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Management of tuberculosis during pregnancy: first line anti-tuberculosis drug

Abstract

Tuberculosis is a widespread, infectious disease caused by various strains of mycobacteria, commonly Mycobacterium tuberculosis. Tuberculosis not only responsible for an important proportion of the global burden of disease, but it is also an important contributor to maternal mortality, with the disease being among the three leading causes of death among women aged fifteen to forty five years. The main goals of tuberculosis treatment are to cure the patients, to prevent maternal and perinatal complications and to minimize the possibility of transmission of the bacillus to healthy individuals. First-line anti-tuberculosis treatment for medicine-sensitive tuberculosis can be highly effective; however, in absence of well-controlled studies in pregnant women, first-line tuberculosis medications have been listed as United States Food and Drug Administration pregnancy category C (ie, no adequate well-controlled human studies have been performed, but benefits may be acceptable despite potential risks) except ethambutol categorized as pregnancy category B. Rifampicin can be highly used by pregnant women; due to it is believed to be safe for pregnancy and no teratogenic effects has been observed. Neonates who born from mothers who have been taken rifampicin combination therapy may be developed an increased risk of haemorrhagic disorders in the new-born (postpartum hemorrhage); to avoid this postpartum hemorrhage supplemental vitamin K (10mg/day) should be given for the last four to eight weeks of pregnancy.

Keywords: anti-tuberculosis drugs, first line, management, pregnancy, tuberculosis

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Abbreviations: AIDS, Acquired immunodeficiency syndrome; DOTS, directly Ob-served therapy short course; HIV: human immuno deficiency virus; TB, Tuberculosis; WHO, World Health Organization; USFDA, United States food and drug administration

Introduction

Tuberculosis is a widespread, infectious disease caused by various strains of mycobacteria, commonly Mycobacterium tuberculosis. Mycobacterium tuberculos is, an aerobic, non-spore-forming, non-motile bacillus, is one of five members of the Mycobacterium tuberculosis complex, others being M. bovis, M. ulcerans, M. Africanum, and M. microti, though M. tuberculosis is the major human pathogen. Tuberculosis is an airborne infection.[1,2] Tuberculosis is not only responsible for an important proportion of the global burden of disease, but also it is an important contributor to maternal mortality, with the disease being among the three leading causes of death among women aged fifteen to forty five years.[3] Pregnant women's with active TB typically have the similar clinical manifestations as non-pregnant individuals with active TB; which involve chest pain, fever, cough, fatigue, weight loss, night sweat, and dyspnea and TB symptoms could be masked by physiological symptoms of pregnancy. Fatigue and malaise perhaps characterized during pregnancy is more difficult to recognize as weight loss.[4] Pregnant women with active TB represented an important challenge for both women and fetuses.[5] TB can be transmitted from mother to newborn neonate can be happened by very rare transmission called vertical transmission of TB by transplacental transmission through umbilical veins to the fetal liver and lungs or aspiration and swallowing of infected amniotic fluid in utero-or intrapartum causing primary infection of fetal lungs and gut. Transplacental infection occurs late in pregnant women and aspiration from amniotic fluid occurs in the perinatal period. In the postpartum period a horizontal spread of tuberculosis by droplet from mother or undiagnosed family member is most frequently proposed.[6,7]

Four first line anti-tuberculosis therapy during pregnancy

The main goals of tuberculosis treatment are to cure the patients, to prevent maternal and perinatal complications and to minimize the possibility of transmission of the bacillus to healthy individuals.[8] Prenatal care for pregnant women presents a unique opportunity for evaluation and treatment of latent and active tuberculosis during pregnancy.[9] Individuals with an increased risk of tuberculosis may require medical care only during pregnancy; since pregnancy has not been revealed to elevate the risk of TB, the epidemiology of TB in pregnancy is a reflection of the general incidence of disease.[10] First-line anti-tuberculosis treatment for medicine-sensitive tuberculosis can be highly effective; however, in absence of well-controlled studies in pregnant women, first-line tuberculosis medications have been listed as United States Food and Drug Administration (FDA) pregnancy category C (ie, no adequate well-controlled human studies have been performed, but benefits may be acceptable despite potential risks) except ethambutol categorized as pregnancy category B (no evidence of human risk in controlled studies).[11] There are four first-line anti-tuberculosis therapies such as isoniazid, rifampin, pyrazinamide, and ethambutol. TB treatment is achieved through the use of Directly Ob-served Therapy, Short Course (DOTS); which means the therapy entails the use of combination therapy for at least 6 months, based on the combination of antituberculous agents that are available.[12] This combination includes isoniazide and rifampicin compulsorily, supported by ethambutol and pyrazinamide. Four first line anti-tuberculosis therapies during pregnancy discussed briefly in turn below:

Isoniazid: Isoniazid has been listed as United States Food and Drug Administration (FDA) pregnancy category C. Giving isoniazid for pregnant women is considered to be safe even in the first trimester, though it can cross the placental barrier and cause rare possibility of isoniazid induced hepatic impairment. Prescribing isoniazid in

postpartum period may accelerate the risk of developing hepatitis. The World Health Organization recommended that a supplementation of vitamin-B6 (pyridoxine) 25-50 mg/day or will be given to all pregnant women who receiving isoniazid. Neonates who born from mothers who have been under therapy with isoniazid may be at risk of developing convulsive seizures.[13] Isoniazid adverse effects may be result anywhere from light asymptomatic transaminases to fatal hepatitis, peripheral neurotoxicity or peripheral neuropathy due to a relative pyridoxine deficiency (more likely in slow acetylators, malnutrition, alcoholism, diabetes, AIDS) and lupus like reaction. In pregnancy pyridoxine supplementation with should be prescribed with isoniazid because Vitamin-B6 minimizes the excretion pyridoxine; which is being excessively excreted by isoniazid.[14]

Rifampicin: Rifampicin has been listed as United States Food and Drug Administration (FDA) pregnancy category C. Rifampicin can be highly used by pregnant women; due to it is believed to be safe for pregnancy and no teratogenic effects has been observed. Neonates who born from mothers who have been taken rifampicin combination therapy may be developed an increased risk of haemorrhagic disorders in the new-born (postpartum hemorrhage); to avoid this postpartum hemorrhage supplemental vitamin K (10mg/day) should be given for the last four to eight weeks of pregnancy).[15] Rifampin adverse effects include skin reactions like pruritus, gastrointestinal reactions like nausea, anorexia, abdominal pain, flulike syndrome, and hepatotoxicity, severe immunologic reactions like thrombocytopenia, hemolytic anemia, acute renal failure, and thrombotic thrombocytopenic purpura.[16]

Pyrazinamide: Pyrazinamide has been listed as United States Food and Drug Administration (FDA) pregnancy category C. For a long period of time the use of pyrazinamide for pregnant women has been avoided by many health care givers because of its unavailability of adequate data on its teratogenicity risks. Recently many international organizations such as World Health Organization, International Union against Tuberculosis and Lung diseases, British Thoracic Society, American Thoracic Society, as well as the Revised National Tuberculosis Control Programme of India have been recommended the usage of pyrazinamide for pregnant women because they considered pyrazinamide as it is safe drug to use during pregnancy and no significant adverse events from the usage of this medication has been demonstrated or observed.

Presently, pyrazinamide is use as part of the standard regimen in many countries and particularly indicated in women with tuberculous meningitis in pregnancy, HIV coinfection, and suspected isoniazid resistance.[17] Pyrazinamide adverse effects may result in hepatotoxicity, gastrointestinal symptoms, nongouty polyarthralgia, and asymptomatic hyperuricemia among others.[18]

Ethambutol: Ethambutol has been listed as United States Food and Drug Administration (FDA) pregnancy category B. World Health Organization have been recommended the use of ethambutol combination therapy during pregnancy because they have been considered as it is safe drug if used by pregnant women. Ethambutol has the ability to crosses the placental barrier, and the plasma concentration of ethambutol in the fetus can be as high as 30% of the plasma concentration of the ethambutol in the mother. The retrobulbar neuritis that may complicate the use ethambutol in adults created the fear that it perhaps interferes with ophthalmological development when used by pregnant women; however there is no observed of retrobulbar neuritis in neonates who born from mothers who were under treatment of ethambutol when the standard dose is used.[19] Ethambutol adverse effects may be cause retrobulbar neuritis and peripheral neuritis.

Pharmacokinetics of pyrazinamide, isoniazid, and ethambutol can be summarized as that no changes were required in dosing during pregnancy, as there were no important differences between women antenatal and seven weeks postpartum; however there were very few paired sampling occasions where the woman acted as her own control postpartum: eight for isoniazid and one each for pyrazinamide and ethambutol. This relates to that the four- drug intensive period of TB treatment being only 2 months long; by the postpartum sampling occasion, many women were on the continuation phase of treatment comprising only rifampicin and isoniazid.[20,21]

Table 1 USFDA pregnancy category of first line anti-tuberculosis drug

Drug name	USFDA pregnancy category of anti-tuberculosis drug
Isoniazid Rifampicin Pyrazinamide	C (the pitfall can't be ruled out): The study done in animal model would be shown slight risk to the pregnant animals, but there are no enough evidence in human model or the studies done in animals have shown adverse effects on the fetus (teratogenic or embryocidal, or other); but there are no controlled studies done in women)
Ethambutol	B (no confirmation of pitfall in humans): The study done in animal model would be shown as the drug is safe in pregnant animal; but there is no adequate study for human model or animal studies have not confirmed a fetal risk, but there is no controlled studies in pregnant women or animal studies have reported an adverse reaction that was not confirmed in controlled studies in women in the first trimester

Table 2 First line anti-tuberculosis drug side effects and management during pregnancy[1]

Drug name	Side effects	Management
Isoniazid	Peripheral neurotoxicity, hepatic impairment, lupus like reaction	Vitamin-B6, to minimizes the excretion of pyridoxine
Rifampicin	Postpartum hemorrhage, gastrointestinal disturbances, flulike syndrome, hepatotoxicity, severe immunologic reactions like thrombocytopenia, hemolytic anemia, acute renal failure,	Vitamin K, to avoid postpartum hemorrhage
Pyrazinamide	Hepato-toxicity, gastrointestinal symptoms, nongouty polyarthralgia, joint pains	Acetyl salicylic acid (use of aspirin close to delivery may cause closure of the ductus arteriosus), so use it gingerly
Ethambutol	Retrobulbar neuritis, peripheral neuritis, red-green blindness	Stop it and do ophthalmic evaluation

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Conclusion

Tuberculosis is a widespread, infectious disease caused by various strains of mycobacteria, commonly Mycobacterium tuberculosis. Mycobacterium tuberculos is, an aerobic, non-spore-forming, non-motile bacillus, is one of five members of the Mycobacterium tuberculosis complex, others being M. bovis, M. ulcerans, M. Africanum, and M. microti, though M. tuberculosis is the major human pathogen. Tuberculosis is an airborne infection. Prenatal care for pregnant women presents a unique opportunity for evaluation and treatment of latent and active tuberculosis during pregnancy. For a long period of time the use of pyrazinamide for pregnant women has been avoided by many health care givers because of its unavailability of adequate data on its teratogenicity risks. Recently many international organizations such as World Health Organization, International Union against Tuberculosis and Lung diseases, British Thoracic Society, American Thoracic Society, as well as the Revised National Tuberculosis Control Programme of India have been recommended the usage of pyrazinamide for pregnant women because they considered pyrazinamide as it is safe drug to use during pregnancy and no significant adverse events from the usage of this medication has been demonstrated or observed.

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Availability of data and materials

The datasets generated during the current study are available with correspondent author.

Conflicts interest

The author has no financial or proprietary interest in any of material discussed in this article.

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