WHO recommendations on antenatal care for a positive pregnancy experience: screening, diagnosis and treatment of tuberculosis disease in pregnant women

Evidence-to-action brief

Highlights and key messages from the World Health Organization’s 2016 global recommendations.

Tuberculosis (TB) poses a serious threat to the lives and health of pregnant women and their infants, but is often not recognized during pregnancy and the postpartum period. It is crucial that TB disease and risk for TB progression are recognized and treated, to protect the health of the mother and infant.

Background

Each year, it is estimated that there are over 200 000 cases of TB among pregnant women (1). The global number of TB deaths increased in 2020, most likely as a result of coronavirus disease (COVID-19); it is possible that the impact varied among different subgroups of patients (2).

Even though TB is a leading cause of death among young women in high-burden countries, it is not known how many pregnant and postpartum women die of TB, as these numbers are often not recorded by national TB programmes. These deaths are, therefore, likely to be under-recognized (3). However, it is known that pregnant women are at increased risk of developing TB disease.

There are many potential reasons for this increased risk, including immune system changes in a woman’s body during pregnancy, nutritional stress, hormonal changes and sleep deprivation (4). Additionally, other factors, such as delayed presentation for pregnancy-related health care among marginalized populations (often those more at risk for TB infection), the masking of TB symptoms by what are believed to be pregnancy-related symptoms (e.g. shortness of breath and fatigue), and reluctance by health workers to perform certain diagnostic tests (most often a chest radiograph) during pregnancy, may delay the diagnosis of TB or cause it to be missed (5).

Women who are pregnant or up to six months postpartum are at increased risk of developing TB disease (6). Pregnant women living with HIV are at particular risk from TB. Women living with HIV who develop TB disease in the postpartum period are twice as likely to die during the year following the birth of their infant than similar women who did not develop TB. Their infants are three times more likely to die during their first year of life, and are more likely to become infected with HIV (7).

The babies of women with TB are also at risk of being infected with TB if the mother has untreated TB disease when the baby is born. A baby who is infected with TB has a high chance of quickly developing TB disease. Among these infants (under 1 year old) who do not have HIV, 40–60% will develop TB disease, almost all of them (90%) within a year (8). Infants who are HIV positive are likely to run an even higher risk of developing TB disease.
This brief highlights the context-specific recommendation on TB screening in pregnant women and the policy and programme implications for translating this recommendation into action at the country level.

Refer to the full WHO recommendations on antenatal care for a positive pregnancy experience and to the key resources:

- WHO TB Knowledge Sharing Platform (9);
- WHO consolidated guidelines on tuberculosis
  - Module 1: prevention – tuberculosis preventive treatment (2020) (10);
  - Module 2: screening – systematic screening for tuberculosis disease (2021) (11);
  - Module 3: diagnosis – rapid diagnostics for tuberculosis detection (2021) (12);
  - Module 4: treatment – drug-resistant tuberculosis treatment (2020) (13);
  - Module 4: treatment – drug-susceptible tuberculosis treatment (2022) (14);
  - Module 5: management of tuberculosis in children and adolescents (2022) (15);
- WHO operational handbook on tuberculosis
  - Module 1: prevention – tuberculosis preventive treatment (2020) (16);
  - Module 2: screening – systematic screening for tuberculosis disease (2021) (17);
  - Module 3: diagnosis – rapid diagnostics for tuberculosis detection (2021) (18);
  - Module 4: treatment – drug-resistant tuberculosis treatment (2020) (19);
  - Module 4: treatment – drug-susceptible tuberculosis treatment (2022) (20);

Screening and treatment of TB disease in pregnant women

All pregnant women are at increased risk for developing TB disease during pregnancy and in the six-month period after giving birth. Pregnant women living in areas of high TB burden (a prevalence of 100 cases per 100,000 population or greater) should be screened for TB disease at every contact with a health worker (10,11).

Pregnant women should be screened using the four-symptom screening method (cough, night sweats, fever, weight loss). Screening for weight loss should not just consider absolute weight loss but should also check for failure to adequately gain weight during pregnancy (10,11).

Chest radiography can be used to screen pregnant women for TB disease, as long as good practices are followed to prevent radiation exposure of the fetus (11). The benefit of accurate TB diagnosis outweighs the risks of radiation exposure, although national guidance should be observed.

Women who screen positive require a clinical evaluation with further testing. For this purpose, the TB diagnostic algorithms should be followed to confirm TB before start of treatment (12).

In accordance with WHO guidelines, the tuberculin skin test (TST) or interferon-gamma release assays (IGRA) can be used to test pregnant women for TB exposure as well. It should be noted that, because of immune system changes in pregnancy, these tests may be falsely negative among pregnant women (4,11,12). Recent evidence shows that IGRA may perform better than TST during pregnancy (4).

Sputum analysis for pulmonary TB using molecular WHO-recommended rapid diagnostics should be done following WHO guidelines (12). Pregnant women have a higher rate of extrapulmonary TB, so this should be kept in mind during diagnostic workup.

**Drug-susceptible TB**

Pregnant women with drug-susceptible TB should be immediately started on the standard drug-susceptible TB treatment regimen of two months of isoniazid, rifampicin, ethambutol and pyrazinamide, followed by four months of isoniazid and rifampicin (14,20). These medications are considered safe in pregnancy.

**Isoniazid-resistant, rifampicin-susceptible TB**

The standard treatment for isoniazid-resistant, rifampicin-susceptible TB (HR-TB) is six months of rifampicin, ethambutol, pyrazinamide and levofloxacin, with the addition of isoniazid if rifampicin is only available in combination with isoniazid as a fixed-dose combination tablet (13). Traditionally, fluoroquinolones (e.g. levofloxacin) have not been recommended during pregnancy or breastfeeding.
because of possible adverse effects on the infant. However, these effects may not be as severe as once thought and a treatment regimen including a fluoroquinolone is not absolutely contraindicated. An alternative treatment regimen for Hr-TB is six months of rifampicin, ethambutol and pyrazinamide, with again isoniazid being permissible if it is part of a fixed-dose combination tablet with rifampicin.

Treatment of multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) in pregnant women can be complicated, and studies of the various regimens are ongoing. See Table 1 for more details.

Despite the complications of treating drug-resistant TB in pregnant women, TB treatment should not be delayed; there is a much higher risk of morbidity and mortality to mother and infant from untreated TB than from the side-effects of medication. Any adverse events should be recorded to improve knowledge about TB medicines in pregnancy (13).

Additionally, all pregnant women with TB should be screened for HIV if their HIV status is unknown.

**Table 1. Treatment regimens for drug-resistant TB in pregnant women**

<table>
<thead>
<tr>
<th>Drug resistance profile</th>
<th>Regimen</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid-resistant, rifampicin-susceptible TB (Hr-TB)</td>
<td>6 months of rifampicin, pyrazinamide and ethambutol</td>
<td>Preferred regimen. Addition of isoniazid is acceptable if it is available in combination with rifampicin (13).</td>
</tr>
<tr>
<td></td>
<td>6 months of rifampicin, pyrazinamide, ethambutol and levofloxacin</td>
<td>Alternative regimen. Fluoroquinolones traditionally are not recommended during pregnancy or breastfeeding because of potential adverse effects on infant; however, use is not absolutely contraindicated. Addition of isoniazid is acceptable if it is available in combination with rifampicin (13).</td>
</tr>
<tr>
<td>Multidrug-resistant TB (MDR-TB)</td>
<td>Longer MDR-TB regimen(^b)</td>
<td>Amikacin, streptomycin, prothionamide and ethionamide are contraindicated during pregnancy, so this regimen should be individualized to include medicines with the best safety profile. The safety of bedaquiline in pregnancy is not well known.</td>
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<tr>
<td></td>
<td>Shorter all-oral bedaquiline-containing regimen(^a)</td>
<td>Because it includes ethionamide (which is contraindicated in pregnancy), this regimen is not currently recommended for treating pregnant women (13).</td>
</tr>
<tr>
<td>Pre-extensively drug-resistant TB (pre-XDR-TB)</td>
<td>Bedaquiline, pretomanid and linezolid (BPaL) regimen</td>
<td>There are no data on pregnant women for this regimen so no recommendations can be made. An individualized regimen should be designed that includes medicines that have the best safety profile. Women on this regimen should not breastfeed (4,8).</td>
</tr>
</tbody>
</table>

\(^a\) Please note that upcoming changes to the drug-resistant TB guidelines will be published later in 2022 and the changes are summarized in the Rapid communication: key changes to the treatment of drug-resistant tuberculosis, published in May 2022 and available at: https://apps.who.int/iris/rest/bitstreams/1420701/retrieve. For the shorter all oral bedaquiline-containing regimens, an alternative regimen replacing 4 months of ethionamide with 2 months of linezolid (600 mg) can be used.

\(^b\) Further details of the regimen can be found in WHO consolidated guidelines on tuberculosis. Module 4: treatment – drug-resistant tuberculosis treatment (2020) (13), pp. ix and 17.
TB preventive treatment (TPT) in pregnant women living with HIV

The increased risk of TB among pregnant women who are living with HIV and the increased likelihood of maternal and infant mortality among women living with HIV who develop TB has led WHO to make the following recommendations.

- Pregnant women living with HIV in whom TB disease has been excluded should receive TPT as part of a comprehensive package of HIV care. This should be done regardless of whether the women are on antiretroviral treatment, irrespective of the degree of immunosuppression, and even if testing for TB infection is unavailable (11).

- In settings of high TB transmission, pregnant women living with HIV who have an unknown or positive test of TB infection and who are unlikely to have TB disease should receive at least 36 months of isoniazid preventive therapy (11). This should be given whether or not the woman is on antiretroviral therapy and regardless of her CD4 count or history of previous TB treatment (11).

Pregnant women living with HIV should be screened for TB disease at every visit to a health-care facility or contact with a health worker (10). These women should be screened using the four-symptom screening method mentioned above (10). Pregnant women living with HIV who are not found to have TB disease should receive TPT regardless of the stage of pregnancy.

TPT in pregnant women living with HIV should utilize medicines that are considered safe in pregnancy (11). TPT improves pregnancy outcomes both in women living with HIV and their infants (11). Women can be treated with six months of daily isoniazid monotherapy, or three months of daily rifampicin plus isoniazid, or four months of daily rifampicin monotherapy (see Table 2). The risk of morbidity and mortality to mothers and infants due to the progression to TB disease outweighs the risk of adverse effects from these medicines, including the risk of liver toxicity (11,16,17,22). This advantageous benefit-to-risk balance also applies to prolonged (36-month) TPT with isoniazid (22). There are not enough data on the effects of rifapentine during pregnancy to recommend rifapentine-containing regimens. An affordable regimen that is particularly helpful for pregnant women living with HIV exposed to other opportunistic infections is the use of a fixed-dose combination containing isoniazid 300 mg plus pyridoxine 25 mg plus sulfamethoxazole 800 mg plus trimethoprim 160 mg.

Checking baseline liver function tests in order to screen for possible liver toxicity is encouraged where feasible, but is not essential; routine liver function testing during pregnancy is not necessary unless there is a risk of liver toxicity (11). Vitamin B6 supplements should be given when possible to all women on an isoniazid-containing regimen; if this supplementation is unavailable, however, it should not prevent TPT administration (11).

Table 2. Recommended TPT regimens for drug-susceptible TB in pregnant women living with HIV

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Dose</th>
<th>Additional considerations</th>
</tr>
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<tbody>
<tr>
<td>6 months of daily isoniazid</td>
<td>5 mg/kg/day</td>
<td>If available, give vitamin B6, 10–25 mg daily, for duration of TPT (11).</td>
</tr>
<tr>
<td>4 months of daily rifampicin</td>
<td>10 mg/kg/day</td>
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<tr>
<td>3 months of daily rifampicin plus daily isoniazid</td>
<td>Rifampicin: 10 mg/kg/day Isoniazid: 5 mg/kg/day</td>
<td>If available, give vitamin B6, 10–25 mg daily, for duration of TPT (11).</td>
</tr>
<tr>
<td>36 months of daily isoniazid</td>
<td>5 mg/kg/day</td>
<td>Should be given only in areas of high TB transmission.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If available, give vitamin B6, 10–25 mg daily, for duration of TPT (11).</td>
</tr>
</tbody>
</table>
With regard to prevention of multidrug-resistant TB (MDR-TB) among pregnant women living with HIV, not enough data are available to recommend a regimen; however, levofloxacin may be used if the benefit is considered to outweigh potential harms (11).

**TPT and treatment of TB disease among infants**

Infants have a high risk of developing TB disease if exposed to someone who has pulmonary TB (15,21). If the infant’s mother has untreated pulmonary TB when the infant is born, the infant should be screened for TB.

Symptoms of TB in an infant are different to those in an adult. In addition to the usual symptoms of TB in adults (cough, fever, night sweats, weight loss), infants may not be eating well, may fail to adequately gain weight (instead of losing weight), and may fail to thrive and have reduced playfulness/greater tiredness (15,21). Infants may not cough at all. It is also important to look at infants’ growth charts to see if they have been losing weight or their weight has plateaued, which may indicate TB. Changes on a chest radiograph may be subtle and hard to see if the quality is not optimal. Infants frequently also have extrapulmonary disease, so health workers need to be aware of clinical features of TB outside the lungs.

All infants, regardless of HIV status, who are contacts of a TB patient and who are unlikely to have TB disease based on appropriate evaluation should receive TPT. This should be done even if testing for TB infection is unavailable (11).

Any infant found to have TB should be started on TB treatment immediately.

Further details of the treatment of paediatric TB can be found in the *WHO consolidated guidelines and operational handbook on tuberculosis – module 5: management of TB in children and adolescents* (15,21).

**Considerations for TB screening and treatment and TPT**

**Monitoring and evaluation**

- Household contacts and other close contacts of pregnant women with TB should be systematically screened for TB (10).

- Chest radiography is not mandatory before starting TPT (11).

- Pregnant/postpartum women on TPT should be monitored routinely at monthly encounters with health workers (11).

- Checking baseline liver function tests when isoniazid-containing TPT is given in pregnancy is strongly encouraged when feasible, but is not essential unless there are other risk factors for liver toxicity (11).

- For women with abnormal baseline test results, clinical judgement is required to ensure that the benefit of TPT outweighs the risks. Liver function should be tested routinely in women with abnormal results. Appropriate laboratory testing should also be done for women who develop symptoms while on treatment (e.g. liver function tests for those with symptoms of liver toxicity) (11).

- Women should be asked to contact a health worker at any time if they develop symptoms such as loss of appetite, nausea, vomiting, abdominal discomfort, persistent tiredness or weakness, dark-coloured urine, pale stools, jaundice, confusion or drowsiness while on medication for TB. If a health worker cannot be consulted at the onset of such symptoms, the patient should stop treatment immediately (11).

- In people on MDR-TB preventive treatment, close monitoring for adverse effects and adherence to treatment is essential. Adverse effects from medicines depend on which preventive treatment regimen a woman is on. More details can be found in the operational handbook on TPT (16).

- Vitamin B6 supplementation in pregnant women undergoing isoniazid-containing TPT should be prescribed if available to prevent neuropathy (11). If neuropathy develops, vitamin B6 at a different dose may be given to treat it – see the operational handbook on TPT (16).

**Education and training**

Countries should review and update their policies, standard operating procedures and training curricula as necessary to support adaptation and adoption of the new antenatal care recommendations.
• Screening for TB and assessment for TPT should be integrated into a country’s antenatal and postpartum care algorithms.

• Education regarding TB in pregnancy should be incorporated into the curriculum of all health workers and community health workers who provide care to pregnant women.

• Health workers should be trained and educated about the increased risk of TB in pregnancy and TB treatment guidelines for pregnant women. Health workers should be trained to recognize the signs and symptoms of TB and how it may present in pregnant women (e.g. TB symptoms may be masked by pregnancy; risk of extrapulmonary TB; decreased sensitivity of TST and IGRA during pregnancy).

• All health workers should understand how to properly screen pregnant women for TB. They should understand that chest radiography is safe in pregnancy if done with the correct shielding precautions. Health workers should also understand the diagnostic algorithms that follow a positive screening test. In pregnant women who screen negative, assessment for TPT eligibility is important. Tests for TB infection may have reduced sensitivity in pregnant women, so clinical judgement also needs to be relied upon. (In pregnant women with HIV, testing for TB infection is not necessary before the start of TPT.)

• Depending on the structure of the antenatal and postpartum care, community health workers should be educated about TB during pregnancy and know how to properly refer women, as they may be the workers that pregnant women see most often and are most comfortable talking with.

• All health workers, including community health workers, should take time to counsel pregnant women about TB treatment regimens.

• Women requiring TPT should be informed about the importance of and reasoning behind treating an infection that does not have any symptoms. Women with TB disease should be informed of the treatment regimen they are taking, as well as how long they need to take it. Women should be made aware of the potential adverse effects of TB medication and know to contact a health worker if adverse effects occur. It should also be discussed with women that treating TB (and receiving TPT, in the case of women living with HIV) improves their own and their infants’ chances of survival. Care should be taken to address any questions or concerns the women may have.

• Health workers should be educated about the risk infants have of progressing to TB disease, particularly if their mother has untreated TB at the time of delivery. Health workers should understand how to screen an infant for TB and how symptoms in an infant may be different from those in adults. Health workers should make sure the infant’s mother and/or caregivers understand about TB infection and how it can progress to TB disease, and how important it is to provide TPT to an infant. Health workers should feel comfortable treating TB and providing TPT to an infant, or know how to properly and quickly refer an infant for care.

• Health workers should be educated on how to recognize and manage the adverse effects of TB treatment and TPT, including anorexia, nausea, vomiting, abdominal discomfort, persistent fatigue or weakness, dark-coloured urine, pale stools, jaundice, confusion or drowsiness.

• Health workers should be educated on the possible stigma surrounding TB in the community and be aware of issues this may pose to women undergoing evaluation for TB. Health workers should aim to correct misconceptions surrounding TB and decrease stigma.

**National policy**

• In areas with a high TB burden (a TB prevalence of 100 cases per 100,000 population or greater), at every pregnancy care visit and every other contact with a health worker or community health worker, all pregnant women and women up to six months postpartum should be screened for symptoms of TB, including cough, fever, night sweats, and weight loss or failure to properly gain weight during pregnancy.

Concern for TB should be aggressively pursued with TB diagnostic studies (e.g. samples sent for GeneXpert diagnosis and TB culture, where available), including chest radiography if appropriate. If TB disease is found, women should immediately be started on treatment. If the mother has untreated TB after delivery, appropriate
screening and treatment of the infant and other contacts should be done; the infant is at very high risk of developing TB. These women and infants should be referred to TB treatment clinics if the current provider feels uncomfortable treating TB, and the provider should make sure that the woman follows up with the TB clinic.

- All pregnant women living with HIV should be screened for TB and assessed for TPT as part of comprehensive HIV care and pregnancy care and started on TPT as part of the package of HIV care. This should be done regardless of whether the women are on antiretroviral treatment, irrespective of the degree of immunosuppression, and even if testing for TB infection is unavailable. If a pregnant woman living with HIV is in an area of high TB transmission and has an unknown or positive IGRA/TST (and does not have TB disease), she should receive at least 36 months of isoniazid preventive therapy. This should be given whether or not the woman is on antiretroviral therapy and regardless of CD4 count or history of previous TB treatment.

- In order to provide TB treatment to infants, there should be a network of health workers who are comfortable with and capable of diagnosing and treating infants and can provide guidance to other health workers who may have questions about caring for paediatric patients.

- If possible, people being seen for TPT should be seen separately from people with TB disease (e.g. by having separate clinic days) to minimize risk of further exposing TPT patients to TB disease.

- TPT for pregnant women living with HIV and their infants should be incorporated into the TB preventive care pathway that should already be in place for all people living with HIV.

- National TB programmes should consider separately tracking pregnancy in the register, to allow for a better estimation of the local TB burden in pregnancy.

References


