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Tuberculosis in Pregnancy

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Abstract

Pregnancy is a time of joy and anticipation, but when tuberculosis (TB) enters the picture, it can bring worries and questions. This article explores the impact of TB during pregnancy. When a pregnant woman gets TB, there are risks involved. It's important to detect TB early, and this can be done through regular check-ups. Once TB is found, treatment is available, and it's safe for both the mother and baby. Prenatal care is a must during this time to monitor and manage the disease. Support from doctors, family, and the community is vital. Education about TB and pregnancy empowers women to make informed decisions. In conclusion, while TB during pregnancy may seem challenging, with the right care and support, many women have safely journeyed through it and delivered healthy babies. It's a reminder that even in tough times, medical care can make a big difference in the lives of mothers and their precious little ones.

Keywords: Pregnancy; Tuberculosis; Drug Sensitive Tuberculosis; Multidrug Resistance Tuberculosis

Abbreviations: TB: Tuberculosis; LTBI: Latent TB Infection; PTB: Pulmonary Tuberculosis; EPTB: Extra Pulmonary Tuberculosis; CBNAAT: Cartridge-Based Nucleic Acid Amplification Test; DST: Drug Susceptibility Testing; PCR: Polymerase Chain Reaction; LPA: Line Probe Assays; WHO: World Health Organization; IGRA: Interferon Gamma Release Assay; AFB: Acid-Fast Bacilli; FNAC: Fine Needle Aspiration Cytology; FDC: Fixed-Dose Combination; IP: Intensive Phase; CP: Continuation Phase; MDR-TB: Multidrug Resistant Tuberculosis; TPT: Tuberculosis Preventive Therapy.

Introduction

Globally in the year 2021, it is estimated that approximately 10.6 million individuals were affected with tuberculosis (TB). This represents a significant 4.5% increase compared to the 10.1 million cases reported in 2020. This upturn marks a stark reversal from the trend of gradual decline observed over several years. Likewise, the TB incidence rate, measured as new cases per 100,000 population per annum, is believed to have experienced a 3.6% rise between 2020 and 2021. This stands in contrast to the consistent annual decline of approximately 2% that characterized the past two decades [1].

In the realm of maternal-fetal medicine, one challenging and often overlooked conundrum is the presence of tuberculosis (TB) during pregnancy. While the world makes strides in combating this ancient and persistent bacterial infection, the unique complexities that arise when TB intersects with the delicate journey of pregnancy continue to present a formidable medical puzzle.

Picture, if you will, the intricate dance of life unfolding within a pregnant woman's body. It's a time of immense hope

and anticipation, but it's also a period of vulnerability. This is where the shadow of TB can cast its serious presence. Tuberculosis, caused by the cunning Mycobacterium tuberculosis, has a knack for testing the resilience of the human body. However, when this adversary chooses to infiltrate the body of an expectant mother, it introduces a multifaceted dilemma.

The precise incidence of tuberculosis (TB) during pregnancy remains uncharted in numerous countries, but it is presumed to mirror the prevalence observed in the general population. In one of the study from United Kingdom the incidence rate of tuberculosis (TB) during pregnancy was 12.8 per 100,000 (95% CI, 8 to 19.4). Notably, the TB rate during the 180-day postpartum period was higher at 19.2 per 100,000 (95% CI, 12–29) compared to the rate outside of pregnancy, which stood at 9.1 per 100,000 (95% CI, 7.6–10.8) with a statistically significant difference (P = 0.001). When considering TB events during both pregnancy and the 180 days postpartum, they were notably more common, with a combined rate of 15.4 per 100,000 (95% CI, 11.2–20.6), as compared to the rate outside of pregnancy. This difference is statistically significant, with a crude incidence rate ratio of 1.68 (95% CI, 1.17–2.38, P = 0.02) [2].

These findings underscore the heightened risk and increased incidence of TB during pregnancy and the postpartum period, emphasizing the need for targeted interventions and heightened surveillance during these critical periods of maternal care.

Pregnant women, with their altered immune systems, find themselves at a higher risk of TB infection. The consequences are not confined to the maternal sphere alone; they reverberate through the placenta, impacting the developing foetus. Premature births, low birth weights, and a heightened risk of maternal mortality loom on one side of the equation, while the potential effects of anti-TB medications on the growing baby raise questions on the other.

This article explores into the complex aspects of tuberculosis (TB) during pregnancy, looking closely at how it's diagnosed, treated, and managed. We aim to help you understand the difficult decisions that healthcare providers have to make when trying to keep both the mother and the unborn baby healthy. Through our exploration, we want to emphasize the importance of staying vigilant, acting promptly when needed, and working together with various medical experts to deal with TB during pregnancy. This teamwork is crucial to ensure the best possible outcomes for both the mother and the baby. Even though we live in a time of advanced medicine, TB remains a persistent problem. Despite this challenge, we are committed to safeguarding the health of both mothers and babies, ensuring that new beginnings can be beautiful and healthy, even when faced with this age-old disease.

Pathogenesis

The causative agent is typically Mycobacterium tuberculosis, with occasional cases involving Mycobacterium bovis or atypical mycobacteria [3]. Person inhales airborne droplets containing M. tuberculosis. Bacteria reaches the alveoli of the lungs and their alveolar macrophages attempts to engulf and destroy the bacteria. Some M. tuberculosis bacteria survive inside macrophages because mycobacteria inhibit phagosome-lysosome fusion. Thereafter immune response is triggered and macrophages, T cells, and other immune cells form granulomas around infected cells. Bacteria may become dormant in granulomas, leading to latent TB infection (LTBI). In immunocompromised individuals, bacteria may reactivate casing active TB disease develops with bacterial replication and tissue damage. TB bacteria can spread to other parts of the body. Thus, stronger immune response is initiated. Infected tissue undergoes caseous necrosis, resembling cheese-like material. Active TB can lead to cavity formation in the lungs. Cavity rupture can release infectious bacteria into airways. TB infection can resolve with treatment or persist as a chronic condition with periods of active disease and remission [4].

Interaction Between Tuberculosis and Pregnancy

With the early use of modern anti-tuberculosis treatment, tuberculosis has not shown much adverse effect on the progression of pregnancy and labour. Tuberculosis (TB) is accountable for a significant portion, ranging from 6% to 15%, of maternal deaths, while also significantly increasing the risk of unfavourable pregnancy outcomes. According to a study using a national registry, pregnant and postpartum women face 1.4 and 1.9 times higher TB incidence rates, respectively, compared to their non-pregnant counterparts [5,6]. However adverse pregnancy outcomes are seen in those patients who have more advanced disease, immunocompromised status, presence of extrapulmonary disease and inadequate response to the treatment [7]. A previous meta-analysis addressing active tuberculosis (TB) during pregnancy discovered elevated risks, including maternal health complications, antenatal admissions, miscarriages, anemia, and cesarean deliveries. Additionally, untreated TB correlated with heightened occurrences of preterm births, low birth weight, fetal distress, reduced Apgar scores at 1 minute, birth asphyxia, and perinatal mortality [8]. Expectant mothers with HIV face a 2.56-fold higher risk of contracting tuberculosis (TB) during pregnancy [9]. Additionally, the co-occurrence of TB and HIV elevates the risk of neonatal mortality threefold. Moreover, this co-

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infection increases the likelihood of vertical transmission to newborns by 15% for TB and 10% for HIV [10].

The state of pregnancy itself does not elevate the vulnerability to disease, including the transition from latent to active infection or the reaction to TB treatment [11]. Nonetheless, the presence of pregnancy can complicate TB diagnosis. Medical practitioners may hesitate to conduct radiographic examinations due to concerns about potential harm to the developing foetus. Moreover, the symptoms commonly associated with TB, such as weakness, weight fluctuations, and breathlessness, closely resemble the natural changes and discomforts experienced during pregnancy, further complicating the differentiation between the two conditions [12]. Studies indicate that pregnancy doesn't notably influence the progression of TB, encompassing factors like sputum conversion rate, disease stabilization, and relapse rate. The key lies in prompt and accurate diagnosis and treatment. TB's course during pregnancy hinges on factors such as the disease's extent, the drug sensitivity pattern of AFB, radiographic presentation, and the individual woman's susceptibility to TB [13]. The postpartum phase also represents a heightened vulnerability period, which could be attributed to the immunological alterations associated with pregnancy. This increased susceptibility during pregnancy and the postnatal period may stem from the immune system changes that accompany gestation [7].

Risk Factors for Tuberculosis in Pregnancy

Factors contributing to an increased susceptibility to tuberculosis (TB) during pregnancy encompass various elements, including one's medical and social background. These factors comprise a personal or familial history of TB, migration from less affluent to more prosperous regions, compromised immune systems as seen in conditions like HIV or Diabetes mellitus, extremes of age (particularly younger women whose immune systems are less robust), persistent health challenges, and multi-nutrient deficiencies often associated with lifestyle factors such as substance abuse, alcohol dependency, and homelessness. Furthermore, residing in overcrowded and inadequately ventilated housing environments also heightens the risk of TB transmission [7].

Clinical Presentation

The signs of TB infection during pregnancy often resemble those experienced by non-pregnant individuals. However, it's worth noting that the presence of pregnancy can sometimes obscure actual weight loss, making the failure to gain weight a crucial symptom to be vigilant about. In pregnancy, pulmonary tuberculosis (PTB) stands out as the most prevalent form of TB disease. Nevertheless, a challenging subset, known as disseminated TB, manifests in approximately 5-10% of expectant mothers grappling with TB disease. It's important to underscore that this disseminated form poses a specific risk for the transmission of TB to newborns, potentially leading to congenital TB [14].

In regions where TB and HIV are endemic, it is imperative that all pregnant women undergo a diligent screening process to detect any potential TB symptoms. Furthermore, it is equally essential to conduct HIV testing for pregnant women showing signs that may suggest TB. This comprehensive approach ensures the early identification and appropriate management of both TB and HIV, safeguarding the health of both the mother and the unborn child [14].

Presumptive Pulmonary TB pertains to individuals displaying symptoms and indicators suggestive of TB. These encompass a persistent cough lasting for a minimum of two weeks, a fever persisting for two weeks or more, noticeable weight loss, the occurrence of hemoptysis, or any anomalies detected in chest radiographs. It is crucial to note that individuals in close contact with confirmed TB patients, those living with HIV, individuals with diabetes, those experiencing malnutrition, cancer patients, and individuals under immunosuppressive therapy or steroid treatment should undergo regular screening for signs and symptoms indicative of TB [14].

The following are also to be investigated as presumptive pulmonary tuberculosis:

- Individuals in close contact with microbiologically confirmed TB patients exhibiting any duration of cough.
- Those with suspected or confirmed extra-pulmonary TB, experiencing cough regardless of its duration.
- People living with HIV who manifest any duration of cough symptoms. Presumptive Extra Pulmonary Tuberculosis (TB) encompasses specific organ-related indicators such as lymph node enlargement, joint pain and swelling, neck stiffness, mental confusion, along with general symptoms like substantial weight loss, prolonged fever, and night sweats lasting two weeks or more [14].

Diagnosis

It can be further divided as diagnosis of Pulmonary Tuberculosis and diagnosis of Extrapulmonary Tuberculosis.

Diagnosis of Pulmonary Tuberculosis

PTB encompasses bacteriologically confirmed or clinically diagnosed tuberculosis affecting lung tissue or the tracheobronchial tree. Tuberculosis involving mediastinal/hilar intrathoracic lymph nodes is also considered PTB. Miliary TB, with lung lesions, falls under PTB. On the other hand, EPTB comprises tuberculous pleural effusion without

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lung radiographic abnormalities. If an individual has both PTB and EPTB, they are categorized as having PTB [14].

Microbiological Test

In cases of pulmonary tuberculosis (PTB), sputum samples, whether spontaneously produced or induced, are commonly utilized. These samples are subjected to acid-fast bacilli demonstration through techniques like Zeihl-Neelsen Staining or Fluorescence staining. However, it's important to note that solely relying on staining techniques may lead to missed diagnoses, particularly in smear-negative cases, and in instances of paucibacillary cases or sampling errors [7]. The conventional cultural methods (Gold Standard) often require over four weeks for results, and up to six to eight weeks for phenotypic drug susceptibility testing, leading to considerable delays in both diagnosis and the initiation of treatment [15]. The MGIT-B system, an automated culture platform, is employed for the detection of mycobacterial growth. Typically, culture outcomes are obtainable within a span of 42 days. Following the initial detection of growth in cultures, results for Drug Susceptibility Testing (DST) become accessible in approximately 14-26 days [16].

In today's scenario WHO recommend rapid diagnostic tests such as GeneXpert MTB/RIF, also known as Xpert MTB.Rif, represents a commercially accessible cartridge-based nucleic acid amplification test (CBNAAT) designed for diagnosing Mycobacterium tuberculosis complex infections. This innovative diagnostic tool swiftly provides confirmation, taking just two hours to deliver results. Operating on the principle of polymerase chain reaction (PCR), it analyses various specimens, including biopsies and bodily fluids, searching for genetic markers unique to Mtb. Simultaneously, it identifies the presence of the rpoB gene associated with rifampicin resistance. Manufactured by Cepheid in Sunnyvale, California, USA, it is instrumental in diagnosing tuberculosis, particularly in instances of limited bacterial presence [16]. In 2016, an upgraded version called Xpert MTB/RIF Ultra emerged with improved sensitivity akin to culture assays. Though more resource-efficient and expedient, it has somewhat reduced specificity, necessitating careful interpretation of trace-positive results [17]. Additionally, a forthcoming version, Xpert XDR, will extend its utility by detecting resistance to isoniazid, injectable agents, and fluoroquinolones. However, it's worth noting that while a positive CBNAAT result is informative, a negative outcome doesn't consistently rule out tuberculosis [3].

Another test used for rapid diagnosis is Line Probe Assays (LPA) that identify DNA sequences unique to the Mycobacterium tuberculosis complex and mutations linked to drug resistance. The First Line LPA detects Rifampicin and Isoniazid resistance, while the Second Line LPA identifies Fluoroquinolone and Second-line injectable class resistance. The urine lateral flow lipoarabinomannan (LF-LAM) assay test utilizes immunocapture techniques to identify the presence of mycobacterial lipoarabinomannan antigen in urine samples. While it may not offer high sensitivity, it serves as a valuable, quick diagnostic tool for HIV-positive individuals, particularly in urgent life-threatening situations necessitating swift tuberculosis diagnosis [15].

Serological Test

The World Health Organization (WHO) has issued a firm advisory against the utilization of Commercial Serodiagnostic assays for the detection of both pulmonary and extrapulmonary tuberculosis (TB) [18].

Chest X Ray

Utilizing a chest X-ray as a screening tool is instrumental in enhancing the sensitivity of the diagnostic process. When any abnormalities are observed in the radiograph, further assessment for TB, including microbiological confirmation, is imperative. In cases where microbiological confirmation is lacking, an X-ray can provide valuable supportive evidence for diagnosis. While X-ray interpretation may exhibit variability and lacks specificity for TB, integrating careful clinical evaluation alongside supportive X-ray findings enables the diagnosis of TB, even when culture results may not fully confirm it. Furthermore, X-rays are valuable in diagnosing extrapulmonary TB manifestations such as pleural effusion, pericardial effusion, mediastinal adenopathy, and miliary TB [16]. While chest X-rays during pregnancy are generally considered safe when medically necessary, it is crucial for healthcare providers to carefully weigh the benefits of the diagnostic information against the potential risks to both the pregnant woman and the foetus. Additionally, they should take appropriate precautions to minimize radiation exposure and consider alternative imaging methods when feasible. Pregnant women should discuss any concerns they have about medical procedures, including X-rays, with their healthcare provider to make informed decisions about their care.

Tuberculin Skin Test(Montoux test) and Interferon Gamma Release Assay(IGRA): These tests are safe during pregnancy and are primarily employed for the diagnosis of infection rather than the disease itself. They are particularly valuable for diagnosing latent tuberculosis; however, they should not be relied upon as standalone tools for tuberculosis treatment.

Diagnosis of Extrapulmonary Tuberculosis [16]

Demonstrating the presence of Acid-Fast Bacilli (AFB) in a sample taken from an extra-pulmonary site often proves to

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be a challenging task due to the typically low concentration of these bacteria. When diagnosing extra-pulmonary tuberculosis, it is essential to consider the clinical symptoms associated with the affected organ or system.

For the microbiological confirmation of extra-pulmonary tuberculosis, the preferred diagnostic methods are CBNAAT (Cartridge-Based Nucleic Acid Amplification Test) and Liquid Culture. Nevertheless, various specialized investigations can also aid in the diagnosis. These encompass radiological imaging, cytological or pathological examinations, biochemical analyses, and immunological assessments.

These Investigative Techniques Include

- Fine Needle Aspiration Cytology (FNAC) combined with direct smear examination.
- Excision or biopsy of specimens for histopathological scrutiny.
- Analysis of bodily fluids through cytology, biochemical tests, and smear examination.
- Utilization of X-rays to visualize the affected region.
- Employment of Ultra-Sonography for diagnosing Abdominal Tuberculosis.

It is worth noting that certain forms of extra-pulmonary tuberculosis pose diagnostic challenges due to their diverse symptomatology. Delayed diagnosis can have severe consequences, including potentially fatal outcomes or life-threatening complications, as is particularly evident in cases of meningeal tuberculosis.

Treatment

The objectives of anti-tubercular treatment encompass rendering the patient non-infectious, breaking transmission chains, decreasing infection reservoirs, reducing fatality rates via relapse-free recoveries, and preventing drug resistance development.

Treatment of Drug Sensitive Tuberculosis

The World Health Organization (WHO) suggests that employing fixed-dose combination (FDC) tablets is the preferred approach for treating individuals with drug-susceptible tuberculosis, as opposed to using individual drug formulations [15]. The intensive phase (IP) involves an initial 8-week period with daily doses of isoniazid (H), rifampicin (R), pyrazinamide (Z), and ethambutol (E) administered under direct observation, tailored to weight categories. Following this, the continuation phase (CP) spans 16 weeks with daily doses of isoniazid, rifampicin, and ethambutol. Pyrazinamide is discontinued during this phase. In specific TB forms like CNS TB, Skeletal TB, and Disseminated TB, the CP may extend by 12-24 weeks based on clinical judgment, with extensions beyond 12 weeks necessitating specialist recommendations [16,19].

Treatment of Multidrug Resistant Tuberculosis (MDR-TB)

The landscape of MDR-TB treatment has undergone significant transformations over the past decade, primarily due to the introduction of novel medications and regimens, resulting in considerably shortened treatment durations. Treatment of MDR-TB in pregnancy is quite complex. Pregnancy does not prohibit drug-resistant TB treatment, but it carries significant risks for both the mother and the unborn child. Second-line injectable medications are unsuitable during pregnancy due to potential harm to the fetal auditory nerve. Ethionamide is also avoided in the first 32 weeks due to teratogenic effects. Consequently, the shorter oral Bedaquiline-based MDR -TB regimen cannot be used for pregnant individuals with drug-resistant TB. To address MDR-TB, adherence to the protocols outlined by the National Tuberculosis Program is required [20]. Pregnant individuals diagnosed with active tuberculosis and patients battling multidrug-resistant TB should receive locally accessible, nutrient-enriched or fortified supplemental nutrition.

Treatment of Latent Tuberculosis

Pregnancy should not be a barrier to Tuberculosis Preventive Therapy (TPT) eligibility for women, regardless of their HIV status. Both Isoniazid (H) and Rifampicin are deemed safe for use during pregnancy. However, caution is advised with rifapentine due to limited safety data in pregnancy. For TPT also protocols outlined by the National Tuberculosis Program is required [21].

Postpartum and Breast Feeding

To ensure the well-being of both the breastfeeding mother and her baby while preventing the transmission of TB, it is essential for the mother to complete a full course of TB treatment with appropriate chemotherapy. Continuation of breastfeeding is encouraged throughout this process. After confirming the absence of active TB in the baby, it is advisable to administer a 6-month course of isoniazid preventive therapy. Moreover, it is vital to educate the mother about practicing good cough hygiene to minimize the risk of transmission, including covering her nose and mouth during coughing or sneezing. For mothers and infants on isoniazid, supplementing with vitamin B6 (pyridoxine) is recommended, with a daily dose of 10mg for the mother and 5mg for the infant [16,20].

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Conclusion

In conclusion, tuberculosis during pregnancy is a serious concern that needs attention. It can be tough, but with early detection, proper treatment, and good prenatal care, we can protect both the mother and the baby. Regular check-ups and support from healthcare experts are vital. It's important for everyone to be aware of TB's impact on pregnancy and to provide the right care. With teamwork, we can make sure that pregnant women facing TB have the best chance of a healthy pregnancy and a bright future for their newborns. Together, we can conquer TB and ensure safe pregnancies.

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