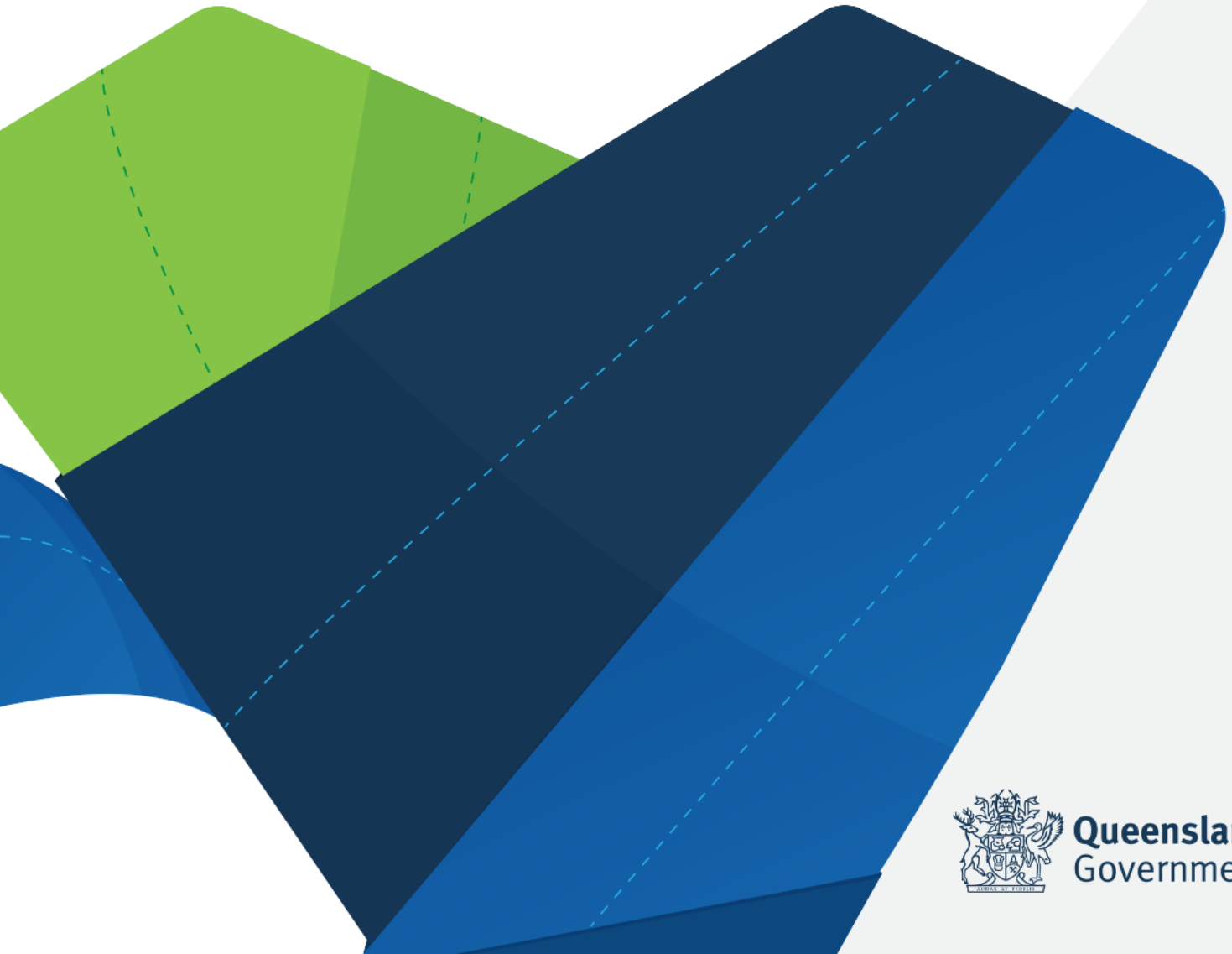
Queensland Health

Management of tuberculosis in pregnant women and newborn infants

Guideline, Version 3.2 - November 2021



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Note, updates after October 2021 are amended in the online version of Management of tuberculosis in pregnant women and newborn infants ONLY
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Contents

1. Key critical points

- The decision to treat tuberculosis (TB) in pregnancy, must consider the potential risks to mother and fetus from medication, versus the benefits to mother, fetus and the community. The benefits of treating TB in pregnancy are widely considered to outweigh the risks of treatment.
- Although small concentrations of some TB drugs are excreted in breast milk, treatment of a woman for TB is not considered a contra-indication to breastfeeding, is not associated with toxicity to the baby and should not be discouraged.
- All infants born to mothers with TB during their pregnancy require evaluation for congenital TB.
- If congenital TB is diagnosed, the infant should receive standardised multidrug treatment for at least 6 months with longer duration considered when there is central nervous system involvement or suspected or confirmed antimicrobial resistance.
- If the mother has pulmonary TB and is potentially infectious at the time of delivery and no evidence of congenital TB is found, infants should have chemoprophylaxis with isoniazid and rifampicin from birth until at least 3 months of age.
- Where the mother is undergoing treatment for pulmonary TB, is unlikely to be infectious at the time of delivery and the infant has no evidence of congenital TB, the infant does not require chemoprophylaxis and can have a Tuberculin Skin Test (TST) performed at 3 months; if the TST is negative, then offer BCG vaccination.
- Where the mother has disseminated or genital tract TB during pregnancy, the infant should commence on standard TB treatment for at least 3 months unless the mother's TB treatment was completed prior to birth. Continue treatment for at least 6 months if there is evidence of TB infection in the child (congenital TB or reactive TST).
- In addition to the infant receiving appropriate chemoprophylaxis, the mother should wear a mask while breastfeeding if she is considered infectious.

2. Effects of TB on pregnancy

Maternal TB has been associated with an increased risk of spontaneous abortion, perinatal mortality, small size for gestational age, and low birth weight. The outcome is unfavourably influenced by delays in diagnosis or treatment.

True congenital TB is a rare complication of in utero TB infection due to maternal haematogenous spread. Congenital TB is difficult to diagnose because it is seldom clinically distinguishable from other neonatal or congenital infections. Symptoms usually arise in the second or third week postpartum. Hepatosplenomegaly, respiratory distress, and fever are common and chest radiography is usually abnormal, with involvement of the liver (site of primary/Ghon focus) being the hall mark of congenital TB where infection crossed the placenta.

All persons diagnosed with active TB, including pregnant women, should be evaluated for HIV infection by serological testing. This is particularly important in pregnancy, given major benefits of appropriate HIV treatment to the mother and her baby.

3. First-line treatment

The International Union Against Tuberculosis and Lung Disease (www.theunion.org) and the World Health Organization (www.who.int) support the use of standard first-line drug regimens in pregnant women with TB.

This guideline endorses the recommendation of the use of standard first-line drugs of isoniazid, rifampicin, ethambutol, and pyrazinamide in pregnant women with TB. Although these TB drugs cross the placenta, these have not been shown to have teratogenic effects and thus are not contra-indicated in pregnancy.

3.1. Isoniazid

Isoniazid is recommended for use in pregnancy. Isoniazid may be associated with an increased risk of hepatotoxicity in pregnant women. Monitoring for hepatotoxicity is with symptom assessment and fortnightly liver function tests during the first 2 months of treatment and then monthly thereafter.

3.2. Pyridoxine (Vitamin B6)

Pyridoxine supplementation is recommended for all pregnant women taking isoniazid as deficiency is more likely to occur than in the general population. Pyridoxine should also be administered if cycloserine or pro/ethionamide is used for treatment of drug-resistant TB in the post-partum period (see below).

3.3. Rifampicin

Rifampicin is recommended for use in pregnancy. Bleeding attributed to hypoprothrombinaemia has been reported in infants and mothers following the use of rifampicin in late pregnancy. Vitamin K is recommended for both the mother and the infant postpartum if rifampicin is used in the last few weeks of pregnancy.

3.4. Ethambutol

Ethambutol is recommended for use in pregnancy without any specific precautions. Its use in high therapeutic doses in neonates/infants is generally discouraged, because of eye toxicity concerns and the availability of better treatment options, but its use in pregnancy is not discouraged.

3.5. Pyrazinamide

Pyrazinamide is recommended for use in pregnancy. No reports of fetal malformations are attributable to pyrazinamide, although no animal or epidemiological studies have been reported. The paucity of such data is the reason that the United States Centers for Disease Control and Prevention (CDC) guidelines continue to not endorse pyrazinamide use in pregnancy. Its use, however, is supported by other TB authorities, including the World Health Organization and The International Union Against Tuberculosis and Lung Disease, and is recommended in this guideline. If pyrazinamide is not used, a 9-month regimen containing isoniazid and rifampicin is recommended, supplemented by ethambutol until drug susceptibility results are available. Treatment with pyrazinamide during pregnancy requires close clinical observation with increased monitoring of at least monthly liver function tests due to the higher risk of hepatotoxicity.

4. Second-line treatment

The management of drug-resistant (DR) cases and the use of second-line agents (both generally and during pregnancy) should only be considered after consultation with an expert in TB management. Teratogenicity has been described with aminoglycosides, capreomycin, and prothionamide, and patients taking these agents should be advised to take measures to avoid pregnancy. Despite a paucity of data regarding their use in pregnancy, fluoroquinolones and the new diarylquinoline (bedaquiline) are considered drugs of preference over other agents with established fetal toxicity profiles. An MDR-TB regimen may be modified post-partum to optimise the regimen depending on clinical circumstances.

4.1. Fluoroquinolones

Increased incidence of abnormalities is not evident in babies of mothers treated with fluoroquinolones. However, animal studies of ciprofloxacin suggest a potential risk of damage to articular cartilage when exposed to high doses. In general, fluoroquinolones can be used safely in pregnant women with drug-resistant TB where the benefits of treatment clearly outweigh the potential risks.

4.2. Amikacin

All aminoglycosides are potentially nephrotoxic and ototoxic to the fetus and their use is not recommended for TB in pregnant women. Maternal drug levels do not appear to correlate with fetal safety. The use of aminoglycosides in pregnancy should be a last resort after due consideration of the risks and benefits.

4.3. Pro/ethionamide

Prothionamide (available in Australia) and ethionamide have been shown to be teratogenic in animal studies and thus there is no controlled data in human pregnancy. Their use is generally not recommended in pregnancy.

4.4. Cycloserine

Although there is no evidence of teratogenicity in rats, there are insufficient studies in humans to confirm the safety of cycloserine in pregnancy. Its use should only be considered in drug-resistant TB where the benefits outweigh the potential risks.

4.5. Clofazimine

Based on the use of clofazimine for the treatment of leprosy in pregnancy, this agent should be considered safe for the treatment of MDR-TB in pregnant women.

4.6. Bedaquiline

Although bedaquiline (BDQ) has a relatively short history of clinical use for the treatment of MDR-TB, there are no early signals of being hazardous in pregnancy. Animal studies cited in the product information did not find any evidence of fetal harm. A recent study of 108 pregnant woman and their babies found no safety concerns in the 54percentof woman who received BDQ. A slight decrease in birth weight in the BDQ group could not be attributed to BDQ, with no remaining differences at one year of age. (Loveday et al)

4.7. Para-aminosalicylic acid

There is limited animal and human safety data relating to the use of para-aminosalicylic acid in pregnancy. It may be associated with embryotoxicity, occipital malformation, and higher incidence of limb and ear abnormalities. Its use should only be considered in drug-resistant TB where the benefits outweigh the potential risks.

4.8. Meropenem and Imipenem-cilistatin

The carbapenem agents meropenem and imipenem-cilistatin, when combined with clavulanic acid (as amoxycillin/clavulanic acid) have utility in treating DR-TB. There is no evidence of harmful effects on the human fetus with either agent, although imipenem-cilistatin has been associated with fetal adverse effects in animal studies with uncertain implications for humans. Animal studies have not identified potential teratogenicity with meropenem.

4.9. Amoxycillin/clavulanic acid

There is no evidence of teratogenicity in animal studies. Amoxycillin/clavulanic acid has been used without problems documented in late pregnancy as prophylaxis in women with prolonged rupture of membranes, but experience with its use in the first trimester is limited. Amoxycillin/clavulanic acid is likely to have a role in the treatment of MDR-TB in pregnancy with concomitant carbapenem use.

5. Treatment of TB in breastfeeding women

Although small concentrations of TB drugs are excreted in breast milk, treatment for TB is not considered a contra-indication to breastfeeding. It is also important to note that the concentrations of TB drugs in breast milk are so low that they cannot be relied on for treatment of the infant. If an infant requires treatment for active disease or primary prophylaxis, adequate weight-based guidelines for children should be followed. It is not considered necessary to administer pyridoxine to a breastfeeding infant whose mother is receiving isoniazid unless the infant is also receiving isoniazid, but standard multivitamin supplementation should be considered. A recent MDR-TB field guide publication, *The Sentinel Project on Pediatric Drug-Resistant Tuberculosis*, recommends that breastfeeding infants of mothers who are on cycloserine or pro/-ethionamide treatment should be considered for pyridoxine (B6) supplementation.

6. TB and the newborn

6.1 Congenital TB

Congenital TB is a rare complication of in utero TB infection that results from maternal haematogenous spread and transplacental transfer. This is most likely where the mother has disseminated TB disease, such as miliary TB/TB meningitis or occult dissemination following primary pulmonary TB (often signified by a recent TB pleural effusion). TB of the genital tract is another risk factor for congenital TB in the infant if the placenta is affected. Women with active pulmonary TB are more likely to infect their babies after, not before, delivery.

Congenital TB is difficult to diagnose because it is difficult to distinguish clinically from other neonatal or congenital infections. Symptoms usually arise in the second or third week postpartum. Hepatosplenomegaly, lymphadenopathy, respiratory distress, poor feeding and fever are typical features; chest radiography is usually abnormal, and involvement of the liver (site of primary/Ghon focus) is the hallmark of congenital TB.

If congenital TB is suspected, CXR, abdominal ultrasound, lumbar puncture and gastric aspirate (GA) must be performed promptly. A second GA must be collected on the following day. An Xpert Ultra MTB/RIF molecular assay should be performed on at least one of the gastric aspirate samples. Treatment should be initiated as soon as possible with standard 3 drug therapy: isoniazid, rifampicin, and pyrazinamide for sensitive TB. Ethambutol may be included if isoniazid resistance is considered likely. Duration of therapy should be at least 6 months, but a longer treatment period or additional drugs may be considered if CNS or drug resistant disease is suspected/confirmed.

Expert advice should be sought, particularly if MDR-TB or other forms of DR are suspected. The placenta should be evaluated with histology and mycobacterial culture.

If congenital TB is diagnosed where the mother was not known to have had TB in pregnancy, a thorough assessment of the mother for TB (including genitourinary TB and HIV co-infection) should occur.

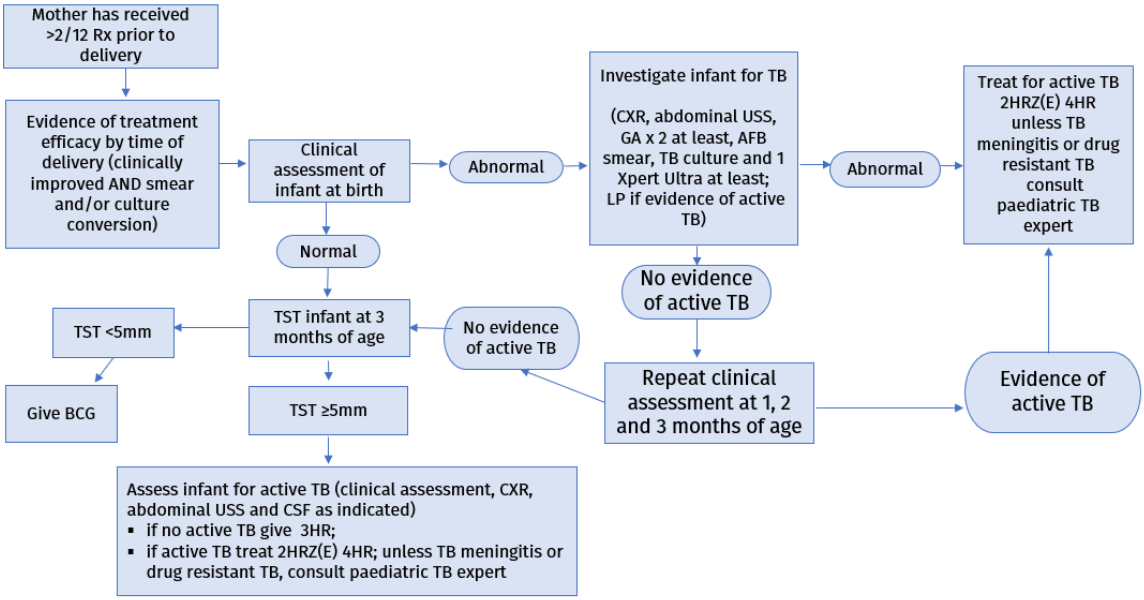
6.2 Mother with Latent TB (LTB) at delivery

Where the mother has LTB (positive TST/IGRA plus normal CXR or abnormal findings on CXR but no evidence of TB disease), the infant should not be separated from the mother and can be breastfed. Treatment of maternal LTB should be considered after the initial postpartum period. The infant does not require treatment.

6.3 Mother with active pulmonary TB during pregnancy who has received sufficient treatment to be considered not infectious at time of delivery

If a mother with pulmonary TB has been on TB treatment for more than 2 months before delivery and has evidence of treatment efficacy (clinical improvement and smear and/or TB culture conversion), she is unlikely to be infectious to her baby or others at the time of delivery. In this scenario and provided there are no clinical features of congenital TB, the infant does not require further investigations or treatment if generally well and thriving. . If cultures are still pending, a substantial decrease in smear positivity may also be indicative of treatment efficacy provided clinical improvement also confirmed. Perform TST on infant at 3 months of age and if negative, offer BCG. In this setting, BCG will provide protection in an environment where there is an increased likelihood of future TB exposure, e.g. should the mother relapse or other close contacts develop active pulmonary TB.

Figure 1. Pulmonary TB in pregnancy – mother unlikely to be infectious due to adequate treatment duration and response



See notes Section 6.7

6.4 Mother with active pulmonary TB during pregnancy who has not received sufficient therapy and likely infectious at delivery

Regardless of smear result, a mother with active pulmonary TB during pregnancy who has not commenced therapy or has received less than 2 months of TB therapy before delivery or has failed to demonstrate adequate response to therapy despite more than 2 months therapy before delivery may still be able to transmit TB to their infant. In this scenario, chemoprophylaxis from birth until at least 3 months of age is recommended unless congenital TB is present.

All infants born to mothers with active TB at delivery require evaluation for congenital TB as above (Section 6.1), although the risk is generally considered to be low. If there is clinical suspicion of congenital TB, see 6.1 for management.

A first gastric aspirate should be obtained from the infant and isoniazid 10mg/kg/day and rifampicin 15mg/kg/day preventive therapy should be commenced promptly and continued for 3 months. If the infant is breastfeeding and isoniazid chemoprophylaxis is commenced, the infant should have pyridoxine supplementation (5mg daily).

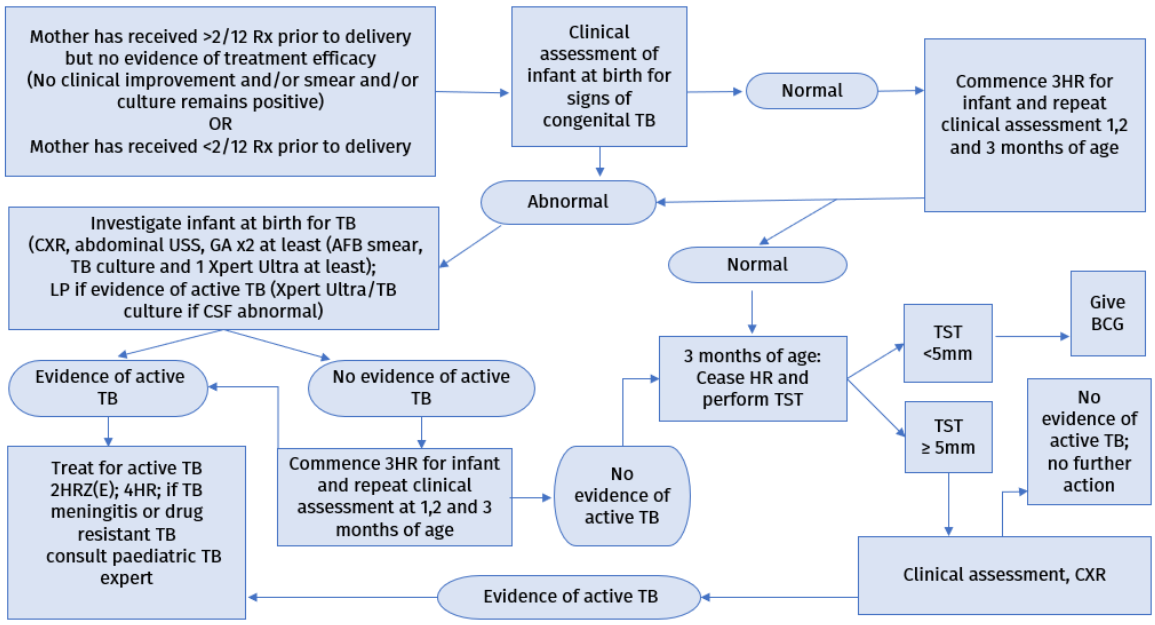
If the gastric aspirate (or any other specimen) grows *M. tuberculosis*, manage as for congenital TB.

The mother should wear a surgical mask when in close contact (including breastfeeding) with her infant from the time of delivery until the mother becomes smear negative and more than 2 months of effective therapy administered. The mother should start appropriate anti-TB therapy as soon as possible, if not already commenced. The infant should be evaluated

monthly. Medication doses should be recalculated according to the infant's body weight. If TST negative at 3 months, the infant should be given BCG.

If the parents decline the recommendation for their child to revieve chemoprophylaxis, monthly clinical assessment should still occur with a TST at 3 months of age. A child with a positive TST who has not recived chemoprophylaxis is at high risk of developing active TB in the first year of life and should be managed with chemoprophylaxis as a high priority (assuming active TB again excluded).

Figure 2. Pulmonary TB in pregnancy – mother likely to be infectious due to inadequate treatment duration or response



See notes Section 6.7

6.5 Mother with extra-pulmonary TB during pregnancy

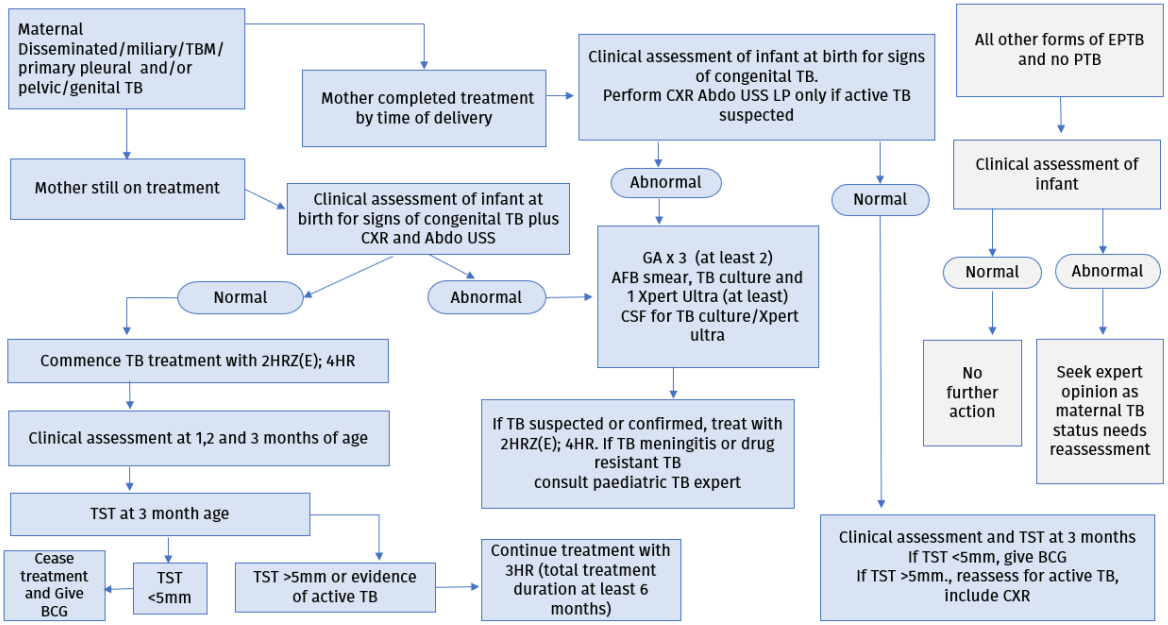
While most forms of extrapulmonary TB are not a transmission risk for the infant, congenital TB in the infant may occur when there is maternal disseminated/miliary TB, TB meningitis, primary TB (often manifested as a pleural effusion in pregnancy), or genital tract TB.

With these forms of maternal extrapulmonary TB, the risk of transmission is in utero or during delivery with acquisition via haematogenous transplacental spread or ingestion/inhalation of infected amniotic fluid. There is not a significant risk of transmission after birth to the infant unless there is also pulmonary TB present and adequate maternal therapy is yet to occur.

Where a full course of therapy has been completed prior to delivery, treatment of the infant for latent or active TB is not required if the infant is assessed as normal on initial

examination. If the mother is still on treatment at delivery – for a disease condition potentially associated with dissemination or placental involvement – the infant should be treated with 2HRZ(E);4HR. At 3 months of age, perform TST and clinical assessment; if TST <5mm and no evidence of active TB, cease treatment and give BCG. If evidence of active TB, continue therapy.

Figure 3. Mother with extra-pulmonary TB during pregnancy



See notes Section 6.7

6.6 Mothers with MDR-TB disease

If the mother has infectious MDR-TB pulmonary disease at delivery, consider on a case by case basis whether the infant should be separated from the mother until she is on appropriate TB treatment. Breast feeding is not contra-indicated, but mother should wear a surgical mask while in contact with her infant until she is culture negative. The infant should not share a room or bed with the mother while the mother is infectious. The infant should be considered for chemoprophylaxis with a fluoroquinolone, but this needs to be discussed to consider likely risks and benefits. If chemoprophylaxis is given, BCG vaccination should be postponed until such treatment is complete and the baby is confirmed to be TST/IGRA negative at least 3 months after exposure ended. All cases should be discussed with a paediatric TB specialist.

6.7 Notes

- Consult paediatric TB/infectious disease expert for all cases of TB in pregnancy and newborn infants.
- Recommendations in sections 6.1 to 6.5 are based on TB proven or assumed to be drug susceptible.
- Wait 1 week after ceasing HR before administering BCG.
- 2HRZ(E);4HR - 2 months of isoniazid, rifampicin, pyrazinamide and ethambutol followed by 4 months of isoniazid and rifampicin. Ethambutol can be omitted/discontinued if susceptibility to HRZ is confirmed/considered likely.
- If rifampicin resistance (including MDR-TB) is proven or strongly suspected, seek expert advice from the Queensland TB Expert Advisory Group (TEAG)
- Recommendations apply to preterm babies as well as term babies.

References

Bothamley G. Drug Treatment for Tuberculosis during Pregnancy: Safety Considerations. Drug Safety. 2001;24(7):553–65.

Centers for Disease Control and Prevention. Treatment of Tuberculosis, American Thoracic Society, CDC, and Infectious Diseases Society of America. MMWR 2003;52(No. RR-11)

Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. Joint Tuberculosis Committee of the British Thoracic Society. Thorax. 1998 Jul;53(7):536–48.

Enarson DA, Rieder HL, Arnadottir T, Trébucq A. Management of tuberculosis a guide for low income countries. 5th ed. International Union Against Tuberculosis and Lung Disease; 2000.

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. J Thorac Dis. 2018 May;10(5):3102–18.

Loveday M, Hughes J, Sunkari B, Master I, Hlangu S, Reddy T, Chotoo S, Green N, Seddon JA. Maternal and infant outcomes among pregnant women treated for multidrug/rifampicin-resistant tuberculosis in South Africa. Clin Infect Dis. 2020 Mar 6:ciaa189. doi: 10.1093/cid/ciaa189. Epub ahead of print.

Management of Drug-Resistant Tuberculosis in Children: A Field Guide. Boston, USA: The Sentinel Project for Pediatric Drug-Resistant Tuberculosis; November 2018, Fourth edition.

MIMS Online. (2020). Available from https://www.mimsonline.com.au

Ormerod P. Tuberculosis in pregnancy and the puerperium. Thorax. 2001 Jun;56(6):494–9.

World Health Organization. Guidance for national tuberculosis programmes on the management of tuberculosis in children. 2nd Ed. Geneva: WHO. 2014

World Health Organization, Stop TB Initiative (World Health Organization), editors. Treatment of tuberculosis: guidelines. 4th ed. Geneva: WHO; 2010.

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