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Effects of antituberculosis treatment on pregnancy outcomes in infertile women with genital tuberculosis: a systematic review

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ABSTRACT

Objectives To evaluate the efficacy of antituberculosis therapy on pregnancy outcomes in infertile women with genital tuberculosis.

Design Systematic review.

Data sources We searched in PubMed/MEDLINE, CENTRAL and EMBASE up to 15 January 2023. Additionally, we manually search the reference lists of included studies.

Eligibility criteria We included randomised controlled trials (RCT), non-RCTs (non-RCT) and cohort studies that evaluated the effects of antituberculosis treatment on pregnancy outcomes in infertile women with genital tuberculosis compared with not receiving antituberculosis treatment or receiving the treatment for a shorter period.

Data extraction and synthesis Two independent reviewers extracted data. We used Cochrane Risk of Bias 1.0 and Risk Of Bias In Non-randomised Studies tools for risk of bias assessment and meta-analysis was not performed. We used Grading of Recommendations, Assessment, Development and Evaluations approach to assess the certainty of the evidence.

Results Two RCTs and one non-RCT were included. The antituberculosis regimens were based on isoniazid, rifampicin, pyrazinamide and ethambutol for 6–12 months. In women without structural damage, very low certainty of evidence from one RCT showed that the antituberculosis treatment may have little to no effect on pregnancy, full-term pregnancy, abortion or intrauterine death and ectopic pregnancy, but the evidence is very uncertain. In women with structural damage, very low certainty of evidence from one non-RCT showed that the antituberculosis treatment may reduce the pregnancy rate (297 fewer per 1000, 95% CI −416 to −101), but the evidence is very uncertain. In addition, very low certainty of evidence from one RCT compared a 9-month vs 6-month antituberculosis treatment regimen showed similar effects between the schemes, but the evidence is very uncertain. Two RCTs reported that no adverse events of antituberculosis treatment were noted or were similar in both groups.

Conclusion The effect of antituberculosis treatment on pregnancy outcomes in infertile women with genital tuberculosis is very uncertain.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ We did not search regional databases from tuberculosis-endemic countries, so some studies may have been missed.
⇒ The evidence is limited and comes from only two randomised controlled trials (RCTs) and one non-RCT with methodological limitations, resulting in a very low certainty of evidence in their results.
⇒ Not all included studies provided detailed information about their methodology, evaluated the effects for all pregnancy outcomes, or reported the adverse events of the therapy.
⇒ A meta-analysis could not be performed due to the small number of studies and heterogeneity among them.
⇒ Clinically relevant outcomes for infertile women and clinicians were included to inform decision-making regarding the use of antituberculosis treatment on pregnancy outcomes, and we used rigorous methods including the Grading of Recommendations, Assessment, Development and Evaluations approach to assess the certainty of evidence.

PROSPERO registration number CRD42022273145.

BACKGROUND

Female genital tuberculosis (FGTB) is a chronic infectious disease that develops mostly secondary to a primary focus in the lungs from where the dissemination of *Mycobacterium tuberculosis* is usually haematogenous or lymphatic.[1] The prevalence of FGTB varies among countries. For example, in an Indian community, the reported prevalence was 45.1 cases per 100 000 women,[2] and in Pakistan, a retrospective study that analysed 410 748 mycobacterial cultures collected from 2007 to 2016, reported 32 culture-positive FGTB cases.[3] In addition, genital tuberculosis in women is a major cause of infertility.[4 5] The

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prevalence of infertility among women with genital tuberculosis varies among reports, ranging from 40% to 80%.[6–8] However, the real burden of FGTB is not well known and probably underestimated due to vague symptomatology, asymptomatic presentation and the heterogeneity in the diagnostic tools used.[6 9]

Infertility in FGTB is developed, mainly, as a result of structural damage in fallopian tubes (fibrosis and lumen obstruction)[6 10]; endometrium (intrauterine synechiae)[11] and ovaries (tubo-ovarian abscess).[12] Infertility could also develop as a result of non-structural damage. Proposed mechanisms are endometrial hostility through increased inflammatory cytokines,[13] oophoritis with poor ovarian reserve and an endocrine disorder in the ovulation induction process.[1]

The main treatment for infertility in FGTB is assisted reproductive technologies (such as in vitro fertilisation and embryo transfer).[14] In addition, previous studies suggest that antituberculosis treatment, given alone or in combination with assisted reproductive technologies, could have a potential benefit to treat infertility in women with genital tuberculosis.[15 16]

Antituberculosis treatment based on, isoniazid, rifampicin, pyrazinamide and ethambutol (HRZE) for 2 months, followed by isoniazid and rifampicin (HR) for the next 4 months[17] should be used to treat drug-sensitive active pulmonary and extrapulmonary tuberculosis.[5] However, the effects of this treatment on pregnancy outcomes in women with genital tuberculosis without active tuberculosis disease are controversial. These drugs could reduce the structural damage of granulomas or have an immunomodulatory role that decreases the hostility of the endometrium,[13 18] but they are not exempt from presenting adverse events such as hepatitis, cutaneous reactions, gastrointestinal intolerance, haematological reactions and renal failure.[19] Therefore, this systematic review aimed to evaluate the efficacy of antituberculosis therapy on pregnancy outcomes in infertility in women with genital tuberculosis.

METHODS

The study protocol has been registered at PROSPERO (CRD42022273145). We followed statements for the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA).

Inclusion criteria

We included randomised controlled trials (RCTs) and expanded the inclusion criteria to non-RCTs, and comparative cohort studies in any language. The decision was made because only a small number of randomised trials could be available as found in the preliminary search that we conducted. We included studies that compared antituberculosis treatment against not receiving antituberculosis treatment or receiving the treatment for a shorter period in infertile women with genital tuberculosis without active tuberculosis disease and reported data on pregnancy outcomes. The antituberculosis treatment of interest was the scheme based on, isoniazid, rifampicin, pyrazinamide and ethambutol (HRZE) for 2 months, followed by isoniazid and rifampicin (HR) for the next 4 months. As detailed in the protocol, we assess pregnancy outcomes including pregnancy, full-term pregnancy, ectopic pregnancy and abortion or intrauterine death, as well as adverse events. We excluded case–control or cross-sectional studies, case reports, reviews, editorials or letters that do not present original results, and articles not available in full text.

Literature search and study selection

We searched in PubMed/MEDLINE, CENTRAL and EMBASE until 15 January 2023, with no restriction on language or publication date. The full search strategy for each database is available in online supplemental file 1. The elimination of duplicates and the selection of studies were performed using online software (Rayyan QCRI, Qatar Computing Research Institute). Two authors (DF-G and SAM-R) independently screened titles and abstracts to identify potentially relevant studies for inclusion. These potential studies were full text reviewed independently by two authors (BC-C and AGG-U). The disagreements were resolved with a third author (KFL). Excluded studies and reasons for exclusion can be found in online supplemental file 2. In addition, we manually search the reference lists of included studies to identify more relevant studies.

Data extraction

Two authors (KFL and KGT) independently extracted the following information from each included study using a previously designed Microsoft Excel sheet: first author, year of publication, country, study design, study period and follow-up, diagnosis of tuberculosis, sample size, age, intervention and comparator details, funding, and outcomes (pregnancy, at-term pregnancy, ectopic pregnancy, abortion or intrauterine death and adverse events). Disagreements were resolved with a third author (DRS-M).

Risk of bias

Two authors (DRS-M and JF-M) independently assessed the risk of bias in the included studies using the Cochrane Risk of Bias (RoB) 1.0 tool for RCT,[20] and the Risk Of Bias In Non-randomised Studies (ROBINS-I) for non-RCT.[21] Disagreements were resolved with a third author (SGL). The Cochrane RoB 1.0 tool consists of seven items: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective reporting of results, and other sources of bias (unbalance in basal characteristics). For each item, the decision may be of low, high or unclear risk of bias.[20] The ROBINS-1 consists of seven items. For each item, the decision may be low risk of bias, moderate risk of bias, serious risk of bias, critical risk of bias and no information.[21] We did not

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use the New-Castle Ottawa Scale tool because no comparative cohort studies were included.

Statistical analysis

We used Stata V.16.0 to calculate risk ratios (RRs) with 95% CIs and Grading of Recommendations, Assessment, Development and Evaluations (GRADE) pro Software to calculate absolute effects with 95% CI for each outcome. We could not perform a prespecified meta-analysis due to the number of included studies and heterogeneity between them in terms of study design, type of comparator and population (women with genital tuberculosis without and with structural damage). In consequence, we could not perform the heterogeneity and publication bias statistical assessment.

We could not perform prespecified subgroup analysis according to country, mode of diagnosis of genital tuberculosis and history of previous tuberculosis treatment due to lack of data. We presented the results separately for women with structural damage, defined as the presence of lesions characteristic of tuberculosis in the ovary, tubes or uterus[4]; and for those without structural damage, defined as having only a positive endometrial PCR test.[22]

Certainty of evidence

We used the GRADE approach to assess the certainty of the evidence for each outcome as high, moderate, low or very low, based on study limitations, imprecision, risk of bias, inconsistency, indirectness and publication bias.[23] With GRADE, RCT and non-RCT designs begin at as high and low certainty of the evidence, respectively.[24] Then, we used the following criteria to rating down the certainty of evidence: regarding imprecision, we used the sample size rather than setting thresholds in a minimally contextualised approach.[25] For this purpose, we followed the criteria proposed by Murad *et al* to rating the certainty of evidence in the absence of a single estimate of effect.[26] We rated down one level for a dichotomous outcome if the study had less than 300 events and two levels if the study had less than 50 events. Regarding the risk of bias, we rated down one level if the study had fewer than six items with a low risk of bias and by two levels if the study had fewer than five items with a low risk of bias. The inconsistency and publication bias could not be assessed because one study was included for each outcome. We presented the results in Summary of Findings tables and followed the GRADE guidance for communicating the results.[27]

Patient and public involvement

Patients and public were not involved in this study.

RESULTS

Selection of studies

We found 1468 articles in the systematic search. After the removal of duplicates, we examined 970 records by title and abstract, of which 20 records were reviewed in full text. Finally, we included three studies.[22 28 29] We did not find additional studies after searching the references of the included studies (figure 1).

Characteristics of the studies

Two studies were RCT,[22 29] and one was non-RCT.[28] The sample size ranged from 78 to 175 participants. One study[22] evaluated infertile women without structural damage with positive endometrial PCR test for tuberculosis and two studies[28 29] evaluated infertile women with structural damage according to the hysteroscopy or laparoscopy findings. The mean age ranged from 28 to 29 years. Two studies[22 28] evaluated the effectiveness of antituberculosis therapy with HRZE for a period of 6–12 months compared with no antituberculosis treatment, followed by assisted reproductive therapies. One study[29] evaluated different regimens of antituberculosis treatment with HRZE comparing the efficacy of treatment for

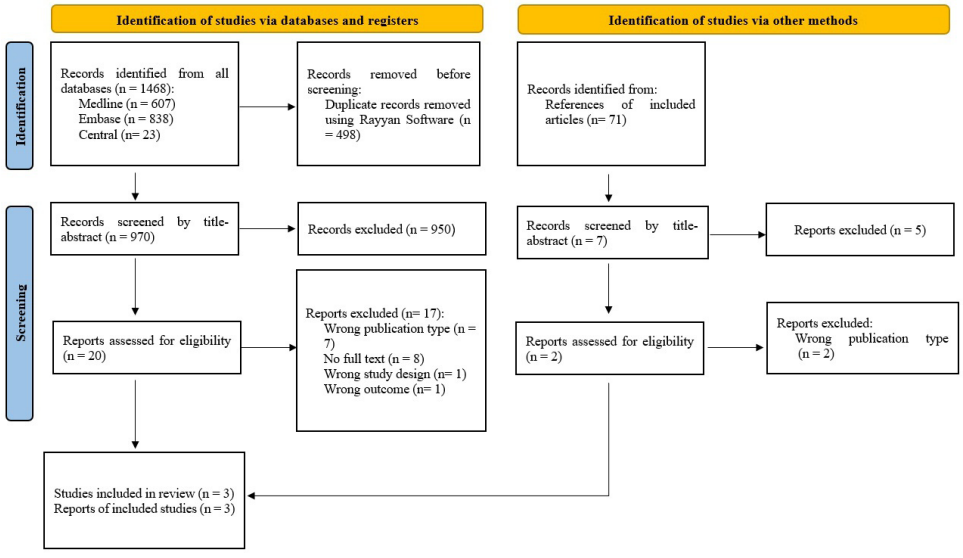


Figure 1 Flow diagram summarising the process of literature search and selection.

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9 vs 6 months. The funding of the studies and other characteristics are listed in table 1.

Risk of bias

Overall, the studies were rated as unclear or high risk of bias. The RCT of Kriplani *et al*[22] presented unclear risk of bias in allocation concealment and a high risk of bias in blinding participants, study personnel and outcome assessors. The RCT of Sharma *et al*[29] presented an uncertain risk of bias in blinding of participants, study personnel and outcome assessors, and selective reporting of results (figure 2).

The non-RCT of Yue *et al*[28] had critical risk in the domain of bias due to confounding and bias due to deviations from the intended interventions. In addition, the study had serious risk in the domains of bias due to participant selection and bias in the classification of interventions. There was no information on bias due to missing data. The risk was moderate in the domain bias in the measurement of outcomes and there was low risk in the bias domain assessing reported outcome selection (figure 2).

Antituberculosis treatment for women with genital tuberculosis without structural damage

Very low certainty of evidence from one RCT (100 participants)[22] shows that at 12 months follow-up, the antituberculosis treatment (HRZE) for 6 months, compared with no antituberculosis treatment, may have little to no effect on pregnancy (71 more per 1000, 95% CI −88 to +311), full-term pregnancy (34 more per 1000, 95% CI −103 to +232), abortion or intrauterine death (11 more per 1000, 95% CI −3 to +36) and ectopic pregnancy (not estimable) but the evidence is very uncertain. In addition, the study reported no adverse events in either group (table 2).

Antituberculosis treatment for women with genital tuberculosis with structural damage

Very low certainty of the evidence from one non-RCT (78 participants)[28] shows that at no detailed follow-up the antituberculosis treatment (HRZE) for 6–12 months, compared with no antituberculosis treatment, may reduce the pregnancy rate (297 fewer per 1000, 95% CI −416 to −101) but the evidence is very uncertain. In addition, the study did not report information about adverse events (table 3).

Other comparisons: 9-month vs 6-month antituberculosis treatment for women with genital tuberculosis

Very low certainty of evidence from one RCT (175 participants)[29] shows that the antituberculosis treatment for 9 months (HRZE), in comparison to antituberculosis treatment for 6 months, have little to no effect on pregnancy (13 more per 1000, 95% CI −56 to +107), at term pregnancy (9 more per 1000, 95% CI −35 to +75), abortion or intrauterine death (1 more per 1000, 95% CI−26 to +52), and preterm pregnancy (1 more per 1000, 95% CI −22 to +48) but the evidence is very uncertain. In addition, the study reported that adverse events were similar in both groups (online supplemental file 3.

DISCUSSION

Summary of main results

We included one RCT and one non-RCT that compared the effectiveness of antituberculosis treatment compared with no antituberculosis treatment in infertile women with genital tuberculosis without and with structural damage, respectively. In infertile women without structural damage, the antituberculosis treatment for 6 months may have little to no effect on pregnancy outcomes and adverse events, but the evidence is very uncertain. In contrast, in infertile women with structural damage, the antituberculosis treatment for 6–12 months may reduce the pregnancy rate, but the evidence is very uncertain. In addition, we included one RCT that compared a 9-month vs 6-month antituberculosis treatment regimen was included. However, the evidence is very uncertain.

Effects in infertile women without structural damage

The use of antituberculosis treatment to improve pregnancy outcomes was proposed based on biological plausibility. However, the included RCT found that the effects of the antituberculosis treatment given for 6 months on pregnancy outcomes are very uncertain.[22] This could be explained because most potentially useful drugs based on biological plausibility ultimately do not cause clinical benefits in patients. However, all can produce adverse events. In this sense, a study that evaluated articles published in six major basic science journals between 1979 and 1983 found that of 101 novel or promising therapies, 27 resulted in the publication of at least one clinical trial, of which 5 were approved for use, and of which only 1 (0.99% of promising therapies) shown clear clinical benefits.[30]

Effects in infertile women with structural damage

The included non-RCT showed that, with very low certainty of evidence, antituberculosis treatment for 6–12 months may reduce the pregnancy rate. This effect could be explained by possible imbalances in the characteristics of the participants and the small sample size of the study. Although no statistically significant differences were found in the characteristics of the participants, women who received antituberculous treatment, compared with those who did not, tended to have a higher frequency of hydrosalpinx (41.3% (19/46) vs 40.6% (13/32)), pelvic adhesions (97.8% (45/46) vs 96.9% (31/32)) and age greater than or equal to 30 years (30.4% (14/46) vs 28.1% (9/32)), respectively.[28] Based on this, the probability of pregnancy could be lower in women who received antituberculosis treatment. It has been described that small studies, without randomisation, and other methodological limitations tend to find

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Table 1 Characteristics of included studies that evaluated antituberculosis treatment in infertile women with genital tuberculosis

Study–year	Country	Study design	Period of study and follow-up	Diagnosis of tuberculosis	Sample size	Age–years (mean±SD)	Intervention details	Comparator details	Funding
Kriplani 2016[22]	India	RCT	November 2010–May 2014, 6 and 12 months postlaparoscopy	Endometrial DNA-PCR positive, with other tests being negative (EA-HPE, AFB, laparoscopy and hysteroscopy)	100	28.5±3.8	Antituberculosis treatment for 6 months: HRZE for the first 2 months followed by HR for 4 months. Then, after 6 months postlaparoscopy: ovulation induction with clomiphene Citrate, follicle monitoring, HCG injection and intrauterine insemination	No antituberculosis treatment. After 6 months postlaparoscopy: the comparator group received the same fertilisation therapy as intervention group	The Indian Council of Medical Research
Sharma 2016[29]	India	RCT	May 2010–April 2014, 12 months after completion of therapy	Laparoscopy, hysteroscopy or PCR with positive findings of structural damage on ultrasound, hysterosalpingography or laparoscopy	175	29.0±4.6	Antituberculosis treatment for 9 months: HRZE for the first 2 months followed by HR for 7 months	Antituberculosis treatment for 6 months: HRZE for the first 2 months followed by HR for 4 months	Government of India
Yue 2018[28]	China	Non-RCT*	November 2005–October 2015, follow-up period not detailed	Laparoscopy and/or hysteroscopy with positive findings of structural damage	78	28.0±3.6	Antituberculosis treatment for 6 to 12 months: HRZE for 2 months, followed by HR for 4–10 months. Some patients underwent in vitro fertilisation or embryo transfer (no detailed data for this group)	No antituberculosis treatment. Some patients underwent in vitro fertilisation or embryo transfer (no detailed data for this group)	Not reported

*The study did not perform an adjustment of covariates.
AFB, acid-fast bacilli; EA-HPE, endometrial aspirate histopathology examination; HCG, human chorionic gonadotropin; HRZE, isoniazid, rifampicin ethambutol and pyrazinamide; RCT, randomised controlled trial.

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A Risk of bias for randomized clinical trials

Bias	Items	Kriplani (2016)	Sharma (2016)
Selection bias	Random sequence generation	+	+
	Allocation concealment	?	+
Performance bias	Blinding of participants and personnel	-	?
Detection bias	Blinding of outcome assessment	-	?
Attrition bias	Incomplete outcome data	+	+
Reporting bias	Selective reporting	+	?
Other bias	Other bias	+	+

B Risk of bias for non-randomized clinical trials

Risk of bias domains	Yue (2018)
Bias due to confounding	!
Bias due to selection of participants	X
Bias in classification of interventions	X
Bias due to deviations from intended interventions	!
Bias due to missing data	?
Bias in measurement of outcomes	-
Bias in selection of the reported result	+
Overall	!

Judgement Critical: ! Serious: X Moderate: - Low: + No information: ?

Figure 2 Risk of bias.

statistically significant and biased results.[31] Therefore, these results should be interpreted with caution.

On the other hand, antituberculosis treatment may not have a significant impact in reducing severe lesions such as adhesions, which would be the main mechanical causes of infertility. In this sense, a Canadian cohort that included infertile women with genital tuberculosis found that the frequency of tubercles in the pelvic peritoneum, fallopian tube and ovary was reduced from 54% to 2.04% after antituberculosis treatment. However, the frequency of pelvic adhesions was similar before and after treatment (42% vs 42.5%, respectively).[10]

Implications

Currently, the treatment of choice to achieve pregnancy in women without active infection is assisted fertilisation techniques. For women without structural damage, less invasive methods such as ovulation induction and timed intercourse are proposed.[6] On the other hand, in women with structural damage to a functional endometrium, in vitro fertilisation and embryo transfer could be the best

Table 2 Summary of findings for the effects of antituberculosis treatment compared with no antituberculosis treatment in infertile women with genital tuberculosis without structural damage

Population	Infertile women with genital tuberculosis without structural damage (only PCR positive)					
Intervention	Antituberculosis treatment (orally isoniazid, rifampicin, pyrazinamide and ethambutol (HRZE) for 6 months)					
Comparator	No antituberculosis treatment					
Outcomes	**No of participants (studies)**	**Antituberculosis treatment**	**No antituberculosis treatment**	**Relative effect (95% CI)**	**Absolute effects**	**Certainty of the evidence (GRADE)**
Pregnancy follow-up: 12 months	100 (1 RCT)	25/50 (50%)	21/50 (42%)	RR: 1.17 (0.79 to 1.74)	71 more per 1000 (from 88 fewer to 311 more)	⨁OOO *,† Very low
Full-term pregnancy follow-up: 12 months	100 (1 RCT)	21/50 (42%)	19/50 (38%)	RR: 1.09 (0.73 to 1.61)	34 more per 1000 (from 103 fewer to 232 more)	⨁OOO *,† Very low
Abortion or intrauterine death follow-up: 12 months	100 (1 RCT)	3/50 (6%)	1/50 (2%)	RR: 1.53 (0.84 to 2.80)	11 more per 1000 (from 3 fewer to 36 more)	⨁OOO *,† Very low
Ectopic pregnancy follow-up: 12 months	100 (1 RCT)	1/50 (2%)	0/50 (0%)	Not estimable	Not estimable	⨁OOO *,† Very low
Adverse events follow-up: 12 months	The study reported no adverse events in either group.					

*We downgraded one level of evidence due to serious risk of bias: No blinding of participants and staff, and no blinding of outcome assessors.
†We downgraded two levels of evidence due to very serious imprecision.
GRADE, Grading of Recommendations, Assessment, Development and Evaluations; RCT, randomised controlled trial; RR, risk ratio.

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Table 3 Summary of findings for the effect of antituberculosis treatment compared with no antituberculosis treatment in infertile women with genital tuberculosis with structural damage

Population	Infertile women with genital tuberculosis with structural damage					
Intervention	Antituberculosis treatment (orally isoniazid, rifampicin, pyrazinamide and ethambutol (HRZE) for 6–12 months).					
Comparator	No antituberculosis treatment					
Outcomes	**No of participants (studies)**	**Antituberculosis treatment**	**No antituberculosis treatment**	**Relative effect (95% CI)**	**Absolute effects**	**Certainty of the evidence (GRADE)**
Pregnancy follow-up: not detailed	78 (1 non-RCT)	11/46 (23.9%)	19/32 (59.4%)	RR: 0.50 (0.30 to 0.83)	297 fewer per 1000 (from 416 fewer to 101 fewer)	⨁OOO *,† Very low
Full-term pregnancy	The study did not report information about full-term pregnancy					
Abortion or intrauterine death	The study did not report information about abortion or intrauterine death					
Ectopic pregnancy	The study did not report information about ectopic pregnancy					
Adverse events follow-up: not detailed	The study did not report information about adverse events					

*We downgraded two levels of evidence due to very serious risk of bias: Inadequate reporting of prospective data collection, failure to report details on consecutive patient inclusion, unbiased assessment of study endpoint, follow-up period, lost to follow-up, prospective calculation of study size, contemporaneous groups and adequate statistical analysis.
†We downgraded two levels of evidence due to very serious imprecision.
GRADE, Grading of Recommendations, Assessment, Development and Evaluations; non-RCT, non-randomised controlled trial; RR, risk ratio.

therapeutic option.[30] If the endometrium is damaged but the ovaries are intact, gestational surrogacy could be the treatment of choice.[4 13] However, these techniques have a pregnancy rate of 60.6%.[16] Given this, the studies proposed using antituberculosis treatment with HRZE before assisted fertilisation techniques to improve pregnancy rates.

With a very low certainty of evidence, the results of this systematic review showed that the effects of antituberculosis treatment on pregnancy outcomes are very uncertain. In contrast, although no frequent adverse events were reported, it is important to note that the adverse events could be underestimated due to small sample size in the studies. In this sense, a multicentric cohort study in Morocco that included 2532 participants, found that the incidence of adverse events of antituberculosis treatment was 10% at 6 months follow-up.[32] In addition, the impact of the treatment's cost could be variable between the different health systems worldwide. A review published in 2015 found the cost of the antituberculosis treatment range from US$14 659 in high-income countries, US$840 in upper-middle-income countries, US$273 in lower-middle-income countries and US$258 in low-income countries.[33]

Finally, the use of antituberculous treatment could delay of 6–12 months in initiating assisted fertility treatments. Therefore, it is likely that the delay in starting assisted fertility techniques could reduce the probability of pregnancy. This would be especially important, as time is a key factor in achieving pregnancy, especially in older women.[22]

Limitations of the included studies

The body of evidence has limitations. The studies were heterogeneous in terms of population, intervention, control groups and outcomes assessed, making comparison difficult.

All the studies were probably underpowered to evaluate adverse events and the reporting of the adverse events was poor. Overall, the certainty of the evidence was very low for all results mainly because of the risk of bias and imprecision. In addition, two studies were conducted in India and one in China, countries with a high burden of tuberculosis,[34] and all the studies had restrictive inclusion criteria. Therefore, the results should be interpreted with caution when extrapolating to other groups.

Recommendations for future studies

Future RCT should be double-blinded and include a larger number of participants to avoid concerns about the risk of bias and imprecision. The effect of the treatment should be evaluated according to whether the patient has structural damage. Finally, the studies should report the type of pregnancy and adverse events.

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Limitations and strengths in the review process

This systematic review has limitations. We did not search regional databases from tuberculosis-endemic countries, so some studies may have been missed. Nevertheless, we searched in three main databases without language restriction, and we extended the search screening references of included studies to find other relevant trials. The evidence is limited and comes from only two RCTs and one non-RCT with methodological limitations, resulting in a very low certainty of evidence in their results. Not all included studies provided detailed information about their methodology, evaluated the effects for all pregnancy outcomes, or reported the adverse events of the therapy. Finally, a meta-analysis could not be performed due to the small number of studies and heterogeneity among them and publication bias was not statistically assessed since less than 10 trials were included.[35]

Strengths of this review include that, to our best knowledge, this is the first systematic review that assesses the effects of antituberculosis on clinically relevant pregnancy outcomes for infertile women with genital tuberculosis without active tuberculosis disease and clinicians to inform the decision-making process. Also, we used rigorous methods according to the Cochrane Handbook for Systematic Reviews of Intervention, including the GRADE approach to assess the certainty of the evidence.[35]

CONCLUSION

We found two RCTs and one non-RCT that evaluated the effect of antituberculosis treatment in infertile women with genital tuberculosis. The effect of antituberculosis treatment on pregnancy in infertile women with genital tuberculosis is very uncertain. RCTs with larger sample sizes and low risk of bias are needed to clarify the balance between the benefits and harms of this therapy.

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Contributors KFL conceptualised, planned, and is the guarantor of the study. KFL, DRS-M and SGL conducted the systematic review. KFL, DRS-M, SAM-R, DF-G, BC-C, JF-M, KGT, JT-P, JA and SGL wrote the paper. All authors read and approved the final version of the manuscript.

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

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