The safety of isoniazid preventive treatment in pregnant and postpartum women: systematic review and meta-analysis

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A 256-character summary:

Studies report conflicting links between isoniazid preventive therapy (IPT) and adverse pregnancy outcomes. Given known harms of active TB in pregnancy, the findings do not support systematic deferral of IPT until postpartum. We need more safety research.

Summary

Background

The World Health Organization recommends TB preventive treatment for high-risk groups. Isoniazid preventive therapy (IPT) has been used globally for this purpose for many years, including in pregnancy. This review assessed current knowledge about the safety of IPT in pregnancy.

Methods

We searched PubMed, Embase, CENTRAL, Global Health Library, and HIV and TB-related conference abstracts, until 15 May 2019, for randomized controlled trials (RCT) and non-randomized studies (NRS) where IPT was administered to pregnant women. Outcomes of interest were 1) maternal outcomes, including permanent drug discontinuation due to adverse drug reactions, any grade 3 or 4 drug-related toxic effects, death from any cause, and hepatotoxicity and 2) pregnancy outcomes, including in utero fetal death, neonatal death or stillbirth, preterm delivery/prematurity, intrauterine growth restriction, low birth weight, and congenital anomalies. Meta-analyses were conducted using a random-effects model.

Results

After screening 1342 citations, nine studies (34 to 51,942 participants) met inclusion criteria. We found an increased likelihood of hepatotoxicity among pregnant women given IPT (RR:1.64, 95%CI 0.78-3.44) compared with no IPT exposure in one RCT. Four studies reported on pregnancy outcomes comparing IPT exposure to no exposure, among pregnant women with HIV. In one RCT, adverse pregnancy outcomes were associated with IPT exposure during pregnancy (OR:1.51, 95%CI 1.09-2.10), but three NRS showed a protective effect.

Conclusions

We found inconsistent associations between IPT and adverse pregnancy outcomes. Considering the grave consequences of active TB in pregnancy, current evidence does not support systematic deferral of IPT until postpartum. Research on safety is needed.

Introduction

Pregnant women with HIV have a high risk of acquiring tuberculosis (TB), which can have severe consequences for both mother and the fetus [1]. Isoniazid has a well-documented safety profile established from its long history of use in pregnant and breastfeeding mothers treated for both latent and active TB.

The 2011 World Health Organization guidelines recommend isoniazid preventive therapy (IPT) in people living with HIV regardless of pregnancy [2]. These guidelines and the 2018 guideline on latent tuberculosis infection (LTBI) advise caution and clinical judgement when deciding the best time to start LTBI treatment in pregnant women [3]. Pregnancy and the postpartum period is a risk factor for drug-induced hepatotoxicity [4] and, although evidence is insufficient, WHO encourages clinical monitoring as well as baseline liver function tests, where feasible, for these groups [3].

A recent clinical trial reported more frequent adverse pregnancy outcomes among women with HIV exposed to IPT during gestation [5]. The study also reported higher frequency of maternal adverse events than expected. There is no systematic review to date that investigated safety of IPT among pregnant women. Therefore, this systematic review assessed the safety of IPT in pregnant and postpartum women compared to other preventive treatment regimens or no treatment.

Material and methods

Search strategy

We performed a systematic review and meta-analysis using the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) [6] and Meta-analysis Of Observational Studies in Epidemiology (MOOSE) [7]. The protocol for this review is registered on PROSPERO (www.crd.york.ac.uk/prospero/; CRD42019136065).

We searched the following databases from inception to 15 May 2019: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (PubMed), Embase, Global Health Library and reviewed

databases listing ongoing RCTs through ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform. We developed the search strategy in consultation with a librarian (Appendix 1). We searched major HIV and TB conferences: International AIDS Conference (AIDS), IAS Conference of HIV Science (IAS), Conference on Retroviruses and Opportunistic Infections (CROI), the UNION World Conference on Lung Health, European Respiratory Society Congress (ERSC), American Thoracic Society Conference (ATS). AIDS and IAS were searched for all available years (2002-2019). For CROI, the UNION, ERSC and ATS, only conferences in the last three years were searched. We did not impose any language or geographic restrictions. We screened bibliographies of included articles and contacted experts and authors of relevant studies to retrieve relevant study information.

Study eligibility and data extraction

Two reviewers independently screened titles and abstracts of studies identified from the search for inclusion. Two reviewers independently screened the full text and assessed their eligibility. Any disagreements were resolved through discussion.

Studies were included when 1) study population included pregnant or postpartum women defined as within 12 months after delivery regardless of HIV status; 2) the intervention was preventive treatment with daily isoniazid alone for 6 months or longer; 3) the comparator was other preventive treatment regimens or no preventive treatment, including the deferred provision until postpartum in a comparison group; 4) the outcomes included permanent drug discontinuation due to adverse drug reactions, any grade 3 or 4 drug-related toxic effects, death from any cause, hepatotoxicity, in utero fetal death, neonatal death, preterm delivery/prematurity, intrauterine growth restriction, low birth weight, and congenital anomalies; and (5) the study design was a randomized controlled trial (RCT) or non-randomized studies (NRS). We initially intended to exclude studies without a comparison group; however, we also included them due to the limited number of studies identified. We excluded studies that included participants with active TB or those who were exposed to multidrug-resistant TB or isoniazid- resistant TB.

Data were extracted independently by two reviewers using standardized extraction forms. The following information was extracted: study design, total duration and date of study, study context (setting, location); number of participants, age, race, ethnicity, body mass index, body weight, education history, HIV status (and antiretroviral status, CD4 counts, and viral load), obstetric history, inclusion criteria, exclusion criteria, comorbidities, results of tuberculin skin test and interferon gamma releasing assays, contact history; type of intervention, comparison, concomitant medications and outcomes. Any disagreements were resolved by consensus. We contacted authors for missing data.

Quality of individual studies and evidence assessment

For the risk of bias of individual studies, we used the revised Cochrane risk-of-bias tool for RCTs (RoB2) [8] and the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool to assess the risk of bias for NRS [9]. GRADE methodology was used to assess and appraise the quality of evidence for each outcome across all studies [10]. We made an overall judgement on the quality of evidence across RCT and NRS separately. The initial rating of the certainty of evidence started with high rather than low and subsequently rated down as recently recommended by the GRADE working group as approach when Robins-I was used [11].

Statistical analysis and meta-analysis

We presented relative risks for dichotomous data with 95% confidence intervals (CI). We conducted meta-analysis with a random effects model using the DerSimonian and Laird method [12] if included studies were clinically and sufficiently homogenous. When at least one study included zero events in one group, we used the Mantel-Haenszel method without continuity correction. Due to inconsistency in the direction of effect indicating a significant heterogeneity by study type, we did not pool data from RCT and NRS. For NRS, we pooled adjusted estimates and if not available, we pooled unadjusted estimates. We did not pool unadjusted and adjusted estimates together. We presented data by HIV status, pregnancy

or postpartum, and preventive treatment regimen given to the control group; however, the limited number of studies precluded meta-analyses by sub-group. We used forest plots to visually assess heterogeneity among the included trials. The small number of studies precluded a sensitivity analysis.

Results

From 1342 records identified, nine studies met our inclusion criteria, including two conference abstracts (Figure 1) [4, 5, 13-19]. Six studies included only women with HIV [5, 13, 15-17, 19] and three included very few or no HIV-positive women [4, 14, 18]. Of the six studies among HIV-positive women, five were conducted in African countries [13, 15-17, 19] and one was conducted in multiple countries with high TB prevalence ≥ 60 per 100,000 population [5]. Eight studies were NRS, three reported data among women who were enrolled in trials of different preventive treatment regimens and became pregnant during the trial [14, 17, 19]; four included pregnant women started on IPT [4, 13, 15, 16] and one included postpartum women [18]; remaining study was a RCT comparing pregnant women with HIV who started 6 months of IPT immediately upon enrollment and those who deferred it until 12 weeks postpartum [5]. Table 1 summarizes study characteristics.

Maternal outcomes

Four studies reported data on hepatotoxicity in pregnant women with HIV [5, 15-17], five studies reported deaths [5, 13, 15-17], two studies reported Grade 3 or 4 adverse events [5, 16] and one study reported treatment discontinuations [5] (Tables 3A-5A). The RCT by Gupta et al [5] reported the highest frequency of hepatotoxicity (6.1% in the immediate IPT arm and 7.1% in the deferred IPT arm) while Karl et al [15] reported only 0.3% and two NRS reported none. Frequency of deaths ranged from none to 2% across studies.

Table 1. Characteristics of included studies

First author	Study design	Setting	Population	INH arm	Comparison
Chang, et al, 2013 [18]	Retrospective cohort	A TB referral center, USA	LTBI patients who began INH treatment including 228 post-partum women	6-9 months of INH (n=228)	No control group who were given no or other regimens
Gupta et al, 2019 [5]	RCT	Eight countries with high TB prevalence ≥ 60 per 100,000 population	HIV-infected pregnant women ≥18 years old. 14-34 weeks gestation. 99.8-100% on cART	Immediate INH (INH started at study entry and continued for 28 weeks) (n=477)	Deferred INH (INH started at 12 weeks post-partum and continued for 28 weeks) (n=479)
Frank et al, 1989 [4]	Retrospective cohort	A clinic, USA	Women enrolled during the first 18 months of the prenatal IPT program	6-12 months of INH (n=3681)	No control group who were given no or other regimens.
Kalk et al, 2018 [15][#]	Retrospective cohort	Routine electronic clinical information systems from public sector health facilities in the Western Cape, South Africa	HIV-infected women on or initiating cART during pregnancy. 41.8% newly initiated on cART and the rest were already on cART.	INH duration unknown. (n=10715) Based on "prescription" in the electronic record.	No treatment (n=41227)
Msandiwa et al, 2009 [19][#]	Sub-analysis of RCT	A hospital, South Africa	Women with HIV who became pregnant during the trial	6 months or continuous INH (n=26)	3-month rifampicin or 3HP (n=8). They were switched to INH alone or discontinued.
Moro et al, 2018 [14]	Sub-analysis of two RCTs	TBTC 26 and 33. (USA, Canada, Brazil, Spain, Peru, South Africa, Hong Kong)	Women who became pregnant during the trial	9 months INH (n=56)	3HP (n=31) No exposure (n=39)
Salazar-Austin et al, 2019 [13]	Prospective cohort	Antenatal clinics and obstetrics wards at a Hospital, South Africa	Pregnant women with HIV≥18 years old 66-78% on cART	6 months INH (n=71), Median gestational age at initiation: 25 weeks (IQR 20-30 weeks)	No INH (n=84)
Taylor, et al, 2013 [17]	Sub-analysis of RCT	Clinics, Botswana	Women with HIV ≥18 years old who became pregnant during the trial 37% on cART and the rest on AZT or AZT/3TC	6-36 months INH (n=103)	No exposure (n=93)
Tiam et al, 2014 [16]	Prospective cohort	Two hospital-based maternal and child health clinics, Lesotho.	Pregnant women ≥14 years old with HIV who presented for their first antenatal clinic visit irrespective of their gestational age. 36.2% on cART and the rest on AZT prophylaxis	6 months of INH (n=124)	No control group who were given no or other regimens

[#]Conference abstracts

RCT: Randomized controlled trial; TB: Tuberculosis; USA: United States of America; LTBI: Latent tuberculosis infection; IPT: Isoniazid preventive therapy; cART: combination antiretroviral therapy; AZT: Zidovudine; 3TC: Lamivudine; INH: Isoniazid; IQR: Interquartile range; 3HP:3-month weekly rifapentine plus isoniazid

Gupta et al provided data on hepatotoxicity compared to placebo by restricting to events occurred until 3 months post-partum before the control group was started on IPT [5] (Table 2). In the analysis, the frequency of hepatotoxicity was higher in women living with HIV given IPT during pregnancy (18/477, 3.8%) than those given placebo (11/479, 2.3%); this difference was not statistically significant (RR 1.64, 95% CI 0.78-3.44) [5]. Kalk et al did not find difference in frequency of hepatotoxicity between the two groups [15].

Table 2 Hepatotoxicity in pregnant women living with HIV in included studies

Study	IPT	Control	Effect (95%CI)
Gupta et al, 2019	18/477 (3.8%)#	Placebo 11/479 (2.3%)#	RR 1.64 (0.78-3.44)
Kalk et al, 2018	30/10715 (0.3%)	No treatment 114/41227 (0.3%)	RR 1.01 (0.68-1.51)
Tiam et al, 2014	0/124 (0%)	NA	NA
Taylor et al, 2013	0/103 (0%)	NA	NA

#The analysis was restricted to events that occurred until 3 months post-partum. Some women were still on IPT and were censored.
IPT: Isoniazid preventive therapy; RR: Risk ratio; CI: Confidence interval

Three studies reported maternal death in pregnant women with HIV who received IPT compared to those who did not [5, 13, 17] (Table 3). The RCT did not show a statistically significant difference in the risk of death between the two groups [5]. Meta-analysis of two NRS suggested a lower risk of death in pregnant women with HIV given IPT (RR 0.65, 95%CI 0.39-1.07).

Table 3 Maternal deaths in pregnant women living with HIV in included studies

	IPT	Control	Effect (95%CI)
Gupta et al, 2019	1/477 (0.2%)	Placebo: 3/479 (0.6%)	RR: 0.33 (0.03 – 3.21)
Kalk et al, 2018	18/10715 (0.2%)	No treatment: 103/41227 (0.3%)	RR: 0.67 (0.41-1.11)
Salazar-Austin et al, 2019	0/71 (0%)	No INH exposure: 2/84 (2%)	RR: 0.24 (95%CI: 0.01- 4.84)
Tiam et al, 2014	2/124 (1.6%)	NA	NA
Taylor et al, 2013	0/103 (0%)	No INH exposure: 0/93	NA

IPT: Isoniazid preventive therapy; INH: Isoniazid; RR: Risk ratio; CI: Confidence interval

One RCT provided data on Grade 3 or 4 adverse events and treatment discontinuations in pregnant women with HIV given IPT compared to placebo [5]. There was no statistical difference in the frequency of treatment discontinuation between the two groups (2.3% vs 1.7%; RR 1.38, 95%CI 0.56-3.40). There was a higher risk of Grade 3 or 4 adverse events in participants given IPT (7.1% vs 4.6%; RR 1.55, 95%CI 0.92-2.61).

For HIV-negative pregnant women, Moro et al reported data on Grade 3 or 4 adverse events, hepatotoxicity, and deaths in pregnant women on IPT (n=56) and 3-month weekly rifapentine and isoniazid (3HP) (n=31) without a significant difference between the two groups [14]. Other studies did not provide data with a control group [4, 16-18].

Pregnancy outcomes

Four provided data on comparison between IPT and no treatment or placebo among pregnant women living with HIV (Table 6A). All of them reported composite pregnancy outcomes including at least low birth weight, preterm delivery, spontaneous abortion, stillbirth, and major congenital anomaly in the composite. Kalk et al additionally included "termination of pregnancy" and neonatal death [15]. Taylor et al additionally included neonatal death [17]. The frequency of these composite pregnancy outcomes among women given IPT ranged from 15.0% to 31.1%. In three studies reporting frequency of individual outcomes, prematurity and low birth weights were commonly observed (10.1-13.4% for prematurity and 8.7-14.9% for low birth weights) in women given IPT [5, 13, 15]. This was similar in women not exposed to IPT (Table 6A).

Results from one RCT and the three NRS were inconsistent (Figure 2). The RCT showed a significantly higher risk of composite adverse pregnancy outcomes in those who initiated IPT during pregnancy (Mantel-Haenszel OR stratified by gestational age, 1.51 95%CI 1.09-2.10) while a meta-analysis of composite outcomes using adjusted estimates from the two NRS suggested a significantly lower risk of

adverse pregnancy outcome (OR: 0.40, 95%CI 0.20-0.74) (Figure 2). Due to substantial heterogeneity (I^2=80%, p=0.002), we did not pool data from the RCT and NRS.

A similar trend was observed when individual outcomes were analyzed (Figure 3 and Tables 7A-10A). In the RCT, women on IPT were more likely to experience still birth, spontaneous abortion, or neonatal death, preterm birth, low birth weight, and congenital anomaly while none of them was statistically significant [5]. Salazar-Austin et al reported a lower risk of low birth weight and preterm delivery in those given IPT [13]. In the study by Kalk et al, IPT was significantly associated with lower risk of individual adverse pregnancy outcomes [15].

In HIV-negative pregnant women, only one study reported data on pregnancy outcomes (still birth, spontaneous abortion, or neonatal death and congenital anomaly) [14]. This study did not find a statistical difference among pregnant women exposed to IPT, 3HP, and no treatment; however the number of women in each group was very small (n=56, 31, and 39, respectively).

Quality of evidence assessment

Tables 1A and 2A in Annex 2 present results of risk of bias assessment. The risk of bias in the RCT by Gupta et al was considered of some concern due to missing outcome data (15.9% in the immediate IPT arm and 17.3% in the deferred IPT arm). Of the four NRS with a control group that reported pregnancy outcomes, all were considered at serious risk of bias.

We rated quality of evidence on a comparison between IPT and no preventive treatment or placebo among pregnant women with HIV (Table 2). Certainty of evidence ranged from low to moderate from the one RCT and very low to low from two NRS.

Table 2. GRADE assessment of evidence. IPT compared to no IPT or placebo for pregnant women living with HIV.

Outcomes (studies)	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants	Certainty of the evidence (GRADE)
	Risk with no IPT or placebo	**Risk with IPT**			
Composite pregnancy outcomes (Low birth weight, preterm delivery spontaneous abortion, stillbirth, or congenital anomaly (1 RCT[1])	170 per 1,000	236 per 1,000 (182 to 300)	**OR 1.51** (1.09 to 2.10)	909	⨁⨁⨁◯ MODERATE [a]
Composite pregnancy outcomes (Low birth weight, preterm delivery, spontaneous abortion, stillbirth, neonatal mortality, or congenital anomaly) (2 observational studies[3,4])	360 per 1,000	209 per 1,000 (101 to 294)	**OR 0.471** (0.199 to 0.742)	347	⨁◯◯◯ VERY LOW [a,b]
Maternal death (1 RCT[1])	6 per 1,000	2 per 1,000 (0 to 20)	**RR 0.33** (0.03 to 3.21)	956	⨁⨁◯◯ LOW [c]
Maternal death (2 observational studies[3,4])	3 per 1,000	2 per 1,000 (1 to 3)	**RR 0.65** (0.39 to 1.07)	52097	⨁⨁◯◯ LOW [b]
Grade 3 or 4 adverse events related to study treatment (1 RCT[1])	46 per 1,000	71 per 1,000 (42 to 120)	**RR 1.55** (0.92 to 2.61)	956	⨁⨁⨁◯ MODERATE [a]
Hepatotoxicity (1 RCT[1])	23 per 1,000	38 per 1,000 (18 to 79)	**RR 1.64** (0.78 to 3.44)	956	⨁⨁⨁◯ MODERATE [a,d]
Hepatotoxicity (1 observational study[2])	3 per 1,000	3 per 1,000 (2 to 4)	**RR 1.01** (0.68 to 1.51)	58242	⨁⨁◯◯ LOW [e,f]
Discontinuation of study drug due to toxicity (1 RCT[1])	17 per 1,000	23 per 1,000 (9 to 57)	**RR 1.38** (0.56 to 3.40)	956	⨁⨁⨁◯ MODERATE [d]

***CI: Confidence interval; IPT**: isoniazid preventive therapy; **OR:** Odds ratio; **RR:** Risk ratio; RCT: Randomized controlled trial.*

***Bibliography**: [1]Gupta et al, 2019; [2]Kalk et al, 2018, [3]Salazar-Austion et al, 2019; and [4]Taylor et al, 2013*

Explanations

a. Optimal information size not met

b. Bias due to confounding is considered serious. Important confounders are not fully accounted for.

c. Large CI including both appreciable benefits and harms and very few events

d. CI includes both appreciable benefits and harms

e. Confounding was not accounted for. Bias due to measurement of hepatotoxicity is considered serious since liver function tests were performed only if clinically indicated, which was likely to be influenced by knowledge of the receipt of IPT.

f. Very large sample size and CI of absolute effect is very narrow.

Discussions

This is the first systematic review that evaluated the safety of IPT among pregnant women. Our review found inconsistent associations between IPT and adverse pregnancy outcomes among pregnant women with HIV in different studies. IPT was associated with more adverse pregnancy outcomes in one RCT while it was protective in three NRS. Frequency of hepatotoxicity was higher in the RCT than NRS.

There are several possible reasons for the discrepancy. First, it may be explained by differences in participant characteristics and settings. In the RCT, almost all of the participants (99.8% in immediate IPT arm and 100% in delayed IPT arm) were already on combination ART (cART) at baseline. However, this was not the case in the three NRS. In the study by Salazar-Austin et al, 72% of women were on ART at delivery while in the study by Taylor et al, only 37% received cART during pregnancy. In the study by Kalk et al, although all women were on cART, 41.8% of them started it during pregnancy. In fact, median CD4 counts were higher in the RCT (491 cells/mm^3 in immediate IPT arm and 496 cells/mm^3 in deferred IPT arm) compared to the other studies with median CD4 counts ranging from 364 to 424 cells/mm^3. Furthermore, the three NRS were conducted in South Africa and Botswana, where TB incidence is estimated to be amongst the highest in the world [20]. In contrast, only one third of the RCT study subjects were enrolled in South Africa and Botswana and the remaining participants were from countries with a lower TB incidence. Women in the NRS may thus have been at a higher risk of TB than those in the RCT. In fact, Kalk et al reported 1.5-fold higher risk of TB in those not given IPT. It is therefore possible that IPT reduced adverse pregnancy outcomes by averting more active TB during gestation. However, Salazar-Austin et al reported no TB cases in the control group during pregnancy and the reason for reduction of adverse pregnancy outcomes in the IPT group thus remains unclear [13]. Secondly, NRS were at higher risk of bias. For example, they did not control for all important confounders such as history of liver disease, alcohol use, and pregnancy history. Thirdly, it is possible that the RCT found more adverse pregnancy outcomes by chance.

The higher frequency of hepatotoxicity observed in the RCT could also be explained by a difference in the uptake of ART. ART causes hepatotoxicity and drug interactions while IPT may increase the risk further [21] [22]. In addition, due to its study design, the RCT measured events that developed while participants were on placebo. Therefore, as the authors discuss, not all hepatotoxic events are attributable to IPT [5]. It is also likely that the rigorous monitoring and systematic laboratory testing during the follow-up may have detected more events than would be observed under routine programmatic conditions. The NRS performed liver function tests only when clinically indicated in accordance with the standard practice recommended by WHO [13, 15, 17]. Asymptomatic liver enzyme elevation may be transient or resolve after completion of treatment without causing clinically significant effects. It is unknown whether routine liver function testing actually prevents clinically significant hepatotoxicity through earlier cessation of a medicine in the field.

Given the findings from the one RCT, deferral of TB preventive treatment may be justifiable in those with low risk for TB after careful consideration of benefits and harms and informed choice of the woman. However, this needs caution. Multiple studies have reported loss to HIV-care after delivery [23-25]. Therefore, deferral of IPT may lead to a missed opportunity to protect women and their babies from TB and deaths. Although data on IPT are limited in pregnant women, this should not be an impediment to giving TB preventive treatment to pregnant women at high risk for progression to active TB. To strengthen confidence in initiating TB preventive treatment during pregnancy, we need safety studies in both HIV-positive and negative pregnant women. This should include different regimens and would preferably be designed as RCTs with appropriate power to measure key pregnancy and maternal outcomes individually. Pooled meta-analysis from person-level data that includes longer-term postpartum surveillance for adverse events in infants would also be helpful.

The strengths of this review include the use of a comprehensive search strategy, explicit inclusion criteria, a systematic approach to data collection and an independent assessment for study inclusion and data extraction. This enabled the first comprehensive assessment of the body of evidence on the safety of IPT

among pregnant women. Our review revealed that the increased risk of adverse pregnancy outcomes due to IPT in a single RCT was not supported by multiple NRS though their risk of bias was serious. This finding and the limited number of studies available signal an urgent need for more research on this important clinical and public health issue.

This review has several limitations. The majority of studies that met inclusion criteria were among pregnant women living with HIV aware of their status. Only three studies provided data on IPT safety among HIV-negative and pregnant women living with HIV unaware of their status and two of them did not include a control group not given IPT. The associations observed among HIV-positive pregnant women are likely to be influenced by the concurrent use of ART and the increased risk of developing TB in these women. The finding is thus not fully generalizable to HIV-negative pregnant women. Second, limited data were available on safety of IPT compared to rifamycin-containing preventive TB regimens among pregnant women. Third, our primary analysis focused on composite adverse pregnancy outcomes because adjusted odds ratios were not available for individual outcomes. The composite outcome was driven by preterm delivery and low birth weight. The frequency of other outcomes (e.g. congenital anomaly and still birth) is usually much lower than those outcomes [26-29]. This was also the case in our review and hence less evidence is available on the impact of IPT on the other outcomes.

In conclusion, a single RCT showed an increased risk of adverse pregnancy outcomes due to IPT while three NRS suggested it has a protective effect. The benefits of IPT may outweigh potential adverse effects from IPT in women at high risk of TB. Therefore, our findings do not support systematic deferral of IPT until postpartum regardless of the risk of TB.

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Figure legends
Figure 1. PRISMA flow diagram

Figure 2. Composite pregnancy outcomes in pregnant women with HIV

Note: The meta-analysis was conducted using adjusted odds ratios.
RCT: randomized controlled-trial; NRS: non-randomized study

Figure 3. Individual pregnancy outcomes in pregnant women with HIV

IPT: isoniazid preventive therapy, CI: Confidence interval, RCT: randomized controlled-trial, NRS: non-randomized study