Association of TB treatment with pregnancy complications: A Systematic Review and Meta-analysis Protocol

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Protocol

Keywords: Pregnancy, Pre-eclampsia, Tuberculosis, Tuberculosis treatment

Posted Date: March 3rd, 2021

DOI: https://doi.org/10.21203/rs.3.rs-274069/v1

Version of Record: A version of this preprint was published at Placenta on September 1st, 2021. See the published version at https://doi.org/10.1016/j.placenta.2021.07.182.

Abstract

Introduction: Tuberculosis is a worldwide health risk factor, especially among immunocompromised groups such as in pregnant women. Diagnosis for TB is complex and appropriate initiation of treatment must be timely and cannot be postponed. This systematic review aims to assess the impact of TB drug exposure linked with pregnancy complications.

Methods: Electronic databases (PubMed, Google Scholar, Elsevier and the Cochrane Library) will be screened that covers original articles published from 2010 to 2020, using medical subject headings (MeSH) and free text searches. Population study of TB-infected pregnant women with control being non-infected pregnant women, defined by maternal age between 15 ≤ 44 years, which reported pregnancy outcomes after exposure to TB treatment during pregnancy will be included. PICOS for research question eligibility, PRISMA-P guidelines and flow diagram will be adhered to and assessed by two independent reviewers. Software manager Zotero v5.0.81 will be used to eliminate duplicates and assess eligibility criteria.

Ethics and dissemination: We anticipate finding a large number of studies reporting on the impact of TB drugs on the incidence of pregnancy complications which, once summarised, will be useful to establishing the link between TB drugs and pregnancy complications induced by these drugs. The protocol for the systematic review will be registered in PROSPERO. The study will be disseminated electronically and in print. It will also be presented to conferences related to TB and pregnancy.

Trial registration: PROSPERO CRD42021226233; Registered on 14 January 2021

Introduction

According to the World Health Organization (WHO), approximately 10 million people developed active tuberculosis (TB) in 2018 (Gupta et al., 2019, Loveday, Hlangu and Furin, 2020), which was 3-fold more TB infections than in 2013 that had about 3.3 million TB cases (Chen et al., 2016). It is believed to be a highly communicable disease. Tuberculosis remains an ever growing public health risk factor for mortality and morbidity, affecting up to 28% (133 per 100,000 individuals) of the general population (LaCourse et al., 2016, Salazar-Austin et al., 2017, Gupta et al., 2019). Active tuberculosis has been the foremost reason of mortality caused by Mycobacterium tuberculosis, which is transmitted via an infected droplet from the affected person, which primarily infects the lungs, but can infect other organs as well (Loto and Awowole, 2012). Some individuals may have an increased risk for TB if they have a weakened immune system due to other diseases such as HIV/AIDS, diabetes and/or cancer etc. Individuals with HIV are at a greater risk to develop active TB (Suresh et al., 2016, van der Walt et al., 2020), either caused by recurrence of an underlying infection or recently developed infection.

In 2017, 1.6 million TB-associated deaths occurred (Gupta et al., 2019), and it has also been suggested to be a major reason of death-related to antimicrobial resistance as well (Mesic et al., 2020). TB-infected individuals, if left untreated may lead to mortality rates of up to 40% (Suresh et al., 2016).

Tuberculosis has the highest burden, especially among racial/ethnic underrepresented groups such as women of childbearing age (15-45 years) and post-delivery period (LaCourse et al., 2016, Salazar-Austin et al., 2017). TB is a major concern as it reckons for approximately 20% (12.8 per 100,000 individuals) among pregnant women (Malhamé et al., 2016, McKenna et al., 2017), with an estimated 216 500 infected cases occurring in pregnant women each year (Salazar-Austin et al., 2017, Gupta et al., 2019). Furthermore TB is a general non-obstetric cause of maternal mortality and is more prominent within highly-burdened and/or poverty stricken countries (Kalk et al., 2020). Co-infection of active tuberculosis in HIV-infected pregnant women is at a greater risk for maternal and neonatal mortality by nearly 300% (Suresh et al., 2016, McKenna et al., 2017).

Even with efforts to reduce tuberculosis prevalence, it is still a primary cause to ill well-being. In a recent cohort study, 80% of TB-infected mothers had more prevalence towards pregnancy complications when matched with uninfected mothers (Jonsson et al., 2019). Obstetric complications of TB developing throughout pregnancy include; pre-eclampsia, eclampsia, hypertension in pregnancy, hypertensive disorders of pregnancy (i.e. gestational diabetes mellitus), high proportions of prematurity (fetal growth restriction), and low birth weight (LBW), miscarriage and spontaneous abortions, specifically if TB is not appropriately treated (Loto and Awowole, 2012, Salazar-Austin et al., 2017, Beck-Friis et al., 2020). Previous research studies indicate inconsistent evidence about the development of TB and TB-treatment among pregnant women and the impact it has on the maternal and post-delivery outcomes (Jonsson et al., 2019, Beck-Friis et al., 2020). In view of the fact, detecting tuberculosis in pregnant women can be quite problematic owing to normal immunological and/or physiological changes throughout pregnancy (Bekker et al., 2016, Jonsson et al., 2019, Kalk et al., 2020). The physiological changes may lead to increased susceptibility to TB infection and/or reactivation.

In addition, pregnancy itself, represses the T-helper 1 (TH1) pro-inflammatory response hiding any pregnancy-related symptoms and overlapping presentations with other infectious diseases, symptoms including extreme tiredness, difficulty in breathing (dyspnea), perspiration, cough or mild fever, which are similar indicators in clinical diagnosis of TB (Bekker et al., 2016, Chen et al., 2016).

TB-drug regimens for treating TB-infected pregnant women have not been conclusive (Jonsson et al., 2019) and only few studies have been published (Beck-Friis et al., 2020). General indecision regarding optimal drug selection, welfare and TB-treatment initiation and safety measures vary by trimester. It remains limited and challenging without clear thought for definite risk and benefits of clinical practice and legal liability (Gupta et al., 2019, van der Walt et al., 2020). Clinical research has a fixed rule of excluding pregnant women from TB drug trials and initiation of TB treatment is usually suggested after the first trimester, to guard the fetus from teratogenic effects (Bekker et al., 2016, van der Walt et al., 2020).

TB-sensitive pregnant women are treated with matching standard treatment (first-line i.e. rifampicin, isoniazid, ethambutol and pyrazinamide) as non-pregnant persons, along with careful monitoring for hepatoxicity and other adverse events (Beck-Friis et al., 2020, Kalk et al., 2020). However guideline

recommendations regarding treatment of drug-resistant TB (DR-TB) and multi-drug resistant TB (MDR-TB) are more difficult as many second-line anti-TB drugs may induce ambiguous, harmful effects and may lead to congenital malformations due to its teratogenic effects (Tabarsi et al., 2011, Beck-Friis et al., 2020). Therefore more research investigating the impact of TB in pregnancy complications is needed in order to improve the diagnosis of TB as well as providing effective guidance on the initiation of appropriate treatment and intervention to promote ideal clinical outcomes (Bekker et al., 2016, Chen et al., 2016) and achieve sustainable development goals, among pregnant women (McKenna et al., 2017).

Hence The objective is to compare safety measurements of TB treatment in early and late pregnancy. Secondly, is to identify the risk of pregnancy complications in women treated with first-line drugs versus women with second-line drugs.

Methods/design

Aim

The main aim for this systematic review is to examine the association of TB treatment with maternal and fetal adverse outcomes.

Objectives

1. To compare the safety measurements of TB treatment in early and late pregnancy.
2. To identify the risk of pregnancy complications in women treated with first-line drugs versus women with second-line drugs.

Design and population

This will be a systematic review of published studies. This protocol is written in line with the recommendations of Preferred Reporting Items for Systematic Review and Meta-analysis for Protocols (PRISMA-P) guidelines and the Cochrane Handbook for Intervention Reviews (Moher et al., 2015). The results will also be reported on the PRISMA 2009 statement, and article screening and selection process will also be demonstrated through a PRISMA-P flow diagram (Table 4).

The eligibility of the research question will be determined by the Population Intervention Comparison Outcomes Study design (PICOS) framework illustrated in (Table 1).

Table 1: PICOS framework for eligibility of research question

Population	Intervention	Control	Outcome(s)	Study design
Tuberculosis-infected pregnant women	Tuberculosis treatment	Tuberculosis non-infected pregnant women	Hypertension in pregnancy	Randomized control trials
			Pre-eclampsia and/or eclampsia	Cohort
			Hypertensive disorders of pregnancy	Matched cohort
			Fetal growth restriction (low birth weight (LBW)	Cross-sectional
			Miscarriage	
			Recurrent spontaneous abortion	

Search strategy and identification of studies

The following databases will be searched for eligible studies: PubMed, Scopus (via Elsevier) and the Cochrane Library. Manual searches through Google Scholar search engine will also be included as a potential resource. Medical subject headings (MeSH) and free text searches will be used on PubMed and the Cochrane Library databases (Table 2). Articles returned by the search will be saved to the citation manager Zotero v5.0.81 (Zotero.org). This software will be used to remove duplicates. The titles and abstracts of the articles remaining after exclusion of duplicates will be assessed for eligibility according to the inclusion and exclusion criteria. The full text of all potentially eligible studies will then be reviewed by two independent reviewers (SJMK and WP), and any disagreement between reviewers with respect to eligible studies for inclusion in the analysis will be settled by a third reviewer. The reference lists of eligible studies and reviews will also be assessed for more eligible studies. A list of potentially eligible studies excluded from the final analysis will be produced with reasons for exclusion mentioned. A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart detailing the number of articles identified, screened, included and excluded will be produced.

Table 2: Search strategy

Database	Search items	Number of Articles found	Date
PubMed	((((((((((((((tuberculosis infected pregnant women) AND (tuberculosis treatment)) OR (first-line drugs)) OR (second-line drugs)) AND (tuberculosis non-infected pregnant women)) AND (hypertensive disorders of pregnancy)) OR (preeclampsia)) OR (eclampsia)) OR (hypertension in pregnancy)) OR (fetal growth restriction)) OR (miscarriage)) OR (recurrent spontaneous abortion)) OR (low birth weight)) AND (randomized control trials)) OR (cohort)) OR (matched cohort)) OR (cross sectional)	13, 116	19 November 2020
Cochrane Library	tuberculosis infected pregnant women (MeSH) in Title Abstract Keyword OR anti-tuberculosis drug in Keyword OR uninfected pregnant women in Title Abstract Keyword OR pregnancy outcomes in Title Abstract Keyword OR studies in Title Abstract Keyword - (Word variations have been searched)	179	23 November 2020

Study selection

Inclusion Criteria

The inclusion criteria included the following: Articles were eligible for review if, (1) articles were of original research publications, available online or through inter-library loan, (2) evidence was published in English and between the year 2010 to 2020 in selected databases, (3) articles were from published global randomized control trials, matched cohort, cohort, and cross-sectional studies of tuberculosis treatment with related pregnancy outcomes/complications, (4) all criteria were mentioned in Table 1; defining the impact of tuberculosis treatment on the incidence of adverse pregnancy and neonatal outcomes (5) participants were women of maternal age between 18 to 45 years old.

Exclusion Criteria

The exclusion criteria included the following: Articles were excluded if, (1) full text was not available, (2) evidence were written in a language not understood by reviewer, (3) evidence were case reports or case studies, expert opinions, viewpoints, reviews and/or meta-analyses, (4) articles were published before the year 2010, (5) study doesn't have the outcomes of interest as objectives, (6) evidence from TB non-pregnant women will be excluded, because the impact of anti-depressants is expected to be evaluated in pregnant women (7) studies that are published in different journals with the same or different title.

Data management

Data collection process

The reviewers SJMK will develop a data extraction form that will be used in the collection relevant data items (Table 3). To reduce data entry errors, selected studies will be independently assessed by two reviewers (SJMK and WNP). As illustrated in (Table 3) below, a data charting table will be used to extract

background information and process the data items from each study selected. To ensure that all pertinent information regarding the relevant aspects for the study is collected, a data charting form will be developed and piloted, and continually updated.

Table 3: Data charting table

Author and date
Study title
Journal full reference
Study design
Average age
Ethnic group
Geographic location
Prevalence of TB
Incidence rate of TB
Screening tool
TB treatment regimen First-line TB treatment Second-line TB treatment
HIV Status
CD4 count
ART therapy
Parity
Duration of gestation 14 to < 24 weeks 24 to ≤ 34 weeks
Primary outcomes (Pre-eclampsia, eclampsia, gestational diabetes, hypertension, miscarriage, treatment failure, maternal death, hepatoxicity)
Secondary outcomes (premature, fetal growth restriction, low birth weight, stillbirth, fetal death)

Risk of bias and quality assessment

The Two independent reviewers (SJMK and WNP) will appraise all included studies and judge the quality of the selected papers using the Cochrane risk of bias tool.

Bias will be evaluated against the following items:

a. How the allocation sequence was generalised;
b. How allocation was concealed from participants, investigators and outcomes;
c. Blinding of participants and investigators;
d. Blinding of outcome assessors;
e. Completeness of outcomes data (number analysed relative to number randomised);
f. Selective reporting: whether all prespecified outcomes are reported.

Table 4: Prisma Flow diagram

Data synthesis

A summary of findings table will be used to provide a synthesis of the main outcomes of included studies. Moreover, if the included studies are homogeneous in terms of the type of immune checkpoint inhibitor used and participant characteristics, data will be analyzed with Rev Manager (Version 5.3) to conduct a meta-analysis. To measure statistical heterogeneity between studies, I^2 and Chi squared statistical tests will be used (14, 15). An I^2 value of >50% will be considered substantial heterogeneity (16). To find the sources of heterogeneity within the included studies, a subgroup analysis and meta-regression comparing the study estimates from different study-level characteristics, quality, intervention type, and the reported effect measure of adverse events will be conducted.

Discussion

This systematic review for linking TB drug exposure with pregnancy outcomes is crucial, as it may cover the gap for potential management and prevention strategies for high TB burden settings especially in underrepresented groups like pregnant women (Salazar-Austin et al., 2017, Kalk et al., 2020). This could possibly create and/or promote ideal clinical outcomes for both mother and fetus (Bekker et al., 2016, Chen et al., 2016). However, due to rooted research rules of excluding pregnant women from TB drug trials, because of ethical dimensions to be considered for the risks involved, creates inconclusive research and/or data and discrepancies among researchers (Bekker et al., 2016, Gupta et al., 2019, van der Walt et al., 2020).

Safety and efficacy guidelines regarding the use of first-line drugs during pregnancy has been recognised to be initiated after the first trimester to avoid harmful teratogenic effects that could ultimately lead to anomalies and/or risk of hepatoxicity in pregnant women (Bekker et al., 2016, van der Walt et al., 2020). Nevertheless, it is still uncertain what the effects of second-line drugs are during pregnancy, as vulnerable

participants are usually excluded from these clinical trials, due to uncertainty of whether benefits outweighs risks (Tabarsi et al., 2011, Beck-Friis et al., 2020, van der Walt et al., 2020).

Therefore better-quality research recording and reporting for TB drug exposure during pregnancy and the possible outcomes, are needed as this could potentially contribute to better assessments of the disease, which could potentially improve maternal TB case finding and obstetric outcomes among mothers and their infants (Salazar-Austin et al., 2017, van der Walt et al., 2020).

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

Not applicable

Competing interests

The authors declare that they have no competing interests

Funding

Not applicable

Authors' contributions

SJMK wrote the protocol for the study with assistance from WN. SJMK is guarantor of the review. All authors have reviewed and approved the final version of this manuscript.

Acknowledgements

Not applicable

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Figures

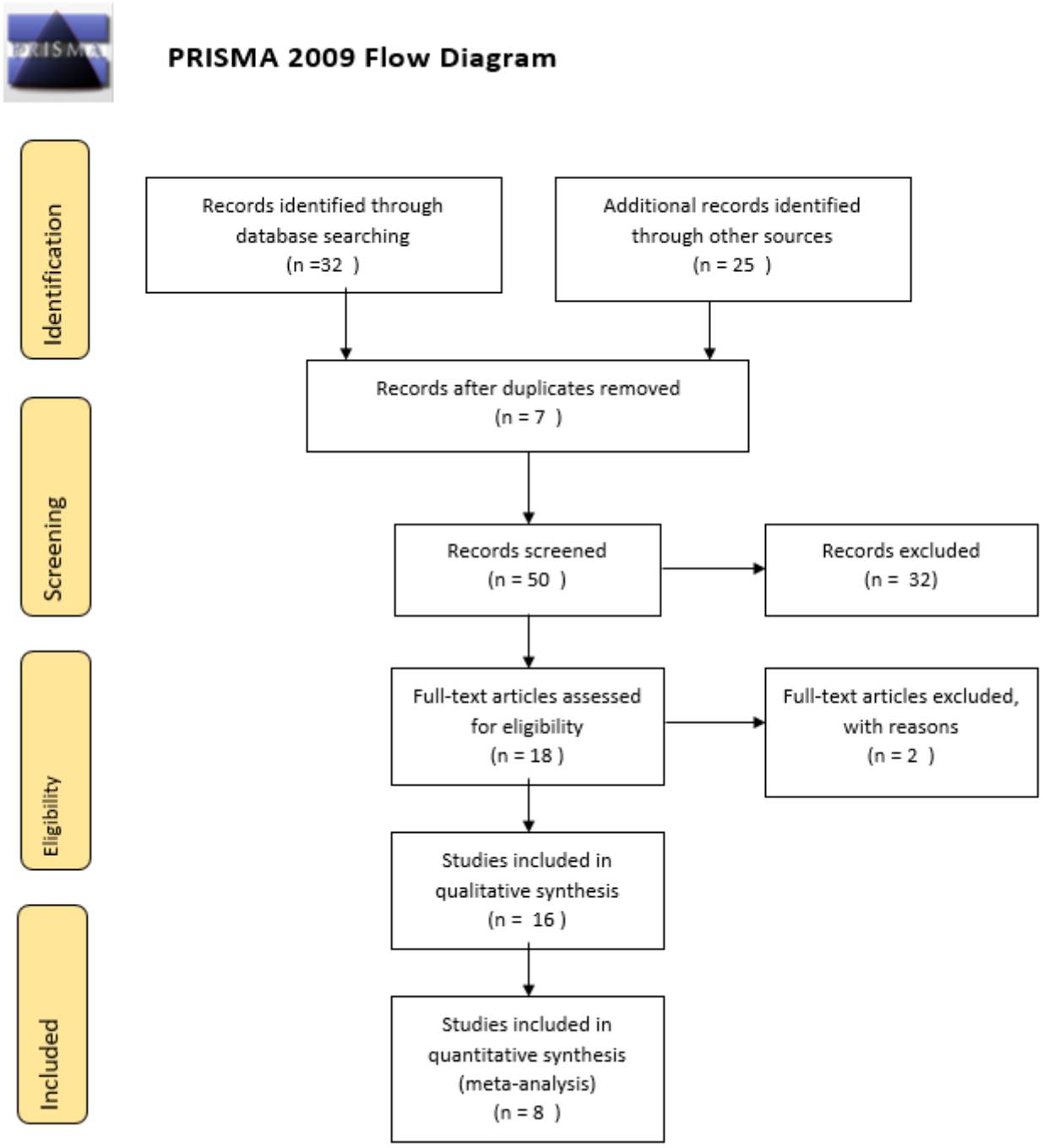

Figure 1

Prisma Flow diagram. m: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Supplementary Files

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- PRISMAChecklist.doc