REVIEW ARTICLE

# Perinatal Tuberculosis

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## Abstract

Tuberculosis (TB) is a major contributor to disease burden globally. Congenital tuberculosis is a life-threatening disease in neonates with higher mortality rate. Perinatal transmission of infection occurs in utero or during delivery. It is difficult to differentiate congenital infection from postnatal. Cantwell criteria is used for the diagnosis of congenital infection. As symptoms are nonspecific congenital tuberculosis has to be actively considered as a possibility to diagnose it. Isolation of *Mycobacterium tuberculosis* organism either in culture or acid-fast bacilli (AFB) smear is very essential for the diagnosis. After the diagnosis of congenital tuberculosis treatment has to be initiated without delay. Breastfeeding should be encouraged among mothers on treatment for latent tuberculosis and after two weeks of treatment for active TB.

**Keywords:** Congenital tuberculosis, Diagnosis, Perinatal transmission, Treatment.

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## Epidemiology

*Mycobacterium tuberculosis* is the causative organism of TB and is a major public health problem. ''The World Health Organization (WHO) in its 2018 report, estimated that out of 10 million cases of TB in 2017, about 1 million occurred among children less than 15 years. There were 234,000 deaths of children due to tuberculosis and 40,000 deaths in HIV infected children''.[1]

## Tuberculosis of Fetus or Newborn

### Definitions

There are two types of neonatal tuberculosis namely congenital TB and postnatally acquired TB. Neonatal TB is a serious infection and the mortality rate is about 50%.[2-4] Congenital TB is contracted during pregnancy or at the time of childbirth and cause disease afterward. Perinatal TB is a preferred term which includes true congenital disease. The diagnostic criteria for congenital tuberculosis were put forth by Beitzke in 1935. It was subsequently revised by Cantwell in the year 1994.[5]

### Diagnostic Criteria[5]

Proven tuberculous lesions plus one of the following:

- The tuberculous lesion in a newborn baby in the first week of life
- Primary liver complex or caseating hepatic granulomas
- Maternal genital tract or placental TB
- Exclusion of postnatal transmission by a thorough investigation of contacts.

Postnatal TB is contracted after birth either by inhalation of TB bacilli or by ingestion of infected breast milk and the infant subsequently present with signs and symptoms of tuberculosis along with radiographic findings.[6]

It is difficult to differentiate between true congenital TB and those acquired postnatally, in general, clinical presentation and management remain the same between two groups.

## Transmission and Pathogenesis

Perinatal transmission of tuberculosis is a possibility through a multitude of ways. Most commonly associated with endometrial tuberculosis or disseminated infection in mother. The hematogenous spread can happen via the umbilical vein or by infected amniotic fluid aspiration, or ingestion of infected secretions.[2,4]

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Primary complex in the liver along with caseating granuloma is the definitive lesion of congenital tuberculosis. The organisms can spread beyond the liver into the systemic circulation causing disseminated infection involving GI tract, spleen, kidney, adrenals, bone marrow, meninges, and skin. Rupture of the placental tuberculous lesion into amniotic fluid may cause primary foci in the lungs or GI tract if the fetus inhales or ingest infected amniotic fluid. Neonate can present as sepsis-like syndrome if there is massive dissemination.[6]

## Clinical presentation/radiographic findings

Perinatal TB usually manifest at a median age of 24 days, but occasionally noted at birth ranging from 1 to 84 days.[5] Hepatosplenomegaly and respiratory distress are the most common presentation of congenital tuberculosis followed by poor feeding, fever, failure to thrive, irritability, lethargy, cough, abdominal distension and low birth weight.[3,6,7] Neonatal TB may present in the form of septicemia, persistent or recurrent pneumonia, meningitis, lymphadenopathy, jaundice, ascites, disseminated intravascular coagulation, otitis media, osteomyelitis, paravertebral abscess and cold abscess.[8]

Sometimes, the initial manifestation is very similar to sepsis, the clinician should have a high index of suspicion if a sick newborn fails to improve with antibiotics and has negative microbiological and serological test results for infections. About 50% neonates have miliary disease pattern in chest X-ray, rests have adenopathy and parenchymal infiltrates.[6]

## Diagnosis

Assessment of maternal risk factor for TB is very important in suspected congenital tuberculosis. Placental examination and culture for TB bacilli should be done if the mother presents with inexplicable bronchitis, pneumonia, meningeal disease, endometritis or unusual uterine bleeding. If the placenta is not available for examination, uterine dilatation and curettage should be considered because endometrial culture often yields positive results.[6] HIV testing for a mother is very important in suspected congenital tuberculosis. The diagnosis of congenital tuberculosis sometimes helps in the detection of undiagnosed maternal TB.[9]

Confirmation of tuberculosis in the neonate is done by testing body fluids for positive acid-fast bacilli smear and cultures such as tracheal aspirates, gastric aspirates, and tissue biopsy. Cerebrospinal fluid analysis for acid-fast bacilli is very essential because tubercular meningitis occurs in 1/3rd cases of congenital TB.[6]

The PCR of bronchoalveolar lavage fluid is an efficient modality for diagnosis in neonates.[10] The Mantoux test in neonates is often negative in the initial stages but frequently becomes positive after a few months. Gastric and tracheal aspirates are far more sensitive than the tuberculin skin test. Gastric aspirates are positive in 80% whereas, Mantoux is positive in less than 15% of cases.[3,5]

"Some newborns may have positive interferon-gamma release assay, but due to the limited data on the reliability of a negative test results IGRA is not recommended by AAP in children less than 2 years of age".[6]

Ultrasound liver is crucial in case of suspected congenital TB. Liver biopsy, though invasive should be considered if abnormal features are found in ultrasound or if there is a diagnostic dilemma to look for caseating granulomas.[11] Liver biopsy is 100% sensitive in the diagnosis of congenital tuberculosis.[3]

Newer methods such as LED fluorescence microscopy and *mycobacterium* growth indicator tube (MGIT) are used for rapid diagnosis in developed countries. LED fluorescence microscopy is more sensitive and specific in the identification of TB bacilli compared to the existing older modalities.[12] Gene Xpert is a rapid diagnostic tool used in highly TB prevalent areas including multidrug-resistant TB.[13]

## Treatment

As soon as proper culture samples are obtained in a suspected neonatal TB, antituberculosis treatment should be started promptly. Currently, there is no specific RNTCP treatment guidelines exist for perinatal tuberculosis. The AAP recommendation for the treatment of neonatal tuberculosis includes four-drug regimen for the first 2 months (intensive phase)—isoniazid (INH), rifampin (RIF), pyrazinamide (PZA) and either ethambutol (EMB) or an aminoglycoside such as amikacin. Amikacin is most commonly used instead of Ethambutol because neonates are at higher risk of developing meningitis or disseminated disease, and Amikacin has better CNS penetration ability and bactericidal activity.[14]

After the completion of the intensive phase, the recommended duration of continuation phase is 7–10 months of Isoniazid and Rifampin therapy. The total duration of treatment for neonatal tuberculosis is usually 9–12 months.[14]

Prednisone (2 mg/kg/day) should be administered for 4–6 weeks if TB meningitis is suspected. The drug is gradually tapered and stopped.[14]

## Prognosis

The mortality rate of congenital tuberculosis even with effective treatment is 25–50%, hence, the prognosis is guarded.[6] There are several reasons for high morbidity and mortality associated with congenital tuberculosis;

- Nonspecific signs and symptoms of the disease, which results in a delay in diagnosis.[3,15,16]
- The false negativity of tuberculin test in newborns poses another challenge compared to in older children, which cause further delay in diagnosis.[8]
- Disseminated diseases such as meningeal and miliary tuberculosis are common in neonates than other age groups.[15,17]
- The immune system is relatively immature in neonates, so they are at risk to develop tuberculosis disease.[18,19]

## Maternal tuberculosis

### Latent Tuberculosis Infection (LTBI) in Pregnancy

Treatment of latent TB in pregnant women should be deferred until 3 months after delivery to reduce the risk of hepatitis.[20]

### Active Tuberculosis Disease in Pregnancy

Active TB in pregnancy is associated with adverse fetal and maternal outcomes. Hence pregnant mother once diagnosed with active TB, prompt treatment should be initiated. Active TB disease treatment in pregnancy includes 2 months of intensive phase with isoniazid, rifampin, and ethambutol, followed by 7 months of isoniazid and rifampin, the total duration of treatment is 9 months.[21,22]

## Management of an exposed neonate

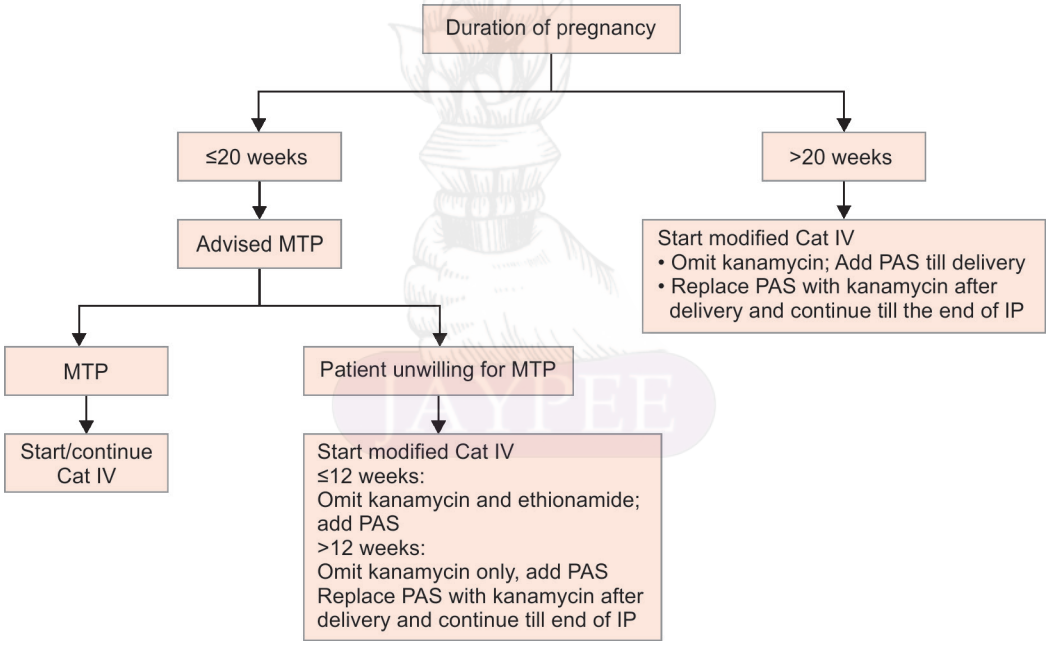
Mother with active pulmonary TB can transmit the infection to her newborn, so at the time of delivery baby born to a mother with suspected or known active disease should be separated until both have been evaluated.[14] Management is summarized in Table 1.

- If both mother and neonate have active pulmonary TB, both should be started on ATT, mother and baby need not be separated as long as both are adherent and mother should use a mask until she is noninfectious.
- If the mother has pulmonary tuberculosis and neonate has a latent infection without active disease, the mother should be treated for active TB disease and baby should be started on Isoniazid prophylaxis. Separation of mother and baby is not required if they are compliant to treatment and mother should follow infection control measures such as to wear a mask.
- If the mother has active pulmonary TB and there is no proof of active TB disease or latent infection in neonate, the mother should be treated with ATT for active disease and baby for latent infection with Isoniazid for 3 to 4 months. Mother and baby can be together provided they are adherent, and the mother should use a mask.
- Once the infant completes 3 to 4 months of Isoniazid prophylaxis, tuberculin skin test should be done:
- If the infant's repeat tuberculin test is positive, investigations should be carried out to look for active disease and the infant should be treated for either active disease or latent infection based on the tests result.
- If the infant's repeat skin test is negative, Isoniazid can be stopped.

**Table 1:** Management of an exposed neonate[14]

| | Mother and baby both—active pulmonary TB | Mother—active TB disease Baby—no disease, skin test positive | Mother—active TB disease Baby—no disease/no latent infection |
|---|---|---|---|
| Treatment | Mother—ATT Baby—ATT | Mother—ATT Baby—Isoniazid prophylaxis | Mother—ATT Baby- INH for 3–4 months followed by MTX test. If MTX negative stop INH by 3 months. If Mtx is positive, search for disease. If the disease is positive then treat as congenital TB, if no disease give INH for 9 months |
| Isolation | Separation avoided Advised if MDR-TB, non-compliant to therapy, the mother has contagious TB before starting ATT | Separation avoided Advised if MDR-TB, non-compliant to therapy, the mother has contagious TB before starting ATT | Separation avoided Advised if MDR-TB, non-compliant to therapy, the mother has contagious TB before starting ATT |
| Barrier method | Face mask | Face mask | Face mask |

**Flowchart 1:** MDR-TB in pregnancy[23]




- If the mother is still contagious, both infant and mother require re-evaluation and consultation with a TB expert
- If MDRTB is suspected, a TB expert should be consulted (Flowchart 1).
- RNTCP, IAP and WHO recommends INH prophylaxis for 6 months for an infant with latent TB infection.[23-25]

## Breastfeeding

Breastfeeding should be encouraged for mothers on latent TB infection treatment and after at least two weeks of treatment for active Tuberculosis.[14]

The first line ATT drugs are secreted in small amount in breast milk (less than 20% of therapeutic infant dose)and will not cause any toxic effects on breastfed infants.[20,21,26]

Infants on exclusive breastfeeding receiving Isoniazid should be supplemented with pyridoxine.[14]

## Prevention

BCG vaccination is protective against tuberculous meningitis and disseminated form of TB. In infants receiving chemoprophylaxis BCG vaccine is recommended.[23,24] American Academy of Pediatrics recommends BCG vaccination after INH prophylaxis and if follow-up

is not possible then at birth itself.[14] Whereas, RNTCP and IAP advocate BCG administration at birth even for those receiving Isoniazid prophylaxis after excluding congenital TB.[23,27] "WHO recommends BCG vaccination for neonates born to mother with pulmonary TB if an infant is asymptomatic, has no immunological evidence of TB and is HIV negative".[28] Children in highly TB prevalent countries are more prone to get infection early in their life, so BCG should be administered as soon as possible.

## Conclusion

Perinatal TB carries a high mortality rate because of the delay in diagnosis and prompt initiation of treatment. A high index of suspicion, a detailed maternal history, and thorough evaluation of mother and baby is very crucial in establishing the diagnosis. Work up for congenital tuberculosis must include CSF analysis to look for tuberculous meningitis and disseminated disease. Early diagnosis and timely commencement of antitubercular therapy are very critical in reducing the morbidity and mortality associated with the disease. If multidrug-resistant TB is suspected consultation with TB expert is very important.

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