Mini-symposium: Transition to adult care: what adult physicians need to know

Tuberculosis in pregnant women and neonates: A meta-review of current evidence

K.J. Snow, A. Bekker, G.K. Huang, S.M. Graham

PII: S1526-0542(20)30015-4

DOI: <https://doi.org/10.1016/j.prrv.2020.02.001>

Reference: YPRRV 1358

To appear in: *Paediatric Respiratory Reviews*

Received Date: 17 December 2019

Accepted Date: 7 February 2020

Please cite this article as: K.J. Snow, A. Bekker, G.K. Huang, S.M. Graham, Tuberculosis in pregnant women and neonates: A meta-review of current evidence, *Paediatric Respiratory Reviews* (2020), doi: <https://doi.org/10.1016/j.prrv.2020.02.001>

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Tuberculosis in pregnant women and neonates: A meta-review of current evidence

Snow KJ^{1,2,3}, Bekker A⁴, Huang GK⁵, Graham SM^{1,5,6}

1. Centre for International Child Health, University of Melbourne Department of Paediatrics and Murdoch Children's Research Institute, Royal Children's Hospital, Melbourne, Australia
2. Centre for Adolescent Health, Murdoch Children's Research Institute, Royal Children's Hospital, Melbourne, Australia
3. Centre for Health Equity, School of Population and Global Health, University of Melbourne, Melbourne, Australia
4. Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Stellenbosch University, Cape Town, South Africa
5. The Burnet Institute, Melbourne, Australia
6. International Union Against Tuberculosis and Lung Disease (The Union), Paris, France

Author for correspondence:

Dr Kathryn Snow

kathryn.snow@unimelb.edu.au

Word count: 3,129

Words in tables / boxes: 508

Tables: 2

Box: 1

Refs: 47

Funding: KS is supported by the Australian Centre for Research Excellence in Tuberculosis (TB-CRE).

The authors declare no conflicts of interest.

Key words: pregnancy, perinatology, congenital tuberculosis, neonatology, tuberculosis, key populations

Abstract

Pregnant women and their infants are a vulnerable but neglected population in tuberculosis (TB) control efforts. Recent advances in TB prevention, diagnosis and treatment have implications for their care, despite their frequent exclusion from research. We have conducted a meta-review of current evidence and clinical guidelines for TB prevention, diagnosis and management in pregnant women and neonates, focusing on review articles published since 2010.

The actual burden of pregnancy-related TB is unmeasured, but has been estimated at 216,500 cases per year. Although the effect of pregnancy on TB risk is uncertain and controversial, two large whole-of-population studies found that pregnancy was associated with a two- to three-fold increase in risk of TB. Congenital TB is rare but extremely serious. Neonates exposed to TB after delivery will be at high risk of disease, and preventive therapy is recommended once disease has been ruled out. At present, there is limited evidence regarding the performance of different screening strategies for pregnant women, appropriate drug dosing for either pregnant women or neonates, and the safety of most second-line drugs in pregnancy. High quality evidence on these topics is needed, as are detailed guidelines to inform efforts by TB control programs and clinicians working with pregnant women and their infants.

Educational Aims

Readers should come to appreciate that:

- The burden of tuberculosis in pregnancy has never been measured, and routine data collection on both incidence and outcomes should be prioritised
- Although TB screening is recommended for pregnant women in high burden settings, clinical presentation in pregnancy is known to be atypical, and there is limited guidance regarding appropriate screening algorithms
- Drug regimens recommended for the treatment and prevention of TB in pregnant women and neonates are similar to the rest of the population, although some drugs should be avoided (aminoglycosides; delamanid) and there are limited safety data for pyrazinamide relative to the other first-line drugs
- Pharmacokinetic and safety studies in pregnant women and neonates are needed to inform detailed guidelines on appropriate dosing

Introduction

Pregnant women are increasingly recognised as an important vulnerable population in tuberculosis (TB) control, but are still very much neglected.¹⁻⁴ Pregnancy-related TB is an important cause of maternal morbidity and mortality in many countries,³ and is associated with significant risks to both the mother and the foetus/infant.⁵ Therefore, recent advances in the diagnosis, treatment and prevention of TB have important clinical and public health implications for pregnant women and neonates. However, despite these recent advances, major knowledge gaps persist. Current guidelines for the care of pregnant women with TB and their infants rely heavily on data from studies in the general population, and from animal studies.⁶ Important questions persist regarding optimal TB prevention, screening, diagnosis, and treatment in pregnancy, especially in the context of co-morbid HIV or drug resistant TB.^{3,6,7}

Methods

We aimed to conduct a critical narrative meta-review of review articles on TB in pregnant women and/or neonates published in the past decade, to synthesise the current evidence on epidemiology and clinical management of TB in these populations.

We searched PubMed on August 29, 2019 with the following strings:

"tuberculosis"[Title] AND "pregnancy"[All Fields] AND Review[ptyp]

("congenital"[Title] OR "neonatal"[Title]) AND "tuberculosis"[Title] AND Review[ptyp]

((("bedaquiline"[Supplementary Concept] OR "bedaquiline"[All Fields]) OR ("OPC-67683"[Supplementary Concept] OR "OPC-67683"[All Fields] OR "delamanid"[All Fields])) AND ("pregnancy"[MeSH Terms] OR "pregnancy"[All Fields])

We included review articles published from 2010 onwards that focused on TB in pregnant women and neonates, including latent TB infection (LTBI) and multi-drug resistant (MDR) TB. We excluded articles that focused on animal research and reviews that focused on the fertility impacts of urogenital TB.

We consulted published clinical guidelines to confirm the information in the included articles. We evaluated the quality of reviews in relation to whether conclusions were appropriately supported by the findings of included studies, and with regard to the geographic coverage of the original research.

Results and Discussion

The three searches returned 159 publications, of which 12 were duplicates. Of the remaining 147, 83 were potentially relevant. We decided to exclude reviews published prior to 2010 to avoid citing numerous reviews that drew on the same source literature, and in order to focus on up-to-date information. This resulted in 42 potentially relevant publications. Of these, 16

were excluded based on title and 12 were excluded based on full text. This left 14 review articles for inclusion in this meta-review [Table 1]. We searched reference lists for additional articles of interest to provide supplementary information for the included studies.

Table 1. Eligible reviews on TB in pregnant women and/or neonates published during or after 2010, listed in chronological order

#	Authors (Year)	Title	Journal
1	Nhan-Chang & Jones (2010) ⁸	Tuberculosis in pregnancy	Clin Obstet Gynecol
2	Burkett & Bradshaw (2011) ⁹	Neonatal tuberculosis: neonatal intensive care unit considerations in the United States	Adv Neonatal Care
3	Mnyani & McIntyre (2011) ¹⁰	Tuberculosis in pregnancy	Brit J Obst Gyn
4	Getahun et al (2012) ³	Prevention, diagnosis, and treatment of tuberculosis in children and mothers: evidence for action for maternal, neonatal, and child health services	J Infect Dis
5	Loto & Awowole (2012) ¹¹	Tuberculosis in pregnancy: a review	J Pregnancy
6	Mathad & Gupta (2012) ²	Tuberculosis in pregnant and postpartum women: epidemiology, management, and research gaps	Clin Infect Dis
7	Nguyen et al (2014) ¹²	Tuberculosis care for pregnant women: a systematic review	BMC Infect Dis
8	Gould & Aronoff (2016) ¹³	Tuberculosis and Pregnancy - Maternal, Fetal, and Neonatal Considerations	Microbiol Spectr
9	Malhame et al (2016) ¹⁴	Latent Tuberculosis in Pregnancy: A Systematic Review	PLoS One
10	Saramba & Zhao (2016) ¹⁵	A Perspective of the Diagnosis and Management of Congenital Tuberculosis	Paediatr Int Child Health
11	Sobhy et al (2017) ⁵	Maternal and perinatal mortality and morbidity associated with tuberculosis during pregnancy and the postpartum period: a systematic review and meta-analysis	J Pathog
12	Chang & Wu (2018) ¹⁶	Congenital tuberculosis: case report and review of the literature	Paediatr Int Child Health
13	Esmail et al (2018) ¹⁷	Management of drug-resistant tuberculosis in special sub-populations including those with HIV co-infection, pregnancy, diabetes, organ-specific dysfunction, and in the critically ill	J Thorac Dis
14	Newberry & Robertson Bell (2018) ¹⁸	Congenital Tuberculosis: A New Concern in the Neonatal Intensive Care Unit	Adv Neonatal Care

TB in Pregnancy

Epidemiology

It has been estimated that 216,500 women experienced TB during pregnancy globally in 2014.¹⁹ However, this is likely to be an underestimate for a number of reasons. Firstly, the estimate was based on global estimates of TB incidence that have since been revised upwards, from 9 million cases per year to 10 million cases per year.²⁰ Secondly, the methodology did not account for the fact that the risk of TB appears to increase by 2- to 3-fold during late pregnancy and the postpartum period,^{21,22} which will increase the burden of pregnancy-related TB. Consequently, the true global burden of pregnancy-related TB is unknown.^{2,3} At present, information on pregnancy is not routinely collected in TB surveillance efforts nationally or internationally, and pregnant women are not routinely screened for TB in most settings.³ There is an urgent need for case-notification data on this issue to better understand the true burden of disease, including in relation to different risk-factors such as age and HIV status as well as by geographic region.

A 2017 systematic review documented disease presentation, treatment outcomes and pregnancy outcomes in 3,384 women who participated in 13 distinct studies and were compared to controls without TB.⁵ Only six of the 13 studies were conducted in low-or middle-income countries,⁵ despite the far greater burden of TB during pregnancy in these settings, highlighting the need for additional data from high-burden settings.

Consequences of TB in pregnancy

In 10 relevant studies in the review by Sobhy, maternal TB was associated with approximately four-fold higher odds of death in both women and their infants.⁵ In the one study reporting on miscarriage, maternal TB was associated with an odds ratio of 9.1 (95% CI: 4.9, 16.7);²³ stillbirth was not addressed as a separate outcome.⁵ Pregnant women with TB were at elevated risk of preterm birth (OR 1.7, 95% CI 1.2–2.4), and their babies were more likely to have low birth weight (OR 1.7, 95% CI 1.2–2.4).⁵ Outcomes were worse in women who were diagnosed later in pregnancy.⁵ Two reviews stated that women with adequately treated TB were not at increased risk of adverse pregnancy outcomes,^{8,13} but these statements were supported with reference to two small studies from the mid-twentieth century,^{24,25} one of which did not actually compare pregnancy outcomes in women with and without active TB.²⁵ It is challenging to confidently assess the extent to which appropriate clinical management of TB mitigates the risk of adverse birth outcomes, as timing of diagnosis for women in published cohorts has varied, along with severity of disease.^{10,11} Adverse birth outcomes may be rare in some cohorts,²⁴ but this does not necessarily imply that TB treatment brings the risk of these events back to background levels. As in other adults, HIV predisposes pregnant women to more severe TB disease and poorer outcomes.^{5,13,26}

Preventing TB in pregnancy

Prevention of TB during pregnancy relies not only on infection control and appropriate use of preventive therapy in pregnant women, but also on the provision of effective contraception to women being treated for TB.^{5,12} Strikingly, in 73% of the cases included in the systematic

review by Sobhy et al, the pregnancy occurred after TB was diagnosed, rather than TB being diagnosed in the course of the pregnancy.⁵ Rifamycins adversely affect the metabolism of contraceptive hormones,²⁷ and women being treated for TB should be provided information about and access to effective contraception (such as injectable depot medroxyprogesterone acetate, which does not appear to be affected by rifampicin, either copper or intrauterine devices, or barrier methods²⁸). There is limited evidence on the impact of rifampicin on the effectiveness of progesterone-only contraception compared to combined oral contraceptive pill.²⁸ Data on contraceptive access and coverage among women of reproductive age being treated for TB would be of value, as would additional real-world data on the failure rates of different contraceptive methods used by these women.

Current guidelines provide limited advice to clinicians considering TB preventive therapy for pregnant women,^{7,29,30} and there is sparse and conflicting evidence on the safety of preventive therapy during pregnancy even from recent studies.³¹⁻³³ Although preventive therapy can be administered during pregnancy,²⁹ the risk-benefit assessment is more complex than in other adults. A recent randomised controlled trial observed more frequent adverse birth outcomes in HIV-positive women who started isoniazid preventive therapy during pregnancy, as opposed to after delivery.³¹ In several studies reviewed by Nguyen et al, the acceptability of preventive therapy in pregnancy appeared to be poor, with much lower uptake and completion rates in pregnant women compared to other adults.¹² Current recommendations emphasise carefully weighing the apparent risk of progression against potential risks. Pregnant or breast-feeding women who do receive isoniazid should receive pyridoxine (vitamin B6) supplementation to prevent peripheral neuropathy.¹⁰

There is currently limited data on the safety of newer rifapentine-based regimens for TB prevention in pregnant women.^{7,34} A post-hoc analysis of 54 women who became pregnant while receiving a 12-dose once-weekly regimen of isoniazid and rifapentine (3HP) and 72 women receiving 9-month daily isoniazid (9H) in two clinical trials did not show increased rates of adverse events in the 3HP group.³² Current guidelines suggest preventive therapy during pregnancy only for women at high risk of progression,^{29,30} and highlight the need for additional safety data. At least one additional study on preventive therapy in pregnancy is currently underway.³⁵

Screening and diagnosis in pregnancy

TB screening and diagnosis in pregnancy can be challenging.³ In general, symptoms are similar to other adults, and pulmonary disease remains the most common manifestation.^{10,13} The basic algorithm for clinical assessment of pregnant women with suspected TB is the same as for other adults, with diagnosis relying on a combination of symptoms, radiography, and laboratory investigations including smear microscopy, molecular tests (e.g. Xpert MTB/Rif) and, if available, mycobacterial culture.^{3,10} Pregnancy is not a contraindication for the use of shielded chest x-ray in TB screening or diagnosis.³⁶

In settings where TB prevalence is ≥ 100 cases per 100,000 population, WHO recommends consideration of TB screening for pregnant women, using either shielded chest radiography or symptom-based screening [Box 1].³⁶ Ideally, screening would be conducted as part of integrated antenatal care, and through services managing pregnant women with HIV.³

Published evaluations of the implementation of TB screening in antenatal care in low and middle income countries would be of value.

Box 1. WHO recommendation on TB testing in pregnancy³⁶

B.1.8: In settings where the tuberculosis (TB) prevalence in the general population is 100/100 000 population or higher, systematic screening for active TB should be considered for pregnant women as part of antenatal care.

Remarks:

Options for initial screening include screening for symptoms (either for cough lasting longer than two weeks, or any symptoms compatible with TB, including a cough of any duration, haemoptysis, weight loss, fever or night sweats) or screening with shielded chest radiography. The use of shielded chest radiography in pregnant women poses no significant risk but the national guidelines for the use of radiography during pregnancy should be followed.

Identifying an optimal algorithm for TB screening in pregnancy is challenging. Symptom screening has limited sensitivity, as a substantial proportion of pregnant women with active TB are asymptomatic.^{8,13} Symptoms may be atypical or masked by the pregnancy, such as weight loss (offset by weight gain during pregnancy), lethargy (common in pregnancy), night sweats and respiratory discomfort.^{11,12} Gould and Aronoff note that various algorithms have demonstrated high negative predictive values in practice.¹³ However, this is to be expected even if an algorithm were quite poor, simply because in most settings, a very large majority of women screened will not have TB. The combination of low population prevalence with the limited sensitivity and specificity of most tests will generate large numbers of false positives (which require resource-intensive investigations), and non-trivial numbers of false negatives (which result in missed opportunities to intervene). The best algorithm will be context specific, depending greatly on the prevalence of disease and the resources available.

Management of Drug Sensitive-TB in pregnancy

Pregnant women with pulmonary drug-sensitive TB may be treated with either the traditional four-drug regimen, or a modified three-drug regimen which excludes pyrazinamide, extending treatment duration to nine months.^{8,37} The WHO recommends that the standard four-drug regimen be used in all adults with drug-sensitive TB and makes no specific recommendations for treatment in pregnancy.²⁹ However, using pyrazinamide in pregnancy has been controversial in some settings (notably the US) due to a relative lack of safety data.^{11,13,37} US CDC guidelines acknowledge that in some circumstances (for example HIV/TB, extrapulmonary disease, or severe disease), the benefits of pyrazinamide use may outweigh the hypothetical risks of toxicity.³⁷ Streptomycin (an aminoglycoside) should not be used due to a high risk of foetal ototoxicity.^{8,11} Pregnancy may increase the risk of isoniazid-induced hepatitis, and liver function should be monitored during treatment.⁸ Vitamin K supplementation is recommended for the infant at birth, in order to reduce the risk of

haemolytic anaemia following exposure to rifampicin via the placenta.⁸ Management of TB during pregnancy in women living with HIV is complex,³⁸ particularly if the woman has not yet started ART. Physicians should consult appropriate up-to-date guidelines with regard to drug-drug interactions, and the safety of ART drugs in pregnancy.¹⁰

Management of drug resistant TB in pregnancy

The management of drug resistant TB in pregnancy is challenging, and there is a very limited evidence base to guide clinicians.³⁹ This is largely because pregnant women are typically excluded from clinical trials due to safety concerns. We identified only two review articles addressing MDR-TB during pregnancy.^{11,17} A third recent publication by Gupta et al reviewed the current state of drug development in several key populations, including pregnant women.⁶ There is sparse evidence on the safety of most second line drugs in pregnancy, and almost all evidence comes from animal studies, with the exceptions of occasional small case series or case reports.^{6,17} Most second line drugs are classified as class 'C' under the previous Food and Drug Administration classification system, meaning that animal reproduction studies have shown a risk and there are no adequate and well-controlled studies in humans, although the benefits of use drug pregnancy may outweigh the potential risks.⁶ Data from routine care and clinical trials are urgently needed to better ascertain the safety of these drugs during pregnancy.³⁹

The aminoglycosides should usually be avoided in pregnancy due to risk of ototoxicity and foetal malformation; ethionamide and prothionamide are potentially teratogenic.¹ For this reason, pregnant women are ineligible to receive the standardized shortened 9-11 month regimen for MDR-TB.⁴⁰ Delaminid has shown evidence of teratogenicity in animal studies, and is not currently recommended in pregnancy.¹⁷ Bedaquiline has not demonstrated risk in animal studies,¹⁷ and case reports of its use in pregnant women are entering the literature.^{41,42} Additional data on clinical outcomes for pregnant women treated in routine care or in clinical trials would be valuable. Both bedaquiline and delaminid have been shown to be excreted in milk in animal studies, a factor which must be considered by breast-feeding women and their clinicians.¹⁷

Congenital and neonatal TB

We identified 5 review articles addressing congenital and neonatal TB.^{9,13,15,16,18}

Epidemiology

To our knowledge, there are no incidence estimates for either congenital or neonatal TB. WHO estimates suggest that approximately 530,000 children aged 0-4 years developed TB in 2017,²⁰ but estimates for neonates and infants are not available. During pregnancy, the foetus may be exposed to TB via either the umbilical vein, or through infected amniotic fluid; infants may also be exposed during delivery.^{9,10,13,15,43} Congenital TB is rare, but has high mortality,^{11,13} and neonates with congenital TB may deteriorate rapidly.⁴³ Following birth, neonates may be exposed to respiratory droplets if the mother or another care-giver has

infectious pulmonary TB, and in this scenario the risk of progression will be very high.^{44,45} Epidemiologic data show that infants under 1 year old are at extreme risk of progression to disease following infection: 70% of infants accidentally inoculated with *Mycobacterium tuberculosis* (*M.tb*) in the Lubeck disaster in 1930 developed clinical disease.⁴⁴

TB prevention in infants

Prevention of congenital TB relies on timely diagnosis and appropriate treatment of the pregnant mother.^{3,8} Likewise, prevention of transmission after delivery can be achieved if the mother's treatment has controlled her own TB sufficiently that she is no longer able to transmit TB.^{3,8} Preventive therapy is recommended for newborns exposed to *M.tb* who have no evidence of TB disease, and BCG is delayed.⁴⁶ Dosage is weight dependent and will require adjustment as the newborn gains weight.⁴⁶ Options for preventive therapy for a newborn exposed to drug-susceptible TB include isoniazid alone or rifampicin-isoniazid combinations, for which there is now a dispersible formulation that allows adjustment for accurate dosing.⁴⁶ Close follow-up is required to monitor weight gain and clinical evidence of TB disease. If there is no evidence of TB, a test for infection (TST) is performed at 3 months after exposure.⁴⁶ If TST negative, then preventive therapy can be ceased and BCG vaccination is provided if the infant does not have HIV.⁴⁶ If the infant is TST positive, then the preventive therapy regimen (at least 6 months of isoniazid alone or 3 months of rifampicin-isoniazid) is completed.⁴⁶

TB diagnosis and management in neonates

TB signs and symptoms in neonates are diverse, and often extend beyond the respiratory system.^{9,15,43} Some neonates may be asymptomatic. Although intrathoracic TB is the commonest manifestation in all age groups, infants are particularly prone to disseminated disease and to TB meningitis.¹⁸ Congenital TB often involves the liver and related organs.^{9,11,15,16,43} There are numerous barriers to diagnostic confirmation in neonates, most significantly the low sensitivity of immunologic and microbiologic tests. Clinical diagnosis relies on symptoms, radiographic results, history of possible exposure, and response to therapy.^{9,18} Clinicians working in low resource settings may have limited access to radiography, immunologic tests, or microbiologic tests.⁴⁶ A high index of suspicion should be maintained in symptomatic and severely ill infants, especially in those with a known TB contact, and absence of diagnostic confirmation should not rule out TB therapy.⁴⁶

Drug regimens for neonates are the same as for other children, although dose adjustments may be required to balance efficacy against toxicity. Ideally, dosing should be managed by a clinician with experience in treating young children for TB, and adjusted as infants gain weight.⁴⁶ Pharmacokinetic studies are increasingly enrolling young children and infants in order to better understand optimal dosing in these age groups.⁶ Drug administration can be challenging in young children, and dispersible fixed dose combinations are not yet universally available.

Future Research Directions

We identified a number of priorities for future research with regards to prevention, detection, and treatment of TB in pregnancy [Table 2].

Table 2. Evidence gaps and required studies

Gaps	Studies needed
Prevention	<p>Randomised controlled trials to establish the safety and optimal timing of preventive therapy regimens in pregnancy and/or post-partum</p> <p>Pharmacokinetic and safety studies to establish appropriate dosing for pregnant women and neonates receiving preventive therapy</p> <p>Data on the efficacy of different contraceptive options, and programmatic data on contraceptive coverage among women of reproductive age receiving TB treatment</p>
Detection	<p>Operational research on the performance of different screening and diagnostic algorithms in diverse settings</p> <p>Evaluation of diagnostic tests for disease and infection in pregnancy</p> <p>Prevalence data from screening studies in antenatal care in diverse settings</p> <p>Routine TB surveillance data recording pregnancy status</p>
Treatment	<p>Pharmacokinetic studies to establish appropriate doses for treatment of disease in pregnant women and neonates</p> <p>Prospective cohort studies and randomised controlled trials of the safety of second-line TB drugs during pregnancy, including in the first trimester</p>

As in other populations, the limitations of current diagnostic tests and the complexity of clinical evaluation present a barrier to timely screening and diagnosis in pregnant women, and especially neonates.³ The optimal screening algorithms for TB in pregnant women will be setting-specific, and evidence is needed from operational research in a variety of settings to guide implementation. Negative predictive value is important, but sensitivity and number needed to screen are also important indicators, and were reported far less often in the literature we reviewed.

Standard tools for TB surveillance do not include any indicators on TB in pregnancy,⁴⁷ and as a consequence, routine data on both incidence and outcomes are lacking. Where feasible, national TB programs could consider including variables to record pregnancy in case based electronic surveillance systems for TB. Electronic medical records used in either TB services or antenatal care services could also be modified to capture data about TB in pregnant women, including adverse drug reactions and pregnancy outcomes for observational studies.

The safety of drugs for drug resistant TB during pregnancy is an open and critical question, given that animal studies suggest a majority of these drugs present some risk.⁶ The authors

are currently working towards establishing an international registry for TB in pregnancy, which will record adverse events and pregnancy outcomes. In addition to drug safety, high quality data on the pharmacokinetics of TB drugs in pregnant women and in neonates are urgently needed to inform appropriate guidance on dosing in these populations.⁶ More studies are needed to settle the question of whether, or in what circumstances, preventive therapy should be deferred until after delivery.³¹

Conclusions

TB in pregnancy is a serious event for both the mother and the foetus, dramatically increasing the risks of miscarriage, maternal death, and neonatal death. Although TB screening during pregnancy is recommended in some settings, reliable algorithms have not yet been identified. Diagnosis can be challenging in both pregnant women and in neonates. There is limited guidance for clinicians regarding appropriate drug dosing for pregnant women or neonates, and almost no data from humans on the safety of second-line TB drugs in pregnancy. High-quality evidence on these topics is needed to inform clearer and more specific guidelines regarding the prevention, detection and management of TB in pregnant women and their infants.

References

1. Gupta A, Mathad JS, Abdel-Rahman SM, et al. Toward Earlier Inclusion of Pregnant and Postpartum Women in Tuberculosis Drug Trials: Consensus Statements From an International Expert Panel. *The Indian journal of surgery* 2016; **62**(6): 761-9.
2. Mathad JS, Gupta A. Tuberculosis in pregnant and postpartum women: epidemiology, management, and research gaps. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2012; **55**(11): 1532-49.
3. Getahun H, Sculier D, Sismanidis C, Grzemska M, Raviglione M. Prevention, diagnosis, and treatment of tuberculosis in children and mothers: evidence for action for maternal, neonatal, and child health services. *The Journal of infectious diseases* 2012; **205 Suppl 2**: S216-27.
4. McKenna L, Frick M, Lee C, et al. A community perspective on the inclusion of pregnant women in tuberculosis drug trials. *Clinical Infectious Diseases* 2017; **65**(8): 1383-7.
5. Sobhy S, Babiker Z, Zamora J, Khan KS, Kunst H. Maternal and perinatal mortality and morbidity associated with tuberculosis during pregnancy and the postpartum period: a systematic review and meta-analysis. *Journal of pathogens* 2017; **124**(5): 727-33.
6. Gupta A, Hughes MD, Garcia-Prats AJ, McIntire K, Hesselning AC. Inclusion of key populations in clinical trials of new antituberculosis treatments: Current barriers and recommendations for pregnant and lactating women, children, and HIV-infected persons. *PLoS medicine* 2019; **16**(8).
7. Borisov AS, Morris SB, Njie GJ, et al. Update of recommendations for use of once-weekly isoniazid-rifapentine regimen to treat latent Mycobacterium tuberculosis infection. *Morbidity and Mortality Weekly Report* 2018; **67**(25): 723.
8. Nhan-Chang CL, Jones TB. Tuberculosis in pregnancy. *Clinical obstetrics and gynecology* 2010; **53**(2): 311-21.
9. Burkett EA, Bradshaw WT. Neonatal tuberculosis: neonatal intensive care unit considerations in the United States. *Advances in neonatal care : official journal of the National Association of Neonatal Nurses* 2011; **11**(6): 376-81.
10. Mnyani CN, McIntyre JA. Tuberculosis in pregnancy. *BJOG : an international journal of obstetrics and gynaecology* 2011; **118**(2): 226-31.
11. Loto OM, Awowole I. Tuberculosis in pregnancy: a review. *Journal of pregnancy* 2012; **2012**: 379271.
12. Nguyen HT, Pandolfini C, Chiodini P, Bonati M. Tuberculosis care for pregnant women: a systematic review. *BMC infectious diseases* 2014; **14**: 617.
13. Gould JM, Aronoff SC. Tuberculosis and Pregnancy-Maternal, Fetal, and Neonatal Considerations. *Microbiology spectrum* 2016; **4**(6).
14. Malhame I, Cormier M, Sugarman J, Schwartzman K. Latent Tuberculosis in Pregnancy: A Systematic Review. *PloS one* 2016; **11**(5): e0154825.
15. Saramba MI, Zhao D. A Perspective of the Diagnosis and Management of Congenital Tuberculosis. *Journal of pathogens* 2016; **2016**: 8623825.
16. Chang CW, Wu PW. Congenital tuberculosis: case report and review of the literature. *Paediatr Int Child Health* 2018; **38**(3): 216-9.
17. Esmail A, Sabur NF, Okpechi I, Dheda K. Management of drug-resistant tuberculosis in special sub-populations including those with HIV co-infection, pregnancy, diabetes, organ-specific dysfunction, and in the critically ill. *Journal of thoracic disease* 2018; **10**(5): 3102-18.
18. Newberry DM, Robertson Bell T. Congenital Tuberculosis: A New Concern in the Neonatal Intensive Care Unit. *Advances in neonatal care : official journal of the National Association of Neonatal Nurses* 2018; **18**(5): 341-9.

19. Sugarman J, Colvin C, Moran AC, Oxlade O. Tuberculosis in pregnancy: an estimate of the global burden of disease. *The Lancet Global Health* 2014; **2**(12): e710-e6.
20. World Health Organization. Global Tuberculosis Report 2018. Geneva, 2018.
21. Zenner D, Kruijshaar ME, Andrews N, Abubakar I. Risk of tuberculosis in pregnancy: a national, primary care-based cohort and self-controlled case series study. *American journal of respiratory and critical care medicine* 2012; **185**(7): 779-84.
22. Jonsson J. Tuberculosis control in Sweden. *Doctoral Thesis* 2018.
23. Bjerkedal T, Bahna S, Lehmann E. Course and outcome of pregnancy in women with pulmonary tuberculosis. *Scandinavian journal of respiratory diseases* 1975; **56**(5): 245-50.
24. Schaefer G, Zervoudakis IA, Fuchs FF, David S. Pregnancy and pulmonary tuberculosis. *obstetrics and gynecology* 1975; **46**(6): 706-15.
25. Mehta B. Pregnancy and tuberculosis. *Diseases of the chest* 1961; **39**(5): 505-11.
26. Bekker A, Schaaf HS, Draper HR, Kriel M, Hesselning AC. Tuberculosis disease during pregnancy and treatment outcomes in HIV-infected and uninfected women at a referral hospital in Cape Town. *PloS one* 2016; **11**(11): e0164249.
27. Simmons KB, Haddad LB, Nanda K, Curtis KM. Drug interactions between rifamycin antibiotics and hormonal contraception: a systematic review. *BJOG* 2018; **125**(7): 804-11.
28. World Health Organization. Medical eligibility criteria for contraceptive use. Geneva, Switzerland: World Health Organization,, 2015.
29. World Health Organization. Compendium of WHO guidelines and associated standards: ensuring optimum delivery of the cascade of care for patients with tuberculosis. 2018.
30. The American Thoracic Society and the Centers for Disease Control and Prevention. Targeted tuberculin testing and treatment of latent tuberculosis infection. *Am J Respir Crit Care Med* 2000; **161**(4 Pt 2): S221-47.
31. Gupta A, Montepiedra G, Aaron L, et al. Isoniazid preventive therapy in HIV-infected pregnant and postpartum women. *New England Journal of Medicine* 2019; **381**(14): 1333-46.
32. Moro RN, Scott NA, Vernon A, et al. Exposure to latent tuberculosis treatment during pregnancy. The PREVENT TB and the iAdhere Trials. *Annals of the American Thoracic Society* 2018; **15**(5): 570-80.
33. Salazar-Austin N, Cohn S, Lala S, et al. Isoniazid Preventive Therapy and Pregnancy Outcomes In HIV-Infected Women in the Tshepiso Cohort. *Clinical Infectious Diseases* 2019.
34. World Health Organization. Latent tuberculosis infection: updated and consolidated guidelines for programmatic management: World Health Organization, 2018.
35. IMPAACT Network. IMPAACT 2001: A Phase I/II Trial of the Pharmacokinetics, Tolerability, and Safety of Once-Weekly Rifapentine and Isoniazid in HIV-1-infected and HIV-1-uninfected Pregnant and Postpartum Women with Latent Tuberculosis Infection. Durham, NC, 2019.
36. World Health Organization. WHO recommendations on antenatal care for a positive pregnancy experience: World Health Organization; 2016.
37. Nahid P, Dorman SE, Alipanah N, et al. Official American thoracic society/centers for disease control and prevention/infectious diseases society of America clinical practice guidelines: treatment of drug-susceptible tuberculosis. *Clinical Infectious Diseases* 2016; **63**(7): e147-e95.
38. Weld ED, Dooley KE. State-of-the-Art Review of HIV-TB Coinfection in Special Populations. *Clinical Pharmacology & Therapeutics* 2018; **104**(6): 1098-109.

39. Nahid P, Mase SR, Migliori GB, et al. Treatment of Drug-Resistant Tuberculosis: An Official ATS/CDC/ERS/IDSA Clinical Practice Guideline. *Am J Respir Crit Care Med* 2019; **200**(10): e93-e142.
40. World Health Organization. WHO treatment guidelines for drug-resistant tuberculosis: World Health Organization; 2016.
41. Taune M, Ustero P, Hiashiri S, et al. Successful implementation of bedaquiline for multidrug-resistant TB treatment in remote Papua New Guinea. *Public Health Action* 2019; **9**(Suppl 1): S73.
42. Jaspard M, Elefant-Amoura E, Melonio I, De Montgolfier I, Veziris N, Caumes E. Bedaquiline and Linezolid for Extensively Drug-Resistant Tuberculosis in Pregnant Woman. *Emerging infectious diseases* 2017; **23**(10).
43. Di Comite A, Esposito S, Villani A, Stronati M. How to manage neonatal tuberculosis. *Journal of perinatology : official journal of the California Perinatal Association* 2016; **36**(2): 80-5.
44. Fox GJ, Orlova M, Schurr E. Tuberculosis in newborns: the lessons of the “Lübeck disaster”(1929–1933). *PLoS pathogens* 2016; **12**(1): e1005271.
45. Marais BJ, Gie RP, Schaaf HS, et al. The clinical epidemiology of childhood pulmonary tuberculosis: a critical review of literature from the pre-chemotherapy era [State of the Art]. *The International Journal of Tuberculosis and Lung Disease* 2004; **8**(3): 278-85.
46. Graham S. Desk-guide for diagnosis and management of TB in children. Paris, France: The International Union Against TB and Lung Disease, 2016.
47. World Health Organization. Standards and benchmarks for tuberculosis surveillance and vital registration systems. Geneva: WHO, 2016.