

Guideline

Treatment of tuberculosis in pregnant women and newborn infants

Version 3.1

Key critical points

- The decision to treat tuberculosis (TB) in pregnancy must consider the potential risks to mother and fetus from medication, and the benefits to mother, foetus and the community. The benefits of treating TB in pregnancy are widely considered to outweigh any risk of treatment.
- Although small concentrations of anti-TB drugs are excreted in breast milk, treatment for TB is generally not considered a contra-indication to breastfeeding, and is not associated with toxicity to the baby.

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, along with disease other than in lymph nodes.

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 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 almost universally abnormal.

First-line treatment

This guideline endorses the recommendation of the use of standard first-line drug regimens in pregnant women with TB. Isoniazid, rifampicin, pyrazinamide and ethambutol are not contra-indicated in pregnancy, but treatment during pregnancy requires close clinical follow-up, with the monitoring of at least monthly liver function tests due to the higher risk of hepatotoxicity.

Isoniazid

Isoniazid is recommended for use in pregnancy (pregnancy category A). Isoniazid may be associated with an increased risk of hepatotoxicity in pregnant women. Symptoms should therefore be assessed, and liver function tests are recommended fortnightly during the first two months of treatment, and then monthly. Isoniazid is considered safe for treatment of latent TB infection (chemoprophylaxis), but is only recommended especially where the risk of developing disease is high, such as with HIV co-infection or a history of recent high-risk contact.

Pyridoxine

Pyridoxine supplementation is recommended for all pregnant women taking isoniazid because deficiency is more likely to occur than in the general population. The routine use of pyridoxine is recommended for all patients taking isoniazid.

Rifampicin

Rifampicin is recommended for use in pregnancy (pregnancy category C).

Rifampicin is indicated for pregnant women with TB. 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.

Ethambutol

Ethambutol is recommended for use in pregnancy (pregnancy category A).

Pyrazinamide

Pyrazinamide is recommended for use in pregnancy (pregnancy category B2). No reports of foetal malformations are attributable to pyrazinamide, although no animal or epidemiological studies have been reported. The absence of such data is the reason that the United States Centers for Disease Control and Prevention (CDC) guidelines do not endorse pyrazinamide in pregnancy. Its use 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 nine-month regimen containing isoniazid and rifampicin is recommended, supplemented by ethambutol until drug susceptibility results are available.

Second-line treatment

The management of drug-resistant 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 ethionomide and patients taking these agents should be advised to take measures to avoid pregnancy.

Fluoroquinolones

Pregnancy category B3 for ciprofloxacin, moxifloxacin and norfloxacin

Increased incidence of abnormalities is not evident in babies of mothers treated with fluoroquinolones. Animal studies of ciprofloxacin suggest a risk of damage to articular cartilage and subsequent juvenile arthritis with short courses of treatment, and the possibility of joint damage with longer courses must be seriously considered.

Fluoroquinolones should only be used in pregnant women with TB where the benefits of treatment outweigh the potential risks.

Streptomycin and amikacin

Pregnancy category D

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

Capreomycin

Pregnancy category C

Studies where capreomycin was given to pregnant rats have shown evidence of teratogenicity. Capreomycin is generally contra-indicated in pregnancy and should only be used following consideration of its risks and benefits.

Ethionamide and prothionamide

Pregnancy category N/A—only available on SAS

These drugs have been shown to be teratogenic in animal studies and their use is not recommended in pregnancy.

Cycloserine

Pregnancy category not listed

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

Para-aminosalicylic acid

Pregnancy category N/A—only available on SAS

There is limited animal and human safety data relating to the use of para-aminosalicylic acid in pregnancy. It may be associated with a slightly higher incidence of limb and ear abnormalities.

Amoxicillin/clavulanic acid

Pregnancy category B1

There is no evidence of teratogenicity in animal studies. Amoxicillin/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. Amoxicillin/clavulanic acid is likely to have a role in the treatment of MDR-TB in pregnancy.

Treatment of TB in breastfeeding women

Although small concentrations of anti-TB drugs are excreted in breast milk, treatment for TB is not generally 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, the weight-based guidelines for children should be followed.

International guidelines

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.

The CDC (www.cdc.gov) does not specifically endorse the use of pyrazinamide in pregnancy, citing the absence of detailed teratogenicity data, but states that it can 'probably be used safely' during pregnancy. An alternative 9(E)HR regimen is endorsed by the CDC.

TB and the newborn

Congenital TB

Congenital TB is a rare complication of in utero TB infection due to maternal haematogenous spread. Women with pulmonary TB are more likely to infect their infant after delivery.

Congenital TB is difficult to diagnose because it is seldom distinguishable 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 features, and chest radiography is almost universally abnormal.

If congenital TB is suspected on clinical grounds, TST, CXR, lumbar puncture and first gastric aspirate must be performed promptly and regardless of the TST result. Treatment should be initiated promptly with standard 4 drug therapy; isoniazid, rifampicin, pyrazinamide and ethambutol for sensitive TB.

Expert advice should be sought, particularly if MDRTB suspected. The placenta should be evaluated with histology and culture.

Newborn infant whose mother has LTB

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 initial postpartum period.

Newborn infant whose mother has TB

The infant should be evaluated for congenital TB and the mother should be tested for HIV infection.

The infant need not be separated from its mother but contact should be limited until both mother and infant are on appropriate therapy. The mother should wear a surgical mask when in close contact with, or breastfeeding her infant from the time of delivery until the mother becomes smear negative. The mother should commence appropriate anti-TB therapy as soon as possible. Breastfeeding is acceptable unless the mother has MDR disease (see below) or poor adherence to therapy.

If there is no clinical suspicion of congenital TB a first gastric aspirate (of three) 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 three months. If the infant is breastfeeding, pyridoxine should also be given (5mg daily). The infant should be evaluated monthly. Medication doses should be recalculated according to the infant's body weight, every two to four weeks, depending on the infant's age, and more frequently if newborn. If TST negative at three months, the infant should be given BCG.

Mothers with MDR-TB disease

The infant should not be breastfed and should be separated from the mother until she is on appropriate TB treatment. The mother should wear a surgical mask while in contact with her infant and until she is smear negative. Further discussions are required with a paediatric TB specialist.

Explanation of pregnancy categories

(See also the Australian Government [Therapeutic Goods Administration website](#))

Category	Explanation
Category A	Drugs that have been taken by a large number of pregnant women and women of childbearing age, without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the foetus having been observed.
Category B1	Drugs that have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the

	frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals ^[1] have not shown evidence of an increased occurrence of foetal damage.
Category B2	Drugs that have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals ^[1] are inadequate or may be lacking, but available data show no evidence of an increased occurrence of foetal damage.
Category B3	Drugs that have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals ^[1] have shown evidence of an increased occurrence of foetal damage, the significance of which is considered uncertain in humans.
Category C	Drugs that, owing to their pharmacological effects, have caused or may be suspected of causing harmful effects on the human foetus or neonate without causing malformations. These effects may be reversible.
Category D	Drugs that have caused, are suspected to have caused, or may be expected to cause an increased incidence of human foetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects.
Category X	Drugs that have such a high risk of causing permanent damage to the foetus that they should not be used in pregnancy or when there is a possibility of pregnancy.
Category A	Drugs which have been taken by a large number of pregnant women and women of childbearing age, without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the foetus having been observed.

Note:

For drugs in categories B1, B2 and B3, human data are lacking or are inadequate and sub-categorisation is therefore based on available animal data. The allocation of a B category does not imply greater safety than the C category. Drugs in category D are not absolutely contra-indicated in pregnancy (for example, anticonvulsants). Moreover, in some cases the D category has been assigned on the basis of 'suspicion'.

Due to legal considerations in Australia, sponsor companies have, in some cases, applied a more restrictive category than can be justified on the basis of available data. In some cases there may be discrepancies between the official product information appearing in MIMS Annual and the information in the Medicines in Pregnancy booklet due to the lead times involved in printing.

^[1] Animal studies submitted in support of new drug applications must conform to the Australian

Revision history

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References

- Bothamley, G. (2001). Drug treatment for tuberculosis during pregnancy: safety considerations. *Drug Safety*, 24 (7), 553–565.
- British Thoracic Society. (1998). Chemotherapy and management of tuberculosis in the United Kingdom: recommendations. *Thorax*, 53, 536–548.
- Centers for Disease Control and Prevention. (2003). Treatment of tuberculosis. *Morbidity and Mortality Weekly Report*, 52 (RR-11), 1–77.
- Enarson, D.A., Rieder, H.L., Arnadottir, T., Trébuçq, A. (2000). Management of Tuberculosis: a guide for low income countries. 5th ed. Paris: International Union Against Tuberculosis and Lung Disease.
- MIMS Online. (2003). Available from <<http://ckn.health.qld.gov.au>>
- Ormerod, P. (2001). Tuberculosis in pregnancy and the puerperium. *Thorax*, 56, 494–499.
- World Health Organization. (2003). Treatment of Tuberculosis: guidelines for national programs. 3rd ed. Geneva: WHO.
- World Health Organization. (2014). Guidance for national tuberculosis programmes on the management of tuberculosis in children. 2nd Ed. Geneva: WHO.