RETRACTED: Safety Evaluation of Antituberculosis Drugs During Pregnancy: A Systematic Review and Meta-Analysis

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Background: Pregnant women are a common group of people with tuberculosis, especially in patients infected with HIV at the same time. Antituberculosis drug prophylaxis is effective in reducing tuberculosis infection in pregnant women and fetuses after pregnancy, but its safety is still worthy of in-depth discussion. In this study, we conducted a systematic review and meta-analysis of reports on the use of antituberculosis drugs during pregnancy in recent years to provide evidence for clinical diagnosis and treatment.

Methods: The PubMed, Embase, Web of Science databases, Ovid, and clinicaltrials.gov were searched. Search for clinical randomized controlled studies and cohort studies on the use of antituberculosis drugs during pregnancy published in the databases from January 2000 to September 2021 was performed using the Stata 16.0 software after screening qualified bodies of literature.

Results: On the basis of the initial search of 408 articles, this study included a total of 8 articles and 2,563 patients after screening; meta-analysis results showed that preventive treatment with antituberculosis drugs did not increase the incidence of serious maternal adverse events \[RR = 0.99, 95\% CI (.88, 1.12), Z = −0.108, P = 0.914\], did not increase drug hepatotoxicity \[RR = 1.13, 95\% CI (.9, 1.43), Z = 1.071, P = 0.284\], did not increase the incidence of peripheral nerve disease \[RR = 1.52, 95\% CI (.85, 2.71), Z = 1.412, P = 0.158\], did not increase maternal mortality \[RR = 0.67, 95\% CI (.27, 1.7), Z = −0.84, P = 0.401\], and could significantly reduce adverse pregnancy outcomes \[RR = 0.78, 95\% CI (0.68, 0.89), Z = −3.581, P <0.0001\].

Discussion: The use of antituberculosis drugs for preventive treatment during pregnancy is safe and can obtain better pregnancy outcomes.

Keywords: pregnancy, antituberculosis drugs, tuberculosis, system review, meta-analysis

INTRODUCTION

Tuberculosis (TB) is a chronic infectious disease caused by Mycobacterium tuberculosis, and can occur at any age, especially when the immunity of a patient is low. Mycobacterium tuberculosis mainly invades the lungs and forms pulmonary tuberculosis; it can also invade organs other than the lungs, such as the liver and kidneys, and lymph nodes, and is often referred to as extrapulmonary
tuberculosis (1). Tuberculosis is a public health problem that endangers human health, and, as of 2018, there are still 10 million new patients worldwide (2). Pregnant women are a common group of people with tuberculosis. Because of maternal autonomic dysfunction and endocrine and metabolic dysfunction in the body, the body’s immunity is reduced. In addition, ovarian hormones increase, the lung is in a congested state; hyperthyroidism and increased metabolic rate; increased cholesterol in the blood; significantly increased secretion of adrenocorticotropic hormone, which easily causes Mycobacterium tuberculosis infection, dissemination, leading to an increased probability of tuberculosis during pregnancy (3). In addition, tuberculosis is a main cause of complications in and death of people with infectious immunodeficiency virus,
| Author               | Year | Type of study                  | Population characteristics                                                                 | Total cases | E/C cases | Intervention characteristics                                                                 | Control group intervention characteristics | Observation time point | Outcome indicators | Quality assessment |
|---------------------|------|--------------------------------|-------------------------------------------------------------------------------------------|-------------|-----------|-----------------------------------------------------------------------------------------------|---------------------------------------------|-----------------------|-------------------|-------------------|
| Mathad et al. (9)   | 2021 | Prospective cohort             | Pregnant HIV-infected Women with age of 14–34 weeks                                         | 50          | 25/25     | Once-weekly doses of RPT (900 mg) and INH (900 mg) for 16 weeks                              | Placebo during pregnancy                   | 34 weeks after delivery | (a) (b) (c) (d) (e) (f) | 8                 |
| Mokhele et al. (10) | 2021 | Prospective cohort             | Women diagnosed with laboratory-confirmed MDR/RR-TB                                         | 35          | 17/18     | At least two second-line agents: Kanamycin/Moxifloxacin                                        | Placebo                                     | N/A                   | (a) (b) (c) (f)   | 8                 |
| Gupta et al. (11)   | 2019 | multicenter, double-blind,     | HIV-infected pregnant women with ART                                                         | 956         | 477/479   | Begin IPT during pregnancy for 28 weeks                                                       | Placebo during pregnancy                   | 48 weeks after delivery | (a) (b) (c) (d) (e) (f) | A                 |
| Taylor et al. (12)  | 2013 | multicenter, double-blind,     | HIV-infected pregnant women with ART                                                         | 196         | 103/93    | (n = 103) 6 months of isoniazid (300–400 mg/day) plus vitamin B6 (25 mg/day) + 30 months isoniazid | (n = 93) 6 months of isoniazid (300–400 mg/day) plus vitamin B6 (25 mg/day) + Placebo      | 30 months after delivery | (a)               | B                 |
| Salazar-Austin et al. (13) | 2020 | Prospective cohort             | Pregnant women living with HIV aged ≥ 18 years and at least > 13 weeks’ gestation           | 155         | 71/84     | 2 months of IPT exposure during pregnancy                                                     | NO IPT                                      | N/A                   | (d) (f)           | 7                 |
| Yang et al. (14)    | 2015 | Randomized controlled trial    | Latent tuberculosis infection patients                                                         | 120         | 70/50     | Isoniazid Combined with rifampicin                                                           | Placebo                                     | N/A                   | (f)               | C                 |
| Theron et al. (15)  | 2021 | multicenter, double-blind,     | Pregnant women living with HIV at > 14 through to ≤ 34 weeks and 6 days’ gestation         | 936         | 456/480   | 28 weeks of IPT during pregnancy                                                            | Placebo during pregnancy                   | 48 weeks after delivery | (f)               | A                 |
| Moro et al. (16)    | 2018 | Prospective cohort             | Pregnant women with high-risk of latent tuberculosis infection                               | 125         | 87/38     | 12-dose once-weekly regimen of isoniazid (H, 900 mg) plus rifampicin (P, 900 mg)            | Placebo during pregnancy                   | N/A                   | (f)               | 6                 |

E/C, experiment/control; MDR/RR-TB, multidrug-resistant and rifampicin-resistant tuberculosis; ART, antiretroviral therapy; IPT, isoniazid preventive therapy; RPT, rifapentine; INH, isoniazid; N/A, not available.

Outcomes: (a) any serious adverse event; (b) hepatotoxicity rate; (c) peripheral neuropathy; (d) maternal death toll; (e) permanent discontinuation of trial regimen because of toxic effects; (f) adverse pregnancy outcomes.
particularly in low- and middle-income countries with a heavy burden of tuberculosis (4). Pregnant women living with HIV are more susceptible to TB, with a reported risk of between 7.7 and 7.9% for active TB (5) compared with 0.6 and 0.53% for HIV-uninfected women. When tuberculosis develops during pregnancy or early postpartum, it will be closely related to maternal health, pregnancy outcomes, and fetal quality, and can cause adverse outcomes such as premature delivery, low birth weight, and congenital or neonatal tuberculosis infection (6). At present, isoniazid and rifampicin are the recommended first-line drugs by the World Health Organization (WHO). Ethambutol, pyrazinamide, and streptomycin are also used in the prevention and treatment of tuberculosis. Considering the utility of isoniazid preventive therapy (IPT) in reducing tuberculosis infection in pregnant women and fetuses after pregnancy, the WHO strongly recommends IPT treatment for latent tuberculosis infection in patients infected with HIV (including pregnant women) (7). The safety of isoniazid prophylaxis was meta-analyzed in the study by Hamada et al. (8), but the final results were not well-documented because of large heterogeneity among the included articles. In this study, more good-quality articles were included for meta-analysis to provide more definitive evidence.

MATERIALS AND METHODS

Literature Inclusion Criteria

① Type of Study: Since There Are not Many Randomized Controlled Studies on This Topic, We Also Included all Observational Cohort Studies Besides Randomized Controlled Studies. We Did not Limit Whether a Cohort Study Is Prospective or Retrospective. We Welcomed Multicenter Studies, but Did not Refuse Single-Center Studies. The Quality of Literature...
Written in English Language Is Better, and We Prefer to Include Studies Written in the English Language. Study Subjects: all Study Subjects Are Women of Childbearing age. Studies on Rats, Rabbits, Monkeys, Dogs, and Other Animals Were Excluded. Although Different Countries Have Different Definitions of age of Women of Childbearing age, Based on Ethical Factors, We Prefer to Include Studies With age of Study Subjects >14 Years. All parturients were potential TB patients or had already been diagnosed with TB. We Did not Rule out Whether a Parturient Is Infected With HIV, Because Both Pregnancy and HIV Infection can Cause Decrease in Human Immunity and Increase the Possibility of Tuberculosis Infection. We Also Did not Rule out Whether a Parturient Is Receiving HIV Antiretroviral Therapy. In Fact, the Sample Size of Potential Patients With TB Alone Is Very Small, and the Number of Such Studies Is Very Small. However, in Some Undeveloped Countries in Africa, the Risk of TB Infection Is Increased Because of HIV Infection, and the Number of Potential Infected Patients Is Large.

③ Intervention Measures: all Randomized Controlled Studies Were Divided Into Control Group and Experimental Group for Intervention. The Experimental Group Took Antituberculosis Drugs (one or More of Isoniazid, Rifampicin, Ethambutol, Pyrazinamide, and Streptomycin). The Control Group Was not Given Antituberculosis Drugs, or Was Only Given Placebo or Was Given Antituberculosis Drugs After Maternal Delivery. We Did not Limit the Time of Antituberculosis Drug Intervention in the Experimental Group. The Dosage and Course of Treatment of the two Groups of Patients Were not Limited. The timing of anti-TB drug intervention may be before pregnancy or early in pregnancy. For Cohort Studies, 2 Groups of Cohorts Must be Found in the Study, Antituberculosis Drug Intervention Cohort and no Antituberculosis Drug Cohort. Requirements for Intervention Measures Are the Same as Those for the RCT Studies. Differently, Cohort Studies Only Observed the Results and Did not Participate in Process Control. ④ Outcome Indicators: We Evaluated the Safety

![Figure 4](image-url) | Comparison of incidence of peripheral nerve disease with antituberculosis drugs.

![Figure 5](image-url) | Comparison of maternal mortality rate with antituberculosis drugs.
of Antituberculosis Drugs With the Following Indicators: (a) Incidence of Serious Maternal Adverse Events (Excluding Death): Placental Abruption, Postpartum Hemorrhage, Hypertension, and Severe Anemia; (b) Hepatotoxicity Rate: Elevation of Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), and Total Bilirubin, and Clinical Symptoms of Hepatitis; (c) Peripheral Nerve Disease Rate; (d) Maternal Mortality; (e) Adverse Pregnancy Outcomes Including Stillbirth, Miscarriage, Premature Delivery, Neonatal Death, Congenital Malformation, low Body Weight, and Macrosomia.

Exclusion Criteria of Literature
① Review Literature, Experience Sharing, Case Analysis, Meeting Minutes, Qualitative Study, and Practice Guidelines, Such Types of Literature Were Excluded, Because They Have no Specific Data; Case-Series Studies and Epidemiological Surveys Were Excluded, Because There Were no Control Groups in Such Studies; ② Nonpregnant Patients With Tuberculosis Patients and Animals Were Excluded; ③ Purely Descriptive Literature; ④ Literature With Nonstandard Outcome Criteria; ⑤ Repeated Publications Literature.

Literature search: ① search strategy: keyword search was performed with search terms (“Isoniazid” or “Rifampicin” or “Ethambutol” or “Pyrazinamide” or “Streptomycin”) AND (“tuberculosis”) AND (“pregnancy”); ② database: the Pubmed, Embase, and Web of Science databases, and Ovid were used as search databases, and we simultaneously searched for clinical control studies on clinicaltrials.gov; ③ filter setting: the publication time of literature was set (January 2000-September 2021).

Selection of Literature
After retrieval of document, we entered the literature data with qualified title into the EndNote X9 software for subsequent management, used the de-duplication function of the software to eliminate repeated documents, read the title, abstract, and full text of literature, and excluded unqualified literature. (2) The researchers independently read the literature according to inclusion and exclusion criteria to determine whether it is qualified or not. In case of any dispute in this process, a third researcher could intervene and coordinate after discussion.

Data Extraction and Conversion
After completing the screening of literatures, 2 researchers read the full text of the literature again, from which the characteristic information of the literature (author, publication time, study type, and study site), information on study subjects (age, pregnancy time, proportion of HIV infection, and proportion of antiretroviral therapy), information on intervention measures (total number of participants, number of groups, group intervention method, and time of antituberculosis intervention), and outcome information (outcome indicators) were extracted.

Literature Risk of Bias Assessment
(a) Quality assessment and grading were performed according to the method of Cochrane Collaboration Handbook of Systematic Reviewers: grade A: random method, allocation concealment, blind method, withdrawal or loss to follow-up, intention analysis, and baseline situation, and all quality standards were met. Grade B: any one or more quality evaluation criteria are only partially met (or unclear). Grade C: anyone or more of them are completely unsatisfactory. (b) The quality of the included

![Figure 6](fncel-14-542552-Dec-16, 2020 Time: 15:27 # 1.png)

**FIGURE 6** | Effect of antituberculosis drugs on the incidence of adverse pregnancy outcomes.
cohort was evaluated using the Newcastle-Ottawa Scale (NOS), from 3 aspects: study population, comparability, and exposure, quantified by star system, with the highest star being 9; <5 stars were considered to be low-quality studies, and 5 stars and above were considered to be of good quality.

**Statistical Methods**

① Stata 16.0 was used as the analysis software; ② discrete indicators (binary classification) were reported using risk ratio (RR) effect size and 95% CI, and P < 0.05 indicated statistical significance; ③ each outcome indicator (incidence of severe maternal adverse reactions, mortality, hepatotoxicity rate, peripheral nerve disease rate, and adverse pregnancy outcome rate) was analyzed; ④ Forest plot was used to show the effect size; ⑤ I² analysis and Q verification literature heterogeneity were used, and I² > 50% or P < 0.1 indicated the presence of heterogeneity; random effect model was used, otherwise fixed effect was used; RR effect size used the Mantel-Labenszel model; ⑥ Labbe plot was used to investigate heterogeneity, and the metaif command provided by the STATA16.0 software was used for sensitivity analysis; ⑦ Egger and Begger analyses were performed on the results to obtain an Egger progressive plot.

**RESULTS**

**Literature Screening Process and Results**

We retrieved 408 articles from the initial search, and after screening, a total of 8 articles (9–16) were included, including a total of 2,563 patients. We excluded studies without groups or cohorts (17), studies without outcome indicators (18), and studies with animals as subjects (19). The document retrieval flow chart is shown in **Figure 1**.

**Basic Characteristics of the Literature**

The basic characteristics, intervention measures, observation time, and outcome indicators of the included literature are shown in **Figure 1**. The minimum total number of cases in the study was 35, and the maximum was 956. There were a total of 4 controlled clinical studies and 4 cohort studies.

**Meta-Analysis Results**

**Incidence of Any Serious Maternal Adverse Event**

Incidence of serious maternal adverse events was reported in the literature (9–12), and there was no statistical heterogeneity in the literature (I² = 0%, P = 0.389). A fixed-effects model analysis was performed to obtain the pooled value [RR = 0.99, 95% CI
Hepatotoxicity Rate
The literature (9–11) reported hepatotoxicity after treatment, but there was no statistical heterogeneity in the studies ($I^2 = 0\%$, $P = 0.401$). A fixed-effect model analysis was performed to obtain the pooled value [$RR = 1.13$, 95% CI (0.9, 1.43), $Z = 1.071$, $P = 0.284$], and the difference had no statistical significance ($P > 0.05$), as shown in Figure 3.

Incidence of Peripheral Nerve Disease
Incidence of peripheral nerve disease after treatment was reported in the literature (9–11). There was no statistical heterogeneity in the literature ($I^2 = 0\%$, $P = 0.845$). A fixed-effect model analysis was performed to obtain the pooled value [$RR = 1.52$, 95% CI (0.85, 2.71), $Z = 1.412$, $P = 0.158$], and the difference had no statistical significance ($P > 0.05$), as shown in Figure 4.

Maternal Mortality
The literature (9, 11, 13) reported maternal mortality during treatment, and there was no statistical heterogeneity in the literature ($I^2 = 0\%$, $P = 0.846$), which was analyzed using a fixed-effect model, resulting in a pooled value [$RR = 0.67$, 95% CI (0.27, 1.7), $Z = −0.84$, $P = 0.401$], and the difference was not statistically significant ($P > 0.05$), as shown in Figure 5.

Adverse Pregnancy Outcomes
The literature (9–16) reported adverse pregnancy outcomes in parturients, and there was no statistical heterogeneity in the literature ($I^2 = 24.8\%$, $P = 0.231$), which was analyzed using a fixed-effect model, resulting in a pooled value [$RR = 0.78$, 95% CI (0.68, 0.89), $Z = −3.581$, $P < 0.0001$], and the difference was statistically significant ($P < 0.05$), as shown in Figure 6.

Heterogeneity Investigation
In the meta-analysis of maternal adverse pregnancy outcomes, a Labbe plot was used to describe the heterogeneity of the literature. Eight bodies of literature deviated from the central axis and had asymmetric distribution. It can be seen that...
there was certain heterogeneity in the literature. The source of heterogeneity may be related to the proportion of maternal HIV infection, proportion of antiretroviral therapy, drugs used for intervention, whether combined intervention, whether to continue intervention after delivery, observation time point, and other factors, as shown in Figure 7.

Sensitivity Analysis
In the meta-analysis of maternal adverse pregnancy outcomes, the results of sensitivity survey are shown in Figure 8.

Analysis of Publication Bias
In the analysis of maternal adverse pregnancy outcomes, Begger’s Test: \( Pr > z = 0.108 \); Egger’s Test: \( P > t = 0.083 \), suggesting that the possibility of publication bias is small, as shown in Figure 9.

DISCUSSION
The application of antituberculosis drugs (isoniazid and rifampicin) in pregnancy can reduce tuberculosis infection, which has been confirmed by studies, but issues of maternal-fetal toxicity and drug safety are still worth exploring (20). Some studies have shown that the first-line anti-tuberculosis drug isoniazid, when used in combination with vitamin B6, can reduce the potential neurotoxicity of the drug to a fetus, but the binding and metabolism of isoniazid and vitamin B6 may cause deficiency in vitamin B6 in the patient’s body and peripheral neuritis; isoniazid can also inhibit the monoamine oxidase of a patient, resulting in excessive accumulation of histamine in the patient’s body, affecting the patient’s blood pressure, respiration and heart rate. In addition, isoniazid can excessively bind cellular proteins in the metabolism of hepatocytes, causing liver cell degeneration or necrosis, forming drug-induced hepatitis, which manifests as abnormal increase in ALT, AST, total bilirubin, and other indicators (21). Gastrointestinal reactions, rashes, visual disturbances, and hyperuricemic reactions caused by anti-TB drugs are also commonly reported (22).

In order to investigate the safety of antituberculosis drugs in pregnancy, this study included 8 controlled clinical studies or cohort studies for analysis, 4 controlled clinical studies and 4 cohort studies. The meta-analysis results showed that the use of antituberculosis drugs during pregnancy did not significantly increase the incidence of serious maternal adverse events, did not significantly increase the incidence of peripheral nerve disease, did not significantly increase the incidence of hepatotoxicity, did not significantly increase maternal mortality, and had fewer adverse pregnancy outcomes compared those who did not use preventive drugs, which indicated that antituberculosis drugs were still safe in terms of preventive effect during pregnancy, which was consistent with the current consensus of the academic community (23), CDC guidelines (24), and guidelines for the prevention and treatment of tuberculosis population (25). Although there are some adverse reactions with the use of antituberculosis drugs during pregnancy, in the case of controlling the time and dosage of the drugs, it will generally not cause a significant impact on patients, and after
drug withdrawal and symptomatic treatment, the symptoms of patient's adverse reactions will gradually disappear, so the safety of antituberculosis drugs is better.

In a prospective cohort study by Nolan et al., (26), the investigators concluded that isoniazid is safe for use as TB prophylaxis with low incidence of hepatotoxicity, which was consistent with the results of this meta-analysis. We believe that the safety of isoniazid prophylaxis is related to its low dose, and the South African HIV treatment guidelines recommend prophylactic isoniazid 5 mg/kg/day (up to 300 mg/day) for 6–12 months in all adults and adolescents infected with HIV, which is much lower than the recommended dose of 5 mg/kg/day for the treatment of tuberculosis (27). Nevertheless, we should be vigilant of the toxicity of antituberculosis drugs and timely observation of the medication process; if the hepatitis index is elevated, liver protection drugs can be used; critically ill patients need to stop antituberculosis drugs.

In this study, due to the small number of included literature, we did not analyze the medication safety of different kinds of antituberculosis drugs. Abdelwahab et al. (28) applied isoniazid, pyrazinamide and ethambutol in the prevention and treatment of pregnant TB patients, and found that there was no significant difference in pregnancy outcomes among the three regimens. However, when a parturient develops resistance to first-line drugs (isoniazid and rifampicin), other types of anti-TB drugs should be replaced in a timely manner.

There are still some limitations in this study, which are reflected in: (a) the number of included literatures is small and the number of patients included is small, which requires a multicenter trial with a larger sample size; (b) different study patient characteristics and intervention characteristics vary greatly, which may increase heterogeneity; adverse reactions are caused by a variety of factors, not only related to the use of anti-tuberculosis drugs, but also related to whether the parturient is infected with HIV and whether the antiretroviral drugs are used.

**SUMMARY**

The use of anti-TB drugs for preventive treatment during pregnancy is safe and can achieve better pregnancy outcomes.

**DATA AVAILABILITY STATEMENT**

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

**AUTHOR CONTRIBUTIONS**

FH was the supervisor of the entire study. All authors of this study made equal contributions, including data collection, literature review, data analysis, and manuscript writing. All authors contributed to the article and approved the submitted version.

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