

Tuberculosis in pregnancy

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ABSTRACT

Tuberculosis (TB) is one of the oldest diseases known to affect human being. In 2012, out of the estimated global annual incidence of 8.6 million TB cases, 2.3 million were estimated to have occurred in India. The disease is responsible for killing more women of reproductive age than all the combined causes of maternal mortality. The exact incidence of TB in pregnancy is not readily available in many countries due to a lot of confounding factors. It is, however, expected that the incidence of TB among pregnant women would be as high as in the general population, with possibly higher incidence in developing countries. Pregnancy has no positive or negative impact on TB. The clinical presentation of TB is similar to nonpregnant woman but the diagnosis is often delayed due to nonspecific early symptoms and has similar constitutional symptoms like malaise and fatigueness found in pregnancy. The bacteriological diagnosis sample should be processed for tests such as ZN-stain, light-emitting diode microscopy, Gene-Xpert, and gold standard test culture. Treatment of non-multi-drug resistance (MDR) patients should be treated by the same regimen as nonpregnant patients except the use of Streptomycin. The most of the second-line anti-TB drugs are teratogenic and so expected mother with MDR-TB should be advised to terminate the pregnancy.

Key words: *Pregnancy, Pulmonary tuberculosis, Teratogenic*

Tuberculosis (TB) is one of the oldest diseases known to affect human being. The first case was described in Egyptian mummies about 7000 years ago, when it was described as “Phthisis” by Hippocrates. It was estimated that about one-third of the world’s population is infected with the TB. Although India is the second-most populated country in the world, one-fourth of the global incident TB cases occurs annually here. The out of global annual incidence of 8.6 million TB cases in 2012, 2.3 million were estimated to have occurred in India [1]. As much as 75% of individuals with TB are within the economically productive age group of 15-54 years. This significantly impairs socio-economic development, thereby perpetuating the poverty cycle [2]. Clinical diagnosis of TB in pregnant women can be difficult due to nonspecific symptoms related to the physiological response to pregnancy [3]. The disease is responsible for killing more women of reproductive age than all the combined causes of maternal mortality [4]. The exact incidence of TB in pregnancy is not readily available in many countries due to a lot of confounding factors. It is expected that the incidence of TB among pregnant women would be as high as in the general population, with probably higher incidence in developing countries. It is best described as a double edged sword, one blade being the effect of TB on pregnancy and the pattern of growth of the newborn, while the other is the effect of pregnancy on the progression of TB. Untreated TB represents a greater hazard to a pregnant woman and her fetus than does

its treatment. Treatment of pregnant women should be initiated whenever the probability of TB is moderate to high. Infants born to women with untreated TB may be of lower birth weight than those born to women without TB and, rarely, the infant may be born with TB. Although the drugs used in the initial treatment regimen cross the placenta, they do not appear to have harmful effects on the fetus. There is little evidence to guide clinicians in the treatment of drug-resistant TB in pregnancy.

Effect of Pregnancy on TB

The TB cavities may collapse as a result of the increased intra-abdominal pressure associated with pregnancy [5] and after that German physician observed that young women with pulmonary TB to get married to slow the progression of diseases. But in the 20th century, people believed that pregnancy has a deleterious effect on TB and to avoid that induced abortion was recommended for such type of problem [6]. TB is believed to get flared up by the stress of pregnancy, especially in association with a poor nutritional status, immunodeficient state, or co-existent diseases [7]. There are some studies which show that pregnancy has no positive or negative impact on TB [8]. Hedvall reported on 250 of his own pregnant patients and found that 9% improved, 7% deteriorated, and 84% were unchanged antepartum, with 9% improving, 15% deteriorating and 76% remaining unchanged postpartum [9]. Studies in London in the 1950s by Priddy and

Stradling showed rates of TB in the pregnant population to be the same as in the nonpregnant population [10].

Effects of TB on Pregnancy

The effects of TB on pregnancy may be influenced by many factors, like severity of the disease, how advanced the pregnancy has gone at the time of diagnosis, the presence of extrapulmonary spread, and HIV coinfection and the treatment instituted. The pulmonary and extrapulmonary forms of TB effect pregnant women in the same way as the nonpregnant ones. If anti-TB treatment (ATT) is started early in pregnancy, the outcome is same as that in non-pregnant patients, whereas late diagnosis and care are associated with 4-fold increase in obstetric morbidity and 9-fold increase in pre-term labor [11]. A higher frequency of abortion, toxemia, and intrapartum complications were reported in another series [12]. There is one Indian study which shows no increase in maternal mortality [13]. Other factors such as poor nutritional states, hypoproteinemia, anemia, and associated medical conditions add to maternal morbidity and mortality. The worst prognosis is recorded in women in whom a diagnosis of advanced disease is made in the puerperium as well as those with HIV coinfection. Other obstetric complications that have been reported in these women include a higher rate of spontaneous abortion, small for date uterus, and suboptimal weight gain in pregnancy [11].

Effect of TB on Perinatal Outcome

There are many reports of variable perinatal outcomes with increased abortion rates, high levels of pre-eclampsia, and increased levels of difficult labor requiring intervention in some studies [7] but overall good fetal outcome in others [12]. In a study of Indian women with pulmonary disease treated for 6-9 months in pregnancy, perinatal mortality was six times higher than in controls and the incidence of prematurity, small-for-date babies, and low birth weight (<2500 g) was doubled [14].

CONGENITAL TB

A fetus can get TB infection either by hematogenous spread through umbilical vein to fetal liver or by ingestion or aspiration of infected amniotic fluid [15].

True congenital TB is believed to be rare. The risk to neonate of getting TB infection shortly after the birth is greater [16,17]. A primary focus subsequently develops in the liver, with the involvement of the periportal lymph nodes. The tubercle bacilli infect the lungs secondarily, unlike in adults where over 80% of the primary infections occur in the lungs. Criteria given by Cantwell et al., for confirming fetal/neonatal TB comprise demonstration of either primary hepatic complex/caseating hepatic granulomas or percutaneous liver biopsy at birth or presence of maternal genital tract/placenta TB or the presence of lesions during first week of life by excluding postnatal transmission by a thorough investigation of all the contacts (including the attendants) [16]. The clinical presentations of congenital TB include hepatosplenomegaly,

respiratory distress, fever, and lymphadenopathy. However, it is always challenges to differentiate from other congenital infections. The possibility of postnatal transmission must be excluded by a thorough investigation of all contacts, including hospital staffs and attendants. An abnormal chest radiograph is found in all such cases, half of whom have a miliary pattern [18]. The overall mortality for congenital TB is 38% in the untreated and 22% in the treated [18].

CLINICAL PRESENTATION

The clinical presentation of TB is similar to nonpregnant woman, but the diagnosis is often delayed due to non-specific early symptoms and has similar constitutional symptoms such as malaise and fatiguability found in pregnancy [19]. The most common site in pregnancy is pulmonary and, in a study, of the 27 pregnancies reported with culture-positive disease, 74% had cough, 41% had weight loss, 30% had fever, malaise or fatigue, and 19% had hemoptysis; 20% were asymptomatic but all had abnormal radiographs [19].

The diagnosis of pulmonary TB is also delayed due to delayed X-ray to avoid radiation toxicity and that investigation of sputum smear negative TB is more difficult [20]. Other studies have found less significant symptoms in pregnant women with TB.

DIAGNOSIS OF PULMONARY TB IN PREGNANCY

Diagnosis of TB based on Revised National Tuberculosis Control Program algorithm and all patients having a cough of more than 2 weeks duration should undergo sputum examination for acid-fast bacilli. At least two sputum samples should be processed for ZN-staining to detect acid-fast bacilli. Microscopic examination of sputum or another specimen by light-emitting diode (LED) fluorescent microscopy has recently been introduced to improve diagnosis. If the facilities for Gene-Xpert are there, the sample should be preferentially processed for detection Gene-Xpert along with ZN-staining. The gold standard for bacteriological test is culture which could be performed by solid L-J media or liquid mycobacteria growth indicator tube method.

TREATMENT

The main concern about TB treatment in pregnancy is the risk of teratogenicity specially in the 1st trimester.

PRINCIPLES

1. ATT should be started promptly as untreated disease presents a hazard to the mother and fetus.
2. The same regimens are recommended for use in pregnancy as for the nonpregnant state except for withholding of streptomycin.
3. A question-mark exists on the safety of second-line drugs in the pregnant state. Therefore, expectant mothers with multi-drug resistance-TB (MDR-TB) should be advised to terminate the pregnancy. If a woman insists on its continuation, the

possible consequences of the same should be discussed with her in detail.

4. The management of pregnant TB women becomes complicated in the presence of HIV infection due to the involved drug interactions. Hence, the regimens and drug dosages need appropriate adjustments.
5. Pyridoxin should be given to all patients receiving Isoniazid to prevent peripheral neuropathy.
6. Newborn should be segregated from if she is having active pulmonary TB not on the treatment of receiving from <2 weeks.
7. Vitamin K should be given prophylactically to newborn at birth to prevent Hemorrhagic diseases of newborn.
8. Neonates born to mothers having infectious TB should be given chemoprophylaxis with isoniazid (INH) for 3 months or till the mother becomes noninfectious. Bacille Calmette-Guérin (BCG) vaccination may be postponed or done with INH-resistant BCG vaccine.

ANTI-TB DRUGS

First-line Drugs

Isoniazid

Pregnancy category A - Recommended for use in pregnancy: Isoniazid has high lipid solubility, a low molecular weight, and crosses the placenta readily to reach fetal levels similar to those of the mother. As isoniazid may be associated with an increased risk of hepatotoxicity in pregnant women, symptoms should be assessed and it is recommended by some that liver function tests be performed fortnightly during the first 2 months of treatment, and monthly thereafter [21].

Rifampicin

Pregnancy Category C - Rifampicin is most powerful anti-TB drug readily absorbed after oral administration with a peak serum concentration of 5-7 mg/l within 1.5-2 h in nonpregnant subjects and good penetration into all tissues despite the fact that 75% is protein bound.

Bleeding attributed to hypoprothrombinemia has been reported in infants and mothers following the use of rifampicin in late pregnancy. The use of rifampicin is indicated in pregnant women with TB, with the recommendation that vitamin K be given to both the mother and the infant postpartum if rifampicin is used in the last few weeks of pregnancy [21].

Ethambutol

Pregnancy Category A - Recommended for use in pregnancy.

Pyrazinamide

Pregnancy Category N/A - There are no reports of fetal malformations attributable to pyrazinamide, although there are additionally no

animal or epidemiological studies reported to support the safety of this drug in pregnancy. The absence of such safety data is the reason that the CDC (USA) guidelines do not endorse pyrazinamide in pregnancy. Its use is supported by other TB authorities, including the IUATLD and the BTS. To date, there are no reports of significant adverse events from the use of this drug in the treatment of TB in pregnant women despite the fact that the drug is used as part of the standard regimen in many countries. However, additionally, insufficient data are available about the number of pregnant women treated for TB in these many settings. If the treating doctor elects not to use pyrazinamide, a 9 months regimen containing isoniazid and rifampicin throughout (supplemented by ethambutol until drug susceptibility results are available) is recommended.

Second-line Medications

Streptomycin has a well-established association with fetal ototoxicity and not recommended for the treatment of TB in pregnant women. There is no evidence of increased incidence of abnormalities in babies of mothers treated with fluoroquinolones. Animal studies of ciprofloxacin suggest that there is a risk of damage to articular cartilage and subsequent juvenile arthritis with short courses of treatment, and the possibility of joint damage with longer courses of treatment used for TB must be seriously considered [21]. Fluoroquinolones should only be used in pregnant women with TB where the benefits of treatment are judged to outweigh the potential risks, and the decision to use such drugs in this setting should only be made after discussion with clinicians experienced in the management of TB. There are insufficient animal and human safety data relating to the use of para-aminosalicylic acid (PAS) in pregnancy. It has been associated with a slightly higher incidence of limb and ear abnormalities in one report involving 123 patients taking PAS with other anti-TB drugs [21]. PAS should not be used to treat TB in pregnant women unless the benefit/risk ratio is favorable. Ethionamide and prothionamide been shown to be teratogenic in animal studies and their use is contraindicated in pregnancy.

Breast Feeding

The first-line anti-TB drugs cross into breast milk in variable amounts. Rifampicin is excreted into breast milk with milk to plasma ratio of 0.2. The amount transferred to the infant (0.05% of maternal dose) does not cause adverse effects. Pyrazinamide excretion into breast milk is minimal with a maximum of 0.3% of the ingested dose reaching the infant [22]. Ethambutol is secreted into breast milk with approximate milk to serum ratio of 1:1. All these anti-TB drugs are thought to be compatible with breastfeeding by pediatric groups such as the American Academy of Pediatrics [23].

CONCLUSION

Untreated TB disease presents a greater risk to a pregnant woman and her fetus. Treatment should be initiated whenever the

probability of TB is moderate to high. Treatment of non-MDR patients should be treated by the same regimen as nonpregnant patients except the use of streptomycin. A pregnant lady with MDR-TB should be advised to terminate the pregnancy. If a woman insists on its continuation, the proper communication made about consequences before putting on treatment.

REFERENCES

1. Central TB. Division, Directorate General of Health Services, Ministry of Health and Family Welfare, Revised National TB Control Programme, Annual Status Report TB India, 2014. Available from: <http://www.tbcindia.nic.in>. [Last accessed on 2015 Dec 07].
2. World Health Organization. Global Tuberculosis Control 2010, Technical Report, (WHO/HTM/TB/2010). Geneva, Switzerland: World Health Organization; 2010.
3. 2010/2011 Tuberculosis Global Fact; World Health Organization. November, Available from: <http://www.who.int/tb/country/en/index.html>. [Last accessed on 2016 Sep 14].
4. Arora VK, Gupta R. Tuberculosis and pregnancy. Indian J Tuberc. 2003;50:13-6.
5. Snider D Jr. Pregnancy and tuberculosis. Chest. 1984;86(3):108-38.
6. Vallejo JG, Starke JR. Tuberculosis and pregnancy. Clin Chest Med. 1992;13(4):693-707.
7. Schaefer , Zervoudakis IA, Fuchs FF, David S. Pregnancy and pulmonary tuberculosis. Obstet Gynecol. 1975;46(6):706-15.
8. Hedvall E. Tuberculosis and pregnancy. Acta Med Scand. 1953;148 Suppl 286:1-18.
9. Pridie RB, Stradling P. Management of pulmonary tuberculosis during pregnancy. Br Med J. 1961;2(5244):78-9.
10. Figueroa-Damian R, Arredondo-Garcia JL. Pregnancy and tuberculosis: Influence of treatment on perinatal outcome. Am J Perinatol. 1998;15(5):303-6.
11. Bjerkedal T, Bahna SL, Lehmann EH. Course and outcome of pregnancy in women with pulmonary tuberculosis. Scand J Respir Dis. 1975;56(5):245-50.
12. Jana N, Vasishta K, Jindal SK, Khunnu B, Ghosh K. Perinatal outcome in pregnancies complicated by pulmonary tuberculosis. Int J Gynaecol Obstet. 1994;44(2):119-24.
13. Jain NK. Safety of anti-tuberculosis drugs in pregnancy. In: Proceedings of the National Conference on Pulmonary Diseases (NAPCON '01). Vol. 33. Mumbai, Maharashtra, 2001.
14. Hamadeh MA, Glassroth J. Tuberculosis and pregnancy. Chest. 1992;101(4):1114-20.
15. Starke JR. Tuberculosis. An old disease but a new threat to the mother, fetus, and neonate. Clin Perinatol. 1997;24(1):107-27.
16. Cantwell MF, Shehab ZM, Costello AM, Sands L, Green WF, Ewing EP Jr, et al. Brief report: Congenital tuberculosis. N Engl J Med. 1994;330(15):1051-4.
17. Ormerod P. Tuberculosis in pregnancy and the puerperium. Thorax. 2001;56(6):494-9.
18. Good JT Jr, Iseman MD, Davidson PT, Lakshminarayan S, Sahn SA. Tuberculosis in association with pregnancy. Am J Obstet Gynecol. 1981;140(5):492-8.
19. Vallejo JG, Starke JR. Tuberculosis and pregnancy. Clin Chest Med. 1992;13(4):693-707.
20. Doveren RF, Block R. Tuberculosis and pregnancy – A provincial study (1990-1996). Neth J Med. 1998;52(3):100-6.
21. Bothamley G. Drug treatment for tuberculosis during pregnancy: Safety considerations. Drug Saf. 2001;24(7):553-65.
22. Holdiness MR. Antituberculosis drugs and breast-feeding. Arch Intern Med. 1984;144(9):1888.
23. American Academy of Pediatrics Committee on Drugs: The transfer of drugs and other chemicals into human milk. Pediatrics. 1994;93(1):137-50.

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