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Management of Drug-Resistant Tuberculosis in Pregnancy: Epidemiology, Challenges, and Treatment Strategies

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ABSTRACT

Pregnancy-related drug-resistant TB poses several difficulties because of the complicated treatment plans, teratogenicity hazards, and the paucity of safety evidence on second-line TB medications. Research trials frequently leave pregnant women out, resulting in a lack of evidence-based recommendations for treating DR-TB. Increased morbidity, premature birth, and low birth weight are just a few of the major health problems the illness poses to both the mother and the newborn. Newer medications like delamanid and bedaquiline have shown encouraging safety profiles during pregnancy, and recent studies have concentrated on improving treatment approaches. To bridge the knowledge gap, recent clinical trials that include pregnant individuals include Smart4TB and Beat-TB. The World Health Organization (WHO) has started to address this problem by updating recommendations to encourage the use of more recent, all-oral regimens. To improve the outcomes for mothers and newborns, a multidisciplinary strategy comprising obstetricians, pulmonologists, and infectious disease specialists is essential. To improve treatment adherence, psychosocial and nutritional assistance are also crucial. Future studies should further include pregnant women in clinical trials to ensure safer and more efficient methods of treating DR-TB during pregnancy.

Keywords: *Drug-resistant tuberculosis, pregnancy, Smart4TB, Beat-TB, bedaquiline, delamanid, pulmonologists, neonatal health.*

1. INTRODUCTION

A significant worldwide health burden, tuberculosis (TB) causes about 10 million infections and 1.3 million deaths each year, with low- and middle-income countries having the greatest prevalence [1]. Drug-resistant tuberculosis (DR-TB), which encompasses extensively drug-resistant TB (XDR-TB) and multidrug-resistant TB (MDR-TB), poses a significant problem as it complicates treatment and increases death rates [2, 3]. Globally, there were an estimated 450,000 MDR-TB patients in 2021, and treatment results were subpar in many places [4]. Because pregnancy alters the body, second-line anti-TB medications may be teratogenic, and there is a chance of negative effects for both the mother and the fetus; managing DR-TB during pregnancy poses special issues [5, 6]. The lack of safety evidence on newer TB medications like bedaquiline and delamanid complicates treatment options [7]. Perinatal death, low birth weight, and preterm delivery are among the issues that pregnant people with tuberculosis are more likely to experience [8, 9]. To assess the available data on the management of DR-TB during pregnancy, this review will concentrate on treatment safety, maternal-fetal outcomes, and research gaps. Optimizing treatment and directing clinical judgment in this susceptible group requires an understanding of these difficulties [10].

2. EPIDEMIOLOGY AND GLOBAL BURDEN

2.1 Prevalence of DR-TB among Pregnant Women

Drug-resistant tuberculosis (DR-TB) is still a major worldwide health issue, especially for susceptible groups like expectant mothers. Studies indicate that tuberculosis (TB) affects between 2–7% of pregnancies in high-burden countries, with

multidrug-resistant TB (MDR-TB) making up an increasing percentage [9, 10], despite the lack of complete data on DR-TB prevalence in pregnancy.

MDR-TB is estimated by the World Health Organization (WHO) to account for 3–4% of new TB infections and 18–21% of those that have already received treatment [11]. 6.5% of pregnant women with a TB diagnosis in South Africa had MDR-TB, according to research, underscoring the significant burden in areas with high prevalence of HIV and TB co-infection [12]. Similarly, studies conducted in Russia and India found that 5–8% of pregnant TB patients had MDR-TB, which reflects regional differences in drug resistance trends [13].

Due to alterations in immune responses and the possibility of TB symptoms overlapping with pregnancy-related diseases, it might be difficult to accurately diagnose DR-TB during pregnancy. Improving maternal and newborn outcomes in impacted communities requires bolstering monitoring systems and incorporating TB screening into prenatal care initiatives [10, 11].

2.2 High-Burden Regions and Risk Factors

Low- and middle-income nations with high TB incidence are disproportionately affected by drug-resistant tuberculosis (DR-TB). The nations with the largest burden of multidrug-resistant TB (MDR-TB), which accounts for more than 50% of cases worldwide, include South Africa, Indonesia, China, India, and the Russian Federation, according to the World Health Organization (WHO) [1]. Because of the lack of prompt diagnosis and treatment, DR-TB in pregnant women in these areas continues to be a significant problem [12]. Several risk factors are responsible for the elevated rate of DR-TB during pregnancy. A significant risk factor for the development of drug resistance is prior TB treatment, especially insufficient or inconsistent therapy [14]. Furthermore, HIV co-infection heightens vulnerability to DR-TB, particularly in sub-Saharan Africa, where tuberculosis continues to be a major cause of maternal death [9]. Pregnant women are more susceptible to DR-TB due to socioeconomic variables such as poverty, overcrowding, malnutrition, and inadequate access to healthcare [13]. To lessen the burden of DR-TB in high-risk groups, it is imperative to improve access to quick diagnostic techniques, boost TB control programs, and include TB screening into prenatal care services.

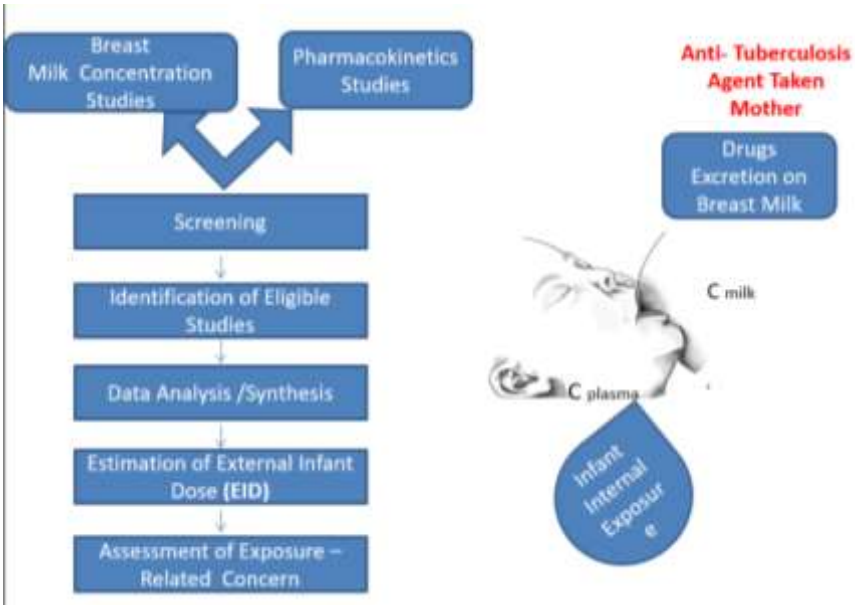

Figure 1

2.3 Impact of DR-TB on Maternal and Neonatal Health

Drug-resistant tuberculosis (DR-TB) increases morbidity and mortality and presents serious health hazards to both mothers and newborns. Preterm labor, intrauterine growth restriction, and maternal mortality are among the consequences that pregnant women with DR-TB are more likely to experience, especially if they get insufficient therapy or a delayed diagnosis [10, 12]. Pregnancy-related physiological changes, such as compromised immune function and elevated cardiac output, may worsen the course of tuberculosis and result in severe clinical symptoms [14]. Negative consequences, such as low birth weight, preterm delivery, and perinatal death, are possible for infants whose mothers have DR-TB. According to studies, the risk of intrauterine growth restriction is doubled for newborns whose mothers have active tuberculosis [9]. Furthermore, while uncommon, congenital TB may develop if the infection spreads after birth or transplacentally [13]. Because second-line anti-TB medications used for DR-TB, such as aminoglycosides and fluoroquinolones, have the potential to have teratogenic effects, treatment issues further complicate outcomes for mothers and newborns [12]. Uncertainty surrounds the

best course of therapy during pregnancy due to a lack of safety evidence on more recent TB medications. Therefore, to lessen the effects of DR-TB on both mother and child, prompt diagnosis, careful observation, and a multidisciplinary approach are crucial.

3. PATHOPHYSIOLOGY AND DIAGNOSIS OF DR-TB IN PREGNANCY

3.1 Mechanism of Drug Resistance in Mycobacterium tuberculosis

Mycobacterium TB (M. tuberculosis) develops drug resistance as a result of genetic mutations that provide resistance to anti-tubercular medications, mostly via spontaneous chromosomal changes rather than horizontal gene transfer [15]. Resistance to at least isoniazid and rifampin is known as multidrug-resistant TB (MDR-TB), while extensively drug-resistant TB (XDR-TB) also involves resistance to fluoroquinolones and at least one second-line injectable medication [11]. Mutations in the katG and inhA genes, which affect drug activation and target binding, respectively, are often linked to isoniazid resistance [16]. Mutations in the rpoB gene cause rifampin resistance by altering the RNA polymerase β-subunit and impairing drug binding [17]. Mutations in the gyrA and gyrB genes, which change DNA gyrase activity and decrease medication effectiveness, are primarily responsible for fluoroquinolone resistance [18]. Mutations in the rrs and eis genes, which alter ribosomal RNA or enhance drug efflux, are responsible for aminoglycoside resistance, which includes kanamycin and amikacin [19]. Physiological changes during pregnancy, such as immunological modulation and altered drug metabolism, may impact the effectiveness of TB therapy and result in suboptimal drug concentrations, which may raise the chance of acquired resistance [20]. Comprehending these processes is essential for creating efficient diagnostic instruments and refining treatment plans for DR-TB pregnant patients.

3.2 Challenges in Diagnosing DR-TB during Pregnancy

Pregnancy-related physiological changes, altered immunological responses, and a lack of diagnostic techniques make diagnosing drug-resistant tuberculosis (DR-TB) very difficult. Clinical identification of atypical TB manifestations might be challenging due to pregnancy-induced immunomodulation [20]. Diagnosis is delayed because symptoms including exhaustion, weight loss, and dyspnea often coexist with typical pregnancy-related changes [9]. Sputum smear microscopy, culture, and molecular tests are the three main methods used in microbiological confirmation of DR-TB. Sputum collection might be challenging in pregnant women, especially those with extrapulmonary or paucibacillary TB [21]. More tests are needed to check for resistance to fluoroquinolone and second-line injectable medications because quick tests like GeneXpert MTB/RIF can find TB quickly but might not detect resistance to other drugs besides rifampin. Although culture-based drug susceptibility testing (DST) is still the gold standard, it takes a long time and delays the start of therapy. The restricted use of chest radiography because of worries about prenatal exposure to ionizing radiation is another significant obstacle. Reluctance to conduct imaging often leads to missed or delayed diagnosis, even if shielding reduces risk [13]. Timely identification of DR-TB in pregnant women is further complicated by the lack of access to modern diagnostics in many TB-endemic countries.

3.3 Available Diagnostic Tools for DR-TB

Drug-resistant tuberculosis (DR-TB) in pregnancy must be diagnosed accurately and promptly to be effectively managed and to enhance outcomes for both the mother and the unborn child. There are several diagnostic technologies available for identifying Mycobacterium tuberculosis and drug resistance patterns, such as GeneXpert MTB/RIF, culture-based techniques, and molecular tests. Within two hours, the GeneXpert MTB/RIF fast molecular test may identify M. tuberculosis and rifampin resistance. The World Health Organization (WHO) recommends it as the first diagnostic test for TB, particularly DR-TB, in high-burden areas because of its excellent sensitivity [1]. However, it only detects rifampin resistance; further testing is necessary to detect other drug resistances [21]. The gold standard for diagnosing tuberculosis and testing for drug susceptibility (DST) is still culture-based techniques, such as liquid culture in the Mycobacteria Growth Indicator Tube (MGIT) system. These techniques are very sensitive, but they take weeks for bacteria to develop, which delays the start of therapy [22]. Faster than culture-based DST, line-probe assays (LPAs) are molecular tests that identify mutations linked to resistance to rifampin, isoniazid, and second-line medications [23]. However, their availability in environments with limited resources is limited due to their need for specialist labs. Although whole-genome sequencing (WGS) is a new technique for thorough resistance profiling, it is not yet generally available in areas where tuberculosis is prevalent [24].

4. LIMITED SAFETY DATA ON SECOND-LINE TB DRUGS IN PREGNANCY

The lack of safety information on second-line anti-TB medications makes treating drug-resistant tuberculosis (DR-TB) during pregnancy more difficult. Many of these drugs may be harmful to the mother and the fetus, which makes treatment choices questionable. Even though untreated DR-TB can be very dangerous for mothers and babies, we still don't know much about how safe some second-line medications are because ethical issues limit clinical studies in pregnant women.

When administered during pregnancy, aminoglycosides (such as amikacin, capreomycin, and kanamycin) may cause fetal hearing impairment due to their ototoxicity and nephrotoxicity [26]. The WHO advises pregnant women to avoid aminoglycosides wherever feasible due to studies showing an increased risk of congenital deafness with in utero exposure

[27].

Although fluoroquinolones, such as levofloxacin and moxifloxacin, are crucial parts of DR-TB regimens, it is unclear whether they are safe to use while pregnant. Studies on animals raise the possibility of cartilage toxicity, but there is not enough information on humans to demonstrate teratogenic consequences [28]. Nevertheless, when advantages exceed disadvantages, fluoroquinolones are often prescribed [29]

Although there is very little information on the safety of bedaquiline and delamanid during pregnancy, these more recent TB medications have shown promise in treating DR-TB. Bedaquiline has been associated with QT prolongation, potentially endangering the cardiovascular health of both the mother and the fetus [30]. There aren't many case studies on delamanid's effects on pregnancy [31].

4.1 Teratogenic Effects of Medications Like Aminoglycosides and Fluoroquinolones

Using second-line anti-TB medications like aminoglycosides and fluoroquinolones during pregnancy can be risky because they might cause birth defects. These drugs are necessary for treating drug-resistant tuberculosis (DR-TB), but their usage must be carefully considered since they may harm a fetus.

The Aminoglycosides

Nephrotoxicity and ototoxicity in mothers and babies are linked to aminoglycosides like amikacin, kanamycin, and capreomycin. Once these substances cross the placenta and accumulate in fetal tissues, they cause congenital hearing loss, particularly sensorineural deafness [32]. According to studies, aminoglycoside exposure during pregnancy greatly raises the chance of hearing damage, which is why the World Health Organization (WHO) advises against using them unless there are no other options [33]. Due to the renal immaturity of growing neonates, nephrotoxicity is nevertheless a concern even if it is less well-documented in fetuses [34].

The Fluoroquinolones

Because they may cause musculoskeletal abnormalities and cartilage toxicity, fluoroquinolones (such as levofloxacin and moxifloxacin) are concerning. Studies on animals have shown that fluoroquinolones harm cartilage and joint development, which may increase the incidence of prenatal arthropathy [35]. However, these effects haven't been clearly proven in human studies, and some past evaluations suggest that using fluoroquinolones doesn't lead to major birth defects. Despite this, pregnant women often avoid fluoroquinolones unless the benefits outweigh the risks, particularly in cases of severe DR-TB [29].

Pregnant women who need DR-TB therapy must follow alternate regimens that prioritize safer medications, continuous fetal monitoring, and multidisciplinary management in light of these possible teratogenic consequences. To improve safety regulations for these important drugs, further research is required.

4.2 Drug Interactions and Side Effects

Multiple second-line medications are used to treat drug-resistant tuberculosis (DR-TB) during pregnancy, which raises the possibility of drug interactions and side effects that might affect the health of the mother and fetus.

Drug Reactions:

The main TB drug rifampin, commonly used with other treatments, affects cytochrome P450 enzymes, which lowers the effectiveness of hormonal birth control, antiretrovirals, and some blood thinners. Antacids and multivitamins that include magnesium, calcium, or iron may interact with fluoroquinolones like levofloxacin and moxifloxacin, decreasing the absorption of the medicine [39]. When taken with other medications that can prolong the QT interval, the newer TB drugs bedaquiline and delamanid raise the chance of heart rhythm problems.

Adverse effects:

Aminoglycosides, such as kanamycin and amikacin, may be ototoxic and nephrotoxic, which may result in congenital hearing loss in newborns [42]. Although there is conflicting evidence from human research, fluoroquinolones have been connected to gastrointestinal issues and possible cartilage damage in animal studies [43]. Bedaquiline has to be closely watched since it might induce hepatotoxicity and QT prolongation [44].

Careful medication selection, dosage modifications, and routine monitoring are necessary for managing DR-TB during pregnancy in order to reduce side effects and guarantee successful therapy.

4.3 Psychosocial and Economic Barriers to Treatment Adherence

Numerous psychological and financial obstacles might affect pregnant women's and fetuses' health outcomes by affecting their adherence to drug-resistant tuberculosis (DR-TB) therapy.

Psychosocial Obstacles:

A woman with DR-TB who are pregnant often face prejudice and stigma, which makes them feel alone and discourages them from getting treatment [45]. Treatment non-adherence may be caused by fear of social rejection, particularly in cultures where tuberculosis is strongly stigmatized [46].. Pregnant women with DR-TB also often suffer from mental health conditions such as anxiety and depression, which makes it more difficult for them to follow long and harmful treatment plans [47].

Economic Barriers:

A major financial burden is caused by the high cost of second-line TB drugs, lost wages from sickness, and frequent medical visits (48). Pregnant women find it challenging to attend routine follow-ups due to limited access to healthcare facilities, particularly in low-resource areas, which raises transportation expenses [49].

5. CURRENT TREATMENT STRATEGIES

5.1. WHO Guidelines for Treating DR-TB in Pregnancy

The World Health Organization (WHO) offers detailed guidelines for treating drug-resistant tuberculosis (DR-TB) during pregnancy that strike a balance between the safety of the fetus and the health of the mother. WHO stresses customized, interdisciplinary methods, although treatment is difficult because of the lack of safety evidence on second-line medications [50]. Since untreated TB increases the risk of problems for both the mother and the unborn child more than possible medication toxicities, WHO advises pregnant women with DR-TB to get treatment right away [51]. Because aminoglycosides such as amikacin and kanamycin are linked to congenital deafness, it is preferable to employ all-oral regimens to reduce toxicity [52]. When possible, a shorter treatment plan that only uses pills (lasting 6–9 months) is recommended, typically including bedaquiline, linezolid, moxifloxacin, clofazimine, and cycloserine. However, the safety of medications such as bedaquiline and delamanid during pregnancy remains limited, necessitating close monitoring. When the advantages of fluoroquinolones exceed the hazards, they may be utilized [5]. Improving maternal and newborn outcomes requires frequent fetal monitoring, nutritional assistance, and comprehensive prenatal care. To improve treatment safety for expectant mothers, WHO emphasizes the need for pharmacovigilance studies.

5.2 Safe and Effective Drug Regimens (Bedaquiline, Delamanid)

Drug-resistant tuberculosis (DR-TB) is now much better managed because of the development of bedaquiline and delamanid, which provide safer and more efficient treatment choices, especially for expectant mothers. Aminoglycosides, which are linked to fetal ototoxicity and nephrotoxicity, are not necessary with these all-oral regimens [55].

5.2.1 Bedaquiline

A diarylquinoline called bedaquiline interferes with the generation of energy in Mycobacterium TB by targeting its ATP synthase. Research has linked it to better treatment results and lower fatality rates in individuals with DR-TB [56]. Pregnancy-related electrocardiographic monitoring is necessary due to worries about QT prolongation, which may raise the risk of cardiac arrhythmias [44]. WHO indicates that the advantages often exceed the hazards, particularly in instances of severe DR-TB, despite the paucity of evidence on fetal safety [57].

5.2.2 Delamanid

A nitroimidazole called delamanid breaks down the TB cell wall by preventing the formation of mycolic acid. With a favorable safety profile, it has shown encouraging outcomes in shorter, all-oral regimens for DR-TB [41]. Delamanid is considered safer during pregnancy and has a lower risk of QT prolongation than bedaquiline, despite the need for further pharmacovigilance research [58].

5.3 Multidisciplinary Approach (Obstetricians, Pulmonologists, Infectious Disease Specialists)

To guarantee the best possible results for both the mother and the fetus, managing drug-resistant tuberculosis (DR-TB) during pregnancy requires a multidisciplinary strategy comprising obstetricians, pulmonologists, infectious disease experts, and other medical professionals [7].

Obstetricians' role

Obstetricians play a crucial role in watching how the baby develops and handling pregnancy problems related to DR-TB, like early delivery and slow growth of the baby in the womb. Additionally, since TB-related malnutrition increases the risk of unfavorable pregnancy outcomes, they guarantee adequate nutritional care for the mother [60].

The function of pulmonary specialists

In order to optimize treatment plans and evaluate medication acceptability, pulmonologists supervise the respiratory care of DR-TB. They use sputum cultures and imaging to assess therapy response and coordinate lung function monitoring [61].

The function of experts in infectious diseases

Drug selection is guided by infectious disease experts, who minimize teratogenic hazards and ensure adherence to WHO-recommended all-oral regimens [62]. Additionally, they monitor patterns of resistance and medication interactions, modifying treatment as needed. Maternal and newborn health outcomes are improved, adherence is increased, and complications are decreased using a cooperative, patient-centered approach. For DR-TB to be successfully managed during pregnancy, multidisciplinary case evaluations and thorough prenatal and postnatal care are necessary [63].

5.4 Nutritional and Psychosocial Support

To improve treatment adherence and the results for both mothers and newborns, extensive nutritional and psychological support is necessary for the effective management of drug-resistant tuberculosis (DR-TB) during pregnancy.

Assistance with Nutrition

Malnutrition puts pregnant women with DR-TB at risk for low birth weight, premature labor, and intrauterine growth restriction (IUGR) (60). For optimal fetal development and to maintain the mother's immune system, proper nourishment is crucial. The World Health Organization (WHO) suggests micronutrient support, such as iron, folic acid, and vitamin D, and balanced energy-protein supplements to prevent the malabsorption effects of TB medicines (64). Furthermore, dietary counseling and food assistance programs may enhance nutritional status and general health outcomes [65].

Support for Psychosocial

In pregnant women with DR-TB, psychosocial factors such as stigma, anxiety, and financial difficulties have a major influence on treatment adherence (66). Peer support groups, community-based therapy, and mental health therapies may all assist in overcoming these obstacles. Incorporating mental health treatments into TB treatment programs ensures comprehensive care (67). In addition, social support—such as financial aid and family participation—is essential for maintaining adherence and lessening the psychological toll of the illness [68].

6. CONCLUSION

Managing drug-resistant tuberculosis (DR-TB) during pregnancy remains a significant challenge due to the limited safety data on second-line TB drugs and the exclusion of pregnant women from clinical trials. This lack of evidence-based guidelines increases risks for both maternal and neonatal health. However, emerging research and clinical trials, such as Smart4TB and Beat-TB, are working to bridge this gap by assessing the safety and efficacy of newer drugs like bedaquiline and delamanid. The World Health Organization (WHO) has also taken steps to support the use of all-oral regimens to improve treatment outcomes. A multidisciplinary approach involving obstetricians, pulmonologists, and infectious disease specialists, along with psychosocial and nutritional support, is essential for optimizing maternal and neonatal health. Future research should continue prioritizing the inclusion of pregnant women in clinical trials to develop safer, more effective treatment strategies for DR-TB in pregnancy.

REFERENCES

[1] World Health Organization. WHO Global Task Force on TB Impact Measurement: report of a subgroup meeting on methods used by WHO to estimate TB disease burden, 11-12 May 2022, Geneva, Switzerland. World Health Organization; 2022 Oct 10.

[2] World Health Organization. Global tuberculosis report 2021: supplementary material. World Health Organization; 2022 Mar 31.

[3] Dheda K, Gumbo T, Maartens G, Dooley KE, McNerney R, Murray M, Furin J, Nardell EA, London L, Lessem E, Theron G. The epidemiology, pathogenesis, transmission, diagnosis, and management of multidrug-resistant, extensively drug-resistant, and incurable tuberculosis. The lancet Respiratory medicine. 2017 Apr 1;5(4):291-360.

[4] Migliori GB, et al. Eur Respir J. 2020;55(6):1902106. Migliori GB, Zellweger JP, Abubakar I, Ibraim E, Caminero JA, De Vries G, D'Ambrosio L, Centis R, Sotgiu G, Menegale O, Kliiman K. European union standards for tuberculosis care.

[5] Parums DV. updates from the World Health Organization (WHO) on global treatment recommendations for drug-susceptible and multidrug-resistant tuberculosis. Medical Science Monitor: International Medical Journal of Experimental and Clinical Research. 2021 Aug 9;27:e934292-1. WHO. Multidrug-resistant tuberculosis: 2021 update. Geneva: WHO; 2021.

[6] Palacios E, Dallman R, Muñoz M, Hurtado R, Chalco K, Guerra D, Mestanza L, Llaro K, Bonilla C, Drobac P, Bayona J. Drug-resistant tuberculosis and pregnancy: treatment outcomes of 38 cases in Lima, Peru. Clinical infectious diseases. 2009 May 15;48(10):1413-9.

[7] Mathad JS, Gupta A. Tuberculosis in pregnant and postpartum women: epidemiology, management, and research gaps. Clinical infectious diseases. 2012 Dec 1;55(11):1532-49.

[8] Loveday M, Sunkari B, Marais BJ, Master I, Brust JC. Dilemma of managing asymptomatic children referred with 'culture-confirmed'drug-resistant tuberculosis. Archives of disease in childhood. 2016 Jul 1;101(7):608-13.

[9] Gupta A, et al. Maternal tuberculosis: a risk factor for perinatal mortality. Lancet Glob Health. 2014;2(9):e537-46.

[10] Mathad JS, Gupta A. Tuberculosis in pregnant and postpartum women: epidemiology, management, and research gaps. Clin Infect Dis. 2012;55(11):1532-49

[11] World Health Organization. WHO Global Task Force on TB Impact Measurement: report of a subgroup meeting on methods used by WHO to estimate TB disease burden, 11-12 May 2022, Geneva, Switzerland. World Health Organization; 2022 Oct 10.

[12] Loveday M, et al. Maternal and infant outcomes among pregnant women treated for multidrug-resistant tuberculosis in South Africa. Int J Tuberc Lung Dis. 2016;20(12):1610-14.

[13] Singh N, et al. Maternal and perinatal outcomes in pregnant women with tuberculosis: a retrospective analysis. Int J Tuberc Lung Dis. 2016;20(3):362-70.

[14] Sinha P, et al. Predictors of multidrug-resistant tuberculosis in children and adolescents: a systematic review and meta-analysis. Clin Microbiol Rev. 2020;33(3):e00129-19.

[15] Zhang Y, Yew WW. Mechanisms of drug resistance in *Mycobacterium tuberculosis*. Int J Tuberc Lung Dis. 2009;13(11):1320-30.

[16] Ramaswamy SV, Musser JM. Molecular genetic basis of antimicrobial agent resistance in *Mycobacterium tuberculosis*: 1998 update. Tuber Lung Dis. 1998;79(1):3-29.

[17] Campbell EA, et al. Structural mechanism for rifampicin inhibition of bacterial RNA polymerase. Cell. 2001;104(6):901-12.

[18] Ginsburg AS, et al. Fluoroquinolone resistance in *Mycobacterium tuberculosis*: Mechanisms and implications for treatment. Clin Infect Dis. 2003;37(8):1103-9

[19] Zaunbrecher MA, et al. *Eis*, an aminoglycoside acetyltransferase from *Mycobacterium tuberculosis*, confers resistance to kanamycin and amikacin. Proc Natl Acad Sci USA. 2009;106(47):20004-9.

[20] Mathad JS, Gupta A. Tuberculosis in pregnant and postpartum women: Epidemiology, management, and research gaps. Clin Infect Dis. 2012;55(11):1532-49.

[21] Theron G, et al. The diagnostic accuracy of the GeneXpert MTB/RIF assay for pulmonary tuberculosis in a high HIV prevalence setting: A prospective study. PLoS Med. 2011;8(7):e1001061.

[22] Boehme CC, et al. Rapid molecular detection of tuberculosis and rifampin resistance. N Engl J Med. 2010;363(11):1005-15.

[23] Hillemann D, et al. Rapid molecular detection of extrapulmonary tuberculosis by the Genotype MTBDRplus assay. J Clin Microbiol. 2007;45(5):1476-9.

[24] Walker TM, et al. Whole-genome sequencing for prediction of *Mycobacterium tuberculosis* drug susceptibility and resistance: A retrospective cohort study. Lancet Infect Dis. 2015;15(10):1193-202.

[25] Nahid P, et al. Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America clinical practice guidelines: treatment of drug-resistant tuberculosis. Clin Infect Dis. 2019;69(7):1117-1140.

[26] Shin S, et al. Treatment outcomes in patients with multidrug-resistant tuberculosis: a systematic review and meta-analysis. Lancet Infect Dis. 2008;8(8):440-9.

[27] World Health Organization. WHO consolidated guidelines on tuberculosis: module 4: treatment: drug-resistant tuberculosis treatment: online annexes. InWHO consolidated guidelines on tuberculosis: module 4: treatment: drug-resistant tuberculosis treatment: online annexes 2020.

[28] Chen CY, et al. Safety of fluoroquinolones in pregnant women: a meta-analysis. Clin Infect Dis. 2021;72(1):e96-e106.

[29] Sturkenboom MC, et al. Drug safety in pregnancy: the fluoroquinolone example. Pharmacoepidemiol Drug Saf. 2008;17(9):897-901.

[30] Pontali E, et al. Bedaquiline and multidrug-resistant tuberculosis: a systematic and critical analysis of the evidence. Eur Respir J. 2017;49(4):1601815.

[31] Modongo C, et al. Successful pregnancy outcomes in women treated for multidrug-resistant tuberculosis in Botswana. Int J Tuberc Lung Dis. 2014;18(9):1059-64.

[32] Lerner SA, et al. Ototoxicity and nephrotoxicity of aminoglycosides: A review. J Infect Dis. 1981;144(1):3-8.

[33] World Health Organization. WHO consolidated guidelines on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment. Geneva: WHO; 2020.

[34] Tunkel AR, et al. Aminoglycoside nephrotoxicity: Risk factors and mechanisms of injury. Antimicrob Agents Chemother. 2003;47(3):929-40.

[35] Domachowske JB, et al. Effects of fluoroquinolones on pediatric cartilage: Implications for treatment of multidrug-resistant tuberculosis. Pediatr Infect Dis J. 1998;17(4):287-9

[36] Padberg S, et al. Safety of fluoroquinolone use during pregnancy: A meta-analysis of observational studies. Clin Infect Dis. 2021;72(8):1442-51.

[37] Mathad JS, Gupta A. Tuberculosis in pregnancy: Epidemiology, management, and research gaps. Clin Infect Dis. 2012;55(11):1532-49.

[38] Tran JH, et al. Rifampin-drug interactions: A systematic review. Clin Pharmacokinet. 2020;59(2):143-58

[39] Van Ingen J, et al. Fluoroquinolones in tuberculosis treatment: WHO recommendations and recent developments. Int J Antimicrob Agents. 2012;39(2):112-20.

[40] Pontali E, et al. Bedaquiline and multidrug-resistant tuberculosis: A systematic review. Eur Respir J. 2017;49(4):1601815.

[41] Skripconoka V, et al. Delamanid improves outcomes in multidrug-resistant tuberculosis. Eur Respir J. 2013;41(6):1393-400.

[42] Duggal P, et al. Aminoglycoside toxicity: A review of nephrotoxicity and ototoxicity. Clin Kidney J. 2021;14(1):1-9.

[43] Padberg S, et al. Safety of fluoroquinolone use during pregnancy: A meta-analysis of observational studies. Clin Infect Dis. 2021;72(8):1442-51.

[44] Guglielmetti L, et al. QT prolongation and cardiac toxicity in patients treated with bedaquiline and delamanid. Emerg Infect Dis. 2018;24(3):491-94

[45] Courtwright A, Turner AN. Tuberculosis and stigmatization: Pathways and interventions. Public Health Rep. 2010;125(Suppl 4):34-42.

[46] Datiko DG, et al. The impact of stigma on treatment adherence among TB patients: A systematic review. BMC Infect Dis. 2020;20(1):1-12.

[47] Sweetland AC, et al. Depression: A silent driver of the TB epidemic. Int J Tuberc Lung Dis. 2017;21(7):S6-S10.

[48] Ukwaja KN, et al. Health care financing for TB patients in developing countries: A systematic review. PLoS Med. 2013;10(2):e1001316.

[49] Horter S, et al. “I can also serve as an inspiration”: A qualitative study of the TB & HIV treatment-seeking experiences of patients diagnosed with multidrug-resistant tuberculosis in South Africa. PLoS One. 2020;15(5):e0233459.

[50] World Health Organization. WHO consolidated guidelines on tuberculosis: module 4: treatment: drug-resistant tuberculosis treatment: online annexes. InWHO consolidated guidelines on tuberculosis: module 4: treatment: drug-resistant tuberculosis treatment: online annexes 2020.

[51] Mathad JS, Gupta A. Tuberculosis in pregnant and postpartum women: epidemiology, management, and research gaps. Clinical infectious diseases. 2012 Dec 1;55(11):1532-49.

[52] Shin S, et al. Adverse effects of second-line anti-tuberculosis drugs in multidrug-resistant TB treatment: A systematic review. Lancet Infect Dis. 2008;8(8):440-9.

[53] Ahmad N, et al. Treatment of multidrug-resistant tuberculosis: An updated WHO guideline-based approach. Clin Microbiol Infect. 2021;27(1):139-48.

[54] Pontali E, et al. Bedaquiline- and delamanid-containing regimens for multidrug-resistant tuberculosis: A systematic review and meta-analysis. Eur Respir J. 2017;49(4):1601815.

[55] World Health Organization. WHO consolidated guidelines on tuberculosis: Module 4 – Treatment: Drug-resistant tuberculosis treatment. Geneva: WHO; 2020.

[56] Pontali E, et al. Bedaquiline-containing regimens improve treatment outcomes in multidrug-resistant tuberculosis: A systematic review. Eur Respir J. 2017;49(4):1601815.

[57] Ahmad N, et al. WHO’s updated approach to MDR-TB treatment: The role of new drugs. Clin Microbiol Infect.

2021;27(1):139-48.

[58] Hwang H, Kang H, Kwon YS, Jeon D, Shim TS, Yim JJ. Outcomes of multidrug-resistant tuberculosis treated with bedaquiline or delamanid. Clinical Infectious Diseases. 2021 Oct 15;73(8):1362-9

[59] Espinal MA, et al. The impact of multidrug-resistant tuberculosis on maternal and perinatal outcomes. Int J Tuberc Lung Dis. 2017;21(7):791-97.

[60] Nunes JT, et al. Malnutrition and tuberculosis: A syndemic perspective in pregnancy. Eur J Clin Nutr. 2020;74(2):264-72.

[61] Nahid P, Mase SR, Migliori GB, Sotgiu G, Bothamley GH, Brozek JL, Cattamanchi A, Cegielski JP, Chen L, Daley CL, Dalton TL. Treatment of drug-resistant tuberculosis. An official ATS/CDC/ERS/IDSA clinical practice guideline. American journal of respiratory and critical care medicine. 2019 Nov 15;200(10):e93-142.

[62] World Health Organization. WHO consolidated guidelines on tuberculosis. Module 4: treatment-drug-resistant tuberculosis treatment, 2022 update. World Health Organization; 2022 Nov 30.

[63] Sugarman J, et al. Multidisciplinary care models for tuberculosis in pregnancy: A global perspective. Lancet Infect Dis. 2021;21(5):e103-e112.

[64] World Health Organization. Nutritional care and support for patients with tuberculosis. Geneva: WHO; 2013.

[65] Bhargava A, Chatterjee M, Jain Y, Chatterjee B, Kataria A, Bhargava M, Kataria R, D'Souza R, Jain R, Benedetti A, Pai M. Nutritional status of adult patients with pulmonary tuberculosis in rural central India and its association with mortality. PloS one. 2013 Oct 24;8(10):e77979.

[66] Courtwright A, Turner AN. Tuberculosis and stigmatization: pathways and interventions. Public health reports. 2010 Jul;125(4_suppl):34-42.

[67] Sweetland AC, Kritski A, Oquendo MA, Sublette ME, Norcini Pala A, Silva LR, Karpati A, Silva EC, Moraes MO, Silva JR, Wainberg ML. Addressing the tuberculosis–depression syndemic to end the tuberculosis epidemic. The International Journal of Tuberculosis and Lung Disease. 2017 Aug 1;21(8):852-61.

[68] Horter S, et al. The role of family and social support in TB treatment adherence: A qualitative study. PLoS One. 2020;15(5):e0233459.