Tuberculosis, human immunodeficiency viruses and TB/HIV co-infection in pregnant women: A meta-analysis

Atieh Yaghoubia,b, Sepideh Salehabadici, Hossein Abdeahadd, Seyed Mahdi Hasaniani, Amir Avane, Masoud Yousefia,b, Saeid Amel Jamehdara,b, Gordon A. Fernsf, Majid Khazaiee, Saman Soleimanpouro,b,*

a Antimicrobial Resistance Research Center, Buali Research Institute, Mashhad University of Medical Sciences, Mashhad, Iran
b Department of Microbiology and Virology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
c Department of Pathology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
d Department of Medical Biochemistry, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
e Metabolic Syndrome Research Center, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
f Brighton & Sussex Medical School, Division of Medical Education, Falmer, Brighton, Sussex, BN1 9PH, UK

ARTICLE INFO

Keywords:
HIV
Tuberculosis
Pregnancy
HIV/TB co-Infection
Mycobacterium tuberculosis

ABSTRACT

Background: Acquired Immunodeficiency Syndrome (AIDS) and tuberculosis (TB) represent major public health problems. The aim of this systematic review and meta-analysis is the assessment of the prevalence of tuberculosis, human immunodeficiency viruses (HIV), and co-infection of both, in pregnant women.

Methods: We searched the literature in PubMed, Scopus, EMBASE, Web of Knowledge and MeSH, from all years of study until 25 April 2018, for articles and abstracts describing tuberculosis, HIV, and co-infection of HIV/TB during the pregnancy. Risk ratio (RRs) and 95% confidence interval (CI) for each outcome were combined, using a random-effects model. Eighteen studies met our inclusion criteria.

Results: There was not an association between the incidence risk of tuberculosis during pregnancy in women without any underlying disease. (Risk ratio = 2.43, 95% CI = 0.97–6.08, p = 0.056, I² = 88.636, df (Q) = 4, Q-value = 35.198). Pregnancy does not increase the incidence risk of HIV (Risk ratio = 1.27, 95% CI = 1–1.6, p = 0.00, I² = 81.024, df (Q) = 17, Q-value = 89.589). The prevalence of HIV has been investigated in three age groups of pregnant women [18–24 years (RR = 1.38), 25–34 years (RR = 1.12), and 35–44 years (RR = 1.71)], but there was not any significant association between the incidence of HIV and the age of the pregnancy. The risk ratio of tuberculosis in HIV positive pregnant women was 2.56 (summary: 95% CI = 1.57–4.17, p = 0.055, I² = 56.744, df (Q) = 4, Q-value = 9.247), and pregnancy in HIV positive women increased the incidence risk of tuberculosis.

Conclusions: Pregnancy in HIV positive women was associated with an increased tuberculosis risk. Thus, prevention of tuberculosis incidents in these pregnant women would be critical for reducing vertical transmission from mother to child.

1. Background

Human Immunodeficiency Virus (HIV) and Mycobacterium tuberculosis (Mt) represent the major public health problems and remain significant contributors to maternal mortality. In 2016, about 10.4 million new cases of TB were reported worldwide, of which 6.2 million were in men, 3.2 million in women, and 1 million in children. Individuals with HIV are estimated to account for 10% of the total number. Nearly half a million women died from TB infection in 2015.

HIV epidemics have increased the rate of TB, among women in reproductive age, as HIV infection weakens the immune system. Approximately, 140000 deaths were found among women who were HIV-positive in 2015.2–5 Pregnancy leads to the activation of latent TB, thus, pregnant women are at high risk of TB infection, especially if they are also HIV positive.6 TB and HIV co-infection has detrimental impacts on maternal and child health, and there is a risk of mother-to-child transmission (MTCT) of HIV and TB. Additionally, risk of MCTC of TB that is more...
than twice the risk of MTCT of HIV significantly increases the risk of mortality for the neonate. Congenital TB is caused by the transmission of *Mycobacterium tuberculosis* bacilli from mother to embryo through the placenta, by either haematogenous spread via the umbilical vein, or by aspiration of infected amniotic fluid.

TB is the leading infectious cause of death in women and now ranks alongside HIV as the leading cause of communicable disease-related death globally. In 2016, 1.7 million people died from TB, including 0.4 million among HIV positive individuals. The mortality rate of HIV positive pregnant women is due to either an increased risk of direct obstetric problems or progression of HIV disease during the pregnancy.

TB/HIV co-infection in pregnant women has also been shown to increase the MTCT of HIV. Even when TB is not transmitted to an infant, it has adverse consequences for neonatal health, including increased risk of premature birth, fetal growth restriction, low birth weight and mortality.

This study aimed to review systematically the literature on the prevalence of HIV, TB, and co-infection of both in pregnant women. We performed a systematic review and meta-analysis to determine whether pregnancy increases the incidence rate of TB and HIV among this group. We also examined whether pregnancy in HIV positive women accelerates the risk of TB.

2. Methods

2.1. Search strategy and inclusion criteria

A systematic and comprehensive search was performed by two people individually in the following databases: PubMed, Scopus, EMBASE, Web of Knowledge and MeSH. Another reviewer examined the finding articles to identify suitable articles for this meta-analysis. Then reviewing the reference lists of relevant papers to locate additional studies that were not identified by the database searches. To conduct the data we used the Meta-analysis of Observational Studies in Epidemiology (MOOSE) as a guideline for reviews of observational studies.
<table>
<thead>
<tr>
<th>author/year</th>
<th>Country</th>
<th>Study period (Y)</th>
<th>Study type</th>
<th>Sample Size or Person-Years</th>
<th>Study population</th>
<th>TB diagnoses</th>
<th>HIV diagnoses</th>
<th>Treatment</th>
<th>RR (CI 95%)</th>
<th>RR (CI 95%)</th>
<th>NOS Score</th>
<th>Ref Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrie Bekker 2016</td>
<td>South Africa</td>
<td>2011</td>
<td>Cohort</td>
<td>74</td>
<td>The mean of women age who enter into the study was 29 years</td>
<td>Smear for microscopy for AFB, cultured from sputum, chest radiography</td>
<td>ELISA</td>
<td>TB (INH, RMP, PZA) HIV (TDF, 3 TC, FTC, NVP)</td>
<td>TB1.54 (0.57–4.16)</td>
<td></td>
<td>7</td>
<td>39</td>
</tr>
<tr>
<td>Amira El-Messidi 2016</td>
<td>United States</td>
<td>2003–2011</td>
<td>Cohort</td>
<td>2064</td>
<td>Pregnant women who were 25–34 years of age and of Hispanic ethnicity</td>
<td>Smear for microscopy for AFB, cultured from sputum</td>
<td>ND</td>
<td>TB 8.42 (5.769–12.289)</td>
<td></td>
<td></td>
<td>8</td>
<td>40</td>
</tr>
<tr>
<td>Kancheya 2014</td>
<td>Lusaka, Zambia</td>
<td>Not reported</td>
<td>Cohort</td>
<td>5033</td>
<td>All pregnant women ≥ 18 years of age presenting for TB screening</td>
<td>Smear for microscopy for AFB, cultured from sputum</td>
<td>Uni-Gold HIV Rapid Test HIV-1/HIV-2 Rapid Screen</td>
<td>ND</td>
<td>TB 1.4 (0.6–2.9)</td>
<td>TB/HIV 1.05 (0.402–2.739)</td>
<td>7</td>
<td>41</td>
</tr>
<tr>
<td>Dominik Zenner 2011</td>
<td>United Kingdom</td>
<td>1996–2008</td>
<td>Cohort</td>
<td>15.4 per 100,000 PY</td>
<td>The minimum age included in the study was woman that reaching the age of 13 years</td>
<td>Cultured from sputum, chest radiography</td>
<td>ND</td>
<td>TB 1.95 (1.239–3.68)</td>
<td></td>
<td></td>
<td>7</td>
<td>42</td>
</tr>
<tr>
<td>Sylvia M. LaCourse 2016</td>
<td>western Kenya</td>
<td>2013–2014</td>
<td>Cohort</td>
<td>306</td>
<td>Median maternal age was 25 years</td>
<td>Smear for microscopy for AFB, cultured from sputum, Xpert, LAM, TST</td>
<td>INH</td>
<td>TB 1.66 (0.19–14.37)</td>
<td></td>
<td></td>
<td>8</td>
<td>43</td>
</tr>
<tr>
<td>Appolinaire Tiam 2014</td>
<td>Africa</td>
<td>2011–2012</td>
<td>Cohort</td>
<td>1763</td>
<td>The minimum age for the women included in the study was 14 years</td>
<td>Smear for microscopy for AFB, cultured from sputum, Xpert, chest x-ray.</td>
<td>ND and vitamin B6</td>
<td>TB/HIV 4.8 (2.474–9.314)</td>
<td></td>
<td></td>
<td>7</td>
<td>44</td>
</tr>
<tr>
<td>Muzyka 2000</td>
<td>Malawi</td>
<td>1998</td>
<td>Cohort</td>
<td>633</td>
<td>Women of child-bearing who were 15–49 years of age</td>
<td>ND</td>
<td>ELISA</td>
<td>INH, RMP, PZA</td>
<td>TB/HIV 3.587 (1.054–12.212)</td>
<td></td>
<td>7</td>
<td>45</td>
</tr>
<tr>
<td>Celine R. Gounder 2011</td>
<td>South Africa</td>
<td>2008–2009</td>
<td>Cohort</td>
<td>3963</td>
<td>All pregnant women ≥ 18 years of age presenting for TB screening</td>
<td>Smear for microscopy for AFB, cultured from sputum</td>
<td>Uni-Gold HIV Rapid Test, ELISA</td>
<td>ND</td>
<td>TB/HIV 3.415 (1.17–9.973)</td>
<td></td>
<td>7</td>
<td>34</td>
</tr>
<tr>
<td>Adeola Falana 2017</td>
<td>United States</td>
<td>2002–2014</td>
<td>Cohort</td>
<td>4053</td>
<td>The minimum age for the women included in the study was 13 years</td>
<td>Smear for microscopy for AFB, cultured from sputum</td>
<td>ND</td>
<td>ND</td>
<td>TB/HIV 2.06 (1.674–2.536)</td>
<td></td>
<td>7</td>
<td>46</td>
</tr>
<tr>
<td>First Author</td>
<td>Study period (Y)</td>
<td>Study type</td>
<td>Country</td>
<td>Sample Size</td>
<td>Study population</td>
<td>HIV diagnoses</td>
<td>RR (CI 95%)</td>
<td>Age group</td>
<td>NOS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------</td>
<td>-----------------</td>
<td>------------</td>
<td>---------</td>
<td>-------------</td>
<td>------------------</td>
<td>--------------</td>
<td>-------------</td>
<td>-----------</td>
<td>------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shujuan Yang</td>
<td>2009–2015</td>
<td>Cohort</td>
<td>China</td>
<td>6780</td>
<td>The average age of study population was &lt; 25–34 years.</td>
<td>-</td>
<td>1.72 (1.17–2.52)</td>
<td>35–44</td>
<td>42</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Michael Kiptoo</td>
<td>2005–2006</td>
<td>Cross-sectional</td>
<td>Kenya</td>
<td>4638</td>
<td>The minimum age of women included in the study was 21 years</td>
<td>-</td>
<td>1.93 (1.01–3.67)</td>
<td>18–24</td>
<td>44</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guthrie S. Birkhead</td>
<td>2010–2016</td>
<td>Cohort</td>
<td>New York</td>
<td>3102</td>
<td>The minimum age of women included in the study was 20 years</td>
<td>-</td>
<td>1.93 (1.01–3.67)</td>
<td>18–24</td>
<td>44</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oladeinde</td>
<td>2009–2010</td>
<td>Cohort</td>
<td>Nigeria</td>
<td>480</td>
<td>The age range of study population ranged from 15 to 47 years.</td>
<td>-</td>
<td>1.83 (1.23–2.73)</td>
<td>18–24</td>
<td>44</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Victoria Iyun</td>
<td>2011–2012</td>
<td>Cohort</td>
<td>South Africa</td>
<td>2105</td>
<td>The median age of women who entered into the study was 28 years</td>
<td>-</td>
<td>1.83 (1.23–2.73)</td>
<td>18–24</td>
<td>44</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Joel Manyahi</td>
<td>2011–2015</td>
<td>Cohort</td>
<td>Tanzania</td>
<td>396–98</td>
<td>The minimum age of women included in the study was 20 years</td>
<td>-</td>
<td>1.93 (1.01–3.67)</td>
<td>18–24</td>
<td>44</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tegenaw Asmamaw</td>
<td>2013–2015</td>
<td>Cross-sectional</td>
<td>Ethiopia</td>
<td>212</td>
<td>The minimum age of women included in the study was 20 years</td>
<td>-</td>
<td>1.93 (1.01–3.67)</td>
<td>18–24</td>
<td>44</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: HIV = human immunodeficiency virus; RR = risk ratio; CI = confidence interval; NOS = Newcastle-Ottawa Scale; PI = Pregnancy Index; Ref = reference; Year = Year; EIA = enzyme immunoassay; PCR = DNA.
estimates were used if adjusted estimates were not presented. The $I^2$ value and $p$-value from the test of heterogeneity were calculated, to assess whether there was any evidence of a between-study variation in the individual effect estimates that were not due to random variation. The values of $I^2$ (more than 50%) and $p$-value (less than 0.05) demonstrate heterogeneity among the included studies. Thus, despite some articles that recommended the fix-effects model, in this study, we used random-effects to consider heterogeneity. Since the number of articles included in our study for each group was less than 10, then use of Funnel plots to assess the possible publication bias was not worth it.21
3. Result

3.1. Study selection and characteristics

Among the 8478 studies identified, 7730 were excluded by the assessment of the titles and abstracts. About 748 full-text papers were reviewed, but only eighteen met our citation and included in the final analysis. The study characteristics included in the meta-analysis and data summaries are presented in Tables 1 and 2. Five studies provided information on the prevalence of TB among pregnant women (n = More than five million people), eight of them provided data for HIV in pregnancy, (n = 57375) and five studies examined HIV and TB co-infection in pregnant women (n = 15445).

3.2. TB incidence rates during the pregnancy

Five studies compared the TB incidence rate, during the pregnancy with the incidence rate of non-pregnant women. The results were shown in Fig. 2. The risk of TB acquisition among pregnant women was (summary: RR 2.43, 95% CI = 0.97–6.08, p = 0.056, I2 = 88.636, df (Q) = 4, Q-value = 35.198). The incidence rate of TB among pregnant women was not significant, in comparison to non-pregnant women.

3.3. Pregnancy and HIV

Eight studies reported HIV incidence rates during the pregnancy. The strength of the association between pregnancy and HIV progression is summarised in Fig. 3. The prevalence of HIV has been investigated in three groups of pregnant women. The results were as follows: The odds ratio of HIV prevalence among pregnant women in the age group of 18–24 years (n = 637) (1.38), 25–34 years (n = 17736) and 35–44 years (n = 3892) were 1.38, 1.12 and 1.71, respectively (Table 3). However, no significant association between the incidence of HIV and pregnancy age was observed. Pregnancy was not associated with progression and incidence of HIV (summary: RR 1.27, 95% CI = 1–1.6, p-value = 0.041, I2 = 81.02, df (Q) = 17, Q-value = 89.589). Therefore, there was no evidence that pregnancy was associated with an increased risk of HIV incidence, compared to non-pregnant women.

3.4. Incidence rates of TB and HIV co-infection among pregnant woman

The strength of association between pregnant women, living with HIV and TB incidence was reported in five studies (Fig. 4). There is evidence that pregnancy in HIV positive women was associated with 1.56 times of the risk of TB acquisition (summary: RR 2.56, 95% CI = 1.57–4.17) with low between-study heterogeneity (summary: I2: 56.74%, p-value = 0.00, df (Q) = 4, Q-value = 9.247), so HIV infection in pregnant women is a risk factor in acquiring TB.

3.5. Sensitivity analysis and publication bias

To evaluate publication bias we use Egger's test and check the symmetry of funnel plots for each group. The result of Egger's test for these three groups as follows, the group of TB and pregnancy (p = 0.33), group of HIV and pregnancy (p = 0.02), and last group incidence rate of HIV/TB in pregnant women (p = 0.59). The results of Egger's test for all three groups show the publication bias and the funnel plot of all three groups illustrate an. To do more, a sensitivity analysis was done and it demonstrates that there is no point estimate of the omitted individual dataset lay outside the 95% CI of the combined analysis based on the overall RR (Figs. 5–7). Furthermore, to find potential sources of heterogeneity we performed subgroup analysis on three different groups and the NOS score of included studies.

4. Discussion

TB is a common infection globally and it is the leading cause of mortality and morbidity. Also, one-third of cases occur among women. TB infection in pregnant women affects the health of both mother and child and increases the risk of both maternal and infant morbidity and mortality.22 The HIV epidemic has significantly influenced the epidemiology of TB, and is a well-known risk factor for progression to active TB, among those infected with *Mycobacterium tuberculosis*.23 Concurrent

### Table 3

<table>
<thead>
<tr>
<th>Age group</th>
<th>Sample Size, No.</th>
<th>OR 95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, 18–24yr</td>
<td>637</td>
<td>1.38 0.884–1.167</td>
<td>0.24</td>
</tr>
<tr>
<td>Age, 25–34yr</td>
<td>17736</td>
<td>1.12 0.75–1.67</td>
<td>0.55</td>
</tr>
<tr>
<td>Age, 35–44yr</td>
<td>3892</td>
<td>1.71 1.20–2.44</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Abbreviations: CI = confidence interval; OR = odds ratio; HIV = human immunodeficiency virus.
TB infection is also a significant contributing factor to maternal mortality, in HIV-infected pregnant women. An increased risk of MTCT is also expected. Infants born to HIV positive mothers with active TB shows an increased risk of TB during their first year of life, and there is a 2.5-fold risk of HIV transmission in neonates. Previous studies show that TB, during the pregnancy, drastically increases the risk of pre-term delivery, also infants born to TB infected women, have a significantly lower birth weight, compared to others. It is also thought that whilst TB affects the health of mother and infant during the pregnancy, also pregnancy may play a role in TB progression. TB spreads from mother to embryo through the placenta via haematogenous, then by the umbilical vein to the fetal liver. Hence, the
studies of HIV-infected women show that CD4+ Th1 counts decrease faster during pregnancy.31 The studies included in this meta-analysis focused on different periods of pregnancy (early and late stages of pregnancy) to recognize the association between pregnancy, HIV and TB risk due to variable levels of hormones during different stages of pregnancy, however, no evidence was found for further confirmation.32

Due to the prevalence of latent TB in the world, and the possibility of advancement of TB to the active form during the pregnancy, the diagnostic test (such as IFN-γ release assay, commonly known as IGRA) is a necessity. This test is recommended for young women who are planning for a pregnancy, especially in HIV positive women, as there is a significant association between TB incidence and pregnancy in HIV positive women. However, to the best of our knowledge, this is the first meta-analysis study to assess the prevalence of TB, HIV and TB-HIV co-infection in pregnant women. In our study, we did not find any significant association between the TB incidence during pregnancy in women without any underlying disease, as has been observed in a cohort study conducted in the UK. The result of this study demonstrates that there was no significant increase during pregnancy (IRR, 1.29; 95% CI, 0.82–2.03), whereas the incidence of TB diagnosis is significantly increased postpartum.33

This result is the same as our meta-analysis finding and means that pregnancy in women without any underlying disease does not have a higher rate of incidence to TB during pregnancy in comparison to the pregnant women who have an underlying disease such as HIV. The result of our study may be due to a low number of studies on the prevalence and incidence of TB during pregnancy; despite our comprehensive search, just five studies meet our inclusion criteria. Additionally, there is no evidence that pregnancy is associated with an accelerated progression and incidence of HIV, similar to the previous finding.34 The association of HIV and pregnancy among women of reproductive age (15–44 years’ age group), reported in eight studies, were investigated and included in this meta-analysis. Due to these findings and the previous one, pregnancy by itself cannot increase the risk of HIV, despite changes in the immune response during the pregnancy.

We found a significant association between the TB incidence in pregnant women who live with HIV, so there is an association between HIV positive pregnant women and TB risk. Pregnancy increases the incidence rate of TB, among HIV positive women and it increases the risk of MTCT, premature birth, the mortality rate of mother and foetus. Some studies have found that pregnancy by itself is not a risk factor for TB.35 Other studies have indicated an increased risk of TB, during the pregnancy of HIV positive women. A study from South Africa shows a high prevalence of active TB, among HIV-positive pregnant women.36–38

Two other studies in Soweto, South Africa in 2003 and 2006 screened HIV-infected pregnant women for symptoms of active TB. The result of these two studies demonstrated that the incidence rate of TB among HIV-seropositive pregnant women are high.39,40 Women with active TB are at higher risk of giving birth to a child with low birth weight. Additionally, the presence of AIDS/HIV and a reduced immune response during pregnancy are two risk factors, which increase the risk of TB infection in pregnant women. In addition, the risk of latent TB progressing to the active form in pregnant women is very high. Furthermore, there is a risk of transmission to the child, leading to mortality in pregnant women. This increase in mortality rate in pregnant women because of TB infection may be due to a lack of knowledge about the incidence of TB during pregnancy, between obstetrician and midwife staff, and the necessity of TB diagnosis among pregnant women.
5. Conclusion

According to the results of this meta-analysis, pregnancy in HIV positive women increase the incidence rate of TB during this period. Due to our findings, designing a program for screening and diagnosing TB in women who are planning a pregnancy, by using the diagnostic test, such as IGRA, is highly recommended, especially in HIV positive women, since there is a significant association between the TB incidence and pregnancy in HIV positive women.

In addition, further investigations are necessary to find out about: (i) Prevalence of active and latent TB in pregnant women; (ii) Design and development of cost-effective assays to differentiate active TB from latent TB in pregnant women, especially women who live with HIV; (iii) Prevalence and handling of active form and latent form of TB in a baby born to mothers with TB.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of competing interest

None.

References