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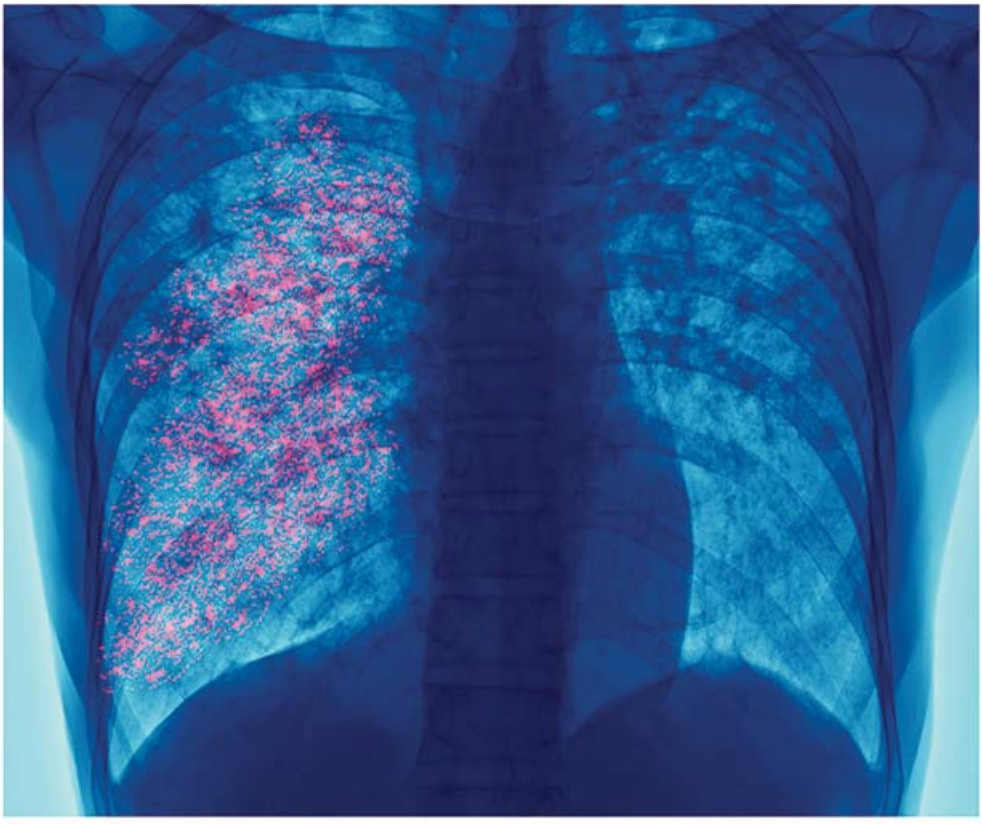
The Tuberculosis Association of India

Update on
MDR Tuberculosis



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Section 5: Associated Diseases

CHAPTER

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Multidrug-resistant Tuberculosis during Pregnancy

Namita Chopra

Abstract

Multidrug-resistant tuberculosis (MDR-TB) is known since drugs for treatment of tuberculosis were discovered and are a challenge for healthcare providers in managing it among females of child-bearing age group. As limited experience of use of second-line drug is available, so MDR-TB management during pregnancies poses a challenge.

Keywords: Tuberculosis, multidrug resistant, pregnancy

INTRODUCTION

Multidrug-resistant tuberculosis (MDR-TB) is defined as *infection with M. tuberculosis* strain resistant to rifampicin and isoniazid. MDR-TB is found in nearly every country. In India, the incidence of MDR-TB is reported to be between 1 and 3% among previously untreated TB cases and between 12 and 17% among those undergoing next time treatment according to National Tuberculosis Elimination Program (NTEP).[1] Biological and immunological changes in pregnancy may cause subclinical infection to lead to active tuberculosis.[2] Also, teratogenic risk of reserve drugs is also not clear. Therefore, effective contraception is strongly advocated for all nonpregnant women receiving treatment with reserve drugs. But, MDR-TB, if left untreated or undiagnosed in pregnancy, can cause higher maternal morbidity, mortality, and increased risk of transmission of TB to fetus. There is increased risk of obstetrical complications such as spontaneous abortions, growth retardation, oligohydramnios, preterm labor, and increased neonatal mortality. Treatment with reserve drugs is required for managing these cases. Standard treatment regimens for drug-resistant tuberculosis (DR-TB) also require some replacement of drugs during pregnancy.

- Treatment of MDR-TB is as such very challenging but if associated with pregnancy, it is still a bigger challenge to manage. This is due to the fact that second-line drugs used for MDR-TB are very toxic and often causes vomiting, which is already a concern in pregnancy. So, it is better to counsel a presumptive MDR-TB to avoid pregnancy till MDR treatment is complete. But, if the patient is already pregnant, advise her to get medical termination of pregnancy (MTP) as permitted in law (up to 24 weeks' pregnancy).
- If the patient is not willing for MTP or the period of gestation is more than permissible limit for MTP, treatment should be started with adequate precautions (like streptomycin) to be avoided during first trimester and ethionamide up to 32 weeks because of suspected teratogenic effects. Newer drugs bedaquiline (Bdq) and delamanid (Dlm) are avoided as their safety profile in pregnancy is still not clear.

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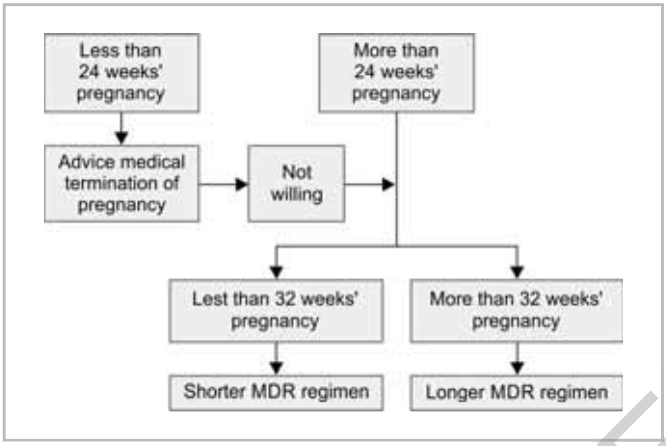

FLOWCHART 1: Management of MDR-TB case during pregnancy.

Notes:
- Ethionamide may be used after 32 weeks' pregnancy.
- Amikacin may be considered in postpartum period.

(MDR-TB: multidrug-resistant tuberculosis)

- The following **Flowchart 1** presents the management of MDR-TB case during pregnancy.
- Pregnant women initiated on Bdq must be encouraged to provide formula feed to their newborn child, till further evidence on the safety of this drug during lactation is available.

These are two-drug regimens used for such cases.

1. *Shorter regimen:* Consisting of 4 months intensive phase with seven drugs (Bdq, levofloxacin, clofazimine, pyrazinamide, and ethambutol followed by 5 months of levofloxacin, clofazimine, pyrazinamide, and ethambutol).

   (4–6) bedaquiline (Bdq) (6 months), levofloxacin (Lfx), clofazimine (Cfz), Z, E, H^h, Eto/(5) Lfx + cfz + Z + E
2. *Longer regimen:* (18–20) levofloxacin (Lfx), bedaquiline (Bdq) (6 months or longer) linezolid (LZD), clofazimine (Cfz), and cycloserine (Cs)

Pregnant patients with MDR-TB who receive effective treatment regimens can achieve a high success rate in treatment and positive pregnancy outcomes.

MULTIDRUG-RESISTANT TREATMENT OUTCOMES DURING PREGNANCY

- The use of treatment regimens recommended under the NTEP including newer drugs—including Bdq, Dlm, and linezolid—for the management of MDR-TB with pregnancy lead to enhance treatment success rate.
- In a study it was found that the treatment success rate was significantly higher among patients on linezolid-containing regimens (85.0%) as compared to patients without linezolid-containing regimens (65.6%). However, these results may be influenced or affected with the administration of additional drugs like Bdq and Dlm.
- Past review studies have indicated that linezolid has increased treatment success rates less number of adverse outcomes among patients taking MDR-treatment. These studies suggest that linezolid used to treat MDR-TB during pregnancy.
- Potential teratogenicity of ethionamide (Eto) in the first trimester and risk of hypothyroidism in the infant in second trimester precludes its use during the first 32

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weeks' pregnancy. As a result, pregnant woman cannot receive a shorter oral regimen with Bdq for MDR/rifampin-resistant tuberculosis (RR-TB) before reaching 32 weeks' pregnancy.

- Second-line injectables are contraindicated throughout pregnancy as they affect the 8th cranial nerve (auditory) of the fetus.
- Hypothyroidism with p-amino salicylic acid (PAS) and myelo suppression with linezolid (Lzd) should also be kept in mind.
- A recent study has shown promising results for the use of Bdq in pregnancy (with an association with low birth weight only). The World Health Organization (WHO) hence recommends that a longer oral MDR or extensively-drug resistant (XDR) TB regimen should be individualized with inclusion of drugs with an established safety profile.
- In patients with DR-TB, women with pregnancy <24 weeks should be counseled for discontinuation of pregnancy (MTP). If the patient is unwilling, shorter oral Bdq containing MDR/RR-TB regimen should not be given in pregnancies <32 weeks' gestation. Either a shift to or continuation of longer oral Bdq containing MDR/XDR-TB regimen (as the case be) is necessary.[3]
- Well-being of the developing fetus should be monitored by the use of ultrasound sonography (USG) scans, particularly at 18 and 32 weeks' gestation.
- Breastfeeding should be encouraged if the patient is smear/culture negative. However, Bdq and Dlm are not recommended during lactation, and hence, formula feed may be given to the baby.

ADVERSE EVENTS

Adverse events are common among pregnant women with MDR-TB, with more than half of the patients experiencing at least one type of drug-related adverse event. With gastrointestinal disorders, ototoxicity, and psychiatric disorders being the most common. The high frequency of adverse events among pregnant women receiving MDR-TB drugs should be monitored closely and managed immediately for adverse effects.

PREGNANCY OUTCOMES

- Teratogenic effect of radiography and antitubercular drugs on the developing fetus needs to be considered. [Teratogenic potential of drugs in the drug-resistant TB (DR-TB) regimen needs to be strictly considered in decision making.]
- Women of child-bearing age, awaiting results of culture and drug-susceptibility tests receiving DR-TB drugs should be strongly counseled to use birth control measures (oral contraceptives should be avoided due to drug–drug interactions and chances of decreased efficacy as a result of vomiting). Testing for pregnancy should be done routinely during pretreatment evaluation and while on treatment. A decision regarding continuation/termination of pregnancy may be done in consultation with the gynecologist/obstetrician, after weighing potential risks to the fetus.
- Most frequently observed adverse pregnancy outcomes were preterm birth, low birth weight and pregnancy loss. The prevalence of preterm birth among patients with MDR-TB to 9.5–11% as compared to the prevalence of preterm birth among patients with drug-susceptible TB (8.0%).[4]
- The chances of still birth in the study (1.9%) were comparable to as reported for patients with other diseases such as coronavirus disease 2019 (COVID-19) (1.4%) and among nonpregnant females (1.8%).[5]
- Primary causes of pregnancy loss were miscarriage and therapeutic abortion.

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BREASTFEEDING

It is concluded that although pregnancy possesses many challenges in the treatment of MDR-TB, the advantages of continuing treatment with modifications outweigh risks to both mother and fetus. Status of pregnant women and the period of gestation and severity of disease are deciding factors before start of the treatment and to achieve at least sputum conversion before delivery.[6]

- Breastfeeding should be continued if patient is sputum smear negative because only a meager fraction of therapeutic dose of drugs is excreted in milk and the impact on infants of such exposure throughout the entire course of MDR-TB treatment has not been determined.
- Nevertheless, if the mother is sputum smear-positive, infant care should be done by family members until she becomes sputum negative, if possible.
- Different countries have various recommended policies regarding whether child should be separated from the mother and the use of breast milk or top milk. In well-resourced settings, providing infant formula can be an alternative to breastfeeding. However, the evidence supporting this approach is limited.
- All efforts should be made to provide breastfeed to the child. Breast milk can be expressed in a mother who is MDR-TB.
- Congenital tuberculosis is very rare and the risk is the highest right after birth. According to the WHO guidelines, newborns should receive the Bacillus Calmette–Guérin (BCG) vaccine at birth. The importance of isoniazid (INH) prophylaxis for infant born with MDR-TB mother is not well established.[7]

CONCLUSION

To conclude, in pregnant women, strict counseling needs to be done for MTP, especially regarding the risk of delaying treatment, the potential effects of new drugs on the fetus including fetal abnormalities (if MTP is not opted) and the need for more intense maternal-fetal-neonatal follow-up. Appropriate counseling and an informed decision-making process for consent needs to be undertaken in each case.

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Update on MDR Tuberculosis

This comprehensive compilation provides updated information on drug-resistant tuberculosis (DR-TB), covering all essential aspects of the disease. The book encompasses general information, diagnostics, therapeutics, and preventive guidelines approved by the National TB Programme. It sheds light on the growing burden of DR-TB, its spread, and the latest diagnostic tools and medications available. Notably, it includes a unique discussion on preventive aspects and TB preventive treatment. The chapters on associated diseases and conditions offer valuable insights into unique clinical manifestations and treatment precautions necessary when managing comorbidities. This resource will serve as an excellent update for resident doctors, faculty members, and private practitioners seeking to enhance their knowledge on DR-TB. Moreover, this handbook will prove invaluable for busy private practitioners and faculty members from departments beyond chest and TB, providing concise information.

Salient Features

- It is edited by editors having a vast experience in managing drug-resistant tuberculosis and academics as authors and reviewers for national and international peer-reviewed journals.
- It is a multiauthor book, authored by renowned specialists working in the field of drug-resistant tuberculosis diagnostics and management.
- It includes chapters by faculty involved in teaching of specialists and superspecialists in the field of tuberculosis and respiratory diseases.
- The chapters have been made interesting by including flowcharts, diagrams, and tables.
- All chapters contain latest references about the topics covered.



VK Arora is a trailblazer in India's fight against tuberculosis (TB), revolutionizing treatment and control through his pioneering work. As a renowned pulmonologist, he played a crucial role in establishing the DOTS strategy in India and introducing the DOTS Plus strategy for multidrug-resistant (MDR) TB. His achievements are impressive, with notable contributions as a WHO member, helping prepare Standard TB Guidelines in India and securing Green Light Committee Clearance for MDR TB in National Institute of Tuberculosis and Respiratory Diseases (NITRD). Dr Arora's editorial contributions are equally remarkable. As Emeritus Editor, he published many special issues on various aspects of MDR TB. He has authored numerous books and research papers, including 251 papers in indexed journals, both national and international. His work has been recognized with various awards and honors, including the Lifetime Achievement Award from the Tuberculosis Association of India. Currently, Dr Arora serves as Chairman of TB Association of India and President of the South-East Asian Region of Union. He is also the executive editor of the Indian Journal of Tuberculosis and has held key positions, including Additional Director General of Health Services and Vice Chancellor of Santosh University, NCR Delhi. With his extensive experience and contributions, Dr Arora is a leading expert in TB control and research, both nationally and internationally.



Kamal Chopra is presently consultant in New Delhi Tuberculosis (NDTB) Centre and TB Association of India. He is working in the field of respiratory medicine and tuberculosis for the last 37 years. He has been trained in TB control and elimination by WHO (diploma course conducted in Japan). He has been Director of NDTB Centre for 14 years. He has around 200 publications in peer-reviewed international and national journals. His name is among 2% scientists in the world in the list released by Stanford University and Elsevier. Currently, he is academic editor of PLoS One and Associate Executive Editor of Indian Journal of Tuberculosis. He has received many awards and orations. Dr Chopra is Chairman of Ethical Committee of two national reputed institutions: Rajan Babu Institute of Pulmonary Medicine and Tuberculosis (RBIPMT) and National Institute of Tuberculosis and Respiratory Diseases (NITRD), New Delhi. He has been part of national committees for formulation of guidelines under National TB Programme. He is a trainer at national and state levels for medical and paramedical staff. His achievements are impressive in preparation of National Strategy Plan for TB Control in India, Guidelines for STDC, Standards of TB Care India, and blueprint for upgradation of NDTB Centre. During his tenure, NDTB Centre has been recognized as the best STDC in India, both in infrastructure and in activities.

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