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Review Article

Tuberculosis During Pregnancy: An Updated Narrative Review

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ABSTRACT

Tuberculosis is a major global cause of morbidity and mortality, affecting over 200,000 pregnant women each year, although the epidemiology of tuberculosis in pregnancy is not well understood. This article aims to provide an overview of tuberculosis during pregnancy and in the postpartum period. A narrative review of published articles on tuberculosis and pregnancy was conducted through March 2023. Special attention was given to studies published between 2000 and 2023. The following themes were covered: epidemiology, pathophysiology, diagnostic tests, treatment of active and latent tuberculosis, drug-resistant tuberculosis, maternal and perinatal outcomes, and postpartum aspects. Pregnancy-related immunological alterations may contribute to an increased susceptibility to tuberculosis, but may play a minor role in relation to several socio-demographic and clinical factors. Active tuberculosis is associated with an increased risk of maternal mortality, morbidity, and anemia, as well as adverse perinatal outcomes such as premature birth and low birth weight, particularly if associated with HIV infection or if treatment is inadequate. Screening for tuberculosis is based primarily on clinical evaluation, chest X-ray, and immunological tests, with nucleic acid amplification and culture used for definitive diagnosis. In drug-sensitive tuberculosis, first-line anti-tuberculosis drugs are considered safe and effective during pregnancy; however, a personalized all-oral regimen including bedaquiline and linezolid is recommended for multidrug-resistant tuberculosis. Treatment of latent tuberculosis in pregnancy should be individualized according to the risk of tuberculosis progression and potential liver damage. Particular considerations in the postpartum period include breastfeeding and postnatal assessment of the baby. The review concluded that more clinical trials involving pregnant women are needed and that the approach to tuberculosis treatment during pregnancy should be standardized to reduce health inequalities.

Key words: tuberculosis, pregnancy, pregnant women, postpartum period, tuberculin test, latent tuberculosis, multidrug-resistant tuberculosis, interferon-gamma release tests, antitubercular agents

INTRODUCTION

Tuberculosis remains one of the top 10 causes of death worldwide and the leading cause of death from a single infectious agent. Globally, in 2024, an estimated 10.7 million people fell ill with tuberculosis, and 1.23 million died from the disease. The tuberculosis incidence rate was 131 per 100,000 population per year, with a case fatality rate of 11.5%. [1]

The true burden of tuberculosis among pregnant and postpartum women is not well understood. Tuberculosis during pregnancy is rarely reported separately, leaving substantial gaps in data and understanding. Each year, over 200 million women become

pregnant globally. [2] It is estimated that more than 200,000 of them develop tuberculosis during pregnancy, but this is likely an undercount. In many parts of the world, tuberculosis remains hidden, undetected, and underdiagnosed, especially among pregnant and postpartum women. [3] The unique biological changes, including alterations in the immune system, that take place in a woman's body during pregnancy and the postpartum period [4] raise the question of whether these changes affect the epidemiology of tuberculosis.

Understanding the pathogenesis of tuberculosis in pregnant and postpartum women is critical, as physiological adaptations within the maternal immune system are theorized to modulate both susceptibility to and the progression of the disease. [4,5] However, the clinical interpretation of these biological mechanisms remains debated. Epidemiological data regarding pregnancy-associated susceptibility are inconsistent, and some evidence suggests that pregnancy does not independently elevate the risk of *Mycobacterium tuberculosis* infection or exacerbate disease progression compared to non-pregnant populations. [2]

This narrative review presents a revised synthesis of the epidemiology, pathophysiology, diagnosis, treatment, and specific complications of tuberculosis during pregnancy. The management of active tuberculosis disease and latent tuberculosis infection (LTBI) is examined separately, given the significant differences in their presentations and treatment approaches. Additionally, we explore emerging issues for women, including drug-resistant tuberculosis, postpartum considerations, and key areas for future research.

METHODS

Study Design

In this study, we present an updated version of the narrative review of the literature on tuberculosis and pregnancy and postpartum. Moreover, a narrative review was selected as the preferred method since it allows a wider and more clinically focused consideration of the literature compared to a systematic review. Indeed, a narrative review provides a greater scope for synthesizing various types of information and evidence, evaluating the existing body of knowledge, and drawing clinical conclusions.

Search Strategy

The comprehensive search for relevant literature was performed in PubMed/MEDLINE, Embase, Global Health, Cochrane Library, and Web of Science databases. The search covered the period from January 2000 to March 2026. Thus, the majority of the included studies were published in the last 10 years to ensure the clinical relevance of the findings. The following set of keywords and Boolean operators was applied:

> For "TB during pregnancy or postpartum": ("tuberculosis" OR "*Mycobacterium tuberculosis*" OR "TB") AND ("pregnancy" OR "pregnant" OR "antenatal" OR "perinatal" OR "postpartum" OR "postnatal").
>
> For "Latent TB infection": ("latent tuberculosis" OR "LTBI" OR "tuberculosis infection") AND ("pregnancy" OR "pregnant").
>
> For "Drug-resistant TB": ("multidrug-resistant tuberculosis" OR "MDR-TB" OR "rifampicin-resistant" OR "RR-TB" OR "bedaquiline") AND ("pregnancy" OR "pregnant").
>
> For "Outcomes": ("maternal outcome" OR "perinatal outcome" OR "preterm birth" OR "low birth weight" OR "congenital tuberculosis") AND ("pregnancy" AND "tuberculosis").

The search results were complemented with a manual search of the references of the included studies, reviews, and guidelines. The following websites were prioritized for the manual search: World Health Organization (WHO), the Centers for Disease Control and Prevention (CDC), and the national tuberculosis programs.

BACKGROUND AND EPIDEMIOLOGICAL CONTEXT

Tuberculosis prevalence during pregnancy and the postpartum period is a global concern, with great variation among study locations. According to a recent systematic review analyzing studies on *Mycobacterium tuberculosis* infection prevalence during pregnancy, 47 included studies reported infection rates as high as 57.0% in certain populations. [6] Another systematic review and meta-analysis included 87 studies of pulmonary tuberculosis and 2965 participants across 27 countries. The researchers found that the most prevalent diagnosis during pregnancy was pulmonary tuberculosis. However, the majority of the included studies did not aim to specifically estimate population prevalence. [7] In a population-based cohort study conducted in Sweden, researchers found increased risks of incident tuberculosis during pregnancy and postpartum, mainly among those originating from high-tuberculosis–incidence countries. [8] The researchers concluded that tuberculosis prevalence during pregnancy largely depended on population group and geographical location rather than pregnancy-related factors.

PATHOPHYSIOLOGY AND RISK FACTORS

Pregnancy is a unique immune disease due to the changes caused to accommodate a growing baby. One of the changes is providing new immune regulation. One consideration with new immune regulation is that host cells become susceptible to new infections. While the old Th1-Th2 cell model illustrates the shift poorly, new evidence shows expanded cell regulation, increased interleukin, with the accompanying dysfunction of antigen-presenting cells. [9,10] The postpartum period shows immune reconstitution with increased inflammatory responses and a conduct shift reversal following delivery. [5,10] These changes illustrate the immune response shifts and changes related to the risk of tuberculosis during pregnancy and postpartum, as seen in **Figure 1**.

Although the physiological reasoning explaining the increased tuberculosis susceptibility of pregnant and postpartum women due to immune system changes is understood, clinical evidence remains limited. [5–8] Likewise, the literature does not firmly establish pregnancy as a factor in the increased incidence of tuberculosis among women. Currently available studies show that increased susceptibility is, in the majority of cases, a result of social and epidemiological conditions rather than pregnancy itself, even though the presence of pregnancy

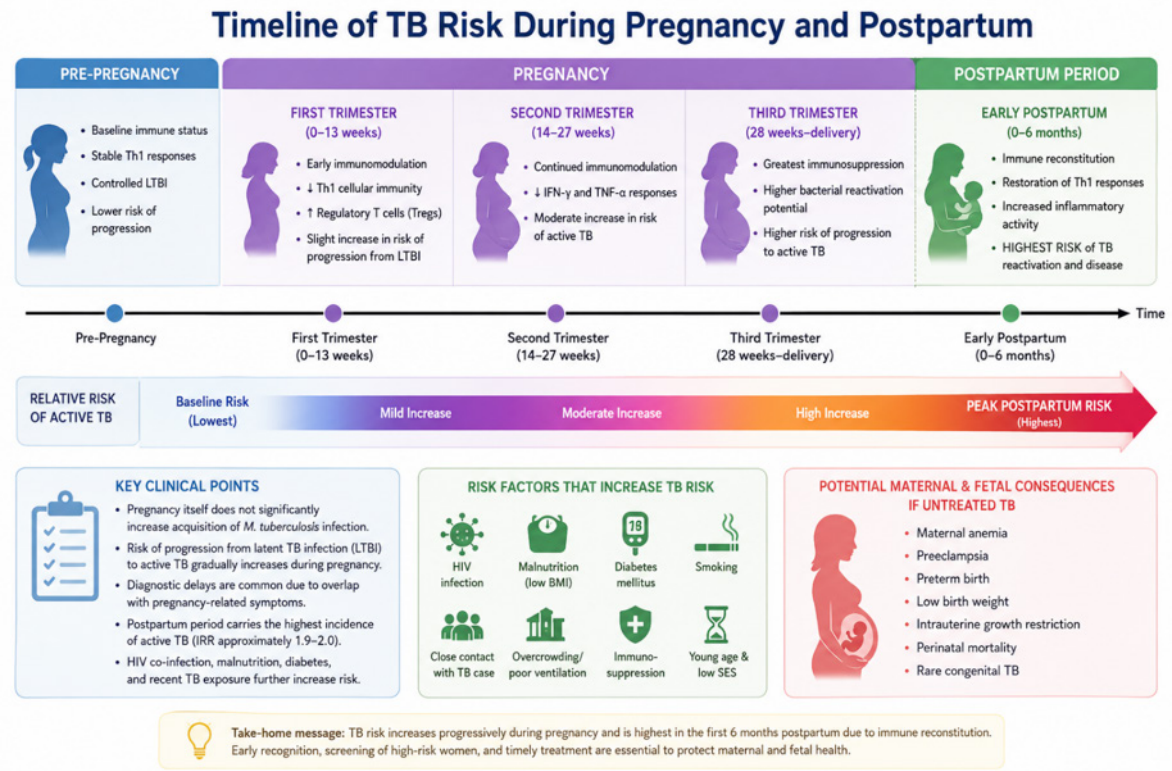

Figure 1: Timeline of tuberculosis risk during pregnancy and postpartum period.

does add a level of complexity to clinical management and diagnosis. [11]

The clinical susceptibility of pregnant women to tuberculosis results from an intersection of unique host factors and socio-economic and environmental conditions. The risk factors include tuberculosis, HIV, malnutrition, diabetes, immunosuppression, close household contact, poverty, and residing in a tuberculosis-endemic country. [10,12] The presence of HIV further complicates the diagnosis and treatment of tuberculosis during pregnancy and greatly increases the risk of pregnant women with LTBI progressing to tuberculosis in the postpartum period. [13,14] Of these risk factors, the mechanisms of tuberculosis in pregnancy are illustrated in **Table 1**.

MATERNAL AND PERINATAL COMPLICATIONS ASSOCIATED WITH TUBERCULOSIS DURING PREGNANCY

Active tuberculosis is a major contributor to indirect maternal mortality, particularly in regions with high tuberculosis prevalence, where it is frequently associated with HIV and other comorbidities. [15,16] A comprehensive global systematic review and meta-analysis of 13 studies with 3384 pregnancies consistently showed negative maternal and perinatal outcomes in women with active tuberculosis compared to women without the disease. [17] Pregnant women with active tuberculosis have a significantly increased risk of death (odds ratio 4.1), and approximately half of these deaths involve HIV-positive women. [13,17] Furthermore, hospital admissions during pregnancy are nine times more frequent in women with active tuberculosis. [17]

Table 1: Risk factors and pathophysiological mechanisms that elevate susceptibility to tuberculosis during pregnancy.

Risk factor	Effect on tuberculosis risk
HIV infection	Major increase in progression to active tuberculosis [13]
Malnutrition	Impaired cellular immunity [13]
Diabetes mellitus	Reduced macrophage and lymphocyte function [13]
Close tuberculosis exposure	Increased likelihood of infection [13]
Poverty and overcrowding	Increased transmission [13]
Immunosuppressive therapy	Reduced host defense [13]
Postpartum immune rebound	Possible reactivation/unmasking [14]

Clinically, active tuberculosis is associated with several serious maternal complications, including maternal anemia, placental chorioamnionitis, gestational hypertension, ruptured alveoli, postpartum hemorrhage, sepsis, and an increased need for intensive care. [13,16–18] Perinatally, tuberculosis during pregnancy correlates with adverse outcomes such as low birth weight, preterm birth, intrauterine growth restriction, small for gestational age (SGA), and increased perinatal mortality. [13,16,18] The risk is particularly high if maternal tuberculosis is not diagnosed or is diagnosed late, if the disease is disseminated or cavernous, or if there is HIV coinfection.

[13,16,18] Although rare, congenital tuberculosis can occur in cases of disseminated or poorly controlled maternal disease and poses a high risk of neonatal mortality if not detected early. [16,19] Complications of tuberculosis during pregnancy are summarized in **Table 2**.

SCREENING AND DIAGNOSTIC EVALUATION FOR TUBERCULOSIS DURING PREGNANCY AND THE POSTPARTUM PERIOD

Tuberculosis in pregnancy presents a diagnostic challenge. Early diagnosis and intervention are crucial to reduce the risk of maternal and perinatal illness or death. Screening protocols are used to detect active disease and/or latent infection in its early stages (when treatment is most effective and can interrupt transmission). However, a positive screening result alone is not sufficient for a definitive diagnosis but is merely one part of the diagnostic process. [5,20,21] Therefore, every positive screening test should be followed by comprehensive diagnostics to confirm or rule out active tuberculosis as part of the overall clinical assessment. [5,21]

Systematic Screening Protocols

Current screening protocols are based on the identification of risk factors. These factors include HIV status, residence in an endemic area, contact with tuberculosis patients, and conditions that weaken the immune system. [21–23] However, universal screening is controversial in areas where the disease is rare. There, protocols target specific pregnant women from at-risk groups to detect cases early and prevent the spread of the disease. For example, in Denmark, doctors diagnosed over 90% of tuberculosis cases during pregnancy and the postpartum period in migrant women. Many of these women were from Africa and had lived in Denmark for a median of less than three years. [24] In Sweden, an increased risk was found only in women who came from countries with a high prevalence of tuberculosis. [8] Systematic screening protocols use various tools, including symptom assessment, chest X-rays, and immunological tests.

Screening Tools

Symptom Screening

While the four-symptom screening method remains a standard starting point, it is increasingly recognized as insufficient for detecting active tuberculosis in pregnancy. Screening protocols for weight loss, for instance, require evaluating not only absolute weight loss but also the failure to achieve expected gestational weight gain. [18,25,26] Nonetheless, diagnostic challenges persist; the positive predictive value of symptom-based screening in pregnant populations is notably low, underscoring the urgent need for more robust, objective screening methodologies. [25] Physiological adaptations characteristic of pregnancy-such as fatigue, weight fluctuations, and dyspnea-frequently overlap with the clinical manifestations of tuberculosis, thereby masking the disease and leading to significant diagnostic delays. [18] Additionally, the systematic exclusion of many pregnant women from routine tuberculosis screening programs contributes to widespread underdiagnosis and late clinical presentation, representing a substantial gap in maternal care protocols. [7,25,26]

Chest Radiography Screening

Chest radiography remains a critical diagnostic instrument for the detection of pulmonary tuberculosis in pregnancy. Current clinical standards affirm that when contemporary equipment

Table 2: Maternal and perinatal complications associated with tuberculosis during pregnancy.

Category	Summary of findings	Key citations
Maternal mortality	Active tuberculosis is a major contributor to indirect maternal mortality in high-burden countries, particularly when associated with HIV co-infection and other comorbidities. Pregnant women with active tuberculosis had a higher mortality risk (odds ratio, 4.1 [95% CI, 0.65–25.2]). [1,11,13]	[1,11,13]
Maternal morbidity	Active tuberculosis during pregnancy is associated with increased antenatal hospital admissions, maternal anemia, placental chorioamnionitis, gestational hypertension, rupture of pulmonary bullae, postpartum hemorrhage, sepsis, and ICU admission in severe disease. [12,15–17]	[12,15–17]
Impact of HIV co-infection	Approximately half of maternal deaths among pregnant women with tuberculosis occurred in women living with HIV, highlighting the major impact of tuberculosis-HIV co-infection on maternal outcomes. [15]	[15]
Adverse perinatal outcomes	Tuberculosis in pregnancy increases the risk of low birth weight, preterm delivery, intrauterine growth restriction (IUGR), small-for-gestational-age (SGA) infants, and perinatal mortality. [12,16,17]	[12,16,17]
Factors associated with poor prognosis	Adverse maternal and fetal outcomes are more common when tuberculosis is undiagnosed or diagnosed late, when disease is disseminated or cavitary, or when HIV co-infection is present. [12,16,17]	[12,16,17]
Congenital tuberculosis	Congenital tuberculosis is rare but may occur in disseminated or poorly controlled maternal disease and is associated with high neonatal mortality if not identified and treated early. [17,18]	[17,18]
Evidence base	A systematic review and meta-analysis including 13 studies and 3384 pregnancies demonstrated consistently worse maternal and perinatal outcomes among women with active tuberculosis compared with women without tuberculosis. [15]	[15]

and appropriate abdominal shielding are employed, fetal radiation exposure remains minimal-well below established teratogenic limits-thereby alleviating the anxieties that often prompt clinicians and patients to delay necessary imaging. [27] Notwithstanding these reassurances, radiographic evaluation faces barriers, including the persistence of radiation-related apprehensions that can lead to diagnostic delays. Moreover, while radiographic manifestations can occasionally be subtle or atypical, particularly in the context of early disease or HIV co-infection, chest X-ray provides indispensable diagnostic insights that are not afforded by symptom-based screening alone. [21,26,27]

Immunological Tests

The WHO recognizes the tuberculin skin test (TST) and interferon-gamma release assays (IGRAs) as validated methods for detecting latent tuberculosis infection. Crucially, to mitigate the diagnostic challenges posed by the overlapping physiological symptoms of pregnancy and the limited specificity of symptom-based screening, current WHO guidelines advise integrating molecular WHO rapid diagnostic tests (mWRDs) into clinical protocols. [28]

- Tuberculin skin test (TST)

The TST is considered safe during pregnancy and is utilized to screen for latent tuberculosis infection in women at high risk. [25] However, the TST cannot distinguish between latent infection and active tuberculosis, limiting its utility as a diagnostic tool for active disease. Its accuracy may also be compromised by false-negative results, particularly in individuals co-infected with HIV who may exhibit cutaneous anergy. Furthermore, false-positive results can occur due to cross-reactivity from nontuberculous mycobacterial infections or prior Bacille Calmette-Guérin vaccination, a concern that is more pronounced in regions where BCG vaccination is widespread. [28,29]

- Interferon-gamma release assays (IGRAs)

IGRAs, such as QuantiFERON-TB Gold and T-SPOT.TB, are considered safe for use during pregnancy, with the significant clinical advantage that their accuracy is not compromised by prior BCG vaccination. [25] This renders them more specific than the TST in populations with high BCG coverage. Nevertheless, clinicians should exercise caution, as IGRAs may exhibit reduced sensitivity in pregnant women and individuals with HIV, potentially leading to inconclusive or false-negative findings. [30]

- Molecular WHO rapid diagnostic tests (mWRDs)

The WHO recommends not to depend exclusively on symptom-based screening for tuberculosis. It is advised that the Molecular WHO Rapid Diagnostic Tests be utilized as per the WHO guidelines. The molecular rapid diagnostic tests that have received endorsement from WHO include Xpert MTB/RIF, Xpert MTB/RIF Ultra, and Truenat MTB. These tests provide the advantage of rapid results-typically within 90 minutes-and the capability to identify rifampicin resistance. [28]

Notably, none of the approved rapid diagnostic tests can distinguish between latent tuberculosis infection and tuberculosis disease. Therefore, it is important to seek consultation and consider other diagnostic procedures such as chest X-rays, especially if the results of these rapid tests are positive. A schematic overview of a risk-based approach to tuberculosis screening in pregnant and postpartum women is summarized in **Figure 2**.

Diagnosis of Active Tuberculosis

If the screening test is positive, further diagnostic tests should be performed to confirm or rule out active tuberculosis. These typically include:

Sputum and other samples smear microscopy: Although smear microscopy remains a rapid, cost-effective, and foundational laboratory technique for identifying *Mycobacterium tuberculosis*, it suffers from substantial diagnostic limitations. Its sensitivity is notably low, particularly in paucibacillary cases and in the context of HIV co-infection, and it is unable to distinguish *Mycobacterium tuberculosis* from nontuberculous mycobacteria, necessitating further confirmatory testing. [31]

Culture: Mycobacterial culture-utilizing either solid or liquid media-remains the diagnostic gold standard, as it is indispensable for the definitive identification of *Mycobacterium tuberculosis* and for performing comprehensive drug susceptibility testing. For cases of suspected extrapulmonary tuberculosis, appropriate clinical specimens, including urine, cerebrospinal fluid, or tissue biopsies, should be obtained for culture. However, this methodology is significantly constrained by a protracted turnaround time, often requiring several weeks, which inherently delays clinical decision-making. Furthermore, the reliance on specialized laboratory infrastructure represents a critical barrier to implementation in resource-limited settings where antenatal care is frequently provided. [32]

Nucleic acid amplification tests: Unlike traditional culture techniques, nucleic acid amplification tests can be performed directly on sputum and other clinical specimens, enabling the rapid detection of *Mycobacterium tuberculosis* and rifampicin resistance within 24 to 48 hours. [33] Given these diagnostic capabilities, the WHO endorses Xpert MTB/RIF and Xpert MTB/RIF Ultra as the initial diagnostic tests for suspected tuberculosis cases, including those involving pregnant women. [34,35] Despite these clinical advantages, significant systemic challenges persist, as access and financial limitations continue to pose substantial barriers to their implementation in low-resource antenatal settings. [34]

Imaging: Ultrasound serves as a safe, non-ionizing modality of choice for evaluating extrapulmonary tuberculosis, including abdominal and lymphatic disease. [29] Although computed tomography entails ionizing radiation, it remains an essential diagnostic tool for complex cases; its use is clinically justified when the maternal benefit outweighs the potential risk to the fetus, provided that strict dose-reduction protocols are employed. [28,30]

Histopathology: Fine-needle aspiration cytology and tissue biopsy remain indispensable diagnostic tools, particularly for extrapulmonary tuberculosis, where the often low bacillary load complicates microbiological confirmation. These procedures may reveal characteristic histopathological features, such as granulomatous inflammation with caseous

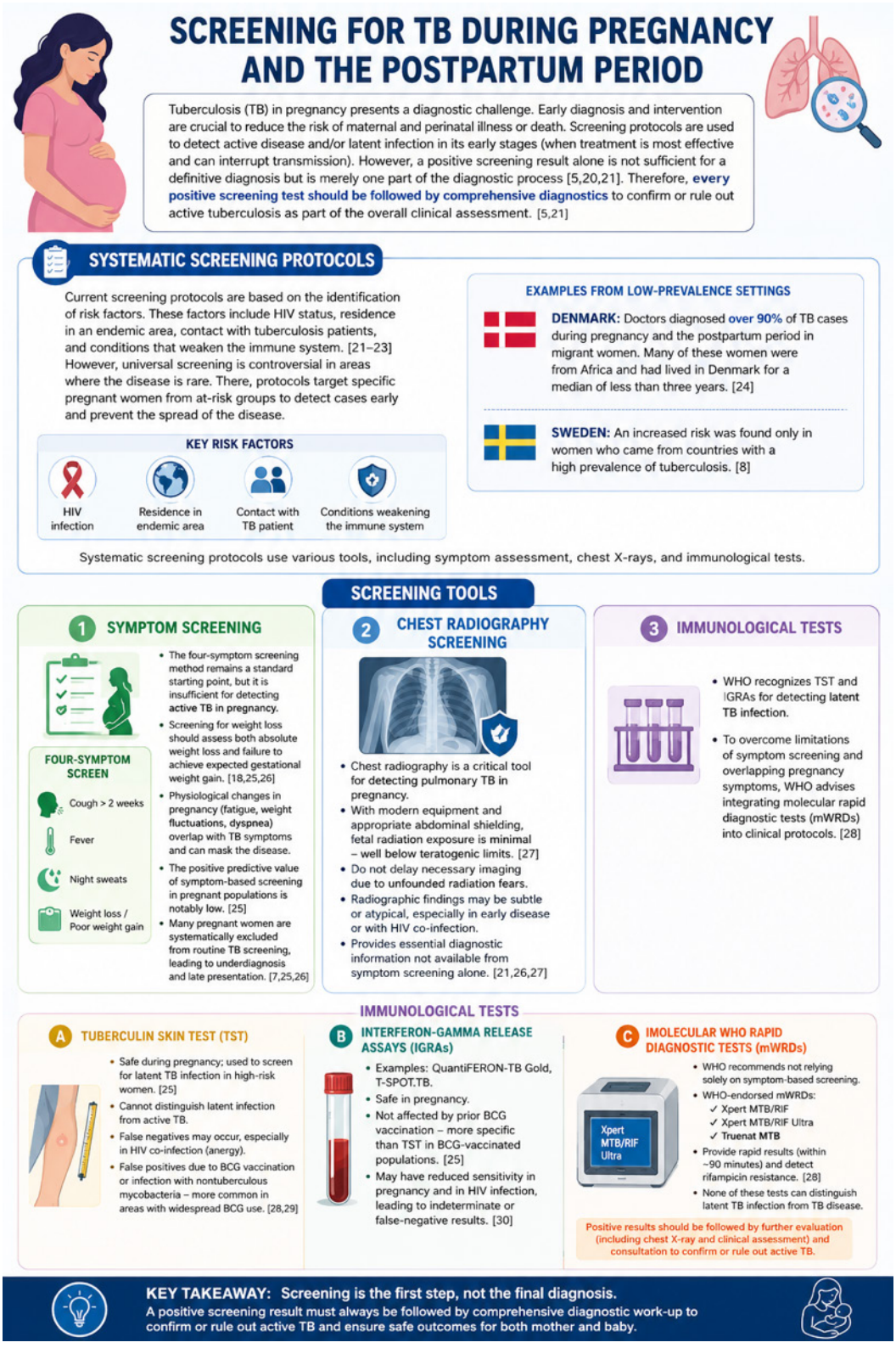

Figure 2: Screening for tuberculosis during pregnancy and the postpartum period.

necrosis, providing essential diagnostic clarity. Consequently, histopathological evidence serves as a critical modality for confirming tuberculosis affecting lymph nodes, the pleura, the musculoskeletal system, the abdomen, and disseminated forms of the disease, especially when other diagnostic tests yield inconclusive or negative results. [36,37] **Figure 3** summarizes the screening and diagnostic workup for tuberculosis in pregnant women.

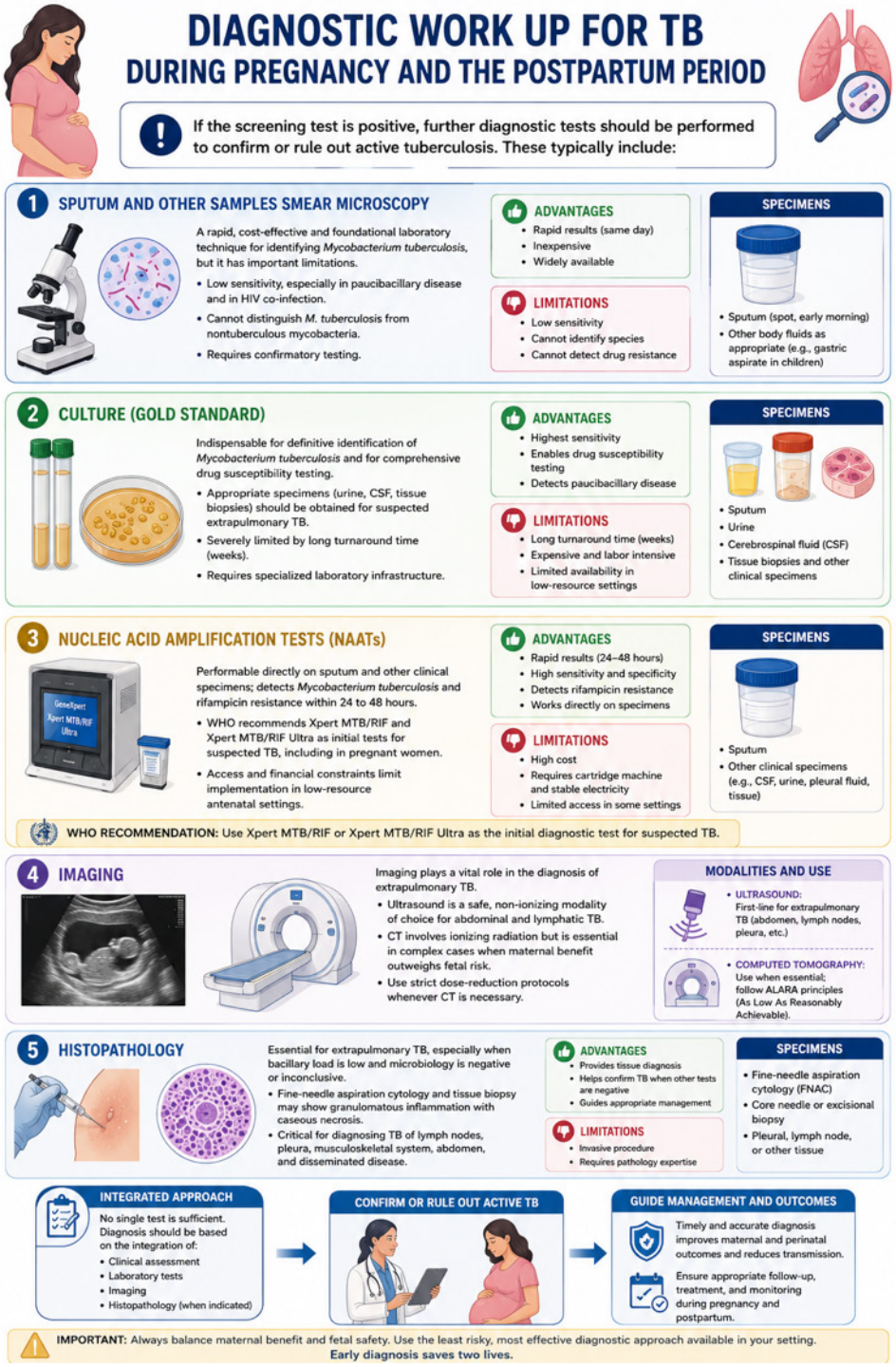

Figure 3: Diagnostic work-up for tuberculosis during pregnancy and the postpartum period.

MANAGEMENT OF ACTIVE TUBERCULOSIS DISEASE DURING PREGNANCY

Initiating treatment for active tuberculosis is imperative for both pregnant and non-pregnant individuals. Clinical evidence underscores that untreated tuberculosis poses a significant, established threat to pregnancy, frequently resulting in severe maternal complications-including irreversible organ damage and mortality-as well as adverse fetal outcomes, such as miscarriage, preterm birth, and vertical transmission. [38,39]

Management of Drug-Sensitive Tuberculosis (Pulmonary and Extrapulmonary Tuberculosis)

The standard of care for treating active, drug-sensitive tuberculosis during pregnancy aligns with nonpregnant protocols, reflecting the clinical consensus that the significant risks of untreated maternal tuberculosis-including preterm birth, low birth weight, and vertical transmission-far outweigh the minimal risks associated with standard anti-tuberculosis therapy. [39] This approach comprises a 6-month regimen: an

initial 2-month intensive phase involving isoniazid, rifampicin, pyrazinamide, and ethambutol, followed by a 4-month continuation phase of isoniazid and rifampicin. [21,40] These first-line agents have an established safety profile with no demonstrated teratogenic effects, supporting their continued use as the cornerstone of therapy in this population. [41]

For pulmonary tuberculosis, non–life-threatening Extra Pulmonary Tuberculosis (EPTB) (e.g., lymph node, pleural), a 6-month course is generally adequate, while bone/joint or miliary tuberculosis may require 9 to 12 months, while maintaining the standard 2-month intensive phase. [40] Pyridoxine (vitamin B6, 25 mg daily) should be co-administered with isoniazid to reduce the risk of neonatal neuropathy and seizures. [40,41] **Table 3** summarizes the first-line anti-tuberculosis drugs in pregnancy with important considerations.

Management of Multidrug-Resistant/Rifampicin-Resistant Tuberculosis (MDR/RR-TB)

Managing MDR/RR-TB in pregnancy is complex yet treatable, necessitating a rigorous assessment that balances the significant dangers of untreated disease against potential treatment-related risks. While second-line medications were historically avoided due to presumed teratogenicity, contemporary clinical evidence strongly supports prompt, aggressive intervention. Untreated MDR/RR-TB poses a substantial, established threat, including high rates of maternal mortality, miscarriage, preterm birth, and vertical transmission. [38,39] Current WHO and CDC guidelines now emphasize that pregnancy should not preclude access to effective treatment-which may include newer agents like bedaquiline-and note that the majority of first- and second-line medications have not demonstrated consistent teratogenic effects. [39,42] Supporting this therapeutic approach, observational studies demonstrate that MDR/RR-TB treatment outcomes in pregnant women are comparable to those in nonpregnant individuals, [38,43] particularly when utilizing optimized, all-oral regimens that prioritize safety and efficacy. [44]

Current WHO and CDC guidelines emphasize that pregnancy should not preclude access to the most effective MDR-TB treatment regimens, including newer agents like bedaquiline. [39,42] Clinical evidence consistently demonstrates that the profound risks of untreated MDR/RR-TB-including significant maternal morbidity and adverse fetal outcomes-far outweigh the potential, often manageable, risks of treatment. [39] Contemporary management strategies prioritize all-oral regimens that minimize fetal exposure to toxic injectable agents while maintaining therapeutic efficacy. [44] Given the complexity of navigating these therapeutic decisions, consultation with an infectious diseases specialist is essential for all suspected or confirmed cases of drug-resistant tuberculosis in pregnant patients. [38]

Clinical guidelines and field guides for managing drug-resistant tuberculosis in pregnant and peripartum individuals emphasize a critical preference for all-oral treatment regimens. [44] By excluding injectable agents-which are associated with significant risks of fetal ototoxicity and nephrotoxicity-these regimens prioritize maternal health while minimizing fetal harm. [44] In alignment with WHO and CDC recommendations, treatment must be individualized to balance the severe risks of untreated MDR/RR-TB against potential therapeutic risks. [39,42] When clinical indications necessitate, safer second-line medications-such as bedaquiline, linezolid, clofazimine, delamanid, and fluoroquinolones-may be employed, as current clinical evidence indicates these agents generally lack consistent teratogenic effects. [38,45–47] **Table 4** provides an overview of second-line anti-tuberculosis drugs categorized for use during pregnancy, based on current international guidance, CDC recommendations, and recent observational studies.

Key Considerations for Initiating Anti-Tubercular Treatment Regimens

- Preferred second-line regimens for MDR/RR-TB during pregnancy prioritize all-oral agents-including bedaquiline, linezolid, clofazimine, delamanid, and fluoroquinolones like levofloxacin-which clinical evidence suggests lack consistent teratogenic effects. [38,44–47] Standardized WHO-recommended regimens, such as the six-month all-oral BDLLfxC, are increasingly recognized as viable options for eligible pregnant patients. [48]
- Agents generally avoided include ethionamide and prothionamide due to maternal intolerance and potential teratogenicity; linezolid is often preferred as a substitute. [48] The use of pretomanid remains restricted outside of research settings due to insufficient safety data. [44]
- Injectable agents-including aminoglycosides (e.g., amikacin, streptomycin, kanamycin) and polypeptides (e.g., capreomycin)-are contraindicated throughout pregnancy because of significant risks of fetal ototoxicity and nephrotoxicity. [44]
- Management must be highly individualized and multidisciplinary, balancing the severe risks of untreated MDR/RR-TB against therapeutic risks, and guided by drug-susceptibility testing, disease severity, and gestational age. [39,42]

Table 3: First-line anti-tuberculosis drugs in pregnancy.

Drug	Pregnancy safety	Important considerations
Isoniazid	Generally safe	Give pyridoxine supplementation
Rifampicin	Generally safe	Monitor for bleeding risk near delivery
Ethambutol	Generally safe	Monitor visual symptoms if prolonged therapy
Pyrazinamide	WHO recommends use	Limited teratogenic evidence
Streptomycin	Contraindicated	Risk of fetal ototoxicity

Table 4: Second-line anti-tuberculosis drugs that may be used during pregnancy.

Drug	WHO Group	Pregnancy safety	Potential fetal/maternal concerns	Clinical recommendation during pregnancy
Bedaquiline (Bdq)	Group A	Can be used when indicated	Limited human pregnancy data; QT prolongation; limited data during breastfeeding	Recommended as part of individualized all-oral MDR/RR-TB regimens when benefits outweigh risks. Increasing evidence supports its use.
Levofloxacin (Lfx)	Group A	May be used with caution	Historical concerns about fetal cartilage toxicity (not confirmed in humans); maternal tendinopathy and QT prolongation	Preferred fluoroquinolone when required for MDR/RR-TB. Benefits generally outweigh theoretical risks.
Moxifloxacin (Mfx)	Group A	May be used with caution	Similar concerns as levofloxacin; QT prolongation	Acceptable alternative when susceptibility testing supports its use.
Linezolid (Lzd)	Group A	Can be used with careful monitoring	Maternal myelosuppression, peripheral neuropathy, optic neuropathy, lactic acidosis with prolonged use	Frequently included in individualized MDR/RR-TB regimens. Monitor complete blood count and neurologic toxicity.
Clofazimine (Cfz)	Group B	Generally acceptable	Reversible skin discoloration in mother and infant; gastrointestinal adverse effects	Considered relatively safe and commonly included in all-oral MDR/RR-TB regimens.
Cycloserine (Cs)/ Terizidone	Group B	May be used with caution	Neuropsychiatric toxicity, seizures, depression	Can be used when necessary with pyridoxine supplementation and close neurological monitoring.
Delamanid (Dlm)	Group C	Limited but increasing evidence	Limited human pregnancy data; QT prolongation	WHO allows use in individualized regimens when expected benefits outweigh potential risks. ECG monitoring is recommended.
Ethionamide (Eto)	Group C	Generally avoided	Severe maternal gastrointestinal intolerance; possible teratogenicity reported in animals	Avoid whenever effective alternatives exist, particularly during the first trimester. WHO recommends substituting linezolid when appropriate.
Prothionamide (Pto)	Group C	Generally avoided	Similar adverse effects and theoretical teratogenic risk as ethionamide	Not routinely recommended during pregnancy unless no safer effective alternative is available.
Para-aminosalicylic acid (PAS)	Group C	May be used when necessary	Gastrointestinal intolerance; hypothyroidism with prolonged use	Acceptable as an alternative when constructing individualized regimens for resistant disease.
Imipenem–cilastatin	Group C	Limited experience	Limited pregnancy safety data; intravenous administration	Reserved for highly resistant or complicated MDR/XDR-TB under specialist supervision.
Meropenem (with clavulanate)	Group C	May be used when required	Limited pregnancy data; generally well tolerated	Considered an option for extensively drug-resistant tuberculosis when few alternatives exist.
Amikacin	Injectable	Contraindicated	Fetal ototoxicity and nephrotoxicity	Avoid during pregnancy.
Kanamycin	Injectable	Contraindicated	High risk of congenital hearing loss	Contraindicated.
Capreomycin	Injectable	Contraindicated	Ototoxicity and nephrotoxicity	Contraindicated.
Streptomycin	Injectable	Contraindicated	Irreversible congenital deafness	Absolutely contraindicated during pregnancy.
Pretomanid	Group BPaL component	Not recommended	Insufficient human pregnancy data	Avoid outside research settings until more safety data become available.

Regimen Selection in Pregnancy: Shorter All-Oral Regimen Versus Individualized Longer All-Oral Regimen

For pregnant patients with drug-resistant extrapulmonary tuberculosis, a systematic clinical approach is critical to optimizing maternal and fetal outcomes. This necessitates rapid confirmation of the resistance profile via drug-susceptibility testing and a rigorous assessment of disease severity, particularly when distinguishing between localized and severe extrapulmonary disease, such as miliary

tuberculosis or central nervous system involvement. [48] Clinicians should prioritize the construction of an individualized, all-oral regimen that effectively treats the infection while avoiding agents with known teratogenic risks, ensuring that management is conducted within a multidisciplinary framework to balance the severe risks of untreated disease against potential therapeutic toxicities. [39,44]

Shorter all-oral regimen: The 2025 WHO guidelines identify the six-month all-oral BDLLfxC regimen-comprising bedaquiline, delamanid, linezolid, and either levofloxacin or clofazimine-as the preferred treatment option for eligible individuals with MDR/RR-TB, including pregnant women. [48] Alternatively, a nine-month all-oral regimen is considered an appropriate option for eligible pregnant patients when the standardized shorter regimen is not indicated; in such instances, clinical management should involve tailored adjustments, such as substituting linezolid for ethionamide, based on drug-susceptibility testing and individualized patient needs. [48]

Strict adherence to eligibility criteria for the shorter regimen is essential; this requires confirmed fluoroquinolone susceptibility and less than 1 month of prior exposure to any constituent medication, parameters designed to minimize the risk of treatment failure and the emergence of acquired resistance. Furthermore, patients with severe extrapulmonary tuberculosis or extensive disease burden are excluded from this standardized approach, as these complex clinical presentations necessitate individualized, longer-term treatment strategies to ensure therapeutic efficacy and patient safety. [48]

Individualized longer all-oral regimen for MDR/RR-TB during pregnancy: Individualized longer all-oral regimens are essential for managing complex MDR/RR-TB during pregnancy, particularly for extrapulmonary tuberculosis, where standardized, shorter-course regimens are frequently contraindicated. For severe presentations-such as miliary tuberculosis or tuberculosis meningitis-the 9-month standardized regimen is insufficient. Furthermore, WHO guidelines underscore the necessity of longer regimens for conditions like osteoarticular or pericardial tuberculosis, where reduced drug perfusion and limited clinical data on shorter protocols preclude their use. Consequently, clinical management of severe EPTB in pregnancy demands a tailored, individualized approach rather than an attempt to conform to standardized shorter regimens. [48] When such standardization is not feasible, extended treatment courses-often lasting 18 to 20 months-are required to ensure therapeutic efficacy in complex MDR/RR-TB cases. [49]

Corticosteroids: Adjunctive corticosteroids are indicated for tuberculosis meningitis, regardless of pregnancy status. [50,51] While these agents are a standard of care, it is imperative to acknowledge the significant evidence gap regarding their use during pregnancy; this population has been systematically excluded from clinical research on the topic, leaving management strategies largely dependent on extrapolations from non-pregnant cohorts rather than pregnancy-specific data.

Gaps in Evidence

The primary evidence gap is the systematic exclusion of pregnant patients from randomized clinical trials; current knowledge relies heavily on observational cohorts and small case series, which often lack the granularity required to guide management for severe extrapulmonary disease. [44] Although pretomanid-containing regimens show promise for MDR/RR-TB, pregnancy-specific safety data remain critically insufficient. [44] Consequently, the literature mandates a departure from standardized protocols in favor of highly individualized, multidisciplinary care that carefully weighs the severe risks of untreated disease against potential therapeutic toxicities. [39,48] The resulting clinical decision-making pathway is illustrated in **Figure 4**.

MANAGEMENT OF LATENT TUBERCULOSIS INFECTION (LTBI) IN PREGNANCY

Upon confirmation of latent tuberculosis infection, clinical management requires a rigorous, individualized assessment that weighs the maternal and fetal risks of progression to active disease-particularly in the near term-against the potential for drug-induced hepatotoxicity. [52,53] The primary clinical objective is to effectively prevent reactivation while minimizing adverse fetal-maternal outcomes, a process that demands a nuanced approach to treatment timing and patient-specific risk profiles. [54]

When to Treat LTBI During Pregnancy

When to treat LTBI during pregnancy? Deciding whether to initiate treatment for latent tuberculosis infection during pregnancy requires a meticulous, personalized assessment of the maternal and fetal risk-benefit profile, particularly given the limitations of existing evidence. [52–54] A robust clinical framework for this decision relies on estimating the patient's near-term risk of progression. Immediate treatment is prioritized in cases of recent exposure, advanced immunosuppression, or other indicators of recent infection, as the risk of progression to active tuberculosis infection is highest during this window. [55] Conversely, when infection is remote and the maternal risk is low, deferring therapy to the postpartum period is a reasonable and evidence-supported strategy consistent with current CDC guidance. [39]

Treatment Regimens

The CDC identifies three primary LTBI regimens suitable for consideration during pregnancy: four months of daily rifampin (4R), three months of daily isoniazid plus rifampin (3HR), and six or nine months of daily isoniazid (6H/9H) with mandatory pyridoxine supplementation. [39] Selecting the optimal regimen requires an individualized clinical assessment, carefully balancing the urgency of preventing maternal progression to active tuberculosis-particularly in high-risk scenarios-against potential treatment-related toxicities, such as hepatotoxicity. [52,53]

Monitoring and Safety

Clinical management during LTBI treatment in pregnancy necessitates a proactive monitoring strategy, specifically targeting clinical indicators of hepatotoxicity, consistent medication adherence, and rigorous review of concomitant prescriptions. [56] While hepatotoxicity concerns frequently justify the deferral of preventive therapy until the postpartum period, clinical decisions must be individualized based on maternal risk profiles. The current evidence base remains constrained; a systematic review identified a potential

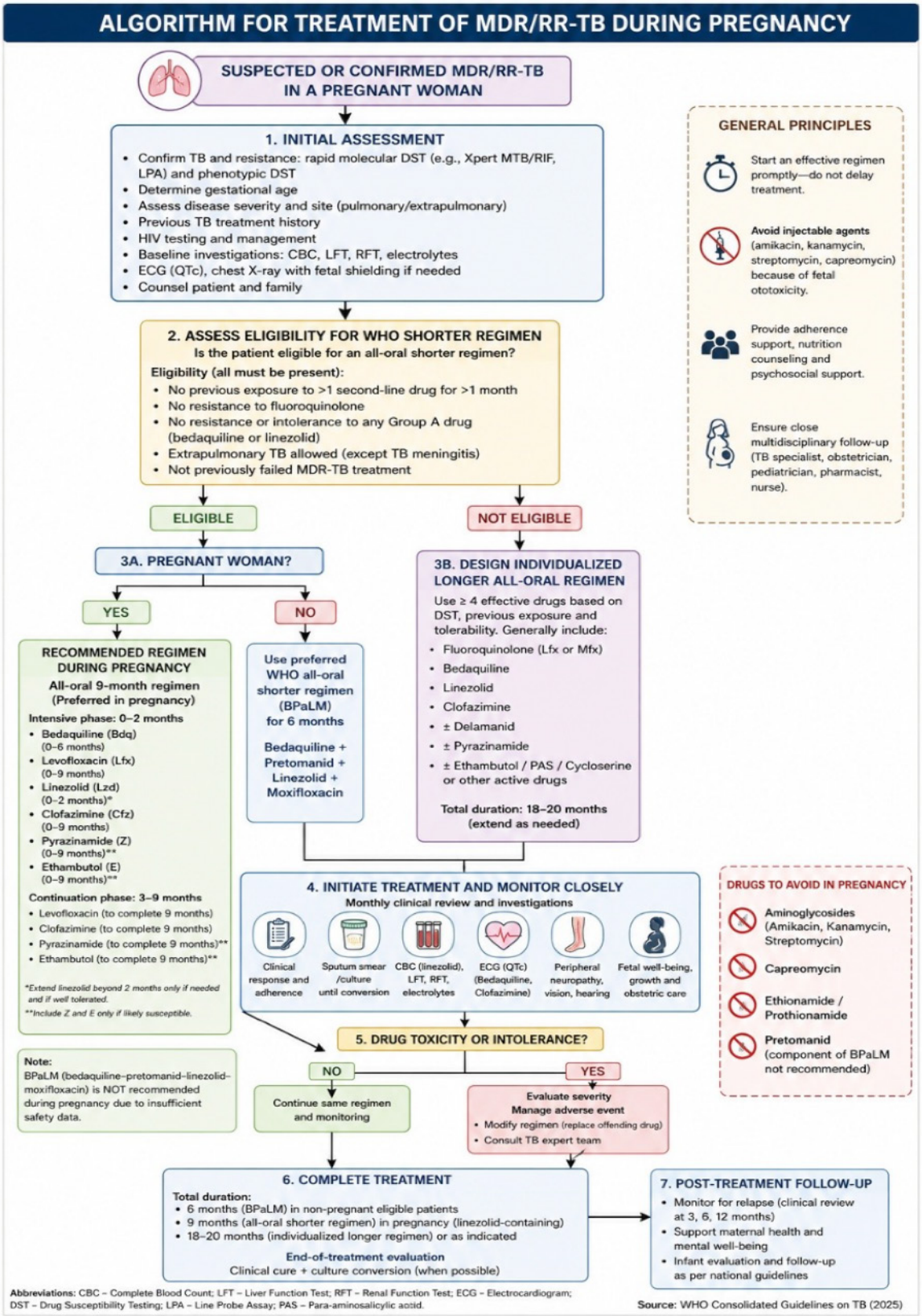

Figure 4: Algorithm for treating MDR/RR-TB during pregnancy.

association between isoniazid use during the pregnancy/postpartum period and hepatotoxicity, yet these findings are derived from sparse and imprecise data. Consequently, there is an urgent requirement for more robust, pregnancy-specific safety data regarding both isoniazid and newer preventive regimens. [52,53]

POSTPARTUM CONSIDERATIONS

The period following childbirth requires enhanced vigilance due to the confluence of stressors specifically related to the puerperium and common postpartum medical management disruptions, both of which elevate the risk of tuberculosis disease. [11] The postpartum period should be considered a high-risk period for developing tuberculosis due to a combination of immunological changes and the competing demands of childcare. It is therefore recommended that postpartum care be provided as a continuation of pregnancy care to ensure appropriate management of the health status of the woman across the perinatal period. This recommendation is supported by WHO guidelines, which state that pregnancy and postpartum should be viewed as a continuum to ensure the provision of integrated, comprehensive services to the mother and the newborn. [57]

Key Postpartum Issues

Breastfeeding: According to the recommendations of the CDC, breastfeeding while on first-line therapy is encouraged since the amount of medication passed to the infant through breast milk is not considerable enough to cause serious side effects. However, when it comes to the use of second-line medication, breastfeeding should be decided individually for each woman due to the lack of relevant clinical information. [58] Therefore, a decision regarding breastfeeding while on anti-tuberculosis treatment should be made by an infectious disease specialist who can carefully consider the benefits and risks of treatment for both mother and neonate. [18]

Mother-infant separation: For mothers with infectious pulmonary tuberculosis on standard treatment, separation is recommended only until sputum smear conversion to prevent transmission. [39] Thereafter, strict infection control measures are deemed sufficient.

Infant evaluation: Infants who are born to mothers who have active tuberculosis at birth need to be subjected to an accurate assessment for congenital tuberculosis because the identification of the infection at an early stage is essential for the effective outcome of the infant treatment. Those who do not exhibit signs of the illness can be prescribed isoniazid as a preventive measure for 3 to 6 months and then reviewed to ascertain the need for further treatment. [58] It is recommended that breastfeeding should be allowed if a mother has received adequate anti-tuberculosis therapy to ensure that the milk is not contaminated. [59]

Immune reconstitution inflammatory syndrome: In HIV-coinfected women initiating or resuming antiretroviral therapy during the postpartum period, the emergence of IRIS can lead to a paradoxical worsening of tuberculosis symptoms due to the rapid recovery of the immune system. This condition presents a complex diagnostic challenge that warrants heightened clinical vigilance, as severe inflammatory manifestations may necessitate the administration of corticosteroids. [51]

CONCLUSIONS

Pregnancy-related tuberculosis is one of the most important social, medical, and health policy issues in the world. The main problem in treating tuberculosis in pregnancy is the lack of knowledge on the safety and efficacy of new tuberculosis drugs and treatments and prevention methods. Studies on these topics should be carried out to provide information on tuberculosis prevalence in pregnant women, standardize treatment and prevention approaches, and ensure access to healthcare for pregnant women with tuberculosis. These issues are complex and multidimensional, and their positive resolution requires a long-term, far-reaching, and high-level study. Pregnant women should also be included in clinical trials, as they have traditionally been excluded from research studies. Another problem is the low level of awareness and understanding of tuberculosis among pregnant women and the general public. The social factor is one of the most important and crucial factors in the control of tuberculosis in pregnancy. Although significant progress has been made in the global fight against tuberculosis, there are still differences in access to healthcare and in the results of treatment for women in different populations. These problems can only be addressed through tuberculosis eradication programs that take into account the different social and healthcare environments in each country.

Until definitive results and evidence-based solutions are found for the identified problems, each clinical case must be approached individually, taking into account existing guidelines, recommendations, and the common views of the treating physician and patient. Thus, tuberculosis eradication cannot be achieved unless the issue of eliminating health inequalities is addressed at the global level. This concern underlines the importance of addressing the needs of women who are pregnant or recently given birth during the planning and implementation phases of tuberculosis programs at all levels.

AUTHORS' CONTRIBUTIONS

All authors contributed substantially to the conception and design of the study, data acquisition and analysis, drafting and revising of the manuscript, final approval of the version to be published, and are accountable for all aspects of the work.

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