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Review

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Tuberculosis and Pregnancy: An Updated Systematic Review

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ABSTRACT

Tuberculosis (TB) affects women, especially in the child-bearing years. TB is associated with a poorer outcome of pregnancy, although this may be due to the general risk factors for TB, namely poverty, malnutrition and overcrowding. New studies have shown that symptom screening has a low sensitivity and specificity, but is improved by the addition of a tuberculin skin test (TST) or interferon-gamma release assay (IGRA) or, in high incidence areas, DNA amplification tests (e.g. Xpert MTB/RIF). TB-HIV co-infection is a common cause of mortality and morbidity in pregnancy. The diagnostic process remains the same in pregnancy, but non-specific symptoms and extra pulmonary disease demand a higher level of suspicion of TB. Standard first-line treatment is safe in pregnancy. Data on second-line drugs in pregnancy is still limited, but injectable drugs may affect the hearing and balance of the fetus. The IGRA responses appear to change during pregnancy, with more positive responses after delivery. The increasing incidence of drug-resistant TB, especially in Eastern Europe and Central Asia, requires an evaluation of the safety of second-line drugs in pregnancy.

KEYWORDS: Tuberclosis; Pregnancy; Mycobacterium tuberculosis; Maternal mortality.

ABBREVIATIONS: TB: Tuberculosis; TST: Tuberculin Skin Test; MeSH: Medical Subject Heading; IGRA: Interferon-Gamma Release Assays; PLHIV: People Living with HIV; QFT: QuantiFERON Gold-in-Tube; BCG: Bacille Calmette-Guérin; CXR: Chest X-Ray; LTBI: Latent Tuberculosis Infection.

INTRODUCTION

Tuberculosis (TB) remains an important disease, despite effective treatment for the last 50 years. The number of cases remains high at 8.6 million new cases and 1.3 million TB deaths (WHO, 2012).[1] Although TB affects men more commonly than women, there were still 2.9 million cases and 410,000 deaths among women, predominantly in the 15-44 year age group, which coincides with the age of childbearing.[1] In 2011, there were an estimated 216,500 (95% uncertainty range 192,100 to 247,000) active tuberculosis cases in pregnant women.[2] Pregnancy itself appears to be a risk factor for developing TB.[3] The increased susceptibility to TB may be due to immunological changes in pregnancy. Pregnancy partially suppresses the T-helper 1 (Th1) cell mediated immunity, in favour of the antibody response (Th2 mediated), perhaps to protect the fetus from immunological rejection.[3] Cell-mediated immunity has the dominant role in protection against *Mycobacterium tuberculosis* and active TB is associated with a dominant Th2 immune response.[3]

This review updates our knowledge about TB in pregnancy, with particular reference to studies since January 2012.

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METHODS

The biomedical databases MEDLINE, through the search engine PubMed, and EMBASE (Elsevier) were searched. The time limit was May 2014 - Jan 2012. The Medical Subject Heading (MeSH) terms "tuberculosis", "pregnancy", "maternal mortality" and "women's health" were combined as a major topic in PubMed MEDLINE. A common search strategy was used for all databases, employing a combination of the following terms: "pregnancy", "maternal", "tuberculosis", "congenital", "latent tuberculosis infection", "multidrug resistant tuberculosis". The research was limited to English-language articles and human studies. Case reports and conference abstracts were excluded. Titles and abstracts were reviewed and irrelevant topics were excluded. To complete the search a manual search was made of bibliographic references cited in the original papers included. These articles were then contextualised within current knowledge of TB in pregnancy.

RESULTS

Maternal tuberculosis and pregnancy outcomes

TB disease in pregnancy is associated with adverse pregnancy outcomes.[4] Toxaemia (pre-eclampsia), vaginal bleeding, fetal death at 16-28 weeks, acute fetal distress, prematurity (<37 weeks), small for date, low birth weight (< 2.5 kg), and perinatal death have all been described, but are also associated with poverty, malnutrition and overcrowding - factors themselves associated with TB.[3,4] Adverse perinatal outcomes have been associated with incomplete treatment, delayed diagnosis and advanced pulmonary involvement.[4] A new case-control study conducted in UK showed a lower birth weight in infants born to mothers with TB, especially if pulmonary disease, despite receiving standard treatment.[5] Maternal TB is a risk factor for child TB. Congenital TB is rare,[6] but the risk of transmission to the infant in the postpartum period is higher due to inhalation of aerial droplets coughed out by the mother. One study in South Africa detected TB in 16% of neonates born to mothers with suspected or proven TB.[7] In Kenya, infants with early TB infection (T-SPOT.*TB* positivity in 6 month old children born from HIV positive mothers) had a 15.5-fold increased odds of having a mother with active TB (P = 0.04).[8]

TB and ectopic pregnancy

An association between acute ectopic gestation and genital tuberculosis has been suggested. In a group of 17 adolescents with acute presentation of ectopic pregnancy, 6 out of 17 (35, 29%) had genital tuberculosis compared with 5% in the control groups (1 out of 20, p=0.03).[9]

Symptom screening active TB in pregnant women

A four symptom screening (cough, fever, night sweat and weight loss) has been proposed by the WHO as a first step in finding TB in people living with HIV (PLHIV).[10] A meta-analysis estimated a sensitivity of 79% and specificity of 50% for these symptoms.[11] However, when tested in 799 pregnant women from India, the sensitivity was 54.5%, and only reached 100% if combined with a tuberculin skin test (TST).[12] A much larger study in South Africa (1415 pregnant women) demonstrated that the WHO four-symptom screen failed to identify most cases of TB in HIV-positive pregnant women[13] as most (73%) were asymptomatic. The sensitivity of having any one of the four symptoms for TB disease was 28%, giving a specificity of 84%, positive predictive value 4.4% and a negative predictive value of 98%. Cough, irrespective of duration, was the most sensitive of the symptoms (23%). In Kenya, screening for the four symptoms in HIV-positive pregnant women was not helpful: 3/26 (12%) symptomatic patients had an abnormal chest X-ray (CXR) consistent with TB, while 7/100 asymptomatic pregnant women who had a CXR were then treated for TB.[14] The same group screened 2980 HIV-positive and HIV-negative pregnant women, 17 of whom were treated for TB on the basis of clinical judgment and/or CXR positivity but just 4 had a one of the following features: a cough of >2 weeks, bloody cough in the past year, fever of >3 weeks, past history of TB diagnosis, history of TB contact in the household, weight loss/failure to gain weight if pregnant in the past year.[15]

The poor performance of symptom screening suggests that additional tests are needed to intensify the effective case finding in HIV pregnant women.

The performance of Tuberculin Skin Test (TST) and Interferon-Gamma Release Assays (IGRAs) in pregnancy

Pregnancy does not appear to alter the performance of the TST.[16] Tests based on the interferon-γ response to proteins that are not found in *Mycobacterium tuberculosis*-Bacille Calmette-Guérin (BCG), were designed to improve the specificity of the diagnosis of TB infection.[17] A comparison of TST and QuantiFERON Gold-in-Tube (QFT) in 199 pregnant women at a US public hospital showed a greater specificity for the IGRA, in that BCG vaccination at birth was an independent predictor of a positive TST but not a positive IGRA.[18] Pregnancy itself appeared not to affect the likelihood of a positive QFT, comparing 140 pregnant and 140 non-pregnant adolescents and young women, and exposure to TB correlated better with the IGRA than with TST.[19] However, there were twice as many indeterminate results due to a low mitogen response in the pregnant compared with the non-pregnant cohort. By contrast, in India, HIV-negative pregnant women, presenting to the antenatal clinic in their late second or third trimester, showed more positive QFT tests than positive TSTs (37% and 14% respectively), even though 5 TU and a cut-off of 10 mm for TST positivity was used as in the US studies.[20]

A cross-sectional study suggested that a positive QFT

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was more likely in the postpartum period, but attempts to perform a cohort study on 60 women were thwarted by the failure of follow-up, such that the initial finding could not be confirmed.[20]

HIV-TB co-infection in pregnancy

The estimated percentage of TB cases living with HIV remains at 13% globally and the African Region accounts for 75% of the estimated number of HIV-positive incident TB cases.[1] Pregnant women with HIV infection have a higher risk of developing active TB than HIV-negative pregnant women.[21,22] TB increases maternal mortality in HIV co-infection.[3,4] An analysis of pregnancy-related mortality in western Kenya found that nearly two-thirds of deaths were due to indirect, non-obstetric causes and HIV/AIDS and TB accounted for 45% and 10% respectively of these deaths.[23] In a rural sub-district in South Africa from 1992 to 2010, the obstetric mortality ratio averaged 185 per 100,000 live births and deaths during pregnancy were 423 per 100,000 live births, the difference being primarily due to HIV/AIDS and pulmonary TB.[24] Furthermore, mothers with HIV co-infection have a higher rate of infecting their children (30%) compared to those with TB alone (12%).[25]

IGRA in HIV-positive pregnant women

One group in Kenya has examined the value of the IGRA T-SPOT. *TB* using cryopreserved peripheral blood mononuclear in a cohort of 327 HIV-positive pregnant women in Kenya.[26,27,28] In the first report, 36% of the HIV-infected women were IGRA-positive during pregnancy, which likely reflects the local rate of LTBI. In multivariate analysis, adjusting for baseline CD4 count, IGRA positivity was associated with a 4.5 (1.1-18.0)-fold increased risk of active TB (p=0.03). Maternal and infant mortality was higher in mothers with a positive IGRA but the difference was not statistically different unless the maternal CD4 count was < 250 cells/mm^3.[26] Eighteen had a positive test and the number of spot counts was highest at 32 weeks, then fell around delivery, followed by a later increase.[27] Nine (3%) women developed TB within 1 year of childbirth, 6/110 (6%) with a positive test and 3/148 (2%) with a negative test at 32 weeks of pregnancy (no significant difference; indeterminate results were found in 52, of whom 8 had <20 spot counts in the positive control). The prognostic sensitivity and specificity improved if the CD4 count was <250 mm^3, although a positive T-SPOT.*TB* test was more common in those with a higher CD4 count.[28]

A cost-effectiveness analysis of IGRA in HIV-positive pregnant women in low TB incidence countries found that testing with TB-SPOT.TB alone was the most cost-effective strategy where the incidence of TB was ≥1.25%, but if the incidence of TB was less than 1,250 per 100,000, screening with TST and then testing with the T-SPOT.*TB* test was better.[29]

Screening for Latent Tuberculosis Infection (LTBI)

The WHO has recommended isoniazid preventive treatment therapy for all HIV infected individuals, including pregnant women.[10] The US Centre for Disease Control and Prevention (CDC) recommend screening for LTBI only in high risk women, i.e. those with known or suspected tuberculosis contact, injection drug use, HIV or other immune suppression, foreign birth and residence in communal settings.[30] Antenatal care is an ideal opportunity to identify pregnant women with LTBI, as it is often the first time healthcare has been accessed, especially in these high risk groups that might find accessing healthcare difficult.[3,31] In high-burden countries, the social conditions of the woman often limit access to healthcare and antenatal care should be integrated with TB screening and treatment.[32]

Isoniazid preventive treatment

Isoniazid is safe in pregnancy and is not teratogenic.[33] Unlike rifampicin, there are no interactions between isoniazid and antiretroviral treatment.[34] A WHO guideline has recommended 6 months preventive treatment on the basis of studies available to them.[10] Clinical trials have suggested an increased benefit by increasing isoniazid preventive treatment to 36 months duration in PLHIV, although none reached statistical significance.[35,36,37] The safety of long-term isoniazid prophylaxis was examined in HIV-infected women who were pregnant during the course of therapy and no adverse pregnancy outcomes were observed compared to the control group.[38]

TB diagnosis in pregnancy

There is no difference in the diagnostic approach between pregnant and non-pregnant women. Sputum examination and a CXR are the most important investigations. Concern about radiation safety in pregnancy has limited the use of chest radiography, but shielding the abdomen and the lower doses of radiation that are now required to obtain a CXR mean that the exposure to the fetus is considered negligible.[39] However, the symptoms of TB are non-specific and are commonly present during normal pregnancy e.g. general malaise, fatigue, appetite loss; extrapulmonary disease, which is more difficult to detect, is also more common in pregnancy.[3,4]

Xpert® MTB/RIF, a PCR test on sputum that detects the presence of *M. tuberculosis* DNA and genetic mutations that indicate resistance to rifampicin, has been proposed as an instrument for active pulmonary case finding[40] and in antenatal clinics in a high TB burden setting.[41] In Zambia, sputum samples from 94 patients admitted with a primary obstetric or gynaecological problem (67% pregnant or < 6 weeks post natal patients and 74% HIV infected patients) were analysed by sputum smear microscopy, culture and Xpert® MTB/RIF assay. Among the participants, 26 had culture-confirmed TB (77% in pregnant or postpartum women). In these circumstances, Xpert® had a sensitivity of 81% and a specificity of 97% compared to sputum culture and was more sensitive than sputum smear microscopy alone (50%).[42]

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TB treatment in pregnancy

The standard first line treatment for pulmonary and extrapulmonary TB does not differ between pregnant and non-pregnant women. The WHO recommend 2 months of isoniazid, rifampicin, pyrazinamide, and ethambutol, followed by 4 months of isoniazid and rifampicin.[43] This regimen is safe to use during pregnancy.[33] Anti-TB therapy should not be a reason to discontinue breastfeeding.[33] Pyridoxine supplementation is recommended for all pregnant or breastfeeding women taking isoniazid. Streptomycin is contraindicated during pregnancy because of damage to the eighth cranial nerve with ototoxicity.[33]

Second line treatment in pregnancy

Multidrug-resistant TB (MDRTB) is defined as TB caused by organisms resistant to isoniazid and rifampicin; extensively drug-resistant TB (XDRTB) is defined as MDRTB resistant as well to any one of the fluoroquinolones and to at least one of three injectable second-line drugs.[44] Globally, in 2012, an estimated 450,000 people developed MDRTB resulting in 170,000 deaths. The highest levels of MDRTB are found in Eastern Europe and Central Asia. In the treatment of MDRTB, WHO advises giving at least four drugs that are known or likely to be effective against the drug-resistant *M. tuberculosis* strain isolated, plus pyrazinamide. If possible, WHO group 2 (amikacin, capreomycin or kanamycin) and WHO group 3 (fluoroquinolones) should be core drugs with the rest (etionamide/protionamide and cycloserine) being accompanying drugs.[44] New drugs, bedaquiline, an oral diarylquinoline which inhibits the proton pump ATP synthase, and delamanid, which is a nitro-dihydro-imidazooxazole derivative with mycobacteria-specific antibacterial activity *in vitro* that inhibit mycolic acid biosynthesis, have been approved for use in the USA since December 2012 and EU since April 2014 respectively, but their use in pregnancy needs evaluation.[45,46]

Although second-line drugs are used during pregnancy, little is known about the safety of these drugs for the fetus and about the outcome in MDRTB cases during pregnancy. The largest study to our knowledge is of 38 pregnant women treated for MDRTB in Peru and outcomes were similar to those of the general local population.[47] The majority of the second-line drugs are in FDA class C (animal studies suggest a problem, but human studies are inadequate), except for aminoglycosides, which are in class D (definite evidence of fetal risk). A TBNET consensus statement on the management of patients with M/XDRTB in Europe states that "safe treatment of M/XDRTB during pregnancy seems possible but needs individual decision-making" and "Pregnancies should not be terminated because of M/XDR-TB";"Aminoglycosides/polypeptides are not recommended for M/XDRTB treatment during pregnancy"; "Patients should be advised to maintain double barrier contraception during treatment of M/XDRTB".[48]

CONCLUSION

There is a need for cohort studies of IGRA in pregnancy in women without HIV to assess the consistency of these tests and any changes that might occur as pregnancy proceeds. The increasing incidence of drug-resistant TB, especially in Eastern Europe and Central Asia, requires an evaluation of the safety of second-line drugs in pregnancy.

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CONFLICTS OF INTEREST: None.

REFERENCES

1. World Health Organization. Global tuberculosis report 2013, 2013. WHO/HTM/TB/2013.11. http://apps.who.int/iris/bitstream/10665/91355/1/9789241564656_eng.pdf?ua=1 Accessed September 12, 2014.

2. Sugarman J, Colvin C, Moran AC, Oxlade O. Tuberculosis in pregnancy: an estimate of the global burden of disease. *Lancet Glob Health*. 2014; 2: e710-e716. doi: http://dx.doi.org/10.1016/S2214-109X(14)70330-4

3. Bothamley GH. Screening for tuberculosis in pregnancy. *Expert. Rev. Obstet. Gynecol.* 2012; 7(4): 387-395.

4. Bothamley GH. Management of TB during pregnancy, especially in high-risk communities. *Expert. Rev. Obstet. Gynecol.* 2009; 4(5): 555-563. doi: 10.1586/eog.09.39

5. Asuquo B, Vellore AD, Walters G, Manney S, Mignini L, Kunst H. A case-control study of the risk of adverse perinatal outcomes due to tuberculosis during pregnancy. *J. Obstet. Gynaecol*. 2012; 32 (7): 635 -638. doi: 10.3109/01443615.2012.704436

6. Peng W, Yang J, Liu E. Analysis of 170 cases of congenital TB reported in the literature between 1946 and 2009. *Pediatr. Pulmonol*. 2011; 46: 1215-1224. doi: 10.1002/ppul.21490

7. Bekker A, Du Preez K, Schaaf HS, Cotton MF, Hesseling AC. High tuberculosis exposure among neonates in a high tuberculosis and human immunodeficiency virus burden setting. *Int. J. Tuberc. Lung Dis*. 2012; 16: 1040-1046. doi: 10.5588/ijtld.11.0821

8. Cranmer LM, Kanyugo M, Jonnalagadda SR, et al. High prevalence of tuberculosis infection in HIV-1 exposed Kenyan infants. *Pediatr. Infect. Dis. J.* 2014; 33: 401-406. doi: 10.1097/INF.0000000000000124

ISSN 2377-1658 Open Journal http://dx.doi.org/10.17140/PRRMOJ-2-109

9. Banerjee A, Prateek S, Malik S, Dhingra D. Genital tuberculosis in adolescent girls from low socioeconomic status with acute ectopic pregnancy presenting at a tertiary care hospital in urban Northern India: are we missing an opportunity to treat? *Arch. Gynecol. Obstet*. 2012; 286: 1477-1482. doi: 10.1007/s00404-012-2487-z

10. World Health Organization. Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings, 2011. http://whqlibdoc.who.int/publications/2011/9789241500708_eng.pdf?ua=1. Accessed September 12, 2014.

11. Getahun H, Kittikraisak W, Heilig CM, et al. Development of a standardized screening rule for tuberculosis in people living with HIV in resource-constrained settings: individual participant data meta-analysis of observational studies. *PLoS Med*. 2011; 8: e1000391. doi: 10.1371/journal.pmed.1000391

12. Gupta A, Chandrasekhar A, Gupte N, et al. Symptom screening among HIV-infected pregnant women is acceptable and has high negative predictive value for active tuberculosis. *Clin. Infect. Dis*. 2011; 53: 1015-1018. doi: 10.1093/cid/cir605

13. Hoffmann CJ, Variava E, Rakgokong M, et al. High prevalence of pulmonary tuberculosis but low sensitivity of symptom screening among HIV-infected pregnant women in South Africa. *PLoS One.* 2013; 8: e62211. doi: 10.1371/journal.pone.0062211

14. Kosgei RJ, Ndavi PM, Ong JO, et al. Symptom screen: diagnostic usefulness in detecting pulmonary tuberculosis in HIV-infected pregnant women in Kenya. *Public Health Action*. 2011; 1(2): 30-33.

15. Kosgei RJ, Szkwarko D, Callens S, et al. Screening for tuberculosis in pregnancy: do we need more than a symptom screen? Experience from western Kenya. *Public Health Action*. 2013; 3: 294-298. doi: 10.5588/pha.13.0073

16. Present PA, Comstock GW. Tuberculin sensitivity in pregnancy. *Am Rev Respir Dis*. 1975; 112: 413-416.

17. Bleknapp R, Daley CL. Interferon-gamma release assays. *Clin. Lab. Med.* 2014; 34(2): 337-349. doi: 10.1016/j.cll.2014.02.007

18. Worjoloh A, Kato-Maeda M, Osmond D, Freyre R, Aziz N, Cohan D. Interferon-gamma release assay compared with tuberculin skin test for latent tuberculosis detection in pregnancy. *Obs. Gynecol*. 2011; 118: 1363-1370. doi: 10.1097/AOG.0b013e31823834a9

19. Lighter-Fisher J, Surette AM. Performance of an interferon-gamma release assay to diagnose latent tuberculosis infection during pregnancy. *Obstet. Gynecol*. 2012; 119: 1088-1095. doi: 10.1097/AOG.0b013e3182546aff

20. Mathad JS, Bhosale R, Sangar V, et al. Pregnancy differentially impacts performance of latent tuberculosis diagnostics in a high-burden setting. *PLoS One*. 2014; 9: 1-8. doi: 10.1371/journal.pone.0092308

21. Pillay T, Khan M, Moodley J, Adhikari M, Coovadia H. Perinatal tuberculosis and HIV-1: considerations for resource-limited settings. *Lancet Infect. Dis*. 2004; 4: 155-165. doi: http://dx.doi.org/10.1016/S1473-3099(04)00939-9

22. Gounder CR, Wada NI, Kensler C, et al. Active tuberculosis case-finding among pregnant women presenting to antenatal clinics in Soweto, South Africa. *J Acquir Immune. Defic. Syndr.* 2011; 57: e77-e84. doi: 10.1097/QAI.0b013e31821ac9c1

23. Desai M, Phillips-Howard PA, Odhiambo FO, et al. An analysis of pregnancy-related mortality in the KEMRI/CDC health and demographic surveillance system in western Kenya. *PLoS One*. 2013; 8: e68733. doi: 10.1371/journal.pone.0068733

24. Garenne M, Kahn K, Collinson MA, Gómez-Olivé FX, Tollman S. Maternal mortality in rural South Africa: the impact of case definition on levels and trends. *Int. J. Womens Health.* 2013; 5: 457-463. doi: 10.2147/IJWH.S45983

25. Gupta A, Bhosale R, Kinikar A, et al. Maternal tuberculosis: a risk factor for mother-to-child transmission of human immunodeficiency virus. *J. Infect. Dis.* 2011; 203: 358-363. doi: 10.1093/infdis/jiq064

26. Jonnalagadda S, Lohman Payne B, Brown E, et al. Latent tuberculosis detection by interferon γ release assay during pregnancy predicts active tuberculosis and mortality in human immunodeficiency virus type 1-infected women and their children. *J. Infect. Dis.* 2010; 202: 1826-1835. doi: 10.1086/657411

27. Jonnalagadda SR, Brown E, Lohman-Payne B, et al. Consistency of *Mycobacterium tuberculosis*-specific interferon-gamma responses in HIV-1-infected women during pregnancy and postpartum. *Infect. Dis. Obstet. Gynecol*. 2012; 2012: 950650. doi: http://dx.doi.org/10.1155/2012/950650

28. Jonnalagadda SR, Brown E, Lohman-Payne B, Wamalwa D, Farquhar C, John-Stewart GC. Predictive value of interferon-gamma release assays for postpartum active tuberculosis in HIV-1-infected women. *Int. J. Tuberc. Lung Dis*. 2013; 17: 1552-1557. doi: 10.5588/ijtld.13.0239

29. Kowada A. Cost effectiveness of interferon-γ release assay for TB screening of HIV positive pregnant women in low TB incidence countries. *J. Infect*. 2013; 68: 32-42. doi: 10.1016/j.jinf.2013.08.009

ISSN 2377-1658 Open Journal http://dx.doi.org/10.17140/PRRMOJ-2-109

30. Centers for Disease Control and Prevention Updated Guidelines for Using Interferon Gamma Release Assays to Detect *Mycobacterium tuberculosis* Infection. MMWR Recomm Rep, 2010. http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5905a1.htm. Accessed October 3, 2014.

31. Nguyen HT, Pandolfini C, Chiodini P, Bonati M. Tuberculosis care for pregnant women: a systematic review. *BMC Infectious Diseases*. 2014; 14: 617. doi: 10.1186/s12879-014-0617-x

32. Jana N, Barik S, Arora N, Singh AK. Tuberculosis in pregnancy: the challenges for South Asian countries. *J. Obstet. Gynaecol. Res*. 2012; 38: 1125-1136. doi: 10.1111/j.1447-0756-.2012.01856.x

33. Bothamley G. Drug treatment for tuberculosis: safety considerations. *Drug Saf*. 2001; 24: 553-565.

34. Cohen K, Meintjes G. Management of individuals requiring ART and TB treatment. *Curr Opin HIV AIDS*. 2010; 5: 61-69. doi: 10.1097/COH.0b013e3283339309

35. Samandari T, Agizew TB, Nyirenda S, et al. 6-month versus 36-month isoniazid preventive treatment for tuberculosis in adults with HIV infection in Botswana: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2011; 377: 1588-1598. doi: 10.1016/S0140-6736(11)60204-3

36. Swaminathan S, Menon PA, Gopalan N, Perumal V. Efficacy of a six-month versus a 36-month regimen for prevention of tuberculosis in HIV-infected persons in India: A randomized clinical trial. *PLoS One*. 2012; 7: e47400. doi: 10.1371/journal.pone.0047400

37. Martinson NA, Barnes GL, Moulton LH, et al. New regimens to prevent tuberculosis in adults with HIV infection. *N Engl J. Med*. 2011; 365: 11-20. doi: 10.1056/NEJMoa1005136

38. Taylor AW, Mosimaneotsile B, Mathebula U, et al. Pregnancy outcomes in HIV-infected women receiving long-term isoniazid prophylaxis for tuberculosis and antiretroviral therapy. *Infect. Dis. Obstet. Gynecol*. 2013; 195637. doi: http://dx.doi.org/10.1155/2013/195637

39. Hart D, Wall BF. Radiation exposure of the UK population from medical and dental X-ray examinations. Natl. Radiol. Prot. Board, Didcot, UK. 2002.

40. Lawn SD, Mwaba P, Bates M, et al. Advances in tuberculosis diagnostics: the Xpert MTB/RIF assay and future prospects for a point-of-care test. *Lancet Infect. Dis*. 2013; 13: 349-361. doi: 10.1016/S1473-3099(13)70008-2

41. Turnbull ER, Kancheya NG, Harris JB, Topp SM, Henostroza G, Reid SE. A model of tuberculosis screening for pregnant women in resource-limited settings using Xpert MTB/RIF. *J. Pregnancy.* 2012; 565049. doi: http://dx.doi.org/10.1155/2012/565049

42. Bates M, Ahmed Y, Chilukutu L, et al. Use of the Xpert® MTB/RIF assay for diagnosing pulmonary tuberculosis comorbidity and multidrug-resistant TB in obstetrics and gynaecology inpatient wards at the University Teaching Hospital, Lusaka, Zambia. *Trop. Med. Int. Health*. 2013; 18: 1134-1140. doi: 10.1111/tmi.12145

43. World Health Organization. Treatment of tuberculosis guidelines. 4th edition, 2010. http://whqlibdoc.who.int/publications/2010/9789241547833_eng.pdf?ua=1. Accessed September 12, 2014.

44. World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis 2011 Update. WHO/HTM/TB/2011.6, 2011. http://whqlibdoc.who.int/publications/2011/9789241501583_eng.pdf?ua=1. Accessed June 12, 2014.

45. Centers for Disease Control and Prevention.Provisional CDC guidelines for the use and safety monitoring of bedaquiline fumarate (Sirturo) for the treatment of multidrug-resistant tuberculosis. *MMWR Recomm Rep*. 2013 62(RR-09): 1-12. http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6209a1.htm. 2013. Accessed September 3, 2014.

46. Ryan NJ, Lo JH. Delamanid: first global approval. *Drugs.* 2014; 74: 1041-1045. doi: 10.1007/s40265-014-0241-5

47. Palacios E, Dallman R, Muñoz M, et al. Drug-resistant tuberculosis and pregnancy: treatment outcomes of 38 cases in Lima, Peru. *Clin. Infect. Dis*. 2009; 48: 1413-1419. doi: 10.1086/598191

48. Lange C, Abubakar I, Alffenaar J-WC, et al. Management of patients with multidrug-resistant/extensively drug-resistant tuberculosis in Europe: a TBNET consensus statement. *Eur. Respir. J.* 2014; 1-41.