Maternal and perinatal mortality and morbidity associated with tuberculosis during pregnancy and the postpartum period: A systematic review and Meta-analysis

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Running title: Outcomes of Tuberculosis in pregnancy

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Word count: 2189

Abstract

Background: There is dearth of data on the epidemiology, clinical features, and outcomes of active tuberculosis (TB) in pregnancy. Current studies of TB in pregnancy have shown varied results and the relationship between TB and adverse pregnancy outcomes remains unclear.

Objectives: We conducted a systematic review and meta-analysis to evaluate pregnancy outcomes associated with TB.

Search strategy: Major databases were searched from inception until December 2015 using terms: "TB', 'pregnancy', 'maternal morbidity', 'mortality' and 'perinatal morbidity', 'mortality'. There was no language or regional restrictions.

Selection criteria: We included studies that compared outcomes of women with TB, with women without TB as controls.

Data collection and analysis: Background and outcome data were extracted. We computed odds ratios for maternal and perinatal complications, and pooled using a random effects model. We assessed for heterogeneity between studies using the I^2 tests and used the Newcastle-Ottawa scale to assess the quality of the studies.

Main results: Thirteen studies, including 3384 pregnancies with active TB and 119448 without TB were eligible for inclusion. Pregnancy with active TB was associated with increased odds of maternal morbidity (OR 2·8, 95% CI 1·7–4·6; I^2=60·3%), anaemia (OR 3·9, 95% CI 2·2–6·7; I^2=29·8%), caesarean delivery (OR 2·1, 95% CI 1·2-3·8; I^2=61·1%), preterm birth (OR 1·7, 95% CI 1·2–2·4; I^2=66·5%), low birth weight (OR 1·7, 95% CI 1·2–2·4; I^2=53·7%), birth asphyxia (OR 4·6, 95% CI 2·4–8·6; I^2=46·3), and perinatal death (OR 4·2, 95% CI 1·5–11·8; I^2=57·2%) compared to pregnant women without Tuberculosis.

Conclusion: Active TB disease in pregnancy is associated with adverse maternal and fetal outcomes. Early diagnosis of TB in the antenatal period is important to prevent significant maternal and perinatal morbidity.

Key words: Active, tuberculosis, maternal, perinatal, pregnancy outcomes.

Tweetable abstract: Active tuberculosis in pregnancy is associated with adverse maternal and perinatal outcomes.

Word count: 278

Introduction

Tuberculosis (TB) is one of the world's deadliest communicable diseases.[1] In 2013, an estimated 9 million people developed active TB and 1·5 million died from the disease, 510 thousand of these were women.[1] TB is one of the leading causes of death in women of reproductive age (15–45 years),[3] globally it is estimated that as many as 216500 pregnant women have active TB.[2] Indirect maternal deaths now account for 28% of total maternal deaths; 15-35% of these deaths are due to TB.[3, 4]

Although the greatest burden of TB infection is in resource-limited countries, resource-rich countries have seen a resurgence of TB, largely as a result of an increase in migrant populations.[5] The areas which have the highest TB burden; South-east Asia, Western pacific and African regions, also have the highest maternal mortality rates.[1]

Studies of active TB in pregnancy have shown varied results and the relationship between TB and adverse pregnancy outcomes remains unclear.[6] Quantitative data synthesis can overcome this deficiency and imprecision. Reviews exist regarding TB in pregnancy, but none has been conducted in a systematic manner or included meta-analysis.[7] We conducted a systematic review to collate the evidence on maternal and perinatal outcomes of pregnancies associated with active TB.

Method

Study selection

Medline, Embase, Web of science and Scopus databases were searched using the subject keywords and MeSH terms for 'TB', 'pregnancy', 'maternal morbidity', 'Maternal mortality' and 'perinatal morbidity', 'perinatal mortality'. We also searched all references of review papers and relevant articles. The search was not restricted by language and included all

articles from inception till December 2015 (Appendix S1). Additionally, we searched the reference lists of the included studies for eligible papers. Two independent reviewers (SS, HK) identified all relevant abstracts using pre-specified inclusion and exclusion criteria in a two- stage process. In the first stage, we screened the titles and abstracts of all citations for potentially relevant papers. In the second stage, we examined in detail the full texts of the retrieved papers. Any discrepancies were resolved after discussion with a third reviewer (KK). Studies were included if they had a cohort of pregnant women with TB and pregnant women without TB as a control group and had pregnancy outcome data included.

Quality assessment of the included studies

The Newcastle-Ottawa scale was used to assess the quality of included studies to evaluate the risk of bias in the selection, comparability of subjects and cohorts, and of the outcome.[8] Two independent reviewers (SS and HK) allocated stars for adherence to a pre-specified criterion. Studies that scored four stars for selection, two stars for comparability and three stars for ascertainment of the outcome were regarded to have a low risk of bias. Studies with two or three stars for selection, one for comparability and two for outcome ascertainment were considered to have a medium risk of bias. Any study with a score of one for selection or outcome ascertainment, or zero for any of the three domains was deemed to have a high risk of bias.

Data extraction and analysis

Using a piloted data extraction form, information on study design, setting, population characteristics, TB diagnosis and treatment as well as maternal and perinatal outcomes were obtained. Two independent reviewers (SS and HK) extracted data in 2×2 tables for comparative dichotomous outcomes.

Standard WHO definitions were used for the following outcomes: maternal mortality, perinatal mortality and preterm birth.[9, 10] Maternal morbidity was defined as any health condition attributed to and/or aggravated by pregnancy and childbirth that had a negative impact on the woman's wellbeing.[11] We accepted the authors' definitions of other fetal complications such as small for gestational age.

We calculated the odds ratios of adverse pregnancy outcomes in women with TB and women without TB for individual studies and pooled them to obtain an overall estimate using a random effects model, as we anticipated heterogeneity between studies. For continuous data, we computed weighted mean difference that was pooled using a random effects model. We assessed for heterogeneity between studies using the I^2 tests. A rough guide to interpretation of I^2 statistics is as follows: 0% to 40%: might not be important; 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent substantial heterogeneity and 75% to 100%: considerable heterogeneity. All analyses were undertaken using Stata SE.12 statistical software.[12]

Results

Characteristics of included studies

Thirteen out of 7521 studies met the inclusion criteria (Figure 1). The studies included 3384 pregnant women with active TB and 119,448 healthy pregnant women as controls. The diagnosis of active TB was made by a combination of clinical and radiological findings supported by microbiological and/or histological confirmation. Of the 3384 women with active TB, 2423 (72%) had pulmonary disease, 199 (5.8%) had extra-pulmonary disease and three patients had both pulmonary and extra-pulmonary disease. The site of TB disease was not stated in 22% of cases.[13] Only 7 women had HIV co-infection. One study excluded patients with HIV.[13] Not all studies included complete data on timing of diagnosis, of 3384

women with TB, timing of diagnosis was included for 1135 women. The timing of diagnosis and treatment varied among this group, 827 (73%) patients were found to have active TB pre-conception, 127 (11%) in the 1st trimester, 135 (12%) in 2nd trimester, 46 (4%) in the third trimester or the post-partum period. Regimens of anti tuberculosis therapy were documented in 62 % of studies, the details of which are provided in table S1. Furthermore, in five studies the precise proportion of patients who received treatment and the regimen received was not recorded.[14-18]

Nearly half of the studies (6/13) were from low-income and middle-income countries. Sixty-one per cent (8/13) of the studies were published after the year 2000. Ten studies reported on preterm birth as an outcome, six studies reported on low birth weight, seven on perinatal death, four on congenital anomalies, three on asphyxia and two reported on small for gestational age and acute fetal distress. Low Apgar score at one minute was reported only by one study. For maternal outcomes, five studies reported maternal death as an outcome, five described maternal morbidity, five reported on delivery by caesarean section and three reported on the presence of anaemia. Miscarriage and antenatal admission were reported by one study each. Study characteristics are shown in table S1.

Quality assessment

The quality of the studies is shown in figure 2. All of the included studies had low or medium risk of bias for study selection, and outcome assessment. 7/13 had low risk of bias for comparability of cohorts. Overall 7/13 of studies had low or medium risk of bias.

150 *Maternal and perinatal outcomes*

151 Maternal and perinatal outcomes were consistently poorer in pregnant women with active TB
152 infection compared to those without. Although not significant, a trend towards more
153 maternal deaths in women with active TB was present (OR 4·1, 95% CI 0·65–25.2; I^2=0%).
154 Of the women who died 50% had HIV co-infection. Maternal morbidity was almost 3 times
155 greater (OR 2·8, 95% CI 1·7–4·6; I^2=60.3%) in pregnant women with TB compared to the
156 control group. The odds of antenatal admission were 9 times greater (OR 9·6, 95% CI; 2·3–
157 40·6). The odds of maternal anaemia were 4 times greater in the TB group compared to
158 control (OR 3·85, 95% CI 2·21–6·71; I^2=29·8%). Caesarean section was performed twice as
159 often in women with TB (OR 2·10, 95% CI 1·17–3·79; I^2=61%). The odds of miscarriage
160 were 9 times greater in women with TB (OR 9·06; 95% CI 4·93–16·67). (Figure 3)

161

162 Of the perinatal outcomes, perinatal death was 4 times more frequent in patients with TB (OR
163 4·2, 95% CI 1·49 –11·83; I^2=57·2%), preterm birth was 1·6 times greater, (OR 1·7, 95% CI
164 1·2–2·4; I^2=66·5%), low birth weight was 1·7 times greater (OR 1·7, 95% CI 1·2 –2·4;
165 I^2=83·1%). Low Apgar score at one minute was 5 times greater (OR 5·71, 95% CI 1·4–22·6)
166 and acute fetal distress was 2·3 times greater (OR 2·34, 95% CI 1·2–4·5; I^2=0%) compared to
167 babies born in the control group. (Figure 4) There was a non-significant difference for the
168 risks of small for gestational age (OR 1·7, 95% CI 0·76–4·2; I^2=83%), and congenital
169 anomalies (OR3·4, 95% CI 0.71–16.7; I^2=73%).

170 Babies born to mothers with TB had a lower mean birth weight (weighted mean difference -
171 278.25g. (95% CI -367.21– -0·189.29; I^2=40.7%) and were born at an earlier gestation
172 (weighted mean difference -0·84 weeks (95% CI -1.22– -0·47), I^2=35.6%) compared to those
173 without TB. (Figure S1)

174

175 *Outcomes by site of disease*

176 With regards to site of TB disease, four studies presented data exclusively on pulmonary
177 disease[16-19]and two studies on extra-pulmonary TB.[15, 20] There was a trend towards worse
178 maternal outcomes with extra-pulmonary TB (Table S2). Additionally in one study[20] among
179 women with extra-pulmonary TB, those that had lymph node disease had no adverse
180 outcomes, but TB at other extra-pulmonary sites did adversely affect pregnancy.

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182 *Outcomes by timing of diagnosis*

183 Breakdown of outcomes by timing of diagnosis and treatment showed better outcomes when
184 treatment was initiated in first trimester in comparison to second and third trimester. In one
185 study none (0/9) of the pregnant women who were treated in the first trimester had preterm
186 birth compared to 33% (4/12) who initiated treatment in second and third trimester.[21] For
187 those who were treated in first trimester, there were no cases (0/9) of perinatal death
188 compared to 23% (3/13) in those treated in the second and third trimesters. In mothers who
189 were treated in the first trimester 28% (2/7) developed complications compared to 60% (6/10)
190 in those who were treated in the second and third trimester. Another study [22] also found that
191 no woman (0/23) who was treated in first trimester had a baby with low birth weight
192 compared to 60% (33/54) in those treated in second and third trimester.

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Discussion

Main findings

Our systematic review highlights that maternal and perinatal outcomes were consistently poorer in pregnant women with active TB compared to those without. There was an increased odds of maternal morbidity, anaemia, perinatal death, preterm birth, low birth weight and fetal distress in pregnant women with active TB. The outcomes appear worse when *anti tuberculous treatment (ATT)* was started late.

Strengths and limitations

To our knowledge, this is the first review that systematically evaluates the risk of active TB in pregnancy, and was carried out in a stringent manner to reduce bias. The strength of this review is that it provides the current best evidence summary exploring studies' characteristics, quality and results, which leads to a deeper insight into the topic than that afforded by individual studies.

Although the studies included a significant number of patients with active TB, not all studies had data available for all maternal and perinatal outcomes. Furthermore although most studies included information on site of disease, and timing of diagnosis, this was not linked to maternal and perinatal outcomes, making subgroup analysis difficult. Between study heterogeneity was moderate for a number of outcomes, and this should be taken to account when interpreting the results. Studies used different treatment regimens, which may be an unexplored source of heterogeneity. 43% of studies had a medium risk of bias, however after excluding these studies in a sensitivity analysis, there was still significantly poorer maternal and fetal outcomes in women with Tb compared to those without.

Interpretation

Clinical diagnosis of active TB in pregnant women can be difficult and there is often a delay in diagnosis due to the non-specific symptoms related to the physiological response to pregnancy[23]. In low and middle income countries, where TB carries the greatest burden, pregnancy maybe one of the few opportunities to assess a woman's health. Pregnancy is therefore an ideal opportunity to screen for active TB disease, this is in line with WHO recommendation of integrating TB screening and investigation into reproductive health services including antenatal and postnatal care in HIV and TB prevalent regions.[4] Different tests have been used in antenatal care such as symptom check, routine sputum examination by smear [24, 25], and the Xpert® MTB/RIF assay[26, 27]. However, there are no guidelines for routine screening for active TB in pregnancy. The tuberculin skin test and the interferon gamma release assays have been used to screen for latent TB infection (LTBI) in pregnancy, however only HIV infected pregnant women are prioritized for LTBI screening according to WHO guidelines.[28]

The effects of active TB on pregnancy may be influenced by many factors, including the extent of the disease, the presence of pulmonary TB vs extra-pulmonary, other comorbidities and the timing of diagnosis and initiation of treatment. Over 50% of maternal mortality occurring in mothers with TB in pregnancy is thought to be due to co-infection with HIV.[29] Unfortunately there were not many women with documented HIV infection included in our review, this may be explained by the fact that a few large studies were conducted before HIV testing was done routinely. It is well known that women with TB / HIV co-infection have poorer outcomes.[30] Although studies on HIV/ TB co-infection have been conducted in pregnancy, these were excluded in our review since they did not include a control group.

Future large prospective studies are needed to further examine the effect of active TB on maternal and fetal outcomes in pregnancy especially from regions with high burden of disease such as Sub-Saharan Africa and Indian Subcontinent. Risk factors affecting maternal and perinatal outcomes such as HIV co-infection, site of disease (pulmonary or extra-pulmonary), timing, type and length of ATT need to be further studied. Congenital TB is an important outcome causing significant morbidity to the infant, unfortunately this was not reported by any of the included studies. Future studies should collect data on this important outcome.

Conclusion

Active TB disease in pregnancy is associated with adverse pregnancy outcomes. Early diagnosis of TB in the antenatal period is important to prevent significant maternal and perinatal morbidity and mortality.

Author contributions:

HK, KSK, ZB and SS were involved in the conception of the research question, and designed the protocol. SS and HK undertook literature search, study selection and data extraction with the help of KSK. SS did statistical analysis with support from JZ. SS designed the tables, figures and appendices, with input from KSK. SS and HK prepared the initial drafts of the manuscript, with additional input from ZB and KSK. All authors contributed to the drafts and final version of the manuscript.

Conflicts of interest:

We declare that we have no conflicts of interest.

Ammalife and Elly Appeal (Barts Charity), Charities with a focus on maternal health research in developing countries funded SS. The Charities had no influence on the

development, conduct or reporting of this work.

Acknowledgement:

We are thankful to Elena Fage and Natalia Hounsome for help with translation of Russian included studies.

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Figure legend

Figure 1: Study selection process for the systematic review on pregnancy outcomes in women with Tuberculosis (TB) and those without TB

Figure 2: Quality assessment using the Newcastle-Ottawa Scale of studies included in the systematic review on pregnancy outcomes in women with Tuberculosis

Figure 3: Maternal outcomes in women with Tuberculosis (TB) compared to those without TB.

Figure 4: Perinatal outcomes in women with Tuberculosis compared to those without TB

Supporting information

Appendix S1: Search Strategy for systematic review on pregnancy outcomes in Tuberculosis

Table S1: Characteristics of studies included in a systematic review on pregnancy outcomes in Tuberculosis

Figure S1: Weighted mean difference for perinatal outcomes (gestation age & birth weight) in women with Tuberculosis compared to those without TB.

Table S2: Outcomes of pregnancy in women with Tuberculosis by site of disease.