

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

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13 **Running title:** Outcomes of Tuberculosis in pregnancy

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22 Word count: 2189

23

24 **Abstract**

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

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

31 **Search strategy:** Major databases were searched from inception until December 2015 using
32 terms: “TB”, ‘pregnancy’, ‘maternal morbidity’, ‘mortality’ and ‘perinatal morbidity’,
33 ‘mortality’. There was no language or regional restrictions.

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

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

40 **Main results:** Thirteen studies, including 3384 pregnancies with active TB and 119448
41 without TB were eligible for inclusion. Pregnancy with active TB was associated with
42 increased odds of maternal morbidity (OR 2.8, 95% CI 1.7–4.6; $I^2=60.3\%$), anaemia (OR 3.9,
43 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
44 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;
45 $I^2=53.7\%$), birth asphyxia (OR 4.6, 95% CI 2.4–8.6; $I^2=46.3$), and perinatal death (OR 4.2,
46 95% CI 1.5–11.8; $I^2=57.2\%$) compared to pregnant women without Tuberculosis.

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

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

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

53 **Word count: 278**

54 **Introduction**

55 Tuberculosis (TB) is one of the world's deadliest communicable diseases.⁽¹⁾ In 2013, an
56 estimated 9 million people developed active TB and 1.5 million died from the disease, 510
57 thousand of these were women.⁽¹⁾ TB is one of the leading causes of death in women of
58 reproductive age (15–45 years),⁽³⁾ globally it is estimated that as many as 216500 pregnant
59 women have active TB.⁽²⁾ Indirect maternal deaths now account for 28% of total maternal
60 deaths; 15-35% of these deaths are due to TB.^(3,4)

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

65

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

72

73 **Method**

74 *Study selection*

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

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

87

88 *Quality assessment of the included studies*

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

98 *Data extraction and analysis*

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

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

108 We calculated the odds ratios of adverse pregnancy outcomes in women with TB and women
109 without TB for individual studies and pooled them to obtain an overall estimate using a
110 random effects model, as we anticipated heterogeneity between studies. For continuous data,
111 we computed weighted mean difference that was pooled using a random effects model. We
112 assessed for heterogeneity between studies using the I^2 tests. A rough guide to interpretation
113 of I^2 statistics is as follows: 0% to 40%: might not be important; 30% to 60%: may represent
114 moderate heterogeneity, 50% to 90%: may represent substantial heterogeneity and 75% to
115 100%: considerable heterogeneity. All analyses were undertaken using Stata SE.12 statistical
116 software.⁽¹²⁾

117 **Results**

118 *Characteristics of included studies*

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

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

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

143

144 *Quality assessment*

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

148

149

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.

181

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.

193

194

195

196 **Discussion**

197 *Main findings*

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

203

204 *Strengths and limitations*

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

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

219

220 *Interpretation*

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

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

243

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

252 **Conclusion**

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

256 **Author contributions:**

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

263 **Conflicts of interest:**

264 We declare that we have no conflicts of interest.

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

267 development, conduct or reporting of this work.

268

269

270 **Acknowledgement:**

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

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359

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.