MERIT RESEARCH JOURNALS
www.meritresearchjournals.org

Merit Research Journal of Medicine and Medical Sciences (ISSN: 2354-323X) Vol. 6(6) pp. 185-190, June, 2018
Available online http://www.meritresearchjournals.org/mms/index.htm
Copyright © 2018 Merit Research Journals

Review

Tuberculosis and Pregnancy

Ioannis K. Thanasas* and Konstantina Balafa

Department of Obstetrics and Gynecology of General Hospital in Trikala, Trikala, Greece

***Corresponding Author's E- Mail: thanasasg@hotmail.com**
Phone: 2431029103 / 6944766469

Abstract

Tuberculosis is common in pregnancy. The most common location of the disease is the lungs. Diagnosis of lung tuberculosis in pregnancy is not easy. The mild clinical manifestations of the disease along with the common delay of a lung x-ray can delay the correct diagnosis of tuberculosis. Despite that, early recognition of the symptoms and the risk factors correlated with the disease along with the contemporary technology allow today the proper diagnosis and treatment. Direct use of the anti-TB drugs is the basis of treatment that aims at avoiding serious adverse effects for the mother and the fetus/neonate. The present paper based on updated literature aims at a brief overview of lung TB during pregnancy as far as diagnosis, prognosis and basic principles of treatment is concerned.

Keywords: Tuberculosis, Pregnancy, Anti- tuberculosis drugs

INTRODUCTION

In general, it is known that during pregnancy normal biochemical and anatomical changes in systematic and local levels are made. Normal adjustment in pregnancy includes a complex of changes in circulatory, hormonal and immunobiological system that are aimed to ensure stable and ideal environment for the development of the placenta and baby and on the other hand, to protect the maternal organization. Furthermore, during pregnancy the function of the respiratory system is influenced by several biochemical and mechanical changes with dyspnoia as the main symptom. The knowledge of these respiratory changes is very important to recognize the pathology of the respiratory system because serious problems can be provoked as concern as the smooth pregnancy progress and delivery.

In this paper, a brief review of management of pulmonary tuberculosis during pregnancy as long as the best outcome for mother and baby is discussed.

Pulmonary tuberculosis during pregnancy

Pulmonary tuberculosis is a pathological situation characterized by acute inflammation of lung parenchyma and it is caused by mycobacterium of tuberculosis, one nonmotile, acid-resistant, aerobic and rod – shaped bacterium. Tuberculosis is a rare condition during pregnancy. Pregnancy is not a risk factor that favors tuberculosis presentation. In addition, the incidence of extra pulmonary tuberculosis in pregnant women is not significantly different from the overall rate of tuberculosis in non pregnant women (Ormrod, 2001). According to World Health Organization (WHO), it is estimated that the incidence of TB has increased in recent years. More specifically, the incidence of TB in population rose from 6.6 million cases in 1990 to 9.4 million in 2008, and the 3.6 millions of new infection concern to women (WHO, 2009). Recently, WHO published that 3.3 million cases of TB in women was reported with 510.000 deaths in 2013. Also, it was estimated that 1/3 of these women were infected by HIV (WHO, 2014).

In general, TB is a severe cause of death in women. It is estimated that TB concerns 700.000 deaths each year. TB is an important non-obstetric cause of maternal mortality. Actually, 1/3 of deaths are caused by TB in women that were infected in childhood and in most cases in non-developed countries (Grange et al, 2010). Kothari and his colleagues, analyzing the results of a multiannual

Table 1. Treatment of pulmonary tuberculosis during pregnancy and breastfeeding.

• Training – information of pregnant women
• Observation of pregnant women's lung function
• Regular fetus observation
• Anti-TB therapy
♦ First line drugs
▪ Ethambutol
▪ Isoniazid
▪ Rifampicin
▪ Pyrazinamide
♦ Second line drugs
▪ Streptomycin
▪ Kanamycin
▪ Amikacin
▪ Capreomycin
▪ Ethionamide
▪ Prothionamide
▪ Cycloserine
▪ fluoroquinolones
• Anti –TB therapy during breastfeeding

study in London, showed that the incidence of TB during pregnancy has increased (Kothari et al, 2006). Recently, Knight and his colleagues published that the incidence of TB in pregnancy in United Kingdom was 4.2 cases per 100.000 pregnancies or about one case per 24.000 pregnancies (Knight et al, 2009). Mathad and Gupta concluded that the incidence of active TB in pregnant women in developed countries (low risk) is 0.06-0.25%. In non – developed countries (high risk) the incidence is about 0.07-0.5% in HIV-negative pregnant women and about 0.7-11% to HIV-positive women (significantly elevated incidence), (Mathad and Gupta, 2012). More recently in 2014, Sugarman and his colleagues, analyzing the results of an epidemiological study showed 216.500 cases of active TB during pregnancy. Furthermore, same researchers in the same study published that the disease concerns people of African countries in 41.3% of patients (Sugarman et al, 2014).

Therapy

Treatment of pulmonary tuberculosis during pregnancy and after labor demands special attention and must be organized by a team of obstetricians-gynecologists and pulmonologists. The ideal treatment of pulmonary tuberculosis during pregnancy includes education and information of pregnant women, observation of pregnant women's breathing function, regular fetus observation and timely administration of anti-tuberculosis drugs in early onset of pregnancy. In this way, best breathing function of these women and best outcome of pregnancy is achieved (table 1). Pregnant women should be well informed that adequate tuberculosis management is a prerequisite for the best pregnancy outcome. Furthermore, pregnant women should be trained to recognize the disease's symptoms and start medication immediately.

In general, none of anti – tuberculosis drugs is proven by studies that is totally safe for the fetus. However, pharmaceutical treatment of tuberculosis during pregnancy is so important and side effects from modern anti TB drugs have low incidence to fetuses. In each case of a moderate clinical suspicion, drug therapy should be initiated. Clinical experience and different studies showed that administration of anti TB drugs during pregnancy is safe. Dangers of non administration of anti TB drugs are more threatening to the fetuses than side effects of same drugs. The choice of the suitable combination of anti TB drugs is a practice that has some special rules that medical practitioner must know. The medical practitioner should be specialized and familiar to the way of administration and side effects of anti-TB drugs (Nguyen et al, 2014). About the safe administration of anti-TB drugs during pregnancy there is a classification from United States Food and Drugs Administration (FDA) (Reproduced with permission from: Lacy CF, Armstrong LL, Goldam MP, Lance LL, Lexi – Comp Drug Information Handbook, 20th Edition, Hudson, OH: Lexi – Comp, 2011), table 2. Most important anti-TB drugs and their classification according to FDA are showed in table 3 (Arbex et al, 2010; Arbex et al, 2010).

Today, the predominant treatment is the administration of ethambutol, isoniazid, rifampicin and pyrazinamide for two months and then administration of isoniazid and rifampicin for four months. If pyrazinamide is not concluded to the first given medical combination, then isoniazid and rifampicin must be administrated for

Table 2. FDA pregnancy categories.

CATEGORY A	Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters).
CATEGORY B	Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women.
CATEGORY C	Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
CATEGORY D	There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
CATEGORY X	Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.

Table 3. Anti – TB drugs and their classification during pregnancy.

Drug Category	Drug	Fda Category
First line anti – TB drugs	Ethambutol	**B**
	Isoniazid	**C**
	Rifampicin	**C**
	Pyrazinamide	**C**
Second line anti – TB drugs	Streptomycin	**D**
	Amikacin	**D**
	Kanamycin	**D**
	Capreomycin	**C**
	Ethionamide	**C**
	Propiothinamide	**C**
	Cycloserine	**C**
Fluoroquinolones	Ciprofloxacin	**C**
	Norfloxacin	**C**
	Gatifloxacin	**C**

seven months. The safety of first line anti-TB drugs (ethambutol, isoniazid, rifampicin, pyrazinamide) for the treatment of tuberculosis during pregnancy is established in recent years (Tripathy and Tripathy, 2003; Efferen 2007).

First line anti – TB drugs

Most of first line anti-TB drugs such as isoniazid, rifampicin and ethambutol are well tolerated from pregnant women and newborns. Isoniazid is considered as class C drug to FDA classification. Isoniazid dosage is 5mg/kg/24h one time as a single dose with empty stomach. Isoniazid totally crosses the placenta but teratogenic effect on fetuses is not proven. Although, in many cases, isoniazid is may related to elevated risk of hepatotoxicity. Also, there are serious suspicions that incidence of hepatitis from isoniazid is elevated directly after birth (Tedla et al, 2010). In each case, symptoms and clinical signs of liver failure should be carefully estimated. Liver function tests in pregnant women are necessary every 15days during the first two months from the beginning of the therapy and next once a month. Furthermore, TB prophylaxis can be succeeding with the administration of isoniazid in 5mg/kg once a day for 6 – 9 months. Indication of chemotherapy prophylaxis is necessary especially to tuberculin skin test positive pregnant women and to those with known risk factor such as HIV positive pregnant women or presence of TB infected person in pregnant women's environment (Bothamley, 2001; Taylor et al, 2013). In each case, isoniazid must be administrated with pyridoxine (vitamin B6) in dosage 50mg daily at the same time to avoid peripheral neuropathy (American Thoracic Society, CDC, Infectious Diseases Society of America, 2001; Tiam et al 2014). In an earlier study, Snider and his colleagues published that the presence of abnormalities in children whose mothers took medication with isoniazid during pregnancy for TB treatment was 1%, less than 1.2%-6% that is about the presence of fetus abnormalities in general population (Snider et al, 1980).

Rifampicin is considered as category C drug in FDA classification. Rifampicin is administrated one time as a single dose of 600mg peros and it crosses less the placenta than isoniazid. This drug is safe during pregnancy but there are also reviews in literature that it can cause abnormalities in fetuses when administrated during organogenesis (Loto and Awowole, 2012). Bothamley in 2001 analyzing the results of his study, showed that children whose mothers took rifampicin in advanced pregnancy can show hemorrhage that can lead to thrombocytopenia. When rifampicin is administrated during the two last weeks of pregnancy, vitamin K must be administrated to mother and newborn directly after birth (Bothamley, 2001).

Ethambutol is considered as category B drug in FDA classification. Ethambutol is administrated in dosage of 15mg/kg daily per os. It is safe during pregnancy but some literature reviews showed that it can cause fetus abnormalities when administrated during prenatal period (Bharathi et al, 2012). Lewit and his colleagues in an earlier experimental study, showed that retrobulbar neuritis in adults, which is a complication of ethambutol, is related to the presence of ophthalmological disorder in each case that ethambutol is administrated in higher than recommended dose during pregnancy to cure TB. (Lewit et al, 1974).

Pyrazinamide is considered as category C drug in FDA classification. The use of pyrazinamide for TB treatment during pregnancy was not indicated for a long time by specialists due to lack of reviews about its safety during pregnancy. Lately, many global organizations such as International Union against Tuberculosis and Lung Diseases (IUATLD), British Thoracic Society, American Thoracic Society, World Health Organization and Revised National Tuberculosis Control Programme of India appreciate that the use of pyrazinamide uring pregnancy is safe. Lately, many global organizations such as Internation Union against Tuberculosis and Lung Diseases (IUATLD), British Thoracic Society, American Thoracic Society, World Heath Organization and Revised National Tuberculosis Control Programme of India indicate that the use or pyrazinamide during pregnancy is safe. The lack of serious side effects of this drug is a reason that pyrazinamide is included in the therapeutic protocols to the anti-tuberculosis treatment during pregnancy. Administration of pyrazinamide is totally indicated to women with tuberculous meningitis, to HIV positive pregnant women and in cases that there is serious evidence of isoniazid resistance (Blumberg et al, 2003; American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America, 2005).

Second line anti – TB drugs

Streptomycin is considered as category D drug in FDA classification. In many cases, streptomycin is incrimimated for fetal ototoxicity and perhaps it causes neonatal deafness (Donald et al, 1991). Other second line anti – TB drugs like kanamycin, capreomycin, cycloserine and amikacin shoud be avoided during pregnancy because their safety to the fetus is not certain. Amikacin is considered as category D in FDA classification. In general there are worries that aminoglycosides may be ototoxic and nephrotoxic to fetuses. It is known that the levels of the drug in maternal blood are not related to the safety of fetus and neonatal (World Health Organization, 2008). The use of aminoglycosides for TB treatment during pregnancy should be considered as last option but first danger and benefits must be counterbalanced by specialists who are aware of possible side effects (World Health Organization, 2008; World Health Organization, 2010). Kapreomycin is considered as category C in FDA classification. Experimental studies showed that there is serious possibility to teratogenesis during pregnancy. Use of kapreomycin is not indicated to TB treatment to pregnant women. Advantages and disadvantages of its use should be considered before making decision to administrate it during pregnancy (WHO, 2008). Also, ethionamide and prothionamide (category C in FDA classification) are considered as teratogenic. Their use should be avoided during pregnancy unless if it is imposed by specialists in multi resistant disease (Morlock et al, 2003, Khilnani, 2004; Shin et al, 2003). Experimental studies showed that the use of ethionamide is related to intrauterine growth restriction (IUGR), central nervous system abnormalities and skelatal fetuses abnormalities (Bothamley, 2001). Cycloserine is considered as category C in FDA classification. Experimental studies did not show teratogenesis but there are no sufficient evidences that cycloserine is safe to pregnant women. Generally, cycloserine is not indicated during pregnancy and its administration should be considered as special therapeutical option (WHO, 2008).

Fluoroquinolones are considered as category C in FDA classification. Studies showed that there is no high risk of fetal abnormalities in neonatals whose mothers took fluoroquinolones during pregnancy. However, studies in animals that took ciprofloxacin showed high risk for damages in fetal articular cartilage. Furthermore, in cases that fluoroquinolones are administrated in higher than ordinary dosages, elevated possibilities of fetal abnormalities and treatment benefits should be counterbalanced by specialists (Bothamley, 2001). However, in each case, the decision of administrating fluoroquinolones during pregnancy should be made by experienced physicians in TB treatment (World Health Organization, 2008).

Breastfeeding in women who are under medication in first line drugs should not be discouraged, because the concentration of these drugs in milk is subtherapeutic and

damages in neonatals can not be caused. The danger of second line drugs is not clarified yet. In each case, it is acceptable that danger is minus if mother breastfeeds before administrating any indicated anti-TB treatment (Maddinemi and Panda, 2008).

Finally, in cases of multi resistant disease, physician should weigh the danger of disease dispersion from mother to neonatal from the danger of side effects of second line anti-TB drugs. Despite few evidence, there are litterature reviews for successful outcome and treatment of disease in pregnant women with multi resistant tuberculosis and administration of second-line anti-TB drugs during pregnancy (Drobac et al, 2005; Palacios et al, 2009; Tabarsi et al, 2011).

Conclusion

TB is not common during pregnancy. This disease is most frequently detected in the lugs. The effect of TB on pregnant women is considered to be an important subject which should concern pregnant women as well as their attending physicians. The existence of a specialized medical team consisted of a lung specialist, a neonatologist and an obstetrician- gynecologist, in close cooperation of course, is absolutely necessary and highly recommended, so that we are given the opportunity to achieve the best possible medical attention of these patients and ensure the best prenatal outcome as much as possible. A successful outcome of TB on pregnant women assumes special training regarding TB:

· They should be kept well informed

· Their breathing functions ought to be objectively attended

· The embryo's condition had better be frequently attended as well and last but not least

· There has to be a firsthand dosage of any necessary medical treatment when required

Every time there is a moderate up to important clinical inkling, some medical treatment against the disease has to start being provided, the battle-front medicine against TB, required to face the disease during pregnancy, is of low danger as far as the embryo's life is concerned but the potential danger for any obstetric complications is still high enough. Second-best medicine against TB, despite the limited bibliographical data, is potentially indicated in the battle against this very impervious disease during pregnancy.

In general, it is estimated that the dangers resulting when no medical treatment is provided are a greater threat against the embryo and the new-born baby when they are compared to the possible, undesirable side-effects resulting from the dosage of the appropriate medical treatment.

Medicine against TB has to be the base of the therapy the objective of which is to avoid any unpleasant, serious complications that will have to do not only with the mother but also with the embryo and the nursing.

REFERENCES

American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America (2005). Controlling tuberculosis in the United States. American Thoracic Society; Centers for Disease Control and Prevention; Infectious Diseases Society of America. Am J Respir Crit Care Med., 172: 1169 – 1227.

American Thoracic Society; CDC; Infectious Diseases Society of America (2003). Treatment of tuberculosis. MMWR Recomm Rep., 52: 1 – 77.

Arbex MA, Varella Mde C, Siqueira HR, Mello FA (2010). Antituberculosis drugs: drug interactions, adverse effects, and use in special situations. Part 1: first – line drugs. J Bras Pneumol., 36: 626 – 640.

Arbex MA, Varella Mde C, Siqueira HR, Mello FA (2010). Antituberculosis drugs: drug interactions, adverse effects, and use in special situations. Part 2: second line drugs. J Bras Pneumol., 36: 641 – 656.

Bharathi KN, Natesh TS, Ashwitha Reddy A (2012). Prenatal exposure to anti – tubercular drugs and postnatal effect on growth, development and cognitive ability in rats. Prog Neuropsychopharmacol Biol Psychiatry., 37: 203 – 209.

Blumberg HM, Burman WJ, Chaisson RE, Daley CL, Etkind SC, Friedman LN, Fujiwara P, Grzemska M, Hopewell PC, Iseman MD, Jasmer RM, Koppaka V, Menzies RI, O'Brien RJ, Reves RR, Reichman LB, Simone PM, Starke JR, Vernon AA; American Thoracic Society, Centers for Disease Control and Prevention and the Infectious Diseases Society. American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America (2003). Treatment of tuberculosis. Am J Respir Crit Care Med., 167: 603 – 662.

Bothamley G (2001). Drug treatment for tuberculosis during pregnancy: safety considerations. Drug Saf., 24: 553 – 565.

Donald PR, Doherty E, Van Zyl FJ (1991). Hearing loss in the child following streptomycin administration during pregnancy. Cent Afr J Med., 37: 268 – 271.

Drobac PC, del Castillo H, Sweetland A, Anca G, Joseph JK, Furin J, Shin S (2005). Treatment of multidrug – resistant tuberculosis during pregnancy: long – term follow – up of 6 children with intrauterine exposure to second-line agents. Clin Infect Dis., 40: 1689 – 1692.

Efferen LS (2007). Tuberculosis and pregnancy. Curr Opin Pulm Med., 13: 205 – 211.

Grange J, Adhikari M, Ahmed Y, Mwaba P, Dheda K, Hoelscher M, Zumla A (2010). Tuberculosis in association with HIV/AIDS emerges as a major nonobstetric cause of maternal mortality in Sub-Saharan Africa. Int J Gynaecol Obstet., 108: 181 – 183.

Khilnani GC (2004). Tuberculosis and pregnancy. Indian J Chest Dis Allied Sci., 46: 105 – 111.

Knight M, Kurinczuk JJ, Nelson – Piercy C, Spark P, Brocklehurst P; UKOSS (2009). Tuberculosis in pregnancy in the UK. BJOG., 116: 584 – 588.

Kothari A, Mahadevan N, Girling J (2006). Tuberculosis and pregnancy--Results of a study in a high prevalence area in London. Eur J Obstet Gynecol Reprod Biol., 126: 48 – 55.

Lewit T, Nebel L, Terracina S, Karman S (1974). Ethambutol in pregnancy: observations on embryogenesis. Chest., 66: 25 – 26.

Loto OM, Awowole I (2012). Tuberculosis in pregnancy: a review. J Pregnancy., 2012: 379271.

Maddineni M, Panda M (2008). Pulmonary tuberculosis in a young pregnant female: challenges in diagnosis and management. Infect Dis Obstet Gynecol., 2008: 628985.

Mathad JS, Gupta A (2012). Tuberculosis in pregnant and postpartum women: epidemiology, management, and research gaps. Clin Infect Dis., 55: 1532 – 1549.

Morlock GP, Metchock B, Sikes D, Crawford JT, Cooksey RC (2003). EthA, inhA, and katG loci of ethionamide – resistant clinical Mycobacterium tuberculosis isolates. Antimicrob Agents Chemother., 47: 3799 – 3805.

Nguyen HT, Pandolfini C, Chiodini P, Bonati M (2014). Tuberculosis care for pregnant women: a systematic review. BMC Infect Dis., 14: 617.

Ormerod P (2001). Tuberculosis in pregnancy and the puerperium. Thorax., 56: 494 – 499.

Palacios E, Dallman R, Muñoz M, Hurtado R, Chalco K, Guerra D, Mestanza L, Llaro K, Bonilla C, Drobac P, Bayona J, Lygizos M, Anger H, Shin S (2009). Drug – resistant tuberculosis and pregnancy: treatment outcomes of 38 cases in Lima, Peru. Clin Infect Dis., 48: 1413 – 1419.

Shin S, Guerra D, Rich M, Seung KJ, Mukherjee J, Joseph K, Hurtado R, Alcantara F, Bayona J, Bonilla C, Farmer P, Furin J (2003). Treatment of multidrug – resistant tuberculosis during pregnancy: a report of 7 cases. Clin Infect Dis., 36: 996 – 1003.

Snider DE Jr, Layde PM, Johnson MW, Lyle MA (1980). Treatment of tuberculosis during pregnancy. Am Rev Respir Dis., 122: 65 – 79.

Sugarman J, Colvin C, Moran AC, Oxlade O (2014). Tuberculosis in pregnancy: an estimate of the global burden of disease. Lancet Glob Health., 2: e710 – 716.

Tabarsi P, Moradi A, Baghaei P, Marjani M, Shamaei M, Mansouri N, Chitsaz E, Farnia P, Mansouri D, Masjedi M, Velayati A (2011). Standardised second – line treatment of multidrug – resistant tuberculosis during pregnancy. Int J Tuberc Lung Dis., 15: 547 – 550.

Taylor AW, Mosimaneotsile B, Mathebula U, Mathoma A, Moathlodi R, Theebetsile I, Samandari T (2013). Pregnancy outcomes in HIV – infected women receiving long – term isoniazid prophylaxis for tuberculosis and antiretroviral therapy. Infect Dis Obstet Gynecol., 2013: 195637.

Tedla Z, Nyirenda S, Peeler C, Agizew T, Sibanda T, Motsamai O, Vernon A, Wells CD, Samandari T (2010). Isoniazid – associated hepatitis and antiretroviral drugs during tuberculosis prophylaxis in HIV – infected adults in Botswana. Am J Respir Crit Care Med., 182: 278 – 285.

Tiam A, Machekano R, Gounder CR, Maama – Maime LB, Ntene – Sealiete K, Sahu M, Isavwa A, Oyebanji O, Ahimbisibwe A, Mokone M, Barnes GL, Chaisson RE, Guay L, Kassaye S (2014). Preventing tuberculosis among HIV – infected pregnant women in Lesotho: the case for rolling out active case finding and isoniazid preventive therapy. J Acquir Immune Defic Syndr., 67: e5 – e11.

Tripathy SN, Tripathy SN (2003). Tuberculosis and pregnancy. Int J Gynaecol Obstet., 80: 247 – 253.

World Health Organization (2008). Guidelines for the Programmatic Management of Drug – Resistant Tuberculosis: Emergency Update 2008. Geneva: World Health Organization, Stop TB Department.

World Health Organization (2009). Global Tuberculosis Control, Epidemiology, Strategy, Financing. Geneva: World Health Organization.

World Health Organization (2010). The Treatment of Tuberculosis Guidelines. Geneva: World Health Organization.

World Health Organization (2014). Global tuberculosis report 2014 (in IRIS). World Health Organization, Geneva.