



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

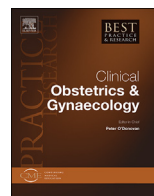
Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



ELSEVIER

Contents lists available at ScienceDirect

Best Practice & Research Clinical Obstetrics and Gynaecology

journal homepage: www.elsevier.com/locate/bpobgyn

4

Tuberculosis in pregnancy

Shuk Yi Annie Hui, MBBS, MRCOG, MSc, Clinical Associate
Professor^{*}, Terence T. Lao, FRCOG, MD, Professor

Department of Obstetrics and Gynaecology, The Chinese University of Hong Kong, Hong Kong SAR, China



Keywords:

Tuberculosis
Pregnancy
Anti-tuberculous drugs
Diagnostic tests
EPTB
HIV

A B S T R A C T

Due to COVID-19 pandemic, the latest progress of the End Tuberculosis (TB) Strategy was far from optimal and services for TB needs to be quickly restored. Pregnancy is a unique opportunity to screen and manage TB, and it is an essential step in TB eradication. Early diagnosis and treatment for active disease can reduce maternal and neonatal morbidities and mortality. The more widespread utilization of newer rapid molecular assays with drug-susceptibility testing has significantly shortened the diagnostic process for active TB disease. First-line anti-TB drugs are proven to be safe in pregnancy. Management of latent TB infection (LTBI) during pregnancy is controversial, but puerperium is a period of increased susceptibility to progress to active disease. Extrapulmonary TB (EPTB), multidrug-resistant TB (MDR-TB) and HIV co-infection remain significant issues surrounding TB management during pregnancy and often require input from a multidisciplinary team including TB experts.

© 2022 Published by Elsevier Ltd.

Introduction

Infection with *Mycobacterium tuberculosis* (TB) is a global health hazard. In 2014, the World Health Organization (WHO) endorsed the End TB Strategy aiming to eradicate TB by 2035 [1], but in 2020, 1.5 million people died from TB, including 214 000 with human immunodeficiency virus (HIV) co-infection, and TB was the second leading infectious killer after COVID-19 [2]. About 90% of the cases are found in South-East Asia, Africa and the Western Pacific, with India, China, Indonesia, the Philippines and Pakistan as the worst-affected countries, and women accounted for one-third of all

^{*} Corresponding author.

E-mail address: anniehui@cuhk.edu.hk (S.Y.A. Hui).

cases, with higher prevalence in the reproductive ages [2]. Globally, 216 500 active TB cases were estimated in pregnant women in 2011 [3], the risk increased by 2.56-fold in pregnant women with HIV infection [4], the commonest co-infection among low- and middle-income countries where most maternal mortality cases occurred [5]. The COVID-19 pandemic led to an 18% fall in TB notifications in 2020, with India, Indonesia and the Philippines accounting for 93% of the drop. However, disruptions in TB and HIV services resulted in a resurgence in TB-related mortality [2]. Pregnancy provides the opportunity to integrate screening for TB, HIV and even COVID-19 [6] into prenatal care [7], hence an update on TB in pregnancy and the puerperium is warranted.

Pathophysiology

Site of infection

The most common form of TB infection is pulmonary TB acquired through the inhalation of tubercle bacilli aerosolized by coughing, sneezing, talking or manipulating infected tissues [8], forming granuloma in lung tissue by recruitment and arrangement of the host's immune cells to contain the pathogen, and undergoing necrosis, caseation, and cavitation, in turn resulting in bacterial spread and disease dissemination [9]. Lymphatic and haematogenous spread can cause extrapulmonary TB (EPTB) [10].

Activity of disease

Latent TB infection (LTBI) is when the initial infection resolves without causing any symptoms but leaving small quantities of TB bacteria dormant in the body, occasionally re-emerging as active TB disease [11]. In healthy adults, the lifetime chance of active disease following an infection is only 5–10%, but the risk escalates to 10% annually with trends toward extrapulmonary spread in immunocompromised patients, particularly HIV-positive patients. The TB disease is an active illness with multiplying TB bacteria and manifestations of symptoms and signs depending on the site of infection, and the person becomes infectious. In between LTBI and active disease is a spectrum of bacterial activity and antagonistic immunological responses described as subclinical TB, in which the patients would be missed on symptom screening but can have positive bacteriological tests [12–14].

Risk factors

Risk factors for the progression of TB infection include past TB infection, contact with infected individuals, immigrants from resource-limited countries, ethnic minorities, poor health and malnutrition, drug abuse, alcoholism, smoking, poor living conditions (homelessness or overcrowded housing), extreme age and immunosuppression (HIV infection and medical problems like diabetes mellitus) [15].

Interaction between TB and pregnancy

Pregnancy per se does not increase disease susceptibility or course, including progression from latent to active infection or response to TB treatment [16].

Nevertheless, TB adversely affects pregnancy outcomes, being influenced by the site and severity of the disease, anti-tuberculous drug treatment response, complications of TB, gestational age at diagnosis and HIV status [16,17]. An earlier meta-analysis on active TB found significantly increased odds of maternal morbidity (Odd Ratio (OR) 2.8), antenatal admission (OR 9.6), miscarriage (OR 9.0), anaemia (OR 3.9) and caesarean delivery (CD, OR 2.1). Without treatment, TB also led to increased preterm delivery (PTD, OR 1.7), low birth weight (LBW, OR 1.7), foetal distress (OR 2.3), low Apgar score at 1 min (OR 5.7), birth asphyxia (OR 4.6) and perinatal death (OR 4.2) [18]. Subsequently, other studies similarly documented increased adverse outcomes. A US national cohort study with 4053 cases of TB in pregnancy demonstrated higher frequency of severe pre-eclampsia and eclampsia (Proportionality Ratio (PR) 1.7 and 3.9, respectively), postpartum haemorrhage (PR 1.8), placenta praevia (PR 1.9), sepsis (PR 6.2), and 37 times higher in-hospital death, compared with TB-negative counterparts but without

racial or ethnic disparities [19]. Furthermore, an earlier US population-based study showed significantly more concurrent HIV in women with TB and an increasing number of EPTB, with increased maternal mortality (OR 6.7) and congenital anomalies (OR 1.8) [20]. In India, significant increase in PTB, anaemia and intrauterine growth restriction (IUGR) were found in pregnancies complicated by TB [17]. A Chinese population-based cohort study showed that TB in the mothers or their partners both posed increased risk of stillbirths (OR 1.89 and 2.13, respectively) compared with TB-negative counterparts [21]. Despite the dispute on association between TB and hypertensive disorders of pregnancy [22], maternal TB remains an important obstetric risk factor.

HIV infection, the most powerful risk factor for active TB disease, increases latent TB reactivation 20-fold [23], and HIV co-infection triggers a substantial suppression of mycobacterium TB-specific IFN- γ responses in a CD4⁺ T cell count-dependent manner, which suggests that the higher risk of active TB disease during pregnancy is due to failure to control the TB infection [24]. Pregnancy in HIV-positive women increases TB acquisition by 2.56-fold [4], and TB and HIV co-infection increases neonatal death 3-folds [25] together with vertical transmission of 15% for TB and 10% for HIV [26].

The puerperium is associated with a greater risk of serious maternal complications including death, and disease transmission to their infants irrespective of HIV status or exposure history [27,28], as active TB disease is increased 95% during the 180 days postpartum [29], attributed to reversion of suppressed T-helper 1 pro-inflammatory responses after delivery resulting in disease exacerbation [30]. Those with LTBI also exhibit increased non-specific T-cell activation, which is a biomarker for progression from LTBI to TB disease [31]. Therefore, postpartum surveillance is important, especially for mothers in the endemic regions.

Extra-Pulmonary TB (EPTB) in pregnancy

EPTB is becoming more prevalent [20] and is found in >60% in India [32]. The sites include the pleura, abdomen, spine, urogenital tract and the central nervous system (CNS) [33,34]. Diagnosis is often delayed due to overlapping symptoms with those from pregnancy, atypical presentations, and reluctance in radiological imaging, biopsy and surgical intervention. EPTB is associated with poorer pregnancy and foetal outcomes, including increased antenatal hospitalization, oligohydramnios, pre-term premature rupture of membranes, LBW, reduced mean birth weight and small for gestational age, depressed Apgar scores, respiratory distress, NICU admission and perinatal mortality [35–37].

The outcome is influenced by the site of TB, with TB lymphadenitis having a favourable pregnancy outcome [38]. CNS infection, found in 5–10% of EPTB cases, is the most devastating form as diagnosis is difficult. Classical symptoms of tuberculous meningitis include fever, headache, neck stiffness, focal neurological deficits, brain abscess and formation of tuberculoma [39–42], while TB spine may cause intractable low back pain, focal neurological signs and even paraplegia that requires surgical treatment [43–45].

The widespread use of infertility treatment has led to an increasing number of pregnant patients with miliary TB after in vitro fertilization combined and embryo transfer (IVF-ET), some developing respiratory failure or acute respiratory distress syndrome and many with deleterious pregnancy outcomes [46,47]. It is prudent for TB screening in couples seeking infertility treatment, especially in the endemic regions, and anti-TB treatment should be commenced prior to IVF-ET in confirmed cases [47,48].

Management of TB in pregnant women

Screening

For regions with a high disease burden, universal screening for TB among pregnant women is preferable; restricting screening to symptomatic women would reduce yield as asymptomatic cases would not be tested [49,50]. For regions with a low disease burden, screening should be targeting selected at-risk pregnant women for early case finding and prevention of spread, as demonstrated in Denmark where >90% of TB in pregnancy and puerperium was diagnosed in immigrants, especially from Africa, with <3 years' median time of stay in Denmark [51], and in Sweden, where increased risk

was concentrated amongst women originating from countries with high TB incidence [52]. Such approach is justified by the high yield of unknown LTBI and mostly asymptomatic active TB with a similarly high rate of treatment completion.

WHO has proposed a four-symptom screening (cough, fever, night sweats and weight loss) as a first step [53], and a pregnant woman with unexplained documented fever ($>38^{\circ}\text{C}$) and coughs for more than 2 weeks is presumed to have TB, but symptom screening in pregnant women is neither specific nor sensitive, despite a good negative predictive value among HIV-infected women [54,55]. In the latest WHO recommendations, case detection can be improved by new technologies such as computer-aided detection to interpret chest radiography (CXR) and molecular rapid diagnostics that are applicable to pregnant women [53]. As TB disease can present as acute lower respiratory tract infection and community-acquired pneumonia with transient improvement following antibiotic treatment, the threshold for screening should be lowered in these women [56,57]. Other rare but important differential diagnoses of pregnant women that can mimic TB or vice versa include gestational trophoblastic disease with lung metastasis and lung cancer [58,59].

Diagnosis of TB disease

Definitive diagnosis is based on laboratory testing. Microscopy has a low sensitivity and cannot distinguish between *Mycobacterium tuberculosis* from other mycobacteria [60]. Traditional culture can take more than 4 weeks to yield a result and 6–8 weeks for phenotypic drug susceptibility testing, thereby significantly delaying diagnosis and treatment [61]. Currently, WHO recommends replacement of microscopy with molecular rapid diagnostic tests as the initial diagnostic test for all individuals with newly presenting signs and symptoms of TB, patients on treatment or have been previously treated, and patients being evaluated for possible rifampicin resistance or a new or continuing episode of TB, for pulmonary TB, EPTB and in prenatal settings [62]. For EPTB, specimens from other sites, such as gastric, tracheal or bronchial lavage, cerebrospinal fluid, lymph node aspirate, pus and tissue biopsied, can all be tested due to test reliability and speedier results from a single specimen [62]. WHO also recommends universal drug sensitivity testing (DST) using these newer rapid molecular tests, with or without liquid culture for all suspected drug-resistant cases. Nevertheless, traditional culture and DST are still gold standard in cases of diagnostic ambiguity and managing multidrug-resistant patients.

The Center for Disease Control (CDC) has also adopted that nucleic acid amplification test (NAAT) as the standard and priority test for TB suspects. However, a negative NAAT does not exclude TB and traditional culture may still be required [63].

Diagnosis of latent TB infection

There is no gold standard method for diagnosing LTBI. WHO has approved the tuberculin skin test (TST) and interferon-gamma release assays (IGRA) as screening tests for LTBI. In the TST (Mantoux test), a single-needle intradermal injection of 0.1 mL (5 Tuberculin units) of purified protein derivative is delivered, and the skin reaction is assessed 48–72 hours later by measuring the maximum diameter of the induration produced. False-negative results can occur from HIV co-infection or other immunosuppressive diseases [64], severe TB, recent viral infections, sarcoidosis, Hodgkin's disease and technical errors [65], while previous BCG vaccination can lead to false-positive results in healthy women. The application of TST requires reagents, trained operators for proper test placement and a return visit within 72 hours, from which about 20–30% of pregnant women would default. Thus, TST is not recommended for screening in areas with high HIV prevalence or BCG vaccination.

The IGRA are blood tests on the immune response of interferon- γ released by T-lymphocytes to specific TB antigens ESAT-6 and CFP-10. The advantages are improved diagnostic accuracy and specificity, decreased cross-reactivity with BCG and the majority of non-tuberculous mycobacteria. Therefore, IGRA is recommended for TB screening of LBTI in populations with high BCG vaccination rate or uncertain vaccination status. Adoption of IGRA can reduce false-positive results from TST and avoid unnecessary isoniazid prophylaxis at the expense of cost, need for blood collection and laboratory facility. A recent cross-sectional study conducted in a high TB and HIV burden setting found that

pregnancy or HIV infection reduced the rate of detection of LTBI by both tests, with the maximum effect observed in HIV-positive pregnant women [64].

In the rapid communication released by WHO in April 2022, a new TB antigen-based skin tests (TBST) have been found to be accurate, feasible and cost-effective, and is an acceptable alternative to TST and IGRAs [66]. TBST uses the two antigens in the IGRA test, ESAT-6 and CFP 10, as the intradermal injection agents. A double-blinded randomized trial reported a promising result of 94% concordance with the IGRA results and similar indurations sizes as the TST [67]. Furthermore, the result is unaffected by BCG vaccination or infection with non-TB or atypical mycobacteria, with a similar safety profile for participants ≥ 5 years-old, with similar sensitivity as TST and IGRA, while specificity was similar to IGRA and better than TST, particularly in populations with high BCG vaccination rates. Its use in pregnant women remains to be examined.

All these three tests are not designed for diagnosing active TB disease and cannot differentiate progressors from non-progressors in LTBI [68].

Imaging studies

Imaging studies can help in screening and diagnosis. CXR is a helpful screening tool for determining the amount of pulmonary involvement [12], with findings include patchy or nodular shadows with loss of volume and fibrosis with or without cavitation visible in the upper lobes. Radiation safety during pregnancy is enhanced with abdominal shield and lower doses of radiation [69]. Combining CXR with sound clinical judgment allows quick diagnosis of smear-negative TB; but CXR can be normal in up to 14% of culture-confirmed TB, and lung shadows can linger after bacteriological clearance. In high prevalent areas, computer-aided CXR screening combined with rapid sputum test for TB and universal HIV screening can achieve a fast and accurate diagnosis of both HIV and TB [70].

In cases of pleural effusion or abdominal TB, ultrasonography can help to determine the optimal location for aspiration. Computerized tomography or magnetic resonance imaging of the spine, abdomen and brain can be used to aid in the identification and assessment of EPTB.

Treatment of TB in pregnancy

Treatment of TB in pregnancy is best handled by a multidisciplinary team with an obstetrician, microbiologist, respiratory physician, primary care physician, neonatologists, specialist TB nurse and public health officials, to achieve cure without relapse, minimize complications, prevent transmission to the newborn, avoidance of drug resistance and ensure optimal pregnancy outcomes. The treatment regime is determined by the disease condition, drug resistance profile and co-morbidities. The medications are summarised in Table 1 [71–73].

Active TB disease

For drug-susceptible TB, a 6-month course of a combination of isoniazid (INH), rifampicin (RIF), ethambutol (EMB) and pyrazinamide (PZA) daily for 2 months, followed by INH, RIF and EMB daily for 4 months (HREZx2 + HREx4) is recommended by WHO as safety in pregnancy of these first-line medications have been proven (Table 1). This regimen will cure 90% of cases with good drug compliance and improve maternal and perinatal outcomes. Supplementation of pyridoxine and vitamin K maybe necessary as INH may increase maternal hepatotoxicity (1%) requiring treatment with n-acetyl cysteine, ursodiol, vitamin K and even liver transplant [74,75]; and peripheral neuropathy, as RIF in the last few weeks of pregnancy can cause maternal and neonatal hypoprothrombinaemia (Table 1). The effect of PZA on the foetus is unavailable, thus although it is recommended by the WHO as part of the standard regime, it is not endorsed by the CDC, except that it is safe for breastfeeding. If PZA is withheld, the treatment duration is extended to 9 months. Evaluation and regular monthly monitoring for liver function to detect hepatotoxicity during treatment is warranted [76].

As pregnant women may be concerned about the adverse foetal effects of treatment, compliance is enhanced by directly observed treatment in the form of daily direct observation of swallowing of the medications by another person [77]. Other means to monitor compliance include a computerized

Table 1
Anti-TB medications.

First line	HREZx2 + HREx4 (drug-susceptible TB)	Second line	For MDR-TB
	Isoniazid (INH) – 2 plus 4 months Rifampin (RIF) – 2 plus 4 months Ethambutol (EMB) – 2 plus 4 months Pyrazinamide (PZA) – 2 months	WHO Group A	Levofloxacin* Moxifloxacin* Bedaquiline Linezolid*
Supplement treatment	Pyridoxine – pregnancy, breast feeding Vitamin K for mother and infant if Rifampin is used before delivery to Prevent hypoprotrombinaemia	WHO Group B WHO Group C	Clofazimine Cycloserine* Terizidone Delamanid** Imipenem-cilastatin Meropenem Amikacin** Streptomycin** Ethionamide** Prothionamide** P-aminosalicylic acid***

*use only when benefits outweigh potential risks; **contraindicated in pregnancy; ***data limited.
Compiled from Refs. [71–73]; MDR-TB = multidrug-resistant TB.

medicine monitor, a short messaging service [78] and a phone or video call can be similarly useful [79]. Extremely unwell women with smear positive are highly infectious, these patients and those with multidrug-resistant TB (MDR-TB) may need hospitalization for treatment.

Other treatment aspects include provision or advice on balanced, nutrient-rich diets including leafy dark green vegetables, antioxidant-rich vegetables, complete grains, unsaturated fats and micro-nutrient supplements. Infection control management is also critical for the protection of staff and family members, with screening if necessary.

Latent TB infection

The merits of treating LTBI during pregnancy in women without HIV infection is still debatable, as the CDC recommends postponing therapy until late postpartum unless there is a substantial risk of active disease progression [80]. In low burden countries such as Sweden, LTBI is usually concentrated among immigrants, and a well-organized national TB program can ensure a high treatment completion rate [81]. When the risk of LTBI progression is high, such as in HIV co-infection, the recommended treatment is INH for 6 months or RIF plus INH for 3 months, which is efficacious in pregnant women [82].

Multidrug-resistant TB

Data on treatment of MDR-TB in pregnancy is limited. In the recent systematic review and meta-analysis that included 174 pregnant women with MDR-TB, the adverse outcomes included maternal death (7.5%), pregnancy loss (10.6%), PTD (12.9%) and LBW (23.7%) [83]. In the recent case series from South Africa, 60.7% of the 28 women completed TB treatment successfully, while 3 (10.7%) died [84]. The available literature suggests that MDR-TB is associated with high risk of adverse maternal and perinatal outcomes. Treatment regimen for MDR-TB preferably consists of at least 4 second-line anti-TB drugs that are likely to be effective plus PZA (Table 1) [85]. However, because of concerns regarding drug safety, counselling on known and unknown foetal risks is necessary. If the mother's condition is stable with minimal radiological disease, treatment may be deferred until the second trimester to avoid teratogenic effect. The construction of individualised treatment regimen using various combinations of anti-TB drugs according to the susceptibility profile and commencing at an acceptable gestation should be explored, as favourable outcomes are still achievable with careful case selection. After delivery, double-barrier contraception is recommended while continuing the course of MDR-TB treatment.

HIV and TB co-infection

Active TB with HIV co-infection increases maternal mortality and morbidity [86]. Untreated TB may deteriorate with antiretroviral treatment (ART), a condition called immune reconstitution syndrome, which is the paradoxical worsening of pre-existing infectious processes following the initiation of ART in HIV-infected individuals, particularly in the first three months of ART [87]. It is therefore recommended to commence TB treatment prior to ART, which should be initiated within the next 2 weeks for patients with CD4 cell counts of $<50/\text{mm}^3$ and in 8–12 weeks for patients with CD4 cell counts of $\geq 50/\text{mm}^3$. An important exception is TB meningitis, in which ART should not be initiated during the first 8 weeks of anti-TB therapy [88]. Adherence issues, polypharmacy and overlapping side effect profiles of anti-TB and ART medications may also complicate the treatment. RIF interacts with non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs), lowering blood levels of several HIV medications, especially Nevirapine. RIF can be replaced with rifabutin to lower the likelihood of medication interactions with ART [89]. Efavirenz is contraindicated in pregnancy due to concerns regarding teratogenicity.

For newly diagnosed MDR-TB with HIV co-infection, WHO recommends the initiation of ART within 8 weeks of commencing effective MDR-TB treatment, which is determined by the drug susceptibility profile except for a few possible drug-drug interactions, irrespective of CD4⁺ count [90].

As pregnancy suppresses anti-mycobacterial protective immune response in CD4⁺ T-cell count, especially when co-existing with HIV infection, there is an increased risk of progression to active TB disease in pregnant women with LTBI and HIV co-infection [91]. Prophylactic treatment with 4 months of daily RIF or rifabutin as the substitute for RIF is recommended, depending on the ART prescribed [88]. A recent trial found higher incidence of stillbirth, spontaneous abortion, LBW, PTD and congenital anomalies (23.6% vs. 17.0%) in pregnant women who received 28 weeks of INH preventive therapy initiated during pregnancy (immediate group) versus women who started therapy at week 12 after delivery (deferred group) [92]. Therefore, optimal timing of commencement of anti-TB therapy remains to be established.

Perinatal TB

This includes the congenital and postnatally acquired infection. Risk factors include high maternal bacillary load, disseminated disease, sputum-positive pulmonary TB, meningeal TB, HIV co-infection, diabetes mellitus, severe malnutrition, smoking, alcohol consumption, short duration of anti-TB therapy, long duration of contact and poor nursing hygiene. Congenital TB results in foetal exposure to TB bacilli through the placenta or via the umbilical vein from a mother with active pulmonary or EPTB, and the bacilli cause hepatic infection followed by secondary haematogenous or disseminated spread; the infection is often undiagnosed, especially in preterm infants, because of undiagnosed maternal disease [93]. Alternatively, ruptured infective foci in the placenta contaminates amniotic fluid, which upon foetal aspiration or ingestion leads to a primary focus in the lungs or gastrointestinal tract. Placental TB infection per se leads to neutrophilic and histiocytic responses causing villitis and intervillitis, tissue injury and even intrauterine foetal death [94]. After birth, neonatal exposure to an open infectious sputum-positive case leads to postnatal infection. In the absence of evidence of perinatal TB, INH prophylaxis with pyridoxine for 3–6 months is recommended [95]. A positive NAAT or culture on stomach aspirate and clinical or radiological signs of active TB indicate for a full course of anti-TB treatment. BCG vaccine is recommended at birth or after completion of prophylaxis in all neonates [96].

Although it can progress to active TB during pregnancy and postpartum, LTBI does not pose a risk of vertical transmission. As well, offspring born to mothers with TB did not demonstrate higher rates of infectious-related morbidity in the long term [97].

Breastfeeding

The decision of breastfeeding should be arrived only following discussion with neonatologist, obstetrician and pharmacologist. Standard first-line anti-TB medications are excreted in breast milk

only in small amounts and have no deleterious effects on the baby, but this also means that drugs in breast milk cannot be relied upon as an effective treatment for TB disease or latent infection in the infant. Breastfeeding should only be started after the mother has been treated for at least two weeks, and she must first put on a face mask and maintain a high degree of personal and cough hygiene, with pyridoxine supplementation if INH is taken. Expressed breast milk is a safe alternative during barrier nursing.

Conclusion

Pregnancy provides a unique opportunity to screen and eradicate TB as women with advanced disease identified late in pregnancy or during the puerperium, with HIV co-infection and non-compliance have the worse maternal and neonatal outcomes. Early and rapid diagnosis is facilitated by the newer rapid molecular assays with drug-susceptibility testing. Prompt treatment with first-line medications has been proven to be safe in pregnancy and prevents significant maternal and perinatal complications. For LTBI, treatment during pregnancy is controversial but may be indicated postpartum due to increased susceptibility. Significant management issues are EPTB, MDR-TB and HIV co-infection. To avoid overlooking the diagnosis and having to deal with the consequences, a high index of suspicion is necessary, especially in high-risk populations and/or in endemic areas.

Practical points

- Early diagnosis and treatment of TB in pregnancy can reduce maternal and neonatal morbidities and mortality.
- Puerperium is a period of increased susceptibility for progression to active TB disease.
- The more widespread utilization of newer rapid molecular assays with drug-susceptibility testing has significantly shortened the diagnostic process for active TB disease.
- First-line anti-TB drugs are safe to treat TB disease in pregnancy.

Research agenda

- The use of new TB antigens-based skin tests for LTBI screening needs further validation in pregnancy.
- Management of LTBI in pregnancy remains controversial, and further research on how to differentiate progressors from non-progressors is required.
- Bedaquiline may be a helpful second-line agent to treat MDR-TB, and its use in pregnancy needs further investigation.

Declaration of competing interest

The authors declare no conflict of interest.

References

- [1] Jeremiah C, Petersen E, Nantanda R, Mungai BN, Migliori GB, Amanullah F, et al. The WHO Global Tuberculosis 2021 Report - not so good news and turning the tide back to End TB. *Int J Infect Dis* 2022. S1201-9712(22)00149-7.
- *[2] World Health Organization. Global tuberculosis report 2021. Geneva: World Health Organization; 2021.
- [3] Sugarman J, Colvin C, Moran AC, Oxlade O. Tuberculosis in pregnancy: an estimate of the global burden of disease. *Lancet Glob Health* 2014;2(12):e710–6.
- [4] Yaghoubi A, Salehabadi S, Abdeahad H, Hasanian SM, Avan A, Yousefi M, et al. Tuberculosis, human immunodeficiency viruses and TB/HIV co-infection in pregnant women: a meta-analysis. *Clin Epidemiol Glob Health* 2020;8(4):1312–20.
- [5] Mofenson LM, Laughon BE. Human immunodeficiency virus, mycobacterium tuberculosis, and pregnancy: a deadly combination. *Clin Infect Dis* 2007;45(2):250–3.

- [6] Dheda K, Perumal T, Moultrie H, Perumal R, Esmail A, Scott AJ, et al. The intersecting pandemics of tuberculosis and COVID-19: population-level and patient-level impact, clinical presentation, and corrective interventions. *Lancet Respir Med* 2022;10(6):603–22.
- [7] Nguyen HT, Pandolfini C, Chiodini P, Bonati M. Tuberculosis care for pregnant women: a systematic review. *BMC Infect Dis* 2014;14:617.
- [8] Centers for Disease Control and Prevention. Basic TB facts: how TB spreads. <https://www.cdc.gov/tb/topic/basics/howtbspreads.htm>. [Accessed 27 June 2022].
- [9] Ehlers S, Schaible UE. The granuloma in tuberculosis: dynamics of a host–pathogen collusion. *Front Immunol* 2013;3:411.
- [10] Rodriguez-Takeuchi SY, Renjifo ME, Medina FJ. Extrapulmonary tuberculosis: pathophysiology and imaging findings. *Radiographics* 2019;39(7):2023–37.
- [11] Centers for Disease Control and Prevention. Basic TB facts: latent TB infection and TB disease. <https://www.cdc.gov/tb/topic/basics/tbinfectiondisease.htm>. [Accessed 27 June 2022].
- [12] Frascella B, Richards AS, Sossen B, Emery JC, Odone A, Law I, et al. Subclinical tuberculosis disease—A review and analysis of prevalence surveys to inform definitions, burden, associations, and screening methodology. *Clin Infect Dis* 2021;73(3):e830–41.
- [13] Rickman HM, Cohn S, Lala SG, Waja Z, Salazar-Austin N, Hoffmann J, et al. Subclinical tuberculosis and adverse infant outcomes in pregnant women with HIV. *Int J Tubercul Lung Dis* 2020;24(7):681–5.
- [14] Tang P, Liang E, Zhang X, Feng Y, Song H, Xu J, et al. Prevalence and risk factors of subclinical tuberculosis in a low-incidence setting in China. *Front Microbiol* 2022;12:731532.
- [15] Centers for Disease Control and Prevention. Basic TB facts: TB risk factors. <https://www.cdc.gov/tb/topic/basics/risk.htm>. [Accessed 27 June 2022].
- [16] Gould JM, Aronoff SC. Tuberculosis and pregnancy—maternal, fetal, and neonatal considerations. *Microbiol Spectr* 2016;4(6).
- [17] Lewis PF, Budhewar AS, Bavdekar NB. Fetomaternal outcome of pregnant women infected with tuberculosis: an analytical study. *J South Asian Feder Obst Gynae* 2021;13(4):197–201.
- *[18] Sobhy S, Babiker Z, Zamora J, Khan KS, Kunst H. Maternal and perinatal mortality and morbidity associated with tuberculosis during pregnancy and the postpartum period: a systematic review and meta-analysis. *BJOG* 2017;124(5):727–33.
- *[19] Dennis EM, Hao Y, Tamambang M, Roshan TN, Gatlin KJ, Bghigh H, et al. Tuberculosis during pregnancy in the United States: racial/ethnic disparities in pregnancy complications and in-hospital death. *PLoS One* 2018;13(3):e0194836.
- [20] El-Messidi A, Czuzoj-Shulman N, Spence AR, Abenheim HA. Medical and obstetric outcomes among pregnant women with tuberculosis: a population-based study of 7.8 million births. *Am J Obstet Gynecol* 2016;215(6):797.e1–6.
- [21] Sun Q, Zhang H, Zhang Y, Peng Z, Lu J, Ma X. Increased risk of stillbirth among women whose partner has tuberculosis. *BioMed Res Int* 2021;2021:1837881.
- [22] Phoswa WN, Eche S, Khaliq OP. The association of tuberculosis mono-infection and tuberculosis-human immunodeficiency virus (TB-HIV) Co-infection in the pathogenesis of hypertensive disorders of pregnancy. *Curr Hypertens Rep* 2020;22(12):104.
- [23] Pawlowski A, Jansson M, Sköld M, Rottenberg ME, Källenius G. Tuberculosis and HIV co-infection. *PLoS Pathog* 2012;8(2):e1002464.
- [24] Ranaivomanana P, Ratovoson R, Razafimahatratra C, Razafimahefa A, Hoffmann J, Herindrainy P, et al. Longitudinal variations of M. Tuberculosis-Induced IFN- γ responses in HIV-negative pregnant women exposed to tuberculosis. *Front Immunol* 2021;12:805157.
- [25] Gupta A, Nayak U, Ram M, Bhosale R, Patil S, Basavraj A, et al. Postpartum tuberculosis incidence and mortality among HIV-infected women and their infants in Pune, India, 2002–2005. *Clin Infect Dis* 2007;45(2):241–9.
- [26] Adhikari M, Jeena P, Bobat R, Archary M, Naidoo K, Coutsooudis A, et al. HIV-associated tuberculosis in the newborn and young infant. *Int J Pediatr* 2011;2011:354208.
- [27] Tasleem A, Mahmood A, Bharat A. An unfortunate case of reactivation of tuberculosis in a postpartum female. *Cureus* 2020;12(11):e11775.
- [28] Zenner D, Kruijshaar ME, Andrews N, Abubakar I. Risk of tuberculosis in pregnancy: a national, primary care-based cohort and self-controlled case series study. *Am J Respir Crit Care Med* 2012;185(7):779–84.
- *[29] Bothamley GH, Ehlers C, Salonga I, Skrahina A, Orcau A, Codecasa LR, et al. Pregnancy in patients with tuberculosis: a TBNET cross-sectional survey. *BMC Pregnancy Childbirth* 2016;16(1):304.
- [30] Singh N, Perfect JR. Immune reconstitution syndrome and exacerbation of infections after pregnancy. *Clin Infect Dis* 2007;45:1192–9.
- [31] Saha A, Escudero J, Layouni T, Richardson B, Hou S, Mugo N, et al. Mycobacterium tuberculosis-specific T cell responses are impaired during late pregnancy with elevated biomarkers of tuberculosis risk postpartum. *J Infect Dis* 2022;225(9):1663–74.
- [32] Chopra S, Siwatch S, Aggarwal N, Sikka P, Suri V. Pregnancy outcomes in women with tuberculosis: a 10-year experience from an Indian tertiary care hospital. *Trop Doct* 2017;47(2):104–9.
- [33] Adhikari EH, Duryea EL, Rac MWF, Sheffield JS. Genitourinary tuberculosis: a rare cause of obstructive uropathy in pregnancy. *Case Rep Obstet Gynecol* 2014;2014:985682.
- [34] Moore AR, Rogers FM, Dietrick D, Smith S. Extrapulmonary tuberculosis in pregnancy masquerading as a degenerating leiomyoma. *Obstet Gynecol* 2008;111(2 Pt 2):550–2.
- *[35] Jana N, Vasishta K, Saha SC, Ghosh K. Obstetrical outcomes among women with extrapulmonary tuberculosis. *N Engl J Med* 1999;341(9):645–9.
- [36] Yadav V, Sharma JB, Kachhawa G, Kulshrestha V, Mahey R, Kumari R, et al. Obstetrical and perinatal outcome in pregnant women with extrapulmonary tuberculosis. *Indian J Tubercul* 2019;66(1):158–62.
- [37] Lewis PF, Budhewar AS, Bavdekar NB, Gurnani D, Kumari A. Comparative analysis of fetomaternal outcome in antenatal women infected with pulmonary and extrapulmonary tuberculosis. *Int J Reprod Contracept Obstet Gynecol* 2020;9(11):4580.

- [38] Clark PC, Yencha MW, Hart AKE. Management of isolated extrapulmonary tuberculosis in a pregnant patient. *Ann Otol Rhinol Laryngol* 2004;113(8):648–51.
- [39] Namani S, Dreshaj S, Berisha AZ. Tuberculous meningoencephalitis associated with brain tuberculomas during pregnancy: a case report. *J Med Case Rep* 2017;11(1):175.
- [40] Muin DA, Wagner K, Burian R, Ghaem Maghami N, Lapaire O. Brainstem tuberculosis in pregnancy. *Case Rep Obstet Gynecol* 2015;2015:179483.
- [41] Singh S, Jose T, Saxena P. A rare case of CNS tuberculosis with pregnancy. *Int J Reprod Contracept Obstet Gynecol* 2015;4(3):911–4.
- [42] Samson Ejiji I, Gomerep S, Johnson M, Basil Bemgba A. Delayed diagnosis of tuberculous meningitis in a pregnant Nigerian: a case report. *Int J Mycobacteriol* 2013;2(1):54–7.
- [43] Srivastava S, Raj A, Agarwal R, Bhosale S, Marathe N. Management dilemma of tuberculous paraplegia in pregnancy - a case report and review of literature. *Surg Neurol Int* 2020;11:470.
- [44] Badve SA, Ghate SD, Badve MS, Rustagi T, Macchiwala T, Parekh AN, et al. Tuberculosis of spine with neurological deficit in advanced pregnancy: a report of three cases. *Spine J* 2011;11(1):e9–16.
- [45] Lowenstein L, Solt I, Fischer D, Drugan A. Spinal tuberculosis with paraplegia in pregnancy. *Isr Med Assoc J* 2004;6(7):436–7.
- [46] Wang K, Ren D, Qiu Z, Li W. Clinical analysis of pregnancy complicated with miliary tuberculosis. *Ann Med* 2022;54(1):71–9.
- [47] Gai X, Chi H, Cao W, Zeng L, Chen L, Zhang W, et al. Acute miliary tuberculosis in pregnancy after in vitro fertilization and embryo transfer: a report of seven cases. *BMC Infect Dis* 2021;21(1):913.
- [48] Samedy V, Field SK, Al Awad E, Ratcliffe G, Yusuf K. Congenital tuberculosis in an extremely preterm infant conceived after in vitro fertilization: case report. *BMC Pregnancy Childbirth* 2017;17(1):66.
- [49] Adjibimey M, Ade S, Wachinou P, Esse M, Yaha L, Bekou W, et al. Prevalence, acceptability, and cost of routine screening for pulmonary tuberculosis among pregnant women in Cotonou, Benin. *PLoS One* 2022;17(2):e0264206.
- [50] Ali RF, Siddiqi DA, Malik AA, Shah MT, Khan AJ, Hussain H, et al. Integrating tuberculosis screening into antenatal visits to improve tuberculosis diagnosis and care: results from a pilot project in Pakistan. *Int J Infect Dis* 2021;108:391–6.
- [51] Nordholm AC, Suppli CH, Norman A, Ekstrøm CT, Ertberg P, Koch A, et al. Pregnancy and post-partum tuberculosis; a nationwide register-based case-control study, Denmark, 1990 to 2018. *Euro Surveill* 2022;27(12):2100949.
- [52] Jonsson J, Kühlmann-Berenzon S, Berggren I, Bruchfeld J. Increased risk of active tuberculosis during pregnancy and postpartum: a register-based cohort study in Sweden. *Eur Respir J* 2020;55(3):1901886.
- *[53] World Health Organization. WHO operational handbook on tuberculosis. Module 2: screening – Systematic screening for tuberculosis disease. Geneva: World Health Organization; 2021.
- [54] Hamada Y, Lujan J, Schenkel K, Ford N, Getahun H. Sensitivity and specificity of WHO's recommended four-symptom screening rule for tuberculosis in people living with HIV: a systematic review and meta-analysis. *Lancet HIV* 2018;5(9):e515–23.
- [55] Gupta A, Chandrasekhar A, Gupte N, Patil S, Bhosale R, Sambarey P, et al. Symptom screening among HIV-infected pregnant women is acceptable and has high negative predictive value for active tuberculosis. *Clin Infect Dis* 2011;53(10):1015–8.
- [56] Wei M, Zhao Yongjie, Qian Zhuoyu, Yang Biao, Xi J, Wei J, et al. Pneumonia caused by *Mycobacterium tuberculosis*. *Microbes Infect* 2020;22(6–7):278–84.
- [57] Grossman RF, Hsueh P-R, Gillespie SH, Blasi F. Community-acquired pneumonia and tuberculosis: differential diagnosis and the use of fluoroquinolones. *Int J Infect Dis* 2014;18:14–21.
- [58] Xiang Y, Huang C, He Y, Zhang Q. Cancer or tuberculosis: a comprehensive review of the clinical and imaging features in diagnosis of the confusing mass. *Front Oncol* 2021;11:644150.
- [59] Pervaiz A, Inany M, Nguyen HQ, Jacques SM, Alshabani K. A pregnant woman with hemoptysis and diffuse pulmonary nodules. *Chest* 2021;160(6):e651–6.
- [60] Schluger NW. The acid-fast bacilli smear: hail and farewell. *Am J Respir Crit Care Med* 2019;199(6):691–2.
- [61] Vongthilath-Moeung R, Poncet A, Renzi G, Schrenzel J, Janssens J-P. Time to detection of growth for *Mycobacterium tuberculosis* in a low incidence area. *Front Cell Infect Microbiol* 2021;11:704169.
- *[62] World Health Organization. WHO consolidated guidelines on tuberculosis: module 3: diagnosis – rapid diagnostics for tuberculosis detection 2021 update. Geneva: World Health Organization; 2021.
- [63] Centers for Disease Control and Prevention. Report of an expert consultation on the uses of nucleic acid amplification tests for the diagnosis of tuberculosis. 2012. https://www.cdc.gov/tb/publications/guidelines/amplification_tests/recommendations.htm. [Accessed 27 June 2022].
- [64] Birku M, Desalegn G, Kassa G, Tsegaye A, Abebe M. Effect of pregnancy and HIV infection on detection of latent TB infection by Tuberculin Skin Test and QuantiFERON-TB Gold In-Tube assay among women living in a high TB and HIV burden setting. *Int J Infect Dis* 2020;101:235–42.
- [65] Pahal P, Sharma S. PPD skin test. StatPearls Publishing; 2022. Retrieved from, <https://www.ncbi.nlm.nih.gov/books/NBK556037/>.
- [66] World Health Organization. Rapid communication: TB antigen-based skin tests for the diagnosis of TB infection. Geneva: World Health Organization; 2022.
- [67] Ruhwald M, Aggerbeck H, Gallardo RV, Hoff ST, Villate JI, Borregaard B, et al. Safety and efficacy of the C-Tb skin test to diagnose *Mycobacterium tuberculosis* infection, compared with an interferon γ release assay and the tuberculin skin test: a phase 3, double-blind, randomised, controlled trial. *Lancet Respir Med* 2017;5(4):259–68.
- [68] Du F, Xie L, Zhang Y, Gao F, Zhang H, Chen W, et al. Prospective comparison of QFT-GIT and T-SPOT.TB assays for diagnosis of active tuberculosis. *Sci Rep* 2018;8(1):5882.
- [69] American College of Obstetricians and Gynecologists. Guidelines for diagnostic imaging during pregnancy and lactation. Committee opinion No. 723. *Obstet Gynecol* 2017;130:e210–6.

- [70] MacPherson P, Webb EL, Kamchedzera W, Joeke E, Mjoli G, Lalloo DG, et al. Computer-aided X-ray screening for tuberculosis and HIV testing among adults with cough in Malawi (the PROSPECT study): a randomised trial and cost-effectiveness analysis. *PLoS Med* 2021;18(9):e1003752.
- [71] Mirzayev F, Viney K, Linh NN, Gonzalez-Angulo L, Gegia M, Jaramillo E, et al. World Health Organization recommendations on the treatment of drug-resistant tuberculosis, 2020 update. *Eur Respir J* 2021;57(6):2003300.
- [72] Bar-Oz B, Moretti ME, Boskovic R, O'Brien L, Koren G. The safety of quinolones—a meta-analysis of pregnancy outcomes. *Eur J Obstet Gynecol Reprod Biol* 2009;143(2):75–8.
- [73] Cegielski JP, Chan PC, Lan Z, Udawadia ZF, Viikklepp P, Yim JJ, et al. Aminoglycosides and capreomycin in the treatment of multidrug-resistant tuberculosis: individual patient data meta-analysis of 12 030 patients from 25 countries, 2009–2016. *Clin Infect Dis* 2021;73(11):e3929–36. <https://doi.org/10.1093/cid/ciaa621>.
- [74] Philipose J, Suchman KI, Aronsky D, Lee T-P. A case of acute liver failure in a patient on isoniazid prophylaxis for latent tuberculosis. *Cureus* 2022;14(2):e22452.
- [75] Lao TT. Drug-induced liver injury in pregnancy. *Best Pract Res Clin Obstet Gynaecol* 2020;68:32–43.
- [76] Saukkonen JJ, Cohn DL, Jasmer RM, Schenker S, Jereb JA, Nolan CM, et al. An official ATS statement: hepatotoxicity of antituberculosis therapy. *Am J Respir Crit Care Med* 2006;174(8):935–52.
- [77] Karumbi J, Garner P. Directly observed therapy for treating tuberculosis. *Cochrane Database Syst Rev* 2015;5:CD003343. <https://doi.org/10.1002/14651858.CD003343.pub4>.
- [78] Lester R, Park JJ, Bolten LM, Enjeti A, Johnston JC, Schwartzman K, et al. Mobile phone short message service for adherence support and care of patients with tuberculosis infection: evidence and opportunity. *J Clin Tuberc Other Mycobact Dis* 2019;16:100108.
- [79] World Health Organization. Handbook for the use of digital technologies to support tuberculosis medication adherence. Geneva: World Health Organization; 2017.
- [80] Centers for Disease Control and Prevention. TB and pregnancy. 2014. <https://www.cdc.gov/tb/topic/populations/pregnancy/default.htm>. [Accessed 27 June 2022].
- [81] Fröberg G, Jansson L, Nyberg K, Obasi B, Westling K, Berggren I, et al. Screening and treatment of tuberculosis among pregnant women in Stockholm, Sweden, 2016–2017. *Eur Respir J* 2020;55(3):1900851.
- [82] Theron G, Montepiedra G, Aaron L, McCarthy K, Chakhtoura N, Jean-Philippe P, et al. Individual and composite adverse pregnancy outcomes in a randomized trial on isoniazid preventative therapy among women living with human immunodeficiency virus. *Clin Infect Dis* 2021;72(11):e784–90.
- *[83] Alene KA, Jegnie A, Adane AA. Multidrug-resistant tuberculosis during pregnancy and adverse birth outcomes: a systematic review and meta-analysis. *BJOG* 2021;128(7):1125–33.
- [84] Mokhele I, Jinga N, Berhanu R, Dlamini T, Long L, Evans D. Treatment and pregnancy outcomes of pregnant women exposed to second-line anti-tuberculosis drugs in South Africa. *BMC Pregnancy Childbirth* 2021;21(1):453.
- *[85] World Health Organization. WHO consolidated guidelines on drug-resistant tuberculosis treatment. Geneva: World Health Organization; 2019.
- [86] Suresh S, Sharath BN, Anita S, Lalitha R, Prasad TJ, Rewari BB. TB-HIV co-infection among pregnant women in Karnataka, South India: a case series. *J Infect Public Health* 2016;9(4):465–70.
- [87] Chelkeba L, Fekadu G, Tesfaye G, Belayneh F, Melaku T, Mekonnen Z. Effects of time of initiation of antiretroviral therapy in the treatment of patients with HIV/TB co-infection: a systemic review and meta-analysis. *Ann Med Surg (Lond)* 2020;55:148–58.
- [88] Centers for Disease Control and Prevention. Treatment of LTBI and TB in persons living with HIV. 2016. <https://www.cdc.gov/tb/topic/treatment/tbhiv.htm>. [Accessed 27 June 2022].
- [89] Centers for Disease Control and Prevention. Managing drug interactions in the treatment of HIV-related tuberculosis. 2013. https://www.cdc.gov/tb/publications/guidelines/tb_hiv_drugs/recommendations02.htm. [Accessed 27 June 2022].
- [90] Esmail A, Sabur NF, Okpechi I, Dheda K. Management of drug-resistant tuberculosis in special sub-populations including those with HIV co-infection, pregnancy, diabetes, organ-specific dysfunction, and in the critically ill. *J Thorac Dis* 2018;10(5):3102–18.
- [91] Birku M, Desalegn G, Kassa G, Tegbaru B, Howe R, Tsegaye A, et al. Pregnancy suppresses Mycobacterium tuberculosis-specific Th1, but not Th2, cell-mediated functional immune responses during HIV/latent TB co-infection. *Clin Immunol* 2020;218:108523.
- *[92] Gupta A, Montepiedra G, Aaron L, Theron G, McCarthy K, Bradford S, et al. Isoniazid preventative therapy in HIV-infected pregnant and postpartum women. *N Engl J Med* 2019;381(14):1333–46.
- [93] Sun J-M, Wang C, Jin D-Q, Deng F. Fatal congenital tuberculosis owing to late diagnosis of maternal tuberculosis: case report and review of congenital tuberculosis in China. *Paediatr Int Child Health* 2020;40(3):194–8.
- [94] Trivedi N, Gupta N, Sood R, Singh A, Tewari A, Agarwal S, et al. A review on placental tuberculosis. *J Adv Med Med Res* 2020;32(15):42–7.
- [95] Mittal H, Das S, Faridi MMA. Management of newborn infant born to mother suffering from tuberculosis: current recommendations & gaps in knowledge. *Indian J Med Res* 2014;140(1):32–9.
- [96] Lubyayi L, Mawa PA, Nabakooza G, Nakibuule M, Tushabe JV, Serubanja J, et al. Maternal latent Mycobacterium tuberculosis does not affect the infant immune response following BCG at birth: an observational longitudinal study in Uganda. *Front Immunol* 2020;11:929.
- [97] Sade S, Wainstock T, Sheiner E, Pariente G. Perinatal outcome and long-term infectious morbidity of offspring born to women with known tuberculosis. *J Clin Med* 2020;9(9):2768.