

# BMJ Open Examining family planning and adverse pregnancy outcomes for women with active tuberculosis disease: a systematic review

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## ABSTRACT

**Objectives** (1) Summarise and evaluate the current evidence of tuberculosis (TB)-associated pregnancy outcomes, (2) evaluate the state of the science of family planning during TB treatment and (3) provide recommendations to move forward to improve care and outcomes during TB disease.

**Design** Systematic review using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.

**Data sources** PubMed, Embase, CINAHL, Cochrane, Web of Science and Scopus were searched from September 2009 to November 2021.

**Eligibility criteria** Studies were included if they assessed pregnant women with active TB, drug-resistant TB (DR-TB) or TB/HIV coinfection and examined pregnancy, maternal, fetal/birth and TB or TB/HIV coinfection outcomes. Studies were also included if they examined family planning services among women initiating TB treatment.

**Data extraction and synthesis** Two independent reviewers extracted data using PRISMA guidelines and conducted quality assessment using the Joanna-Briggs Institute Critical Appraisal Tools. The level of evidence was reported using the Johns Hopkins Evidence-Based Practice guidelines.

**Results** 69 studies were included in this review. Case reports, case series, case controls, cohort studies, secondary data analyses and a service delivery improvement project conducted in 26 countries made up the totality of the evidence. Most studies reported pregnancy complications for mothers (anaemia, postpartum haemorrhage, deaths) and fetuses or newborns (low birth weight, premature birth, and spontaneous or induced abortions). Few studies discussed the value of offering family planning to prevent adverse pregnancy outcomes. One study examined the effect of a provider training on contraceptive use with reported increased contraceptive use.

**Conclusions** Integrating family planning services within a TB treatment programme is essential to reduce adverse TB-associated maternal-child outcomes. Despite well-established adverse pregnancy outcomes, little attention has been paid to family planning to prevent poor pregnancy outcomes for women with TB/DR-TB. Recommendations for clinicians, TB programmes and researchers are provided and reflect evidence presented in this review.

## Strengths and limitations of this study

- A systematic search of six major electronic databases was conducted and results reported per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.
- Inclusion of case reports and case series allows for the synthesis of important clinical data that is often not reported in systematic reviews.
- Review was limited by the inclusion of only peer-reviewed, English journal articles published in the last 11 years, which likely excluded important findings in other languages and important programmatic data at a country level.
- The variability of study designs, outcome definitions and methods across this body of literature made comparison of outcomes difficult and therefore we were unable to conduct a meta-analysis.

## BACKGROUND

In 2018, about 3.2 million women worldwide contracted tuberculosis (TB) and almost 500 000 died from the disease.<sup>1</sup> Although TB affects more men than women, it disproportionately places women at a higher risk of morbidity and mortality.<sup>2</sup> TB is a non-obstetric cause of maternal mortality and is especially dangerous for women of reproductive age in settings with high rates of TB or drug-resistant TB (DR-TB) and HIV coinfection.<sup>2</sup> TB among mothers is associated with a sixfold increase in perinatal deaths and a twofold risk of premature birth and low birth weight (LBW).<sup>1</sup> Risk of maternal and fetal morbidity and mortality increases by 400% when HIV coinfection is introduced.<sup>1</sup>

The potential teratogenic effects of TB and DR-TB treatment may add further risks to these already high-risk pregnancies: most of the first- and second-line TB drugs are categorised per the US Food and Drug Administration (FDA) as pregnancy Class C or D.<sup>3</sup> First-line treatment of drug-susceptible TB includes isoniazid, rifampin, pyrazinamide

and ethambutol, all of which are categorised as pregnancy Class C per the US FDA.<sup>3–7</sup> It is nevertheless recommended pregnant women receive drug-susceptible TB treatment as early in their pregnancy as possible because the benefits of treatment outweigh the potential adverse outcomes.<sup>3</sup> DR-TB occurs in about 10% of patients with TB and can be detrimental to health and survival since treatment regimens are toxic and prolonged (lasting 9–18 months), and unsuccessful in 44% of cases.<sup>3,8</sup> Most of the second-line TB drugs are also categorised as pregnancy Class C or D. It is up to the providers' discretion to provide and individualise drug regimens for the treatment of DR-TB, who may present with advanced disease and therefore are more at risk of adverse outcomes.

Comprehensive family planning services have the potential to reduce women's risk of adverse pregnancy outcomes in the context of TB and DR-TB. Such services would include counselling about the risks associated with becoming pregnant while undergoing TB or DR-TB treatment, providing safe and preferred methods of contraception and referring women to appropriate care if they intend to conceive or become pregnancy during TB treatment.<sup>9</sup> Family planning counselling by a TB or DR-TB provider at initiation of TB or DR-TB treatment is especially important given that there are known drug-drug interactions between first-line TB drugs, rifampicin, antiretroviral drugs (eg, protease inhibitors) and contraceptives such as combined contraceptive pills.<sup>10</sup>

Despite reported poor outcomes among pregnant women with TB, DR-TB and HIV coinfection, they have not been systematically summarised with family planning strategies to reduce risks explored. In addition, there are no international guidelines regarding pregnancy and family planning in the context of drug-resistant TB (DR-TB) management. Country-specific TB and/or DR-TB guidelines recommend family planning counselling, and/or pregnancy testing and contraceptive use<sup>11–13</sup> or avoidance of specific antituberculous drugs.<sup>14</sup> However, they do not describe how to integrate these services into TB care. Without a more comprehensive understanding of the risks to and prevention strategies for childbearing women with TB, DR-TB and/or HIV coinfection, it will be difficult to improve services or guide additional research.

This systematic review examines published research on pregnancy outcomes and family planning strategies for women undergoing treatment for TB and DR-TB. The objectives are: (1) to summarise and evaluate current evidence for TB-associated pregnancy outcomes, (2) to evaluate the state of the science of family planning during TB treatment and (3) to provide recommendations to move forward to improve care and outcomes.

## METHODS

### Review design

We conducted a systematic review of peer-reviewed literature on global TB-associated pregnancy outcomes using the guidelines outlined by the Preferred Reporting Items

for Systematic Reviews and Meta-Analyses (PRISMA).<sup>15</sup> Given the heterogeneity of study designs, outcome definitions and statistical analysis approaches among included studies, we critically reviewed and synthesised findings instead of conducting a meta-analysis.

### Eligibility criteria

A systematic approach guided the search for articles addressing TB-related pregnancy outcomes. Studies were included if they assessed patient population of pregnant women with active TB, DR-TB or TB/HIV coinfection, and primary outcome variables included pregnancy outcomes, maternal or fetal/birth outcomes and TB or TB/HIV coinfection outcomes. Studies were also included if they examined outcomes of family planning services among women initiating TB treatment (counselling of pregnancy risks, pregnancy testing, contraceptive uptake). Pregnancy outcomes were any outcome a study defined as maternal outcome or any maternal complication: pre-eclampsia; eclampsia; anaemia; haemorrhage; placental abruption/previa; premature rupture of membrane; unplanned caesarean section or induction; death; or TB, DR-TB or TB-HIV coinfection outcomes as defined below. Studies were also included if they assessed fetal complications or fetal/birth outcomes, which may include premature birth defined as birth prior to 37 weeks, LBW defined as weight below 2500 g, stillbirth, spontaneous abortions/fetal demise or induced abortions and congenital TB infection in newborns up to 6 months postpartum. TB, DR-TB or TB/HIV coinfection outcomes include cure/treatment completion, treatment failure, lost to follow-up or fetal or maternal death.

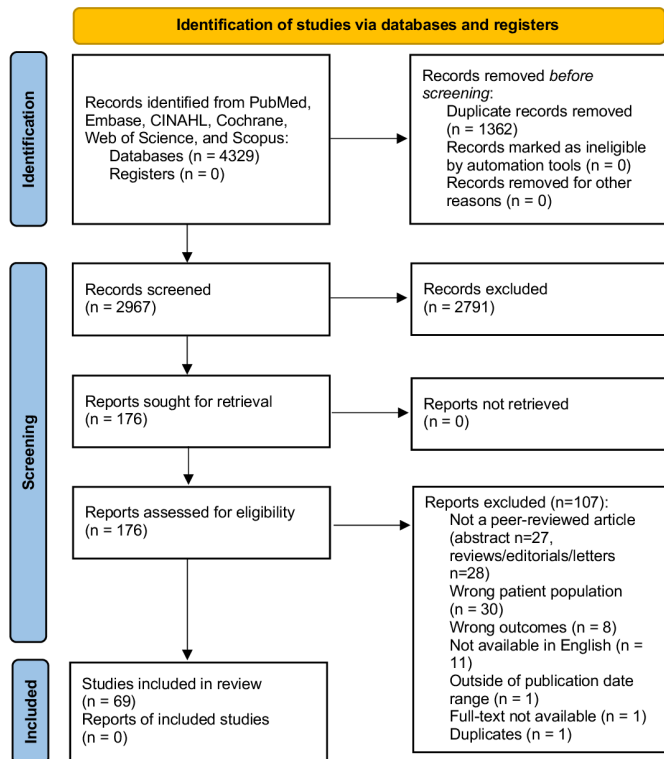
Articles were excluded if they were not peer-reviewed articles (eg, commentaries, communication briefs, editorials, conference abstracts or posters), literature reviews, published prior to 2009; were not written in English and did not include human subjects. We excluded studies older than 2009 to ensure only the most up-to-date evidence was synthesised. We also excluded studies that did not have a primary aim to analyse and discuss pregnancy outcomes as defined above.

### Search and identification process

A Boolean search of the electronic databases PubMed, Embase, CINAHL, Cochrane, Web of Science and Scopus was conducted through 5 November 2021 using the following medical subject heading terms, keywords and associated synonyms in the titles and abstracts: tuberculosis, family planning services, contraceptives, pregnancy outcome, obstetric outcome, fetal morbidity, maternal morbidity, fetal mortality, maternal mortality. The online supplemental appendix provides a full strategy for the search.

### Data extraction and quality assessment

Citations were imported into Covidence and duplicates removed. Two reviewers independently reviewed titles and abstracts. Differences in inclusion of articles were



**Figure 1** Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram: identification and selection of relevant articles.

resolved through consensus. Once the articles for inclusion were finalised, data extraction and quality assessment were performed. The level of evidence of each study was assessed using the Johns Hopkins Evidence-Based Practice (JHEBP) guidelines.<sup>16</sup> The Joanna Briggs Institute (JBI) quality appraisal tools were used to assess the quality of each included citation; studies that fulfilled most to all items of the respective quality appraisal tool indicate they are of high quality and minimal bias.<sup>17</sup> Quality rating assessment was conducted independently by two raters to identify strengths and weaknesses and guide the interpretation of study findings. Any discrepancies were discussed and reconciled by consensus. The critical appraisal of included studies is tabulated in the online supplemental table 1 for review.

### Patient and public involvement

Patients and the public were not involved in this review.

## RESULTS

### Selection of studies

The initial search of all five databases yielded 2967 articles after 1362 duplicates were removed. The full text of 176 articles were thoroughly evaluated to assess eligibility, 107 of which were excluded based on the preidentified exclusion criteria (figure 1).

### Study characteristics

Of the 69 articles included in this review, 68 articles published TB-associated maternal and fetal/neonatal outcomes and 1 article discussed family planning among women with DR-TB. Of these 69 studies, 51 were conducted in low/middle-income countries, with the majority from India (n=12), China (n=10) and South Africa (n=7). Among the high-income countries, the majority (n=8) were from the USA and the UK (n=3).

### Level of evidence and quality appraisal

All studies included were of level III and V evidence per JHEBP guidelines. Level III evidence included non-experimental, observational designs with the majority being retrospective cohort studies (n=15), followed by case-control studies (n=3) and prospective cohort studies (n=3), and secondary data analysis (n=2). Level V evidence included case reports (n=32), followed by case series (n=13) and a service delivery improvement project. There was no experimental (level I), mixed-methods (level II) or qualitative study identified in our search.

The majority of included studies met most or all items of the quality assessment based on the JBI appraisal tool (n=60) with nine fulfilling less than or half of the items of the quality assessment. Because this review aims to provide comprehensive evidence on pregnancy outcomes among women with TB and DR-TB and family planning strategies among this population, we included all studies that met the inclusion criteria regardless of quality or level of evidence. Online supplemental table 1 provides details of the quality assessment and level of evidence of appraised studies. online supplemental table 2 provides details of pregnancy outcomes and other relevant findings for each study included in this review, including study designs, outcome measures and statistical results (online supplemental table 2).

### Current evidence for TB-associated pregnancy outcomes

#### Fetal/newborn outcomes

Overall, reported fetal and newborn outcomes were poor. LBW was a common fetal outcome for TB-infected women with or without HIV coinfection across multiple studies (case reports n=7, case series n=2, cohort study n=8).<sup>18–37</sup> Preterm labour, which adds to the risk of LBW, was reported in multiple studies (case report n=5, case series n=1, case controls n=1, cohort studies n=4) among women with TB infection.<sup>18 21 23 25 26 30 36 38–42</sup> A case-control study found that preterm labour was five times more likely among women with TB (OR 5.9, 95% CI 2.5 to 13.9).<sup>41</sup> One case series and four cohort studies had similar findings: there were higher numbers of preterm births among women with TB versus those who did not.<sup>21 30 36 40 42</sup> A large retrospective cohort study (n=24 149 664) found that pregnant women with TB were more likely to experience preterm labour (13.0% vs 6.8%, p=0.004),<sup>37</sup> and this trend of higher preterm labour rates persisted with other smaller case series and cohort studies.<sup>21 30 40 42</sup>

One large retrospective cohort study (n=2064) found increased congenital anomalies (adjusted OR (aOR)

1.8, 95% C.I 1.24 to 2.62) among newborns of pregnant women with TB.<sup>43</sup> It is unclear if this is attributable to teratogenic effects of TB drugs or other individual variations. A total of eight studies evaluated congenital TB cases. Six case reports of congenital TB discussed babies who were born with LBW, two of which mentioned babies born prematurely and who remained hospitalised for at least 30 days.<sup>22 26 27 44 45</sup> TB outcomes for newborns with congenital TB include: resolution or improvement of TB at follow-up, loss to follow-up, died without TB treatment or unknown.<sup>22 26 28 40 44–46</sup> Other reported poor fetal outcomes included stillbirth (case reports n=1, case series n=2, cohort studies n=3),<sup>30 47 48</sup> spontaneous abortions/fetal demise (case reports n=3, case series n=6, cohort study n=1)<sup>19 29 49–55</sup> or induced abortions (case reports n=4, series n=1, cohort study n=2, other n=1)<sup>42 49 55–60</sup> and fetal growth restriction/retardation (case series n=1, case-control n=1).<sup>41 61</sup> One case series reported stillbirth, spontaneous abortions/fetal demise and induced abortions,<sup>49</sup> and one cohort study reported spontaneous and induced abortions.<sup>62</sup> In contrast, reports of full-term birth, normal vaginal delivery and normal neonatal weight were primarily seen with case reports.<sup>28–32 63–69</sup> Although multiple case reports mentioned good fetal and newborn outcomes, the majority of findings suggest newborns of mothers with TB tend to have poorer outcomes.

### Maternal outcomes

Three large retrospective cohort studies from the USA reported that anaemia and postpartum haemorrhage were more common among women with TB infection as compared with those without TB (n=4053 rate of composite pregnancy complications including anaemia and postpartum haemorrhage 80% higher among women with TB; n=2064 anaemia OR 1.51, 95% CI 1.22 to 1.87; n=4053 rate of postpartum haemorrhage highest in TB only group, 45.5 per 1000 hospitalisations compared with TB and HIV-negative group, 25.8 per 1000, similar to anaemia, 216.6 compared with 102.7 per 1000 hospitalisations).<sup>43 70 71</sup> Two prospective cohort studies found similar findings regarding pregnancy complications including anaemia and pre-eclampsia (n=80, more anaemia in women with TB vs no TB, 27.5% vs 11.0%, p=0.001, pre-eclampsia eightfold more common among women with TB vs no TB, 5.2% vs 0.7%, p=0.03; n=26, 57.7% with adverse events related to TB treatment).<sup>35 62</sup> Anaemia was similarly seen in a case-control study (n=50, anaemia 23% vs 4% control, p-value not reported) and a retrospective cohort study (n=42 among 15 252 pregnant women, anaemia was seen in 83.3% vs 61.9%, p=0.02).<sup>21 41</sup> In the USA, Fernandez *et al*<sup>70</sup> reported highest rates of TB-HIV coinfection (49.9%) among black mothers compared with Hispanic (16.7%) and non-Hispanic white mothers (% data suppressed) in their study. Dennis *et al* proposed that advanced TB disease, commonly seen in ethnic/racial minorities, may be a contributing factor for increased pregnancy complications compared with mothers without

TB.<sup>71</sup> None of the studies stratified analysis of pregnancy complications by race or ethnicity.

A retrospective cohort study (n=2064) reported other pregnancy complications more commonly seen among pregnant women with TB including chorioamnionitis (OR 1.35, 95% CI 1.04 to 1.74), pneumonia (OR 8.42, 95% CI 5.77 to 12.29), acute respiratory syndrome (OR 2.85, 95% CI 1.35 to 6.10) and mechanical ventilation (OR 3.33, 95% CI 1.66 to 6.68).<sup>43</sup> Case reports also found similar pregnancy complications.<sup>56 58</sup> Multiple case reports and case series described delayed TB diagnosis and complicated management of TB and pregnancy.<sup>19 24 28 29 39 44 45 47 49 50 52 54 55 57–59 61 64 66 68 72–76</sup> Some resulted in recommendation and subsequent termination of pregnancy,<sup>56 57 59 77 78</sup> induced abortion<sup>49 62 79</sup> or unplanned caesarean section or induction.<sup>24 25 27 29 36 38 39 53 72 74</sup> For example, one case report described a woman with suspected genitourinary TB prior to pregnancy who suffered from severe pre-eclampsia and postpartum complication of pyelonephritis with unplanned induction.<sup>72</sup>

In regard to TB outcomes, the majority of women in cases reported treatment completion, cure or improvement of clinical symptoms.<sup>23–25 38 39 45 50–52 58 59 63–69 72–75 78 80</sup> Other TB-related maternal outcomes included deaths,<sup>19 21 28 30 32 33 36 41 42 47–49 56 81 82</sup> lost to follow-up,<sup>41 83</sup> TB treatment failure<sup>57</sup> or unknown.<sup>18 22 26 44</sup> Across 16 case series,<sup>19 29 49 53 61 76 77 81 83</sup> a case-control study<sup>41</sup> and cohort studies<sup>31 33 42 62 82 84</sup> that provided descriptive data of TB outcomes, there were a total of 402 cases. Of those, 259 (64%) had an outcome of treatment completed/cured, 49 (12%) were lost to follow-up, 29 (7%) died, 5 (1%) failed treatment, 4 (1%) deteriorated in clinical condition, 5 (1%) with unknown outcome and 46 were on treatment at the time of data collection. Among studies that analysed association of TB and pregnancy outcomes, one study found that women who gave birth to newborns with LBW were 3.83 times more likely to have poor TB outcome such as death, treatment failure or loss to follow-up compared with those delivering newborns with normal weight (95% CI 1.40 to 10.53, p=0.009).<sup>30</sup> El-Messidi and colleagues<sup>43</sup> found that compared with pregnant women without TB, maternal mortality was higher among those with TB (OR 6.27, 95% CI 2.01 to 19.58). Similarly, compared with HIV and TB-negative mothers, those with HIV or TB have significantly higher odds of pregnancy complications (HIV, aOR 1.4, 95% CI 1.32 to 1.47; TB, aOR 1.91, 95% CI 1.64 to 2.23).<sup>70</sup> Although the majority of case reports described favourable TB outcomes for women, they also described difficult management of disease or significant adverse sequelae of TB. Furthermore, larger studies found a large proportion of women with adverse TB outcomes associated with TB disease.

### HIV coinfection outcomes and ART treatment

Across nine studies that analysed data among women with TB-HIV coinfection (one case series, sub-Saharan

Africa; three prospective cohort studies, South Africa; four retrospective cohort studies, USA and South Africa; one secondary data analysis, USA), four reported median age of pregnant women between 29 and 30.1 years (IQR 25–35) and six reported CD4 count at baseline ranging from 11 to 565 cells/mm<sup>3</sup> (IQR 11–565 cells/mm<sup>3</sup>).<sup>30 33 35 41 42 48 62 70 85</sup> These studies found increased maternal mortality and fetal mortality. Bekker *et al*<sup>30</sup> described higher number of deaths among women with TB-HIV coinfection compared with those with TB only (9% vs 0%,  $p=0.313$ ) and 10 fetal deaths ( $n=55$  among mothers with HIV), suggesting higher mortality among this population compared with those with TB only. Similarly, another study found 91% (10/11) of preterm labour were among those with TB-HIV coinfection compared with those with TB only.<sup>42</sup> One study found no statistical significance in association between TB-HIV coinfection and maternal or fetal outcome.<sup>62</sup>

Other pregnancy outcomes included anaemia (27% vs 11%,  $p=0.001$ ), pre-eclampsia (5.2% vs 0.7%,  $p=0.03$ ), LBW (2950 g vs 3060 g,  $p=0.04$ ) and fetal mortality (68 deaths vs 7 per 1000 live births,  $p<0.001$ ) among women with TB-HIV coinfection compared with women with HIV and no TB.<sup>35</sup> One study found that HIV coinfection increased the risk of unfavourable pregnancy outcome of preterm labour and/or LBW (unadjusted HR 3.35,  $p=0.030$ ).<sup>33</sup> Another found that rates of pregnancy were the highest among women with TB-HIV coinfection (331.28 per 1000 hospitalisations) compared with those with HIV alone (272.2 per 1000 hospitalisations).<sup>70</sup>

Our data suggest antiretroviral therapy (ART) is not consistently provided to women with TB and HIV coinfection and of those, few are virally suppressed. ART was initiated at the same time as TB treatment for 19 women (57%,  $n=32$ ).<sup>48</sup> In another study, 29 (55%,  $n=53$ ) women were reported as being on ART at the time of delivery.<sup>30</sup> The highest number of HIV-coinfected women on ART at the time of TB diagnosis was 55 (68.8%,  $n=80$ ); only about 30.8% had an undetectable viral load ( $<200$  copies/mL) compared with those without TB (47.7%,  $p<0.001$ ).<sup>35</sup> Collectively, these studies show that just over half of HIV-coinfected women initiating TB treatment are on some form of ART and much fewer are virally suppressed, which may explain why HIV coinfection contributes additional risk for poor outcomes among women and their babies. Unfortunately, no study analysed pregnancy outcome among pregnant women with TB-HIV coinfection who were on ART versus not on ART, which may limit our understanding of how HIV treatment may impact pregnancy outcomes among this population.

#### DR-TB outcomes

Ten studies evaluate pregnancy outcomes among women with DR-TB.<sup>19 33 42 57 62 72 77 78 82 84</sup> A single case series examined the use of a standardised regimen for DR-TB-infected pregnant women ( $n=5$ ), with a reported cure of TB and good maternal outcomes.<sup>77</sup> In a retrospective cohort study looking at medical records of women with

DR-TB between 2013 and 2017, the authors found that second-line drugs, bedaquiline and levofloxacin, were predictors of LBW (45% vs 26%,  $p=0.034$ ), and that women with HIV coinfection had a higher risk of poor pregnancy outcomes.<sup>33</sup> Four studies reported successful treatment outcome (complete or cure) for the majority of their samples (83.3%, 61%, 65.4% and 88%) and lost to follow-up (11.1%, 28.6%, 26.9% and 12%).<sup>42 62 82 84</sup> The remaining studies, three case reports<sup>57 72 78</sup> and a case series,<sup>19</sup> provide conflicting results on maternal and fetal outcomes: two case studies reported good outcome for mother and baby, one case study reported treatment failure with induced abortion, while the case series noted maternal and fetal/newborn complications and deaths in their descriptive analysis. The validity and generalisability of these studies are limited by their study design and sample size.

#### The state of the science of family planning during TB treatment

The literature search yielded one study which evaluated family planning uptake at initiation of TB treatment among women with DR-TB.<sup>60</sup> This South African study aimed to increase contraceptive use by securing Depo-Provera stock, training healthcare providers to counsel and deliver Depo-Provera injections at initiation of DR-TB treatment and referring women to a tertiary hospital if they intended to conceive or became pregnant during treatment. The authors demonstrated an increase in the number of women initiating Depo-Provera at the time of DR-TB treatment. The authors suggested that these interventions are effective in delaying pregnancies during TB treatment.

Though not specifically examining contraceptive use, six studies that evaluated pregnancy outcomes commented on family planning as crucial to the improvement of health outcomes for women of reproductive age during TB treatment after finding high numbers of pregnancies during the study period.<sup>19 20 41 69 75 78</sup> One study noted 36 out of 38 pregnancies were 'unplanned' among a DR-TB cohort of women, and another reported fetal exposure to two potentially teratogenic TB drugs (ethionamide and levofloxacin) during the first trimester.<sup>19 78</sup> One study recommended risk counselling for women initiating TB treatment.<sup>20</sup> All of these studies, regardless of design or location, recognised one important theme: integrated family planning services, including risk counselling and provision of effective contraceptives, are an important preventative strategy to reduce adverse maternal and fetal/newborn outcomes.

#### DISCUSSION

To our knowledge, this is the first review to evaluate the evidence for TB-associated pregnancy outcomes and the literature for family planning strategies in TB programmes. We found that there were consistent evidence across level III and V studies of poor TB-associated pregnancy outcomes including fetal outcomes (LBW, premature

birth, spontaneous or induced abortions) and maternal outcomes (anaemia, pre-eclampsia and deaths). Despite the findings of poor maternal and fetal outcomes, there is a paucity of family planning research for women with TB and DR-TB. Such a gap in literature may be the rationale for the absence of family planning recommendations in the WHO TB and updated WHO DR-TB guidelines.<sup>86</sup>

Integration of maternal, fetal and infant healthcare in the setting of TB disease is essential. Knowing that TB disproportionately affects women of reproductive age in low-resource settings,<sup>1</sup> there is unquestionably high value in implementing family planning measures as part of TB care. This paucity of research has not gone unnoticed by other scientists. Schnippel *et al*<sup>87</sup> wrote a call-to-action paper suggesting the need for greater integration of family planning services in DR-TB facilities in South Africa; however as to date, only one study specifically evaluated family planning uptake among women initiating DR-TB treatment.<sup>60</sup> This work provided preliminary data on family planning use and the potential benefit of a provider training and contraceptive supply on increasing uptake of Depo-Provera. However, it did not expand on other aspects of family planning services like addressing factors associated with contraceptive use, pregnancy testing, other family planning options beside the injectable Depo-Provera or discussion of counselling of pregnancy risks during treatment, all of which could have an impact on a woman's decision to use contraception.

Given the evidence of outcomes, care and clinical management of pregnant women with TB or DR-TB described in this review, as well as limited data on integrated family planning into TB care, it is imperative for national stakeholders to recommend clear strategies to integrate family planning services into TB care. Our team developed a list of recommendations to guide the integration of family planning into TB and DR-TB services for women of reproductive age, incorporating the evidence from this systematic review, WHO family planning recommendations as well as the US Agency for International Development and Family Health International (FHI) 360 guidelines where relevant (box 1).<sup>88–90</sup>

Due to the limited studies on family planning strategies among women with TB or DR-TB, as well as low level of evidence of included studies (level III and V), it is important for future research to conduct more rigorous studies with higher level of evidence, such as experimental or mixed-methods studies to explore family planning needs and strategies at the individual, programmatic and policy levels. Furthermore, it may be safer and beneficial for pregnant women to have the option to be considered for TB and DR-TB research to facilitate our understanding of how TB and DR-TB treatment may impact maternal child health outcomes and inform future practice.<sup>87 91–93</sup> Specifically, the WHO suggests it would be helpful to compare effectiveness of shorter DR-TB regimens in pregnant women.<sup>94</sup> As of now, the 2020 WHO's guidelines recommend placing pregnant women on longer DR-TB regimen.<sup>94</sup> This is primarily due to the exclusion

### Box 1 Recommendations for integrated tuberculosis (TB)/drug-resistant TB (DR-TB) and family planning services

#### For clinicians\*

- ▶ Women of reproductive age should be tested for pregnancy at initiation of TB or DR-TB treatment as part of quality TB care.<sup>41 69 75 78</sup>
- ▶ Women who are found to be pregnant at treatment initiation should be referred to antenatal care with appropriate follow-ups and more intensive monitoring.<sup>19 20</sup>
- ▶ Women who are not pregnant should be informed of potential risks to maternal and fetal/infant health if they become pregnant during treatment and counselled to delay pregnancy until after completion of treatment.<sup>73</sup>
- ▶ Family planning counselling should be done at baseline, with information provided to women to include options for contraceptive methods depending on the TB or DR-TB regimen they may be on (such as rifampicin inclusive regimen), side effects they may experience on contraceptive of choice and how to switch method or discontinue method. Women should be offered a method which is the most effective, such as a long-acting reversible contraceptive (LARC), that does not interfere with either TB/DR-TB or HIV treatment and is well-suited for her lifestyle and belief.<sup>69 75 88 96</sup>
- ▶ Women who agree to be on an LARC should be educated on the correct use of method and when to follow-up.<sup>88</sup>
- ▶ Women who do not agree to be on a contraceptive should be followed up routinely throughout treatment for changes in relationship status, desire for contraceptive, pregnancy testing and immediate linkage to antenatal care if pregnancy status changes during TB treatment.<sup>88</sup>

#### For TB programmes

- ▶ TB treatment site should keep stock of various contraceptive methods including male and female condoms, oral contraceptives, implants, injectables, intrauterine devices to minimise referring women to outside clinics for family planning.<sup>60 88</sup>
- ▶ TB providers should be trained at least annually on family planning counselling, family planning knowledge and proper techniques to administer contraceptive methods so they may provide these services to women who need them.<sup>60 88</sup>
- ▶ Recommendations for family planning should be standardised and integrated into all TB and DR-TB treatment sites as part of high-quality TB services.<sup>60 87</sup>

#### For researchers

- ▶ Pregnant women should be considered for clinical studies, particularly those looking at the efficacy of shorter regimens compared with longer regimens, which expose women to DR-TB drugs for a longer period of time.<sup>92 93 97</sup>
- ▶ Research, particularly pragmatic and intervention research, should address family planning needs in TB care and the implementation of integrated services.<sup>93</sup>
- ▶ Given a lack of high level of evidence of studies, future research on pregnancy outcomes and family planning among women with TB or DR-TB should prioritise more rigorous study designs where possible, for example, level 1 experimental designs, level 2 mixed-methods design or level 3 prospective cohort studies with larger sample size.

\*Clinicians refer to providers who have direct patient contact including doctors, nurses and pharmacists.

Continued

**Box 1 Continued**

†This citation refers to the companion handbook to the WHO 2014 DR-TB guidelines which were updated in 2020. However, in the updated 2020 guidelines family planning was not mentioned.

of pregnant women from a large randomised controlled trial testing the efficacy of shorter DR-TB regimen (eg, STREAM trial).<sup>95</sup> With a longer treatment regimen, there is a greater exposure time in which women could become pregnant, and longer time pregnant women are being exposed to DR-TB drugs. As of now, there is still no sufficient evidence to support a standardised DR-TB regimen for pregnant women.<sup>91</sup> Research guiding regimen selection in pregnant women is urgently needed in the long term.

In addition to our recommendations for practice, programme and research, local and national level policy action is needed to ensure that family planning services are integrated into TB and DR-TB care settings. Our policy-specific recommendations reflect the evidence from this review and best practices from the field of family planning. FHI 360 created guidance for family planning and HIV integration, which may be used as a blueprint and adapted to TB and DR-TB programmes.<sup>89,90</sup> In brief, policymakers should monitor family planning data such as contraceptive prevalence rate, unmet need and demand for family planning among women with TB and DR-TB to appropriately direct funding and resources. Allocation of resources should prioritise efforts to integrate family planning services into TB and DR-TB programmes and include monitoring and evaluation plan to inform programme and service delivery improvement, as well as scale-up. This could be done by measuring additional indicators specific to family planning and TB integration, including service delivery integration, contraceptive method availability, uptake, informed choice, and training and human resources.<sup>89</sup> Healthcare provider training and ensuring supply of contraceptive methods during TB or DR-TB treatment will also be critical. Finally, subsequent updates to WHO TB and DR-TB guidelines should provide recommendations for family planning as part of quality care for women of reproductive age undergoing treatment. Of note, such a recommendation was offered in the companion handbook to the WHO 2014 DR-TB guideline but absent from the 2020 update.<sup>86,96</sup>

### Strength and limitations of the studies

There were several limitations to our systematic review. This review was limited by the inclusion of only peer-reviewed, English journal articles published in the 11 years. This likely excludes important findings in other languages and important programmatic data at a country level. Most studies in this review were of lower level of evidence, with the majority being case reports, case series and retrospective cohort studies. The inclusion of lower level of evidence such as case reports allow for a

comprehensive view of available clinical data across the globe. Aside from five cohort studies which took place in the USA and China, most had small sample sizes and primarily reported exploratory and descriptive data. This may reduce the ability to generalise results beyond these studies to places that had higher burden of TB, DR-TB and/or HIV coinfection with less access to health resources. Only one study evaluated family planning strategies as part of a quality improvement project. It would be important for future research to consider more rigorous study designs given the low level of evidence of current studies (eg, experimental or mixed-methods studies). This is especially important to consider for studies that evaluate family planning strategies for this high-risk population of women. It is also important that future research prioritise studies with larger sample size in high TB, DR-TB and/or HIV coinfection burden settings to evaluate pregnancy outcomes and family planning strategies since the majority of the larger cohort studies took place in the USA, a high-income country with low burden of disease.

Another limitation of this review is the variability of study design, definitions and methods, which made comparison of outcomes difficult. Definitions of pregnancy outcomes were often heterogeneous across multiple studies; some studies looked at TB, DR-TB, HIV coinfection outcomes as we defined in our review, some looked at fetal/newborn outcomes such as fetal distress, fetal demise versus stillbirth and intrauterine growth restriction or growth retardation rather than LBW or preterm birth without establishing clear definitions. Some failed to discuss TB/DR-TB outcomes of mothers or newborns. There were studies that did not define preterm birth or LBW, and there were studies that explored different pregnancy complications as a composite outcome, all of which made it difficult to cohesively conduct a meta-analysis. We sought to include all relevant studies regardless of methodological designs or quality to further our understanding of the scientific gaps that exist around maternal-child outcomes of women with TB or DR-TB and their family planning needs in both the clinical and research settings. Despite the weakness of the study designs and inclusion of studies of all quality types, the observational evidence consistently demonstrates adverse maternal and fetal/newborn outcomes across the globe in the last decade.

### CONCLUSION

TB in pregnancy is as a major risk factor of maternal and fetal morbidity and mortality, especially in low/middle-income countries where resources are limited. Pregnancy outcomes are worsened in the setting of TB/DR-TB, with or without HIV coinfection, and lack of health resources and access to specialised care. Offering family planning services at TB/DR-TB treatment initiation and education on risk of poor pregnancy outcomes should be considered as part of routine care in women of childbearing age.

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