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LITERATURE REVIEW

MULTI DRUG RESISTANT TUBERCULOSIS IN PREGNANCY

Mualana Muharam, Dewi Wahyu Firina, Dessy Mizarti[1],

Affiliations: *1. Pulmonology and Respirology Department, Faculty of Medicine, Andalas University, Dr. M. Djamil Central General Hospital Padang, West Sumatera, Indonesia*

Abstract

Tuberculosis can develop to multi drug resistant tuberculosis, this will be a serious health problem, not only in Indonesia, also in the world. This disease complexity, length of treatment, adverse effect of drug, make it management become challenging. Pregnancy with physiological changes in it made pregnant woman susceptible to infection, include tuberculosis infection. Data about MDR TB in pregnancy were not much, because TB screening in pregnancy were not often done, also pregnancy it self almost exclude from any trial. Because of MDR TB regiment adverse effect, much of clinician suggest woman in MDR TB treatment to not get pregnant while on it. Management MDR TB on pregnancy use individual regiment, by keep secure and safety aspect of patient, also her fetus.

Keywords*: tuberculosis, multi drug resistant tuberculosis, pregnancy*

INTRODUCTION

Tuberculosis (TB) is an infectious disease that is one of the top 10 deaths, and infection is the leading cause of death, ranking above HIV/AIDS. It is estimated that around 10 million people suffer from TB and cause 1.4 million deaths in 2019. This disease mainly attacks the lungs (pulmonary TB), but can also attack other organs of the body (extrapulmonary TB). TB disease often causes poverty, economic problems, vulnerability, marginalization, stigma, and discrimination. This disease can attack anyone and anywhere. Men are infected with TB more than women. about a quarter of the world's population is infected with TB, 44% of whom are in Southeast Asia. TB cases in Indonesia after being reported at 8.5% of all world cases, the second-largest number in the world, India, with an increase in the number of cases by 69% from 2015 to 2019. According to WHO estimates, there are around 10 cases. % of unreported TB cases in Indonesia.[1]

Drug-resistant tuberculosis (MDR TB) was defined as resistance to at least isoniazid (INH) and rifampin (RMP). This condition is a serious health problem and can be a major threat to world health. There are about 465,000 cases of MDR TB, about half of which are found, with a treatment success rate of 57%. patients with drug-resistant TB were estimated at 3.3% of new TB cases, and 17.7% of previous TB cases. MDR TB cases in Indonesia are estimated at 2.4% of all new TB cases, and 13% of TB patients who have been treated, with an estimated total incidence of drug-resistant TB cases of 8.8/100,000 population.[2]

MDR TB is a major health problem that affects women during their reproductive years.

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Biological changes in pregnancy increase a pregnant woman's risk of developing TB, while pregnancy helps treat TB. The TB mortality rate with untreated pregnancy can be as high as 40%.[3] More aggressive treatment is needed for the treatment of MDR TB. Very little data are available on the treatment of MDR TB in pregnancy, so information about the safety of second-line therapy in pregnant women is lacking.[4]

Pregnancy with MDR TB is more complex, risks can arise as a result of the course of the disease or side effects of using second-line TB therapy, which harms the fetus. The safety of second-line therapy in pregnant women has not been established with certainty. The current WHO MDR TB treatment guidelines recommend individual regimens for the treatment of MDR TB in pregnancy. This recommendation is a conditional recommendation with insufficient data and will continue to be based on available data in the future.[4] Through the discussion of MDR TB in pregnancy, this paper is expected to contribute to the management of MDR TB in pregnancy.

TB-MDR

Definition

Drug-resistant tuberculosis (TBRO) is TB caused by *Mycobacterium tuberculosis* (M.tb) bacteria that have become resistant to anti- tuberculosis drugs (OAT). One of the divisions of drug-resistant TB is Multidrug-Resistant Tuberculosis (MDR-TB), namely TB that is resistant to the most potent drugs, Isoniazid and Rifampicin with or without resistance to other first-line anti-TB drugs such as ethambutol, pyrazinamide, and streptomycin.[5]

Epidemiology

Handling drug-resistant TB has its problems, such as large quantities of drugs, limited drug supply, expensive drug prices, and stronger side effects.[5] Globally in 2016, it was estimated that there were 4.1% of new cases and 19% of new cases. Duration of TB MDR/TB RR. Drug-resistant surveillance data show that there were 240,000 deaths due to MDR TB/RR TB in 2016. Even though the examination was increased, the number of MDR TB/RR TB cases found in 2016 only reached 153,000.[5] In 2019 it is estimated that there will be an increase in MDR TB cases to 465,000 cases, with cases found only 206,030 cases. Treatment was administered in 86% of them, with global treatment success of 57%.[1]

There are not many reports on the incidence of MDR TB in pregnancy. The incidence of TB in pregnancy was estimated at 216,500 in 2014, but this is an estimate of the incidence of TB globally, excluding the possibility of pregnant women suffering from TB increasing by 2 to 3 times. In addition, TB screening was not carried out in pregnant women. As a result, the true incidence rate is unknown.[6] Various case reports of MDR TB in pregnancy indicate an adverse event. The cure rate only reaches 40% of all cases of pregnancy in MDR TB who receive treatment, 40% of them experience death, 10% experience low birth weight births, and 10% experience abortions, or are terminated for health reasons.[7]

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Factors Causing Drug Resistance

The main factor causing M. tb resistance to anti-tuberculosis drugs (OAT) is the result of inadequate or non-standard treatment of TB patients. OAT resistance can be caused by the following 3 factors:[5]

a. Health Care Provider
   - Incorrect diagnosis
   - Treatment does not use the right mix
   - Inadequate dose, type, amount of drug, and duration of treatment
   - Inadequate patient education

b. Patient
   - Does not comply with the recommendations of doctors/health workers
   - Not regularly taking OAT alloys
   - Stopping treatment unilaterally prematurely, usually associated with drug side effects
   - Have impaired drug absorption

c. TB Control Program
   - Insufficient supply of OAT
   - The low quality of the OAT provided

Pathophysiology

Resistance of M. tb bacteria occurs due to spontaneous chromosomal mutations. This mutation weakens the drug-receptor binding on M. tb, so that the drug does not work effectively.[8] TB treatment causes selective inhibition of the M. tb population, the sensitive M. tb population will be killed, while the resistant mutant population will reproduce and cause OAT resistance (acquired resistance). Resistance to OAT in patients who have never received OAT, or have received OAT for less than 1 month is a new resistance (primary resistance). These patients may have been infected by persons with resistant M. tuberculosis. Resistance in patients who have been treated is resistance in patients who have received TB treatment for more than 1 month (secondary resistance), including patients who failed the treatment, patients relapse or return after dropping out of treatment. The possibility of resistance acquired during treatment or experiencing reinfection/primary infection from people with resistant TB bacteria.[5,9]

Criteria for Suspected Drug Resistant TB

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The criteria for suspected drug-resistant TB are all people who have symptoms of TB with one or more history of treatment or the following criteria:[5]

1. TB patients failed treatment with OAT category 2
2. Non-converting category 2 OAT treatment TB patients
3. TB patients who have a history of non- standard TB treatment or use quinolones and second-line injection drugs for at least 1 month
4. TB patients fail treatment with OAT category 1
5. Non-converted category 1 treatment TB patients
6. TB patients relapse after treatment with OAT category 1 or category 2
7. TB patients who return after dropping out of treatment
8. Suspected TB who has a history of close contact with drug-resistant TB patients
9. TB-HIV co-infected patients who do not respond clinically or bacteriologically to OAT administration, if the initial TB diagnosis does not use rapid molecular testing (TCM)

Patients who have previously received TBRO treatment can also become suspected TBRO again, with criteria:[5]

1. Drug-resistant TB patients who fail treatment
2. Drug-resistant TB patients relapse cases
3. Drug-resistant TB patients who return after dropping out of treatment

Patients who meet the above criteria should be diagnosed immediately through a TCM examination.[5]

Diagnosis

Types of Drug-Resistant TB Microbiological Examination

a. Molecular Rapid Test (TCM)
Examination TCM examination with Xpert M. TB/RIF is an automatic nucleic acid amplification test for the detection of M. tb complex bacteria and rifampin resistance genes (rpoB). The results of the examination can be known in approximately 2 hours. Results consist of:[10]
   - M. tb has detected with rifampin results in the form of Rifampicin Resistant detected or “Rif Res” results, Rifampicin Resistant not detected or “Rif Sen” results, Indeterminate Resistant Rifampicin or “Rif Indet” results.
   - M. tb is not detected or the result is “negative”

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- Failed results are invalid, no result, or error

b. Microscopic Examination

The microscopic examination of AFB was performed with Ziehl-Neelsen staining. This test is part of a susceptibility test that is carried out immediately after a patient is confirmed to have rifampin-resistant TB before the patient starts treatment for drug-resistant TB. In addition, the microscopic examination was performed for follow-up culture examination during the treatment period which was carried out as scheduled. The results of the microscopic examination in the form of positive results and negative results.

c. Culture Examination

Culture examination aims to grow and identify M. tb bacteria using solid media (*Lowenstein Jensen*) or liquid media (Mycobacteria Growth Indicator Tube/MGIT). Culture using solid media is relatively cheaper than liquid media but requires a longer time of 3-8 weeks. When using liquid media, culture results can be seen in 1-2 weeks but require a higher cost. The results of the culture examination with solid media were positive (with gradation) or negative, while the results of culture examination with liquid media were positive (without gradation) and negative results.

d. Phenotypic Sensitivity

Test Examination The M. tb complex susceptibility test was carried out to determine the resistance of M. tb bacteria to OAT. Phenotypic method using solid (LJ) and liquid (MGIT) media. Sensitivity test to ethionamide/protionamide can be concluded from the results of molecular susceptibility tests to INH, in the presence of mutations in the inhA gene with first-line LPA. Phenotypic susceptibility tests to cycloserine/terizidone, ethambutol, ethionamide/protionamide, imipenem/meropenem, and PAS were not performed due to low reliability.

e. Second Line LPA Examination

This test is known as Hain Lifescience Genotype M. TBDRplus VER 2.0 (first line LPA) and M. TBDRsl VER 2.0 (second line LPA). LPA examination is one of the sensitivity tests using the genotypic method. First-line LPA can detect resistance to rifampin (rpoB), isoniazid (inhA and katG), and ethionamide/protionamide (inhA) drugs, while second-line LPA is used to detect resistance to fluoroquinolones (gyrA and gyrB) and second-line TB injection drugs (eis and rrs). Currently, the TB program only uses second-line LPA. Examination results can be obtained in approximately 48 hours. LPA results can show:

- *Mycobacterium tuberculosis* detected or *Mycobacterium tuberculosis* not detected
- Fluoroquinolone sensitivity or resistance (levofloxacin, low-dose moxifloxacin, and high-dose moxifloxacin)
- Sensitivity or resistance to second-line injection drugs (kanamycin, amikacin, and

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capreomycin)

TREATMENT

Treatment for drug-resistant TB should be started within 7 days of the diagnosis. Treatment of drug-resistant TB patients is given on an outpatient basis from the start and is monitored daily directly by the Drug Swallowing Supervisor (PMO). Treatment of drug-resistant TB in Indonesia uses a combination of no injection drugs, which is divided into two, namely short-term (9-11 months) and long- term (18-20 months).[5]

The National TB control program has renewed the grouping of drug-resistant TB drugs by 2018 WHO recommendations:[5]

Table 1. Drug Resistant TB Classification

Group	Therapy	Abbreviation
Group A	Levofloxacin/Moxifloxacin	Lfx / Mfx Bdq
	Bedaquiline	Lzd Cfz Cs Trd E
	Linezolid	Dlm Z
Group B	Clofazimine	Ipm-Cln Mpm Amk
	Cycloserine or	S
	Terizidone	Eto Pto PAS
Group C	Ethambutol Delamanid	
	Pyrazinamide	
	Imipenem–cilastatin	
	Meropenem Amikacin	
	or Streptomycin	
	Ethionamide or	
	Prothionamide	
	p-aminosalicylic acid	

The flow of drug-resistant TB treatment is a reference in determining the choice of treatment mix for drug-resistant TB patients based on criteria set by the National TB program.

Short Term TBRO Treatment

Recommendations issued by the WHO in 2019 relate to the use of a non-injectable drug-resistant TB treatment regimen, in which the injection drug kanamycin or capreomycin is replaced by the drug Bedaquiline. The use of injection drugs kanamycin or capreomycin is known to be associated with poor treatment outcomes so that these two injection drugs are no longer used in the treatment of drug-resistant TB.

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1. Not resistant to fluoroquinolones
2. No contact with pre/XDR TB patients
3. Never received second-line OAT for 1 month
4. No resistance or suspected ineffectiveness against OAT in short-term alloys (except INH resistance with inhA or katG mutations)
5. Not pregnant or breastfeeding
6. Not a case of severe pulmonary TB Not a case of severe extrapulmonary TB
7. Drug-resistant TB patients (pulmonary or extrapulmonary) with HIV
8. Children over 6 years old

RR/MDR TB patients who do not meet the above criteria will receive long-term treatment for drug-resistant TB. The composition of the combination of short-term drug-resistant TB treatment without injection consists of 7 types of drugs in the early stages and 4 types of drugs in the advanced stages. The principle of administering a short-term drug-resistant TB treatment regimen without injection is:[5]

1. Before treatment, it is recommended to wait for the results of the drug sensitivity test to fluoroquinolones (second-line LPA results), but if the LPA results are not available until day 7, treatment should be started immediately and the choice of the treatment regimen is based on the results of the history and history of TB/TB treatment previous drug resistance
2. The total duration of treatment is 9-11 months, with the initial stage for 4 months (if there is AFB conversion at or before the 4th month) and the continuation stage for 5 months. Patients with smear results or negative initial cultures can be given the initial stage for 4 months. Clinical and radiological conditions should be monitored to ensure improvement.
3. If BTA conversion has not occurred at month 4, the initial stage of treatment can be extended to month 5 or month 6 (depending on the time of BTA conversion). The second-line LPA examination and drug sensitivity test should be repeated if the results of the smear test at 4 months are still positive.
4. In the short-term regimen, Bedaquiline is still given for 6 months regardless of the duration of the initial stage of treatment.
5. If there is no AFB conversion at 6 months, the short-term combination treatment should be discontinued and the patient's treatment outcome recorded as "treatment failure". Patients were re-registered or referred for long-term drug-resistant TB treatment regimens.

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6. All drugs are taken once a day, 7 days a week (every day), except for Bedaquiline which is taken every day for the first 2 weeks and 3x a week for the next 22 weeks.
7. The composition of the short-term treatment alloy is a standard alloy that cannot be modified. However, in certain conditions, such as the occurrence of side effects, ethionamide can be replaced with protionamide and levofloxacin can be replaced with moxifloxacin. The use of moxifloxacin in short-term combinations. Should be monitored closely for side effects because the concurrent use of moxifloxacin with Bedaquiline and clofazimine can increase the risk of heart rhythm disturbances (QT prolongation).
8. Short-term treatment without injection can not be given if the results of first-line LPA show the presence of mutations in the inhA and katG genes simultaneously indicating resistance to high doses of INH and ethionamide/protionamide.
9. Vitamin B6 (pyridoxine) can be given to patients on a short-term regimen.
10. All drugs must be administered under strict medication supervision during the treatment period

Table 2 Duration of drug administration in short-term drug combinations

Therapy	Early Phase (4-6 Months)	Advance Phase (5 Month)	Total Duration of Treatment
Bedaquiline	V		6 month (regardless of initial stage duration)
Levofloxacin/ moxifloxacin	V	V	9-11 months
Clofazimine	V	V	9-11 months
Ethionamide	V	-	4-6 months
INH high dose	V	-	4-6 months
Pyrazinamide	V	V	9-11 months
Ethambutol	V	V	9-11 months

Long Term TBRO Treatment

Long-term treatment for drug-resistant TB (18-24 months) is given to patients who cannot receive short-term treatment regimens. The combination of long-term drug-resistant TB

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treatment can be modified according to the patient's condition so that it is known as an individualized combination, to increase the effectiveness and safety of this combination.[4]

The principle of long-term guideline without injection:[5]

1. Treatment is started with five TB drugs that are thought to be effective and there are at least three drugs after the use of Bedaquiline is discontinued
2. The ideal treatment regimen consists of three groups A drugs and two group B drugs
3. f group A and Group B do not meet the five drugs, then the drug from group C is taken to complete the number of drugs in the mix.
4. After the administration of Bedaquiline is discontinued (after 6 months), the treatment regimen should consist of a minimum of three drugs Drugs in group C are sorted by recommended use (topmost recommended)
5. In long-term treatment, amikacin or streptomycin injection drugs can be given only when the oral drug choices in group C are not sufficient in the composition of the alloy. Amikacin is given only if it is still proven sensitive, and there is an adequate mechanism for monitoring drug side effects (periodic audiometry).
6. If amikacin is not available, streptomycin can replace amikacin (if streptomycin is also still sensitive)
7. Ethionamide/protionamide and PAS may be added to the treatment regimen when Bedaquiline, linezolid, clofazimine, or delamanide cannot be used and there is no better option for developing a long-term medication regimen.
8. Vitamin B6 (pyridoxine) can be given if the patient is taking linezolid or cycloserine.

The combination of long-term drug-resistant TB treatment should be adjusted to the patient's medical history and clinical condition (including the results of available second-line OAT susceptibility tests, history of intolerance to the disease, and the presence of comorbidities that can cause OAT interactions with other drugs that are also taken)[5]

The recommended treatment in TBRO patients is a short-term treatment. When the patient cannot be given short-term treatment, long-term treatment can be given. Patient criteria for long-term TBRO treatment:[5]

1. RR/MDR TB patients with resistance to fluoroquinolones (pre XDR TB)
2. XDR TB patient
3. Patients failed previous short-term treatment.
4. Drug-resistant TB patients who have received second-line OAT for 1 month.

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5. RR/MDR TB patients with proven or suspected resistance to Bedaquiline, clofazimine, or linezolid
6. MDR TB patients with LPA results have mutations in inhA and katG
7. Pulmonary RR/MDR TB patients with extensive lesions, cavitation in both lung fields
8. Patients with severe extrapulmonary RR/MDR TB or with complications (which must be treated long-term), such as TB meningitis, TB bone, TB spondylitis, miliary TB, TB pericarditis, TB abdomen
9. Drug-resistant TB patients with certain clinical conditions, such as severe allergies/intolerance to drugs in short-term regimens
10. Pregnant, lactating women

Long-term treatment guidelines consist of combinations of drugs, which are by the instructions of the Ministry of Health, as shown in Table 3.

Table 3. Long-term treatment guidelines consist of combinations of drugs

Group Therapy	Therapy
Group A Choose all (three) drugs	Levofloxacin (Lfx) or Moxifloxacin (Mfx) Bedaquiline (Bdq) Linezolid (lzd)
Group B Choose all (two) drugs	Clofazimine (Cfz) Cycloserine (Cs)
Group C If the number of drugs from group A + B is not sufficient for 5 types of drugs, then add 1 or more drugs from group C to complete the treatment mix	Ethambutol (E) Delamanid (Dlm) Pyrazinamide (Z) Amikacin (Am) or Streptomycin (S) Ethionamide (Eto) or Prothionamide (Pto) P-aminosalicylic acid (PAS)

Physiological Changes in Pregnancy

Pregnant women experience decreased immunity, so that latent infection reactivation and sepsis can occur. Pregnant women can tolerate immunity to the fetus while maintaining immunity against infection. This process involves the ability of the fetus to avoid detection from maternal immunity, the release of complement which will reduce the function of the mother's natural killer cells, which affect the thymus and B cells. implantation in early pregnancy can occur. The function of T-helper 2 which produces mask fetal trophoblast antigen is increased, thereby reducing the immunological response of antigens detected by

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TH1.[11]

Significant changes in the immune system in pregnancy function to support normal placentation, and the continuation of a normal pregnancy. These changes affect the ease with which pregnant women become infected with intracellular pathogens such as malaria, tuberculosis, and toxoplasmosis.[11]

Principles of TBRO Treatment in Pregnancy

Patients with MDR TB are strongly advised to use contraception during treatment, because some line 2 OATs are known to harm the fetus Treatment should still be started as soon as the diagnosis is made, taking into account the possible risks.[12] Some principles of drug-resistant TB treatment in pregnant women:[5]

1. Pregnant women do not receive short-term drug-resistant TB treatment combinations
2. Treat with at least 4 types of oral second- line OATs that are thought to be effective.
3. The drugs of choice for the treatment of drug-resistant TB in pregnancy are Bedaquiline and Delamanid (category B), as well as fluoroquinolones, cycloserine, and PAS (Category C).
4. Avoid giving ethionamide or protionamide because it can increase nausea and vomiting in pregnancy, and there is a teratogenic effect in animal experiments.
5. Avoid using aminoglycoside injection drugs because they are ototoxic
6. For drug-resistant TB patients with pregnancy, it is recommended to be treated together with obstetric-gynecological specialists
7. Babies born to mothers who are undergoing drug-resistant TB treatment need to be managed together with a pediatrician drug-resistant TB treatment need to be managed together with a pediatrician

Treatment of MDR TB in Pregnancy

Drug-resistant TB patients who are pregnant are recommended to start treatment as soon as the diagnosis of drug-resistant TB is established, especially in drug-resistant TB patients who are co-infected with HIV. In drug-resistant TB patients who are HIV negative, treatment for drug-resistant TB can be delayed until the second trimester if the patient's condition is stable to avoid teratogenic effects in the first trimester of pregnancy.[5]

The current regimen for MDR TB outside of pregnancy, according to the Ministry of Health guidelines, is a non-injectable regimen, consisting of: 6bdq-Lfx(mfx)-lzd-Cfz-cs/14Lfx(mfx)-lzd-cfz-cs.[5] Consideration and modification needed in using the drug during pregnancy.

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Treatment of TBRO in pregnancy is recommended to be started as soon as possible, especially if the patient is coinfected with Human Immunodeficiency Virus (HIV). If HIV negative, treatment can be postponed until the pregnancy enters the second trimester, if the condition is stable.[5]

Table 4. Category of Drug Safety in Drug-Resistant TB in Pregnancy[5,11]

Group	Therapy	Safety Category	Side Effects
Group A	Levofloxacin (Lfx) or Moxifloxacin (Mfx)	C	Gastrointestinal, insomnia, headache, vaginitis
	Bedaquiline (Bdq)	B	Nausea, vomiting, stomach pain, loss of appetite
	Linezolid (lzd)	C	Nausea, diarrhea, neuropathy
Group B	Clofazimine (Cfz)	C	Jaundice, dry skin, photosensitive
	Cycloserine (Cs)	C	Neurology and psychiatry, headache, restlessness, tremor
Group C	Ethambutol (E)	A	Optic neuritis, gastrointestinal, arthritis
	Delamanid (Dlm)	B	Prolong of QT
	Pyrazinamide (Z)	B	Arthritis, hepatotoxicity, hyperuricemia
	Amikacin (Am) or Streptomycin (S)	D	Proteinuria, irreversible cochlear ototoxicity
	Ethionamide (Eto) or Prothionamide (Pto)	C	Nausea, vomiting, diarrhea, abdominal pain, dysgeusia, hypothyroidism (PAS combination)
	P-aminosalicylic acid (PAS)	C	Nausea, vomiting, diarrhea, hypersensitivity, hypothyroidism (ethionamide combination)

Information:

Security category:[12]

A: Control studies show a low risk of harming the fetus in the first trimester of pregnancy
B: Animal studies have shown no risk to the fetus, but there are no controlled studies in pregnant women, or animal studies have shown that side effects of the drug do not occur in women in the first trimester of pregnancy.
C: animal studies have shown adverse effects on the fetus, there are no controlled studies in pregnant women
D: proven to pose a risk to the human fetus, the benefits if given to pregnant women can still be considered

Impact of MDR TB Treatment on Pregnancy and Fetus

MDR TB is an infection with M. tb bacteria that are resistant to rifampin and isoniazid with or without resistance to other OATs. There have been less than 100 reported cases of MDR TB in pregnancy and the prevalence tends to increase due to the increase in recurrence of TB infection in pregnancy. Biological changes and the immunocompromised state of pregnancy can cause latent infection to develop into active TB infection.[13,14] The teratogenic potential of second-line OATs is still unknown, therefore effective contraception is strongly recommended for all non- pregnant women who are undergoing TBRO

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treatment. . However, MDR TB, if left untreated or undiagnosed in pregnancy, is associated with high morbidity, mortality, and an increased risk of transmission. The risk of obstetric complications such as spontaneous abortion, impaired fetal growth, oligohydramnios, preterm delivery, and increased neonatal mortality is also increased.[6] Appropriate treatment with second-line OATs is required in the treatment of such cases with high virulence and requiring close supervision. Long-term TB treatment, ie 18-24 months after sputum culture conversion, is standard therapy in MDR TB patients with pregnancy.[15,18]

During the treatment of MDR TB in pregnancy, consideration should be given to the use of first-line drugs during pregnancy. The lack of data and the lack of consensus on the management of MDR TB during pregnancy make this a controversial issue. Guidelines for the management of MDR TB in pregnancy are included in the case report.[6,19] Many clinicians recommend that patients delay pregnancy. Often patients do not receive adequate therapy by health care providers because of the challenges in administering MDR TB therapy in pregnancy, namely the lack of data on the safety profile, limitations on the use of rifampin and isoniazid, the timing of starting treatment, strong evidence of toxicity, and fear of fetal complications.[16,20]

Treatment of MDR TB in pregnancy is like a double-edged sword. On the one hand, second-line drugs used for treatment are potentially teratogenic, less effective, and more dangerous; On the other hand, suboptimal treatment can harm the patient. Therefore, the management of these patients involves a multidisciplinary approach with obstetrics, neonatologists, pulmonologists, and public health professionals. The regimen and duration of therapy in these patients require individualized therapy according to the susceptibility pattern of the infection strain. Therapy is usually delayed until well into the second trimester to avoid teratogenic effects of the drug.[14,21]

Most of the second-line drugs are category C drugs in pregnancy except for aminoglycosides which are category D. Several published studies have shown no perinatal side effects, while other studies suggest growth disorders and congenital defects.[14] The study of Palacios et al. pregnant women who underwent MDR TB therapy, 61% recovered, 13% died, and 5% failed treatment. Pregnancy complications occurred in 8 (21%) women, such as spontaneous abortion and vaginal bleeding. None of the infants experienced teratogenic effects. Alene et al's study in South Africa with MDR TB in pregnancy found that 1 in 5 pregnant women treated with MDR TB gave birth to a baby with congenital abnormalities.[4] Fluoroquinolones used during pregnancy have not been shown to increase the risk of malformations in a meta-analysis by Bar-Oz et al. Thus, despite the lack of data on the safety and long-term use of fluoroquinolones, cycloserine, PAS, and amoxicillin/clavulanate in pregnancy, these drugs are still considered as drugs of choice for the treatment of MDR TB during pregnancy.[17,22]

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CONCLUSION

MDR TB cases are still a health problem, with the complexity of the disease, many drugs, expensive drug prices, limited drugs, long treatment times, side effects of drugs, and patient compliance in treatment. Pregnant women with physiological changes caused them to be susceptible to infections, including TB. There are not much data available regarding MDR TB in pregnancy, especially in the use of treatment combinations, so for cases of MDR TB with pregnancy, it is recommended to use an individualized combination consisting of: delamanid- bedaquiline-fluoroquinolone-cycloserine-pas.

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