor or densely populated housing environments (Mehta & Grover, 2022; Miele et al., 2020). Socioeconomic status affects all stages of tuberculosis pathogenesis. The risk of exposure is linked to the disease prevalence and the living environment. This concept involves various interconnected factors, including limited education, low income, overcrowded living conditions, and unemployment, among others (Duarte et al., 2018). Low income impacts TB

incidence as families earning below the regional minimum wage often lack proper nutrition, increasing vulnerability to pulmonary TB.

Home conditions significantly influence pulmonary TB transmission. Poorly maintained roofs, walls, and floors can harbor germs, while dust accumulation on hard-to-clean surfaces creates ideal conditions for bacterial growth. Limited ventilation increases room humidity, providing a favorable environment for the proliferation of TB bacteria (Wikurendra et al., 2021). Both high and low humidity levels can prolong the survival of TB bacteria in the air, raising the risk of exposure for individuals in those environments (Li et al., 2022). High indoor humidity can foster the growth of fungi and bacteria, which can damage lung tissue, making it more susceptible to TB infection. Maintaining optimal humidity in the home supports respiratory health. Low humidity can dry out mucous membranes in the respiratory tract, increasing the risk of infection, while high humidity provides a breeding ground for harmful bacteria. Ideal humidity, along with healthy living conditions and proper ventilation, can help prevent the spread of pulmonary TB (Fahdhienie et al., 2024; Maharjan et al.,2021).

Individuals with low socioeconomic status face a higher risk of TB infection due to restricted access to education, health information, and medical care. Education level is linked to the incidence of pulmonary TB. Those with lower education levels are more likely to contract the disease and face severe outcomes. Higher education levels provide better access to TB-related information, increasing awareness of risks and prevention strategies (Fahdhienie et al., 2024).

Local culture, particularly in terms of preventive behaviors, is strongly linked to the prevalence of pulmonary TB. Both individual and community actions can impact the spread of the disease. The Bacille Calmette-Guérin (BCG) vaccine is a key preventive measure. Active TB patients should cover their mouth and nose when coughing or sneezing to prevent airborne transmission, and regular handwashing with soap and water is crucial in reducing TB risk (Miandad et al.,2016; Puspitasari et al., 2022).

Tuberculosis can affect all stages of the birth process, from reproduction to delivery and beyond. It can lead to infertility through conditions such as uterine synechia, tubal obstruction, implantation issues, and ovarian failure (Pop et al., 2021). Women with tuberculosis after delivery may pass the infection on to their infants (Friedman & Tanoue, 2024). Congenital transmission of TB can occur through amniotic fluid, hematogenous spread, or both. If the placenta becomes infected, the fetus may contract the infection via the umbilical cord, starting from a primary site in the liver with further spread through the bloodstream, or amniotic fluid if the primary infection is in the lungs or gastrointestinal tract (Pop et al., 2021).

Clinical Manifestations

The clinical signs of tuberculosis during pregnancy are similar to those outside of pregnancy (Elkady et al., 2019). Along with general symptoms like fever, night sweats, and weight loss, there are additional clinical features that depend on the organs involved (Mehta & Grover, 2022). Pregnant women with pulmonary tuberculosis show similar symptoms to non-pregnant patients, but weight loss is harder to detect due to pregnancy-related changes (Friedman & Tanoue, 2024; Mehta & Grover, 2022).

Pulmonary Tuberculosis

Pulmonary tuberculosis typically presents with a triad of fever, night sweats, and weight loss. The fever usually occurs in the evening and is mild (<38.5°C). Night sweats are a non-specific symptom. A persistent cough can be productive (with mucus, pus, or blood) or non-productive. Cavity formation or aneurysm rupture in the bronchi can lead to massive hemoptysis. Endobronchial tuberculosis affects the trachea and main bronchi, causing wheezing and shortness of breath (Mehta & Grover, 2022).

Pleural Tuberculosis

Pleural tuberculosis typically follows a primary infection or reactivation of latent tuberculosis. Symptoms include acute fever, cough, and localized pleuritic chest pain. The effusion is usually unilateral and may resolve independently if related to a primary infection. Reactivation during pregnancy carries risks for the fetus and can lead to spread. Parenchymal lesions are detected in 20% of cases with chest X-ray and 80% with chest CT (Mehta & Grover, 2022).

Extrapulmonary Tuberculosis

Extrapulmonary tuberculosis is linked to poorer pregnancy and fetal outcomes (Hui & Lao, 2022; Mehta & Grover, 2022). The most frequent sites of extrapulmonary tuberculosis are the lymph nodes, central nervous system, and bones and joints (Elkady et al., 2019). Lymphadenitis tuberculosis makes up 40% of extrapulmonary tuberculosis cases and typically presents as a palpable mass over 2x2 cm in the cervical, supraclavicular, jugular, or posterior areas (Mehta & Grover, 2022). Tuberculous meningitis (TBM) is the most common manifestation in the central nervous system. TBM is frequently seen in HIV-infected patients and children with miliary tuberculosis (Mehta & Grover, 2022). Typical symptoms of tuberculous meningitis include fever, headache, neck rigidity, focal neurological deficits, brain abscesses, and the formation of tuberculomas. Spinal tuberculosis may lead to lower back pain, focal neurological signs, and paraplegia (Hui & Lao, 2022). Tuberculous pericarditis is a major cause of cardiovascular death in tuberculosis-endemic regions, particularly where HIV infection prevalence is high. Common clinical signs include fever of unknown origin and pericardial friction (Mehta & Grover, 2022).

Other Extrapulmonary Tuberculosis

Extrapulmonary tuberculosis can include arthritis TB, gastrointestinal TB (similar to Crohn's disease), urogenital TB (often asymptomatic but may cause back pain or kidney masses), and laryngeal TB (causing hoarseness, dysphagia, and chronic cough). Diagnosis is made through clinical suspicion and biopsy (Mehta & Grover, 2022).

Screening

The WHO recommends screening for common symptoms, including an unexplained cough lasting over 2 weeks, fever, night sweats, and weight loss, as the initial step (Hui & Lao, 2022). Routine LTBI testing is not necessary for pregnant women who do not have risk factors for developing active tuberculosis (Elkady et al., 2019). High-risk pregnant women include those with close contact to active TB patients, HIV, immunosuppressive conditions, or severe immunocompromised states like lymphoma, leukemia, or organ transplant recipients. For those with other TB risk factors, LTBI treatment may be postponed until two to three months postpartum to reduce the risk of medication side effects (LaCourse, 2024). Pregnant women in areas with high TB prevalence should be screened for TB if they have contact with healthcare providers. Chest X-rays can be used for screening, as long as fetal radiation exposure is minimized. The WHO guidelines recommend using tuberculin skin tests (TST) or interferon-gamma release assays (IGRA) for TB screening during pregnancy, though these tests may yield false negatives due to immune changes in pregnancy. Sputum tests for pulmonary TB with molecular rapid diagnostics may also be suggested (World Health Organization, 2022).

Diagnosis

Diagnosing active TB cases is prioritized in high-burden countries while identifying latent cases is more significant in low-burden regions (Mehta & Grover, 2022). The diagnostic approach for TB in pregnant patients mirrors that of non-pregnant patients, involving clinical history and physical examination (Friedman & Tanoue, 2024). Patients meeting clinical criteria should have a chest X-ray. If TB is suspected, three sputum samples should be collected for smear, culture, and nucleic acid testing. Immunosuppressed patients may need chest X-rays

even with negative tests. Retesting is recommended eight weeks after exposure. Chest X-rays are advised in the first trimester for immunocompromised patients but may be delayed based on risk and clinical judgment (Elkady et al., 2019).

Hematological Examination

Hematological tests in tuberculosis infection are non-specific and reveal lymphocytosis along with elevated erythrocyte sedimentation rates (Mehta & Grover, 2022).

Detection of Tuberculosis Bacilli

In high-burden tuberculosis countries, direct microscopy is the primary test. Bacilli identification involves direct methods like microscopy, culture, nucleic acid detection, or indirect methods such as tuberculin skin tests and interferon-gamma release assays (Mehta & Grover, 2022).

Microscopy

Microscopic examination of sputum for acid-fast bacilli is a fast, affordable, and specific test in high-incidence areas. Common methods include Ziehl-Neelsen, Kinyoun, and fluorescence techniques, which are more sensitive (Elkady et al., 2019; Mehta & Grover, 2022). However, it has low sensitivity (45-80%) and cannot differentiate *Mycobacterium tuberculosis* from other mycobacteria (Hui & Lao, 2022; Mehta & Grover, 2022). The Revised National Tuberculosis Control Programme (RNTCP) recommends collecting a 2 ml morning sputum sample over 2 or 3 days. The first sample detects 85.8% of cases, with an additional 11.9% in the second sample. About 17% of patients with a negative first sample may have false negatives but remain contagious. A repeat smear is done 3 months after treatment. Positive results require culture and drug sensitivity testing. Patients with lung cavity necrosis may release dead bacilli for months but are not contagious. A positive smear after 5 months indicates treatment failure (Mehta & Grover, 2022).

Culture

Culture is the gold standard for diagnosing tuberculosis, offering 30–50% higher sensitivity than smear tests (Mehta & Grover, 2022). Traditional culture testing takes over 4 weeks for results and 6-8 weeks for drug susceptibility testing, significantly delaying diagnosis and treatment (Hui & Lao, 2022). Traditional culture methods use media like Lowenstein Jensen and Middlebrook 7H10/11 (Elkady et al., 2019; Mehta & Grover, 2022). This test is faster than solid culture, taking 9 days for positive and 16 days for negative results, with negatives confirmed after 6 weeks. It offers up to 100% sensitivity and specificity (Mehta & Grover, 2022). Research indicates this test can identify resistance to isoniazid and rifampicin, but not to ethambutol and streptomycin. For tuberculosis meningitis diagnosis, it is the gold standard, detecting 65% of cases within 2-4 weeks (Mehta & Grover, 2022).

Molecular Detection: Nucleic Acid Amplification Tests (NAAT)

The WHO recommends rapid molecular tests as the initial diagnostic for individuals with TB symptoms, treatment history, or possible rifampicin resistance (Elkady et al., 2019; Hui & Lao, 2022). For extrapulmonary TB, samples include gastric lavage, cerebrospinal fluid, or tissue biopsy. The CDC uses NAAT as the standard, but a negative result may still require the conventional culture (Hui & Lao, 2022). NAAT encompasses Polymerase Chain Reaction (PCR), transcription-mediated amplification (Gen-Probe), and the Geno Type Mycobacteria Direct Assay (Elkady et al., 2019; Mehta & Grover, 2022). This test rapidly detects *M. tuberculosis* complex with 85% sensitivity and 97% specificity, aiding in tuberculous meningitis diagnosis but cannot differentiate it from other *Mycobacterium tuberculosis* species (Elkady et al., 2019; Mehta & Grover, 2022). Three NAAT methods are used: CB-NAAT (Cartridge-Based Nucleic Acid Amplification Test), LPA (Line Probe Assay), and LAMP

(Loop-Mediated Amplification). CB-NAAT detects *M. tuberculosis* and rifampicin resistance via semi-quantitative real-time PCR and is approved for diagnosing drug-resistant TB (DR-TB), TB in children, HIV cases, and extrapulmonary TB. It has a sensitivity of 99.8% for BTA-positive samples and 90.2% for BTA-negative, culture-positive samples, with 100% specificity. However, it cannot detect mono-isoniazid resistance (which occurs in 7-11% of first-line treatment failures) or differentiate between live and dead bacilli. For unclear results or suspected false positives, confirmation through culture, drug susceptibility testing (DST), or LPA is recommended. LPA identifies *M. tuberculosis* DNA and genetic mutations related to drug resistance. It has a sensitivity of 98.8% and specificity of 100% for multidrug-resistant (MDR) TB, with rifampicin resistance sensitivity of 98.9% and isoniazid (INH) resistance sensitivity of 97.9%. LAMP is a cost-effective, fast method that allows visual detection of amplification, making it ideal for areas with minimal technical resources. While it detects *M. tuberculosis* complex, it does not identify drug resistance (Mehta & Grover, 2022).

Tuberculin Skin Testing (TST)/Mantoux Test

The Tuberculin Skin Test (TST) involves injecting 2 ml of purified protein from *Mycobacterium tuberculosis* into the forearm and reading the result after 48–72 hours. An induration of 10 mm or more is considered positive. TST is simple, easy, and cost-effective, but it can only detect the presence of infection and cannot distinguish between latent and active TB. It may give false-positive results in BCG-vaccinated children or with repeated testing, and false-negative results in individuals with weakened immune systems (Hui & Lao, 2022; Mehta & Grover, 2022). This test shows a sensitivity of 98% at a 5 mm induration, 90% at 10 mm, and only 50–60% at 15 mm. With higher induration thresholds, the sensitivity drops while the specificity improves (Elkady et al., 2019). The TST is safe to conduct in pregnant individuals (LaCourse, 2024).

Interferon-Gamma Release Assay (IGRA)

The IGRA test detects interferon-gamma release triggered by *M. tuberculosis*-specific antigens (LaCourse, 2024). Earlier versions of IGRA required a 16-hour incubation period, while newer tests like T-spot need only 8 hours for incubation (Mehta & Grover, 2022). IGRA is preferred over TST in low- to moderate-risk cases, patients unlikely to return for follow-up, and those with a BCG vaccination history. It improves diagnostic accuracy, reduces cross-reactivity with BCG and most non-tuberculous mycobacteria, and is recommended for LTBI screening in populations with high BCG vaccination rates or uncertain vaccination status (Elkady et al., 2019; Hui & Lao, 2022; Mehta & Grover, 2022).

The effectiveness of IGRAs in diagnosing latent tuberculosis infection during pregnancy has shown variability across different studies. In both low and high-prevalence regions, IGRAs are considered more specific than the TST because they do not cross-react with the BCG vaccine (Malhamé et al., 2016). Recent evidence indicates that IGRAs are effective predictive tools for active tuberculosis (ATBI). A positive IGRA result or a recent increase in IGRA levels strongly correlates with an elevated risk of reactivation, even among women with significant immunosuppression (Jonnalagadda et al., 2013). In addition, IGRAs play a crucial role in screening for latent tuberculosis infection (LTBI) in low-income areas where follow-up rates are often very low. In such settings, some women may only have a single medical visit in their lifetime, making IGRAs particularly advantageous since they require only one visit, compared to the TST, which requires two visits. The new generation of IGRAs, such as QFT-Plus, offers improved detection of LTBI during pregnancy. This advancement enhances the test's ability to detect interferon-gamma (IFN-γ) secretion from both CD4+ and CD8+ T-cells, providing a more comprehensive assessment of LTBI (König Walles et al., 2018; Yang et al., 2022).

IGRA is more costly and technically challenging than TST, so the WHO advises against using it in high-burden countries for mass screening. RNTCP restricts its use for adult diagnosis in

these regions. Moreover, IGRA cannot differentiate between latent tuberculosis infection and active disease, so it is not suitable for diagnosing active TB (Elkady et al., 2019; Mehta & Grover, 2022). The adoption of IGRA in resource-limited settings remains constrained due to insufficient availability, inadequate infrastructure, and a lack of necessary resources. Limited access to IGRA technology is primarily caused by the absence of testing facilities, inefficient referral systems, and inadequate protocols for sample collection and transport. Additionally, challenges within the healthcare system have led to restricted IGRA testing coverage, including complex laboratory requirements, a shortage of skilled personnel, and prolonged processing times, all of which hinder its application in resource-constrained areas (Barcellini et al., 2016; Kaaba et al., 2021; Paton et al., 2019; Samudyatha et al., 2023). These challenges could be tackled by providing potential solutions such as strengthening healthcare infrastructure, improving referral mechanisms, and enhancing workforce capacity. Expanding diagnostic services, optimizing sample transportation systems, and offering adequate training for healthcare professionals would significantly improve IGRA accessibility. Additionally, the development of more affordable test variants or partnerships with international organizations could support the integration of IGRA into TB control programs in low-resource settings, making testing more widely available and effective in combating the disease.

Point-of-care testing presents a viable solution for improving IGRA accessibility in resource-limited settings. By offering faster and more cost-effective diagnostic results, POCTs can help address challenges related to inadequate laboratory infrastructure and workforce shortages. This approach is especially valuable in areas where access to specialized diagnostic facilities is limited. The ability to provide rapid results can significantly enhance TB diagnosis, particularly for high-risk groups who may have difficulty returning for follow-up testing, such as pregnant women, individuals in remote locations, and those with mobility impairments. Early detection of TB through POCTs is crucial, and several such tests are already in use at primary healthcare facilities to support TB screening efforts. In addition to these established methods, technological advancements have introduced newer approaches that provide accurate and timely results without the need for laboratory access. Various molecular diagnostic tests, including nucleic acid amplification techniques such as GeneXpert and TB-loop-mediated isothermal amplification, are currently employed as POCTs to enhance TB detection (Hong et al., 2022). Integrating POCTs into TB control strategies, including IGRA-based testing, could improve early diagnosis and treatment outcomes, ultimately strengthening TB management in resource-constrained environments.

Chest X-ray

Chest X-ray is a simple, affordable test for diagnosing pulmonary tuberculosis, showing typical signs like focal opacities, consolidation, and pleural effusion. In advanced HIV co-infected patients, radiological findings may be less typical. The American College of Obstetricians and Gynecologists states that single X-ray exposure does not increase the risk of miscarriage or fetal abnormalities, though lead shielding can be used (Elkady et al., 2019; Mehta & Grover, 2022).

Histopathology

In histopathology, tuberculosis is typically identified by caseating granulomatous inflammation with Langhans giant cells. Positive culture results are reported in 60-80% of cases from biopsy samples. Fine-needle aspiration biopsy (FNAB) provides a higher rate of positive diagnoses and has become the preferred diagnostic method over more invasive biopsy techniques (Mehta & Grover, 2022).

Magnetic Resonance Imaging (MRI) and Computed Tomography Scan (CT-Scan)

MRI and CT scans are used to assess tuberculous meningitis (TBM) and spinal tuberculosis. While brain MRI is safe during pregnancy, CT scans are limited due to radiation risks. In TBM,

MRI typically shows basal meningeal enhancement, hydrocephalus, and solitary or multiple tuberculomas. MRI is also effective in detecting intrathoracic lymphadenopathy, pericardial thickening, and pleural or pericardial effusions (Elkady et al., 2019; Mehta & Grover, 2022).

Electrocardiogram (ECG) and Echocardiography

These tests are crucial for diagnosing tuberculous pericarditis. Cardiac tamponade is the key indicator of constrictive pericarditis (Mehta & Grover, 2022).

Cerebrospinal Fluid (CSF) Examination

Cerebrospinal fluid analysis in tuberculous meningitis (TBM) typically reveals lymphocytosis, elevated protein levels, and moderately increased lactate (3-8 mmol/L), whereas bacterial meningitis shows higher lactate levels. Due to TBM's paucibacillary nature, acid-fast bacilli (AFB) are found in only 20% of CSF smear cases (Mehta & Grover, 2022).

Effects of TB Infection during Pregnancy

During pregnancy, immune changes occur to prevent fetal rejection, mediated by estrogen and progesterone. Cellular immunity is suppressed, and humoral immunity is enhanced, increasing the risk of latent tuberculosis reactivation. Increased regulatory T cells reduce Th1 cytokine production, promoting the progression of latent TB to active TB. These changes become more pronounced in the second and third trimesters (Mehta & Grover, 2022). Tuberculosis during pregnancy is linked to worse obstetric and perinatal outcomes. The timing of treatment initiation in pregnancy influences maternal outcomes, with early initiation of anti-tuberculosis therapy (AAT) helping to reduce obstetric morbidity (Mehta & Grover, 2022). Obstetric complications associated with tuberculosis include miscarriage, restricted intrauterine growth, preterm labor, spontaneous abortion, low birth weight, and higher neonatal morbidity and mortality (Elkady et al., 2019; Queensland Health, 2021). A U.S. study of 4,053 pregnant TB cases showed a 37-fold higher risk of severe complications in TB-positive patients. HIV infection increases the risk of active TB and latent TB reactivation by 20 times, while co-infection suppresses the immune response. In HIV-positive pregnancies, TB transmission rises by 2.56 times, with vertical transmission rates of 15% for TB and 10% for HIV (Hui & Lao, 2022). Pregnant women with tuberculosis may experience perinatal outcomes such as preterm birth, low birth weight, lower APGAR scores, acute fetal distress, and neonatal death (Elkady et al., 2019).

The Impact of Pregnancy on the Course of Tuberculosis Disease

Pregnancy does not affect tuberculosis progression, including the transition from latent to active infection or treatment response, as long as it is diagnosed and treated early (Elkady et al., 2019; Miele et al., 2020). Pregnancy can make tuberculosis diagnosis more challenging, as physiological changes during pregnancy can mask typical symptoms (Mehta & Grover, 2022; Miele et al., 2020). Non-specific symptoms like fatigue, dyspepsia, shortness of breath, anemia, weight loss (masked by normal pregnancy weight gain), elevated ESR, and reluctance for chest X-ray can complicate tuberculosis diagnosis during pregnancy (Elkady et al., 2019; Mehta & Grover, 2022; Miele et al., 2020). Pregnancy has not been shown to affect tuberculosis progression or treatment response, but some studies find higher tuberculosis incidence in pregnant and postpartum women compared to non-pregnant individuals (LaCourse, 2024).

Impact of Maternal Tuberculosis on Neonates

Congenital tuberculosis is rare, but mortality rates can reach 35% if left untreated (Mehta & Grover, 2022). Congenital tuberculosis infection occurs due to transplacental transmission through the umbilical vein to the liver and lungs of the fetus. At the end of pregnancy, infected amniotic fluid or aspiration during labor can cause primary infection. The primary infection focuses on the liver, with the involvement of periportal lymph nodes following hematogenous

spread via the umbilical vein (Elkady et al., 2019). Congenital tuberculosis symptoms include fever, abdominal distension, lymphadenopathy, and hepatosplenomegaly. Caseous hepatic granulomas on liver biopsy are a key indicator. Chest X-rays and CT scans are often abnormal. The Cantwell criteria for diagnosis include proven tuberculosis lesions and one of the following: lesions in the first week of life, primary hepatic lesions, maternal genital TB, or excluding neonatal infection through thorough examination (Mehta & Grover, 2022).

Management of Tuberculosis in Pregnancy

Management of pregnant women with pulmonary tuberculosis requires a holistic approach, involving a team of healthcare professionals from various disciplines (Mehta & Grover, 2022). The WHO Tuberculosis Treatment Guidelines emphasize that tuberculosis treatment should not be delayed or restricted during pregnancy, as doing so could result in negative pregnancy outcomes (Friedman & Tanoue, 2024; Mehta & Grover, 2022). Treatment should follow the prescribed regimen, excluding streptomycin due to fetal ototoxicity. Other first-line drugs are safe during pregnancy, and pyridoxine supplementation should be given with isoniazid (Mehta & Grover, 2022). Untreated tuberculosis is more harmful to the mother and fetus than the side effects of treatment (Mehta & Grover, 2022).

Latent Tuberculosis Infection

If immediate treatment is not necessary, latent tuberculosis infection therapy should be postponed for three months after delivery to reduce the risk of hepatitis (Elkady et al., 2019). To avoid unnecessary treatment during pregnancy, latent tuberculosis infection therapy can be delayed for 2-3 months after childbirth. However, treatment should not be postponed due to pregnancy, especially in the first trimester, for women recently exposed to contagious tuberculosis and at high risk of progressing to active tuberculosis. Treatment options include daily Rifampin (RIF) for 4 months (4R), daily Isoniazid (INH) for 3 months with RIF (3HR), and daily INH for 6 or 9 months with pyridoxine (vitamin B6) supplementation (CDC, 2020; Hui & Lao, 2022; Mehta & Grover, 2022). The recommended treatment for latent tuberculosis infection during pregnancy in women not infected with HIV includes Isoniazid (5 mg/kg, up to 300 mg daily) for 9 months or Isoniazid (15 mg/kg, up to 900 mg twice a week) for 9 months. Isoniazid should be accompanied by pyridoxine supplementation (25-50 mg daily) to help prevent isoniazid-induced peripheral neuropathy (Elkady et al., 2019). The Isoniazid and Rifampin (3HP) weekly regimen for 3 months is not advised during pregnancy or for women planning pregnancy, as its safety in pregnant women has not been researched (CDC, 2020; Hui & Lao, 2022; Mehta & Grover, 2022). Individuals with positive TST or IGRA results must be evaluated to exclude the presence of active tuberculosis (Elkady et al., 2019). If screening is positive and the patient has recent contact with an active tuberculosis case, treatment should start during pregnancy. For immunocompromised patients, treatment should begin immediately. Immunocompetent patients should be retested 10 weeks later. A rifampin-based regimen is preferred over isoniazid monotherapy for pregnant women with latent tuberculosis and no HIV, due to shorter duration, better completion rates, and lower hepatotoxicity risk (LaCourse, 2024)

Active Tuberculosis

Active tuberculosis treatment must commence as soon as possible, as leaving it untreated leads to greater health risks for both the mother and the fetus than starting anti-tuberculosis therapy (Elkady et al., 2019). The treatment approach known as Directly Observed Therapy Short Course (DOTS) includes an initial phase that targets and destroys active and semi-dormant tuberculosis bacteria, followed by a continuation phase designed to clear the remaining bacteria, thus minimizing the chances of relapse or treatment failure (Elkady et al., 2019; Mehta & Grover, 2022). The initial treatment consists of isoniazid (INH), rifampicin (RIF), and ethambutol (EMB) daily for two months, followed by INH and RIF for seven months. If

susceptibility results show sensitivity to INH and RIF, ethambutol can be stopped after one month (CDC, 2020; Friedman & Tanoue, 2024; Hui & Lao, 2022). Streptomycin is avoided due to its harmful effects on the fetus, and pyrazinamide (PZA) is not recommended because its fetal impact is unknown. It is generally excluded from first-line TB treatment for pregnant patients due to a lack of teratogenicity data. However, the WHO includes PZA in the standard treatment regimen, and if used, treatment duration may be reduced from nine to six months for most patients (Friedman & Tanoue, 2024). The rifapentine-moxifloxacin-based four-month regimen has not been studied in pregnant patients, so it should not be used. It is known that daily tuberculosis therapy has a higher cure rate compared to the three-times-a-week regimen and can also prevent rifampicin resistance (Mehta & Grover, 2022). Antituberculosis drugs contraindicated during pregnancy include streptomycin, kanamycin, amikacin, capreomycin, fluoroquinolones, ethionamide, and PAS (CDC, 2020; Hui & Lao, 2022; Mehta & Grover, 2022). Monthly evaluations for drug toxicity are necessary, including baseline liver function tests before treatment, followed by assessments for hepatitis symptoms and further liver tests, as pregnancy increases the risk of isoniazid-induced hepatotoxicity. The four first-line drugs; isoniazid, rifampicin, ethambutol, and pyrazinamide are safe during pregnancy and not linked to congenital abnormalities (Elkady et al., 2019). Additional evaluations should include HIV and hepatitis B and C tests, along with a general assessment for chronic liver disease, alcohol use, and exposure to other hepatotoxins (LaCourse, 2024). If no underlying liver disease is present, monthly evaluations for hepatitis symptoms, clinical exams, and liver function tests are required. More frequent monitoring may be needed in cases of liver disease or abnormal liver function tests (Friedman & Tanoue, 2024; LaCourse, 2024). Patients on antituberculosis medication should be educated about hepatitis symptoms and instructed to stop treatment and seek evaluation if symptoms occur. Symptoms include anorexia, nausea, dark urine, jaundice, rash, persistent numbness, fatigue, fever, abdominal pain, easy bruising, and joint pain (LaCourse, 2024).

Coinfection of HIV and Tuberculosis

HIV coinfection significantly increases the risk of latent TB progressing to active disease. The immune response to TB accelerates HIV replication, worsening HIV progression. Over 50% of maternal deaths in TB patients result from HIV coinfection (Mehta & Grover, 2022). The approach to anti-tuberculosis treatment for pregnant individuals with HIV infection generally aligns with that for those without HIV. However, it is essential to monitor and manage potential drug interactions carefully (CDC, 2020; Friedman & Tanoue, 2024; Hui & Lao, 2022). For tuberculosis patients undergoing treatment with rifampicin, only a few antiretroviral drugs can be used simultaneously, as drug interactions can compromise the effectiveness of HIV therapy. Consequently, the policy is to start antiretroviral treatment only after completing tuberculosis therapy (Friedman & Tanoue, 2024; Mehta & Grover, 2022). Rifampicin is known to decrease the serum levels of efavirenz and nevirapine by up to 50%. Therefore, rifabutin is considered a suitable substitute for rifampicin, as it has a milder impact on CYP3A enzymes (Mehta & Grover, 2022). Treatment for TB and HIV coinfection depends on TB transmission rates. In areas with TB rates below 500 per 100,000, TB treatment starts immediately during pregnancy due to the higher risk of progression. For HIV patients on ART, TB treatment is delayed for 2-3 months after childbirth. The Department of Health and Human Services suggests treatment may be postponed until after delivery for people living with HIV. For pregnant women with HIV not on ART, ART should be initiated immediately to reduce the risk of latent TB progressing. In high TB transmission areas, the WHO recommends isoniazid treatment for at least 36 months for those with HIV and a positive or unknown TB test (LaCourse, 2024).

Anti-Tuberculosis Side Effects on Mothers

Isoniazid may increase the risk of hepatitis and peripheral neurotoxicity during the peripartum period. Pyridoxine should be given to pregnant women on isoniazid and to breastfeeding

infants. Rifampicin can cause hepatitis, thrombocytopenia, hemolytic anemia, fever, and rash, and is associated with rare cases of fetal abnormalities and hemorrhagic disease (Elkady et al., 2019; Friedman & Tanoue, 2024). Rifabutin is commonly prescribed as a substitute for rifampicin in patients with HIV who are undergoing antiretroviral treatment (Friedman & Tanoue, 2024). Rifampicin can reduce the effectiveness of hormonal contraceptives by inducing liver metabolism, with this effect lasting up to two weeks after discontinuation. Patients should be advised to use alternative methods (LaCourse, 2024). Side effects of anti-tuberculosis drugs (OAT) include optic neuritis, gastrointestinal issues, thrombocytopenia, ototoxicity, nephrotoxicity, joint pain, dizziness, tinnitus, ataxia, and hearing loss. Patients should be informed about symptoms like nausea, dark urine, jaundice, rash, tingling in hands and feet, fatigue, weakness, fever, abdominal pain, and easy bruising or bleeding (Elkady et al., 2019).

Anti-Tuberculosis Side Effects on the Fetus

Isoniazid is safe in pregnancy, but pyridoxine supplementation is recommended. Rifampicin increases the risk of birth defects and bleeding in newborns, while streptomycin should be avoided. Ethambutol may cause eye toxicity. Pyrazinamide has no significant teratogenic effects. Other drugs like kanamycin and amikacin are not recommended, but accidental use doesn't require pregnancy termination. BCG vaccination should be avoided due to unproven safety (Elkady et al., 2019).

Management of Childbirth

Obstetric management of tuberculosis during pregnancy is similar to typical pregnancies, with cesarean delivery only for obstetric reasons. There is no significant difference in tuberculosis transmission risk to the fetus between vaginal delivery, instrumental delivery, or cesarean section (Elkady et al., 2019).

Management in Neonates

The WHO recommends isoniazid preventive therapy (IPT) for newborns of mothers with less than two weeks of treatment and sputum-positive AFB, with a dose of 5 mg/kg of isoniazid and 5–14 mg/kg of pyridoxine. A tuberculin test should be done at 6-12 weeks; if negative, treatment stops, and BCG vaccination is given. If positive, IPT continues for six months. BCG should be given after IPT as isoniazid reduces its effectiveness. BCG is not recommended for babies of HIV-positive mothers until confirmed HIV-negative. Vitamin K should be given to newborns of mothers on rifampicin. Household contact screening should be done if TB is suspected (Elkady et al., 2019).

Breastfeeding

Breastfeeding is safe for women on first-line anti-tuberculosis drugs, as the drug levels in breast milk are minimal and typically do not cause harm to the nursing newborn (CDC, 2020; LaCourse, 2024; Queensland Health, 2021). Breastfeeding is recommended after at least two weeks of TB treatment, as there have been no documented cases of transmission through breast milk. The WHO supports breastfeeding for mothers with latent or active TB and a negative sputum smear. It helps prevent infections and malnutrition, especially in low-resource settings, with mask use and hygiene practices (Elkady et al., 2019; Friedman & Tanoue, 2024). In severe pulmonary or MDR-TB cases, breastfeeding may be stopped, but expressed milk can be given. The American Academy of Pediatrics allows breastfeeding for mothers treated for two weeks or more, as they are considered non-infectious. The RNTCP recommends breastfeeding regardless of the mother's TB status (Mehta & Grover, 2022). INH doses should be reduced by 20%, as it is highly excreted. Mothers on anti-TB treatment should take their medication after breastfeeding and use formula for the next feed to avoid high plasma levels in the neonate. Routine monitoring of infants is recommended. Pyridoxine supplementation for breastfeeding

infants varies, with WHO and NIHE not recommending it, but The Sentinel Project suggesting it for infants of mothers on cycloserine or prothionamide. Rifampicin may turn body fluids, including breast milk, orange, but it is generally harmless (LaCourse, 2024; Mehta & Grover, 2022; Queensland Health, 2021).

Multidrug-resistant TB (MDR-TB) in Pregnancy

MDR-TB treatment in pregnancy is individualized, with second-line drugs used after evaluating the potential impact on the fetus. Para-aminosalicylic acid, combined with isoniazid, shows no significant teratogenic effects. Women on drug-resistant TB treatment should use contraception due to unclear teratogenic risks of second-line drugs. Obstetric complications like miscarriage, preterm birth, and fetal growth restriction are more common in these patients. TB is not a reason for pregnancy termination, and second-line drugs should be used selectively (Elkady et al., 2019).

Prevention

Improving socio-economic conditions and healthcare access can reduce tuberculosis prevalence. The BCG vaccine is recommended for high-risk individuals and women without immunity traveling to TB-endemic areas, but not during pregnancy. Pregnant women with HIV should be screened for active TB, even without symptoms (Elkady et al., 2019; Mehta & Grover, 2022). Latent tuberculosis affects about 50% of the population. WHO recommends Isoniazid Preventive Therapy (IPT) for HIV-infected individuals to prevent progression to active TB. IPT reduces the risk of infection by 33%. WHO advises that pregnancy should not exclude HIV-positive women from TB screening and receiving IPT (Elkady et al., 2019; Mehta & Grover, 2022). Patients can be treated with isoniazid monotherapy (10 mg/kg/day, max 300 mg for 6 months) and pyridoxine 50 mg/day, or a combination of rifampicin and isoniazid for 3 months, or rifampicin alone for 4 months. Long-term IPT with isoniazid for 36 months is also recommended. An affordable regimen includes a fixed-dose combination of isoniazid, pyridoxine, sulfamethoxazole, and trimethoprim. Liver function tests are advised for screening toxicity. Vitamin B6 supplementation should be provided if possible (Elkady et al., 2019; World Health Organization, 2022).

Conclusion

Tuberculosis (TB) is a major cause of mortality and morbidity in pregnant women, with pregnancy increasing the risk of latent TB reactivation. TB in pregnancy can lead to complications like abortion, preterm birth, low birth weight, preeclampsia, and postpartum hemorrhage. Diagnosing TB is challenging due to overlapping symptoms with pregnancy changes. Early diagnosis is aided by molecular tests, but bacterial culture remains the gold standard. TB treatment during pregnancy should not be delayed, as first-line drugs are safe and help prevent complications. LTBI treatment during pregnancy is controversial but may be indicated post-delivery. First-line anti-TB drugs are safe for breastfeeding.

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