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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

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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,

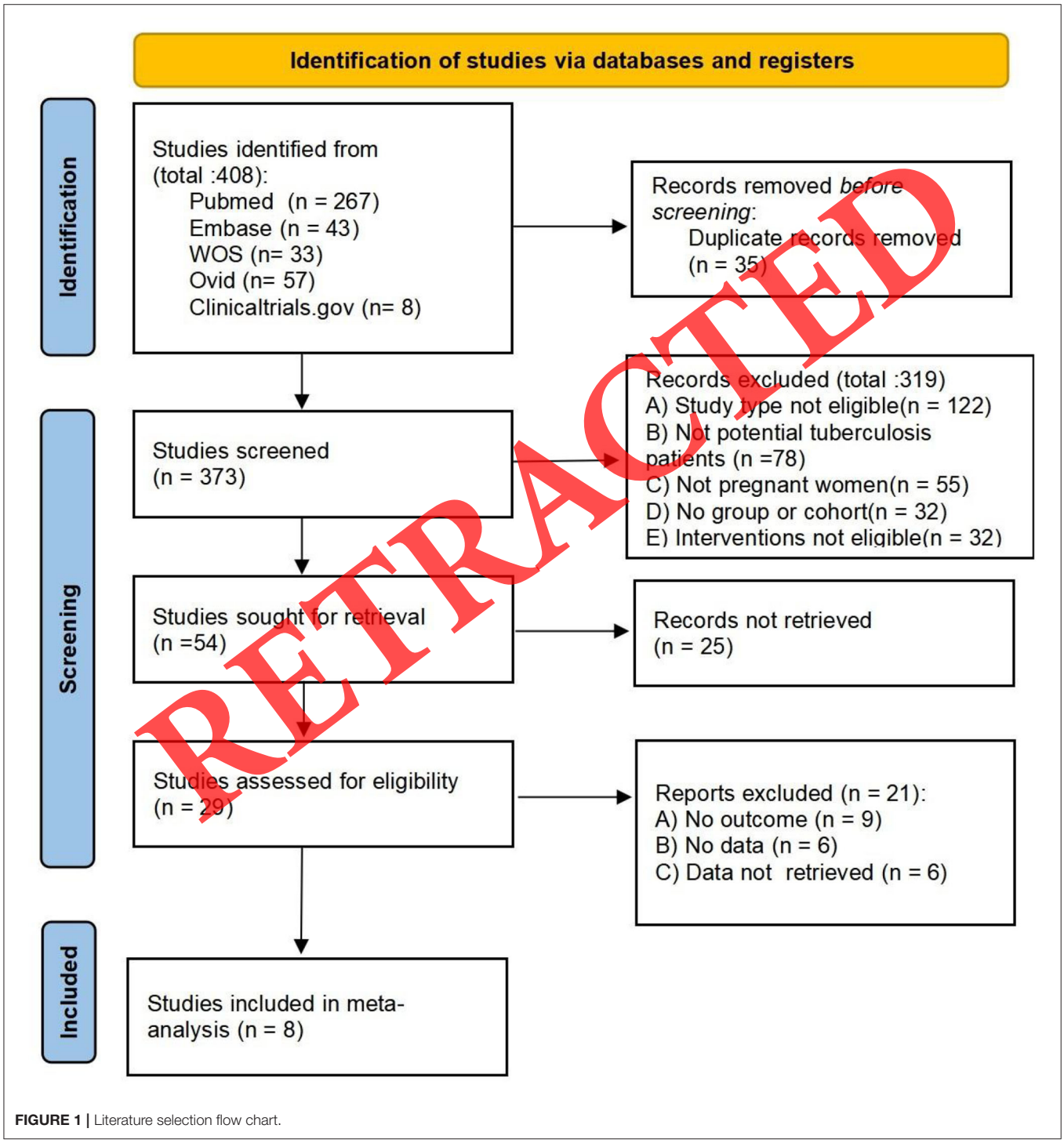

FIGURE 1 | Literature selection flow chart.

TABLE 1 | Basic characteristics, maternal characteristics, intervention measures, observation time, outcome indicators, and quality assessment of the included literature.

Author	Year	Type of study	Population characteristics	Total cases	E/C cases	Experimental group 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 sage 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 laboratoryconfrmed MDR/RR-TB	35	17/18	at least two second-line agents: Kanamycin/Moxifoxacin	Placebo	N/A	(a) (b) (c) (f)	8
Gupta et al. (11)	2019	multicenter, double-blind, placebo-controlled trial	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, placebo-controlled trial	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, placebo-controlled trial	pregnant women living with HIV at ≥14 through to ≤34 weeks and 6 days gestation	926	460/466	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 rifapentine (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 and 7.9% for active TB (5) compared with.06 and.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

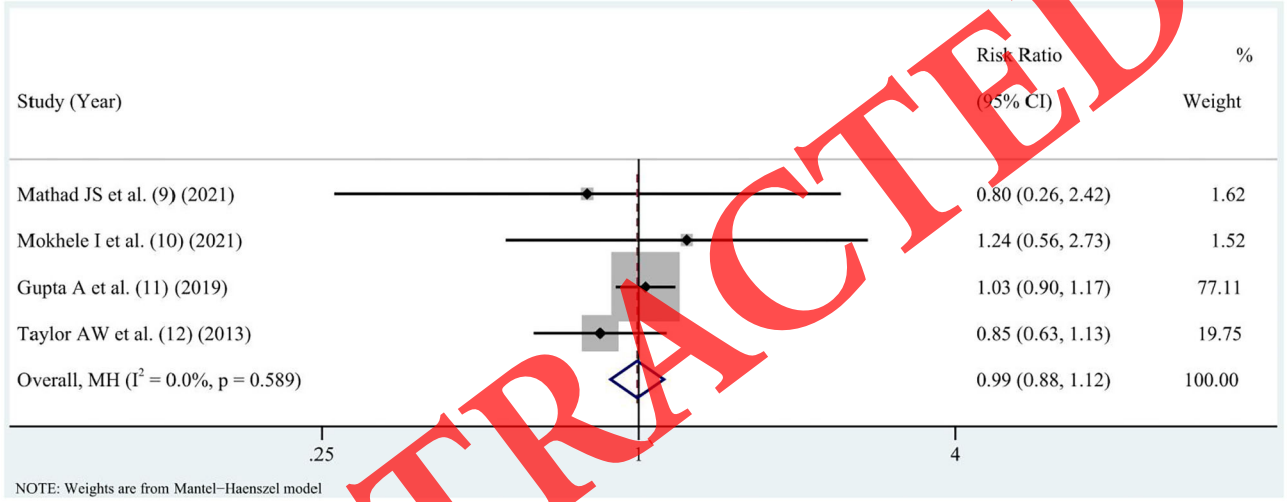

FIGURE 2 | Comparison of incidence of severe maternal adverse reactions to antituberculosis drugs.

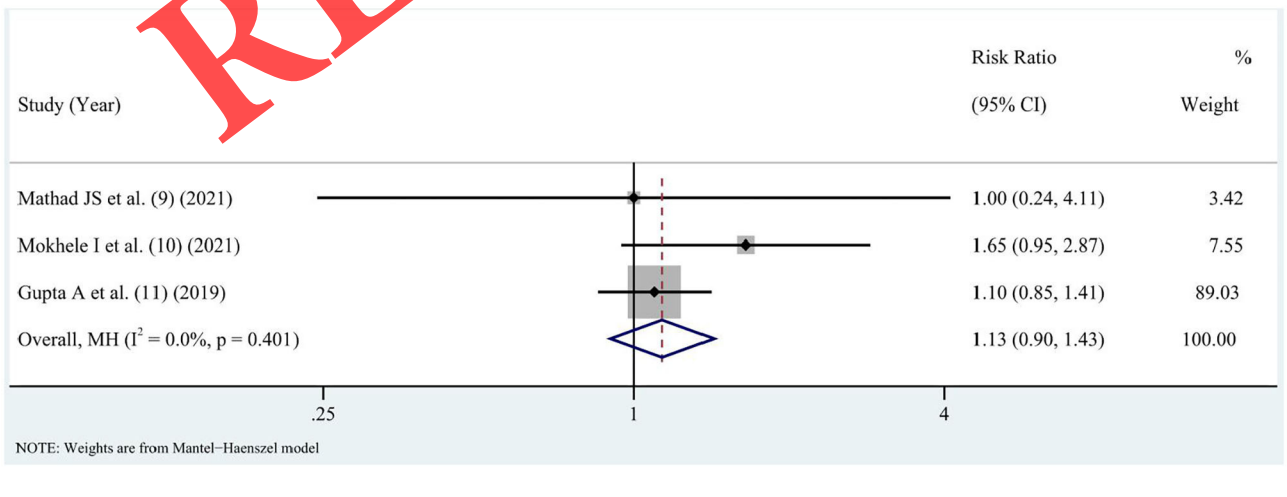

FIGURE 3 | Comparison of hepatotoxicity rates of antituberculosis drugs.

Written in English Language Is Better, and We Prefer to Include Studies Written in the English Language. ② 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 | Comparison of incidence of peripheral nerve disease with antituberculosis drugs.

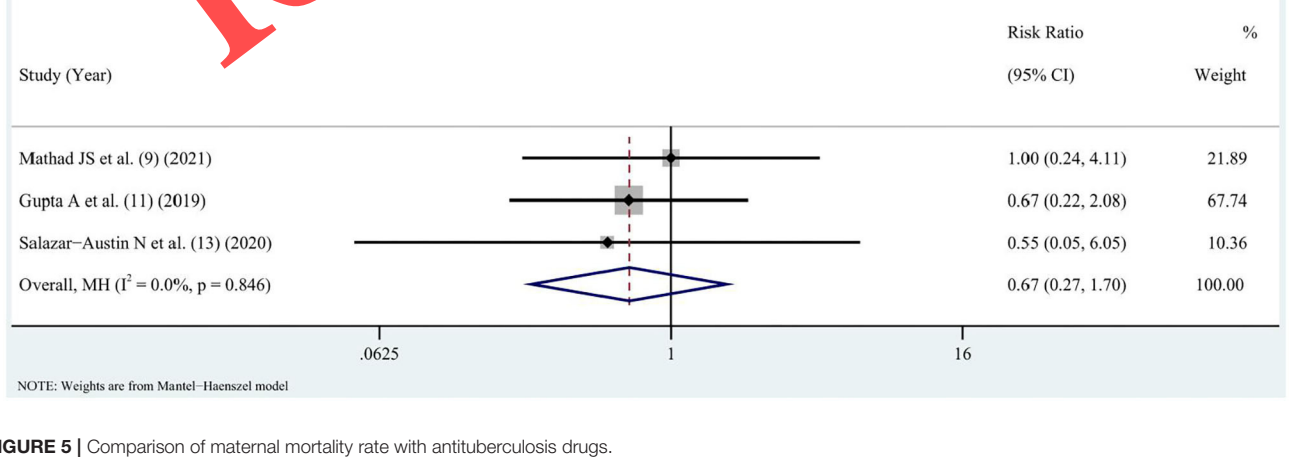

FIGURE 5 | Comparison of maternal mortality rate with antituberculosis drugs.

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

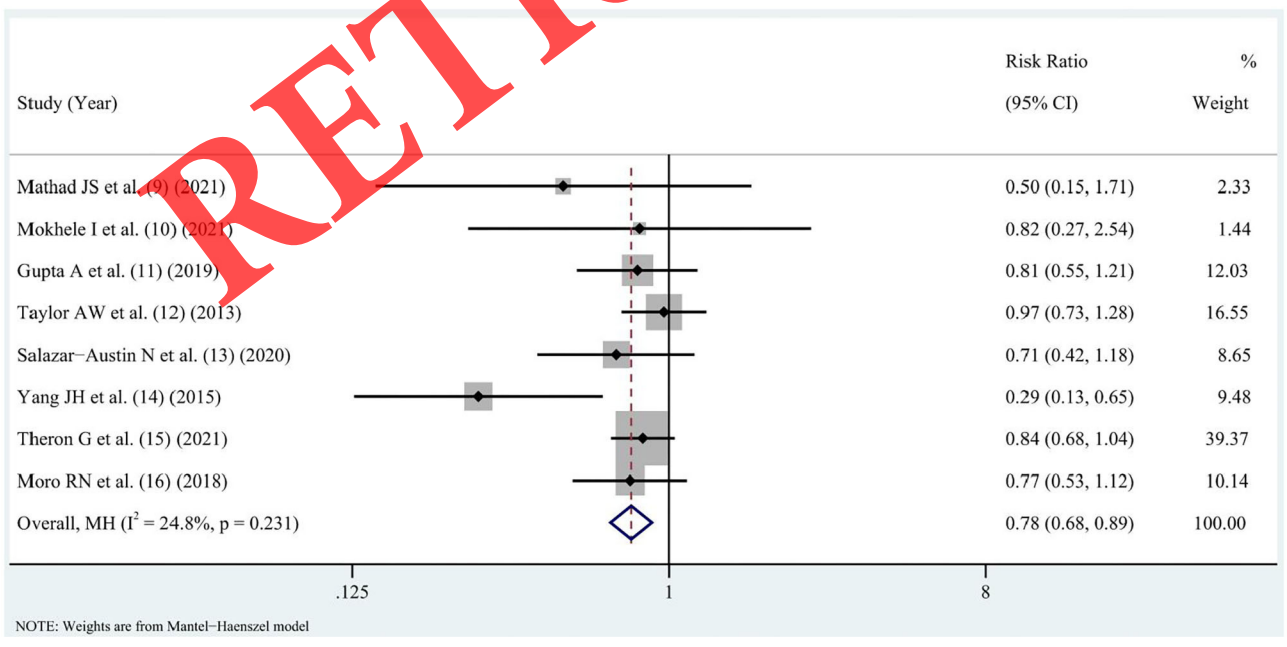

FIGURE 6 | Effect of antituberculosis drugs on the incidence of adverse pregnancy outcomes.

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 I^2 analysis and *Q* verification literature heterogeneity were used, and $I^2 > 50\%$ 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 metanif 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 **Table 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 ($I^2 = 0\%$, $P = 0.589$). A fixed-effects model analysis was performed to obtain the pooled value [$RR = 0.99$, 95% CI

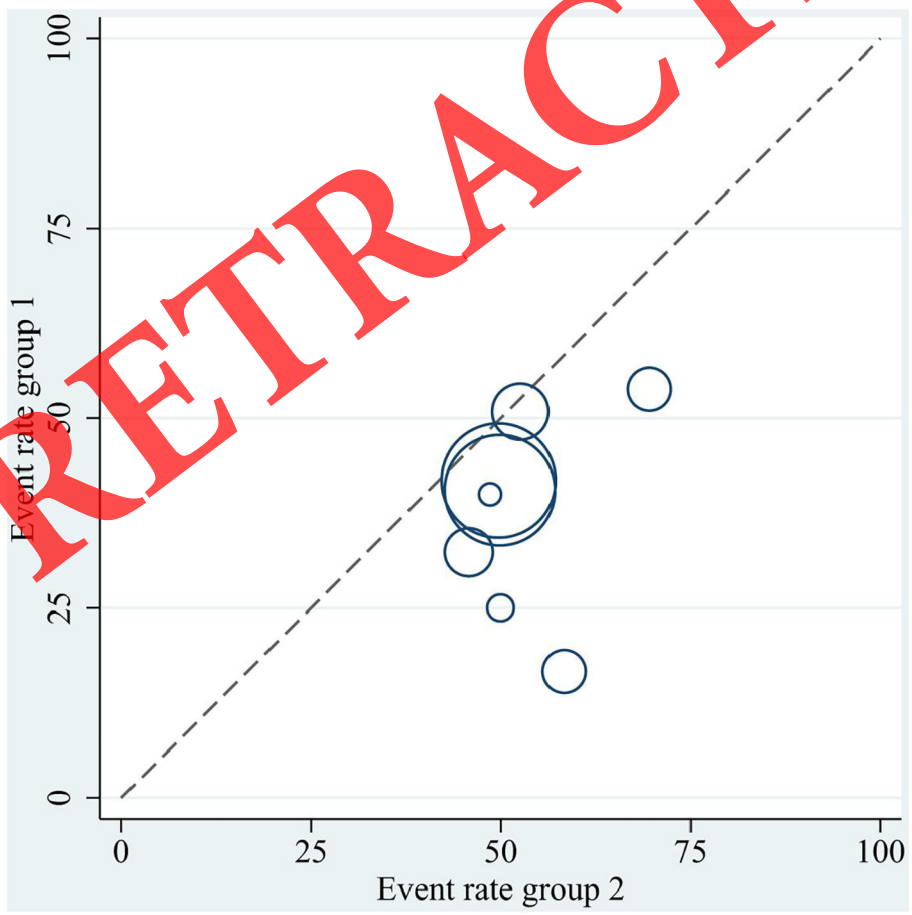

FIGURE 7 | Heterogeneity survey using Labbe plot.

(0.88, 1.12), $Z = -0.108$, $P = 0.914$], and the difference had no statistical significance ($P > 0.05$), as shown in **Figure 2**.

Hepatotoxicity Rate

The literature (9–11) reported hepatotoxicity after treatment, but there was no statistical heterogeneity in the s ($I^2 = 0\%$, $P = 0.401$). 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

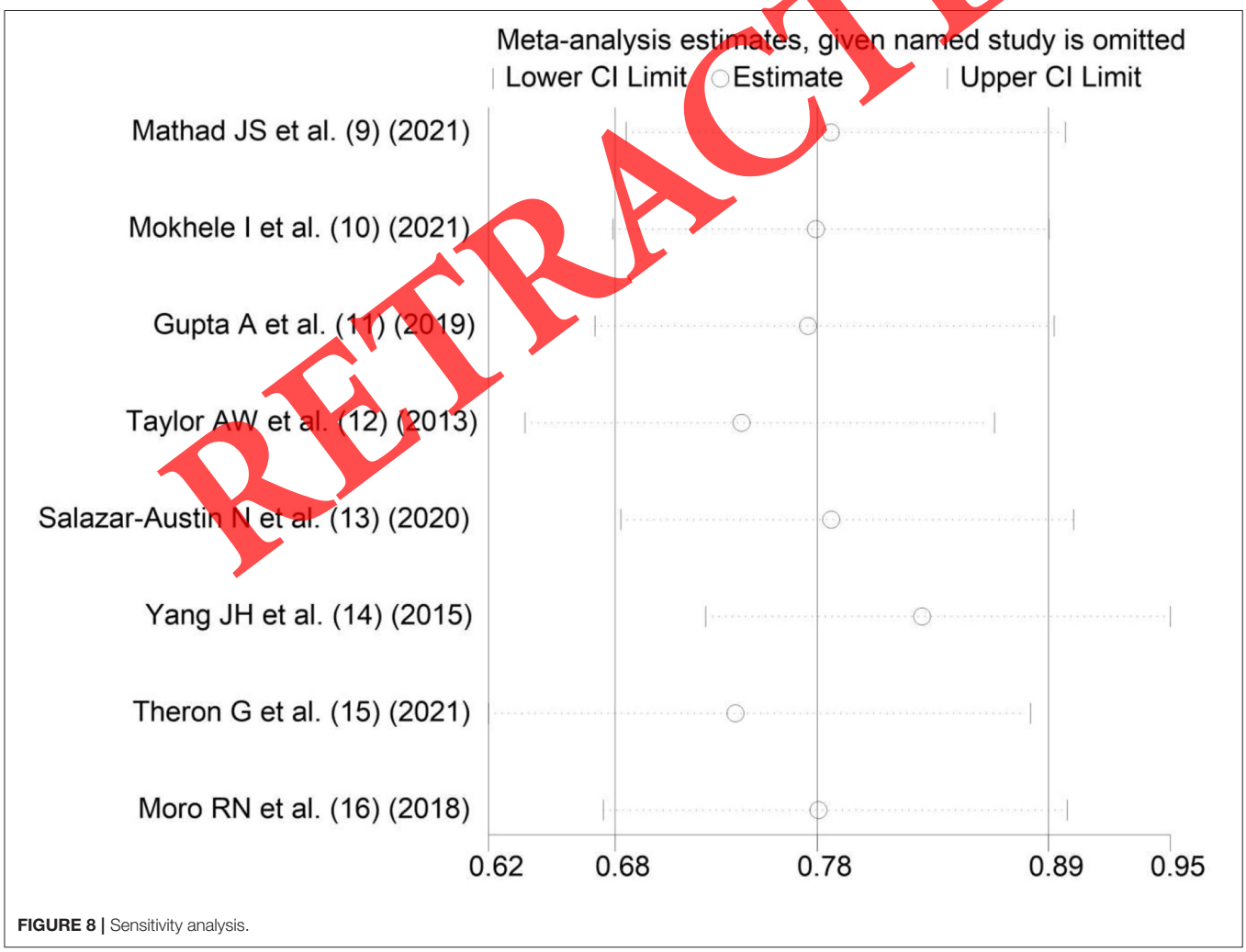

FIGURE 8 | Sensitivity analysis.

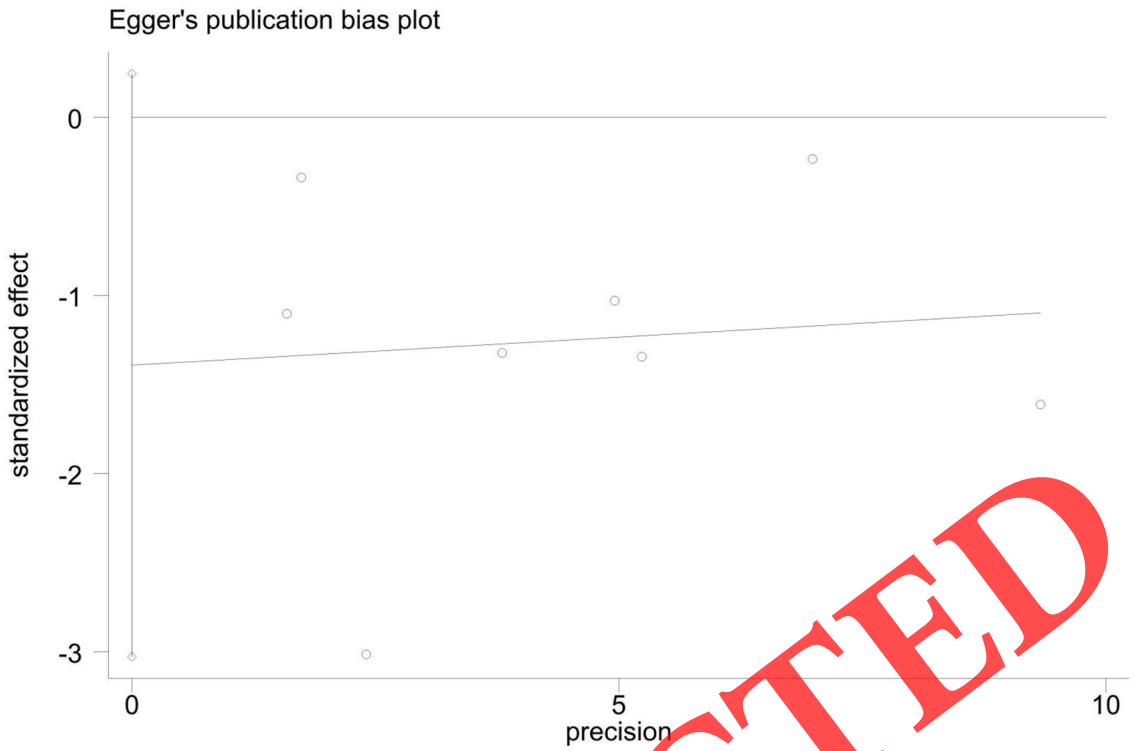

FIGURE 9 | Egger's regression progressive plot.

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 statistics, and manuscript writing. All authors contributed to the article and approved the submitted version.

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