Review

DOI: 10.5582/ddt.2024.01007

Tuberculosis in pregnancy and assisted reproductive technology

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SUMMARY Tuberculosis is a chronic infectious disease caused by mycobacterium tuberculosis infection. In the world, tuberculosis is an important factor affecting women's reproductive health, which can cause reproductive tract anatomy abnormalities, embryo implantation obstacles, ovarian reserve and ovulation dysfunction, leading to female infertility. This group of women usually need to seek assisted reproductive technology to conceive. Latent tuberculosis infection during pregnancy has no clinical manifestation, but may develop into active tuberculosis, leading to adverse pregnancy outcomes. Most pregnant women do not need to be treated for latent tuberculosis infection, unless they are combined with high-risk factors for tuberculosis progress, but they need close follow-up. Early diagnosis and treatment of active tuberculosis in pregnancy can reduce the incidence rate and mortality of pregnant women and newborns, and treatment needs multidisciplinary cooperation.

Keywords tuberculosis, pregnancy, anti tuberculosis treatment, assisted reproductive technology

1. Introduction

Tuberculosis (TB) is a chronic infectious disease caused by mycobacterium tuberculosis (MTB) infection, which is the 13th leading cause of death in the world. According to the summary of the global tuberculosis report in 2023 (*1*), a total of 7.5 million people in the world will be diagnosed with tuberculosis in 2022, which is the highest number since WHO began global tuberculosis surveillance in 1995. Despite an 18% decrease in TB notifications during the COVID-19 pandemic, rates of severe TB and related mortality have continued to rise (*2*). Pregnancy with tuberculosis (PWT) is a collection of diseases caused by MTB infections that occur either during pregnancy or when TB remains untreated during that time. Latent tuberculous infection (LTBI) is a special state in which the host has not yet developed the disease after being infected with MTB. It is characterized by a strong positive purified protein derivative test (PPD) test or a recent transition from negative to positive, without the clinical manifestations and imaging signs of active tuberculosis. LTBI patients have a 5%-10% risk of developing active TB, and most of the rest have no obvious clinical symptoms. The global incidence rate of PWT is between 5-7% according to statistics (*3,4*). Notably, developing countries have a relatively higher incidence rate of tuberculosis compared to developed ones due to differences in economy and medical technology (*1*).

Due to various reasons, the incidence rate of infertility has increased year by year. According to statistics in China, the infertility rate of couples of childbearing age has increased from 2.5%-3% in 1993 to approximately 18% in 2020 (*5*). With the rapid development of assisted reproductive technology (ART), especially *in vitro* fertilization embryo transfer (IVF-ET), more and more infertility patients have achieved their desire to conceive. However, whether IVF increases the risk of TB in infertile patients and its impact on pregnancy outcomes has attracted widespread clinical attention. PWT is not rare in clinical practice. In China, with the relaxation of the three child policy and the increase of IVF, the number of cases of this disease has significantly increased, but its treatment level has mostly stagnated in the 1980s to 1990s (*6,7*).

Worldwide, TB is the leading infectious disease that causes women's deaths, which can cause more than 1 million women's deaths every year. Active TB is also the main disease that causes maternal deaths (*8*). The delayed diagnosis of PWT is the main cause of adverse pregnancy outcomes. To prevent significant severe TB and related mortality, standardized whole process management of PWT is essential. This article will review the pathophysiology, diagnosis, and treatment of PWT after IVF-ET, to provide basis and suggestions for clinical diagnosis and treatment of patients.

2. The relationship among TB, pregnancy and ART

2.1. The effects of TB on female fertility

After MTB infects the lungs, it can infect the internal genitalia within approximately one year, first invading the fallopian tubes (90-100%), then the endometrium (50-80%), ovaries (20-30%), cervix (10 -20%), as shown in Figure 1. This may lead to anatomical abnormalities in the reproductive tract, embryo implantation disorders, reduced ovarian reserve, and ovulation dysfunction, leading to infertility (*9*).

The fallopian tube is the most frequently invaded pelvic organ by MTB. When MTB further infects, causing the fallopian tube to stiffen and thicken, presenting typical bead like changes, and forming cheese like substances in the lumen. When it reaches the level where tuberculosis can be detected, the function of the fallopian tube has basically lost. There are many reports of infertility caused by MTB infection in clinical practice (*10*). Pontifex *et al.* reported the HSG results of 3,773 patients, and found that 37% of the patients with primary infertility had tubal obstruction, and almost half of tubal obstruction originated from tuberculosis (*11*).

Uterine tuberculosis often spreads from fallopian tube tuberculosis through both uterine horns. The endometrium of patients with genital tuberculosis (GTB) exhibits different abnormal manifestations depending on the extent and severity of the lesion, and can affect embryo implantation. Mild endometrial lesions manifest as chronic endometritis and tuberculous granuloma. Moderate manifestation is cheesification or adhesion. Severe manifestations include adhesion of the entire uterine cavity, adhesion of the fallopian tubes, and complete damage to the endometrium, leading to Asherman syndrome. A retrospective study found that the positive rate of acid fast bacilli test on the endometrium of 60 infertile patients was 46.7% (14/60), compared to 13.3% (4/60) in the control group (*12*). Sharma *et al.* conducted a retrospective study on the results of HSG in 70 patients with GTB, and the results showed that, 57.1% of women have normal uterine cavities, 18.5% have irregular cavities, 2.8% have shrunken cavities, and 18.5% have irregular filling defects (*13*). The study by Pan *et al.* showed that, compared with the control group, patients with endometrial latent tuberculosis had fewer retrieved embryos, available embryos, and high-quality embryos (*14*). However, regular anti tuberculosis treatment before assisted reproductive assistance resulted in a similar fresh cycle live birth rate as the control group. A study on assisted reproductive technology results in Indian women with genital tuberculosis showed that after anti tuberculosis treatment, the number of oocytes and grade I embryos obtained from fresh cycles, endometrial thickness, and endometrial blood flow in patients were significantly increased; the thickness of the endometrium and endometrium during the frozen embryo transfer cycle also significantly increased (*15*). Therefore, early diagnosis of FGT and anti-tuberculosis treatment before IVF treatment are the primary measures to increase the probability of pregnancy (*16*).

Tubercul-associated immune abnormalities have an adverse effect on pregnancy. The most significant immune response of the host to MTB is the T cell-mediated cellular immune process, where T lymphocyte subsets and cytokines shift towards the Thl direction, which may affect embryo implantation (*17*). MTB can change the immune response, accompanied by fibrosis and adhesion, thus activating antiphospholipid antibodies and microthrombosis, ultimately leading to embryo implantation failure (*18*).

In addition, MTB infection also affects ovarian reserve and ovulation function. As early as 1985, relevant literature pointed out that tuberculosis infection can lead to a decrease in ovarian reserve function, which is characterized by high basal follicle stimulating hormone, fewer sinus follicles, low inhibin B, slow peak velocity of ovarian blood flow during systole, low pulsatile index, and ultimately low number of retrieved oocytes (*19,20*). Dam *et al.* found that LTBI can lead to ovarian reserve dysfunction, reducing the number of follicles and high-quality embryos (*15*). Although ovarian tuberculosis is relatively rare, in severe cases of tuberculosis infection, tuberculosis nodules, caseous necrosis, and abscesses appear on the surface and inside the ovaries, affecting the blood supply to the ovaries, leading to a decrease in the number and quality of follicles.

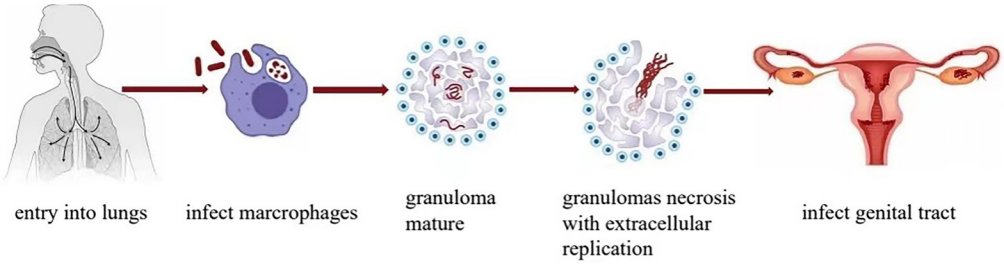

Figure 1. The process of female reproductive tract tuberculosis infection. Tuberculosis infection first infects the lungs and is engulfed by macrophages, gradually forming granulomas. When granulomatous necrosis accompanied by extracellular replication occurs, tuberculosis bacteria can spread to the female reproductive tract, such as the fallopian tubes, endometrium, ovaries, and cervix.

2.2. The interaction between pregnancy and TB

Pregnant women are generally susceptible to MTB. During pregnancy, due to neuroendocrine regulation, the body exhibits a high metabolic state, with mild congestion and edema of the respiratory mucosa, which is conducive to the invasion and reproduction of pathogens. The increase of circulating blood volume of women during pregnancy can reactivate stable tuberculosis foci in the lungs, leading to the recurrence of tuberculosis in the incubation period, and may induce cavity bleeding, leading to secondary infection in the lungs, increasing the difficulty of tuberculosis treatment (*21,22*).

In order to prevent fetal allograft rejection during pregnancy, the maternal immune system has undergone significant changes. The existence of specific immune tolerance and non-specific immunosuppression between mother and fetus may be the reason for the rise of tuberculosis incidence rate during pregnancy (*23*). At the same time, the regulation of estrogen and progesterone during pregnancy maintains maternal fetal immune tolerance, which is one of the reasons for the increased susceptibility to MTB and the possibility of activation of latent tuberculosis. Research suggests an increase in the level and activity of phagocytes and plasma like dendritic cells in pregnant women, downregulation of natural killer (NK) cell toxicity by progesterone induced blocking factors and interleukin (IL-10), and the production of interferon γ (γ-IFN) is also reduced, indicating that cellular responses are generally inhibited, the function of immune cells decreases, and the opportunity for immune escape of Mycobacterium tuberculosis is increased (*24*).

In addition to the increase in susceptibility to tuberculosis due to physiological changes unique to pregnancy, the risk factors of pregnant women infected with tuberculosis are shown in Table 1. PWT seriously threatens the health of mothers and infants. The delay in diagnosis of TB in pregnancy, the progress of the disease, the lack of formal treatment and the combination of extrapulmonary tuberculosis are all important factors leading to the adverse outcome of pregnancy. An American study on obstetric outcomes pointed out that compared with pregnant women without tuberculosis infection, PWT patients were more likely to have chorioamnionitis, premature delivery, postpartum anemia, bleeding, blood transfusion, pneumonia, acute respiratory distress syndrome and mechanical ventilation, and the maternal mortality rate of tuberculosis was significantly increased (*25*). Therefore, standardized whole process management of PWT is essential to prevent major maternal and perinatal complications.

Table 1. High risk factors of tuberculosis

Disease state	High risk factors
TB infection	Contacts with active TB patients People from a country where TB is common, including Africa, Asia, the Caribbean, Eastern Europe, Latin America, Russia Living or working in high-risk environments
LTBI progression	Human immunodeficiency virus infection Tuberculosis infection within the past 2 years Intravenous drug user Immunocompromise No standardized treatment for tuberculosis in the past

2.3. ART increases the risk of PWT

Female pelvic tuberculosis is highly susceptible to tubal infertility, and the recovery of reproductive function is very difficult. It is often necessary to seek assisted reproductive assistance for pregnancy. Some studies report that the changes of hormone levels in the body of infertile women undergoing ART during ovulation induction, the interference of ovum retrieval operation on old pelvic lesions, and the reduction of immune function after pregnancy can all lead to the recurrence of latent tuberculosis foci, and even a large number of MTB multiply into the blood, resulting in acute hematogenous disseminated pulmonary tuberculosis (*26*). IVF superovulation leads to extremely high levels of estrogen in the body, while progesterone luteal support can cause high levels of progesterone. Estrogen and progesterone have a direct inhibitory effect on T lymphocytes in a dose-dependent manner, inducing lymphocyte apoptosis, inhibiting cellular immunity, and leading to transform old and latent tuberculosis into active tuberculosis (*27*).

Addis *et al.* first reported cases of pregnancy complicated with bilateral miliary tuberculosis after IVF-ET (*28*). The patient was 33 years old and underwent IVF-ET for 10 years due to unexplained primary infertility, resulting in a single pregnancy. Intermittent vaginal bleeding occurred during early pregnancy, accompanied by influenza like symptoms and bilateral miliary tuberculosis, and spontaneous abortion occurred at 14 weeks of pregnancy. It is suggested that the IVF-ET treatment process and pregnancy may activate the potential tuberculosis focus, leading to active TB and spontaneous abortion. The research results of Gull *et al.* also showed that both IVF-ET treatment and pregnancy can exacerbate LTBI and even cause life-threatening miliary tuberculosis, leading to spontaneous abortion (*29*). Therefore, it is necessary for infertile patients to screen for tuberculosis before ART treatment to avoid adverse pregnancy outcomes.

3. Diagnosis of PWT

The clinical manifestations of PWT are diverse and lack of specificity. Early diagnosis is very difficult. In addition, clinicians are lack of vigilance, and are prone to misdiagnosis, missed diagnosis and delayed treatment. The key to avoid missed diagnosis and misdiagnosis

Table 2. Diagnostic tools of tuberculosis

Tuberculosis test classification	Investigation
Immunological examination	Purified protein derivative test γ-IFN release test ESAT6-CFPl0 assay
Bacteriology examination	Smear method Culture method
Imaging examination	Chest X-ray, CT, MRI examination Hysterosalpingography
Molecular biology diagnosis	Polymerase chain reaction Gene sequencing Xpert MTB/RIF test
Others	Routine bronchoscopy examination Percutaneous transbronchial biopsy Immunohistochemical diagnosis technology Traditional pathological diagnosis technology

is to strengthen the understanding of tuberculosis in pregnancy and screen suspected patients for tuberculosis in time before IVF-ET. Screening of PWT includes immunology, bacteriology, imaging, molecular biology and other means, which can be selected according to different clinical manifestations and disease progression stages of patients. There are various tools to improve the accuracy of PWT diagnosis, as shown in Table 2.

3.1. Immunological examination

Immunological examination of TB is a rapid examination technique to determine the antibodies and antigens of human TB bacteria. Tuberculin skin test (TST) is an important screening test for TB, especially for high-risk groups. The currently recommended tuberculin for use by World Health Organization (WHO) is PPD. TST results are not affected by pregnancy, so it is recommended for screening PWT (*30*). The advantage of TST testing lies in its simple operation and low cost, but its specificity is relatively poor, and its sensitivity is low for patients with immune deficiency.

γ-IFN release test (IGRAs) plays an important role in the diagnosis of bacterial negative pulmonary tuberculosis and extrapulmonary tuberculosis by stimulating lymphocytes with specific antigens to detect cytokines. Currently, it still cannot distinguish between latent and active tuberculosis infections. It is known as one of the most promising diagnostic techniques for tuberculosis because of its advantages of rapidity, high sensitivity and specificity (*31*). However, its high cost makes it difficult to be widely used in developing countries with high prevalence of tuberculosis.

ESAT6-CFPl0 assay is a newly developed skin test protocol for detecting mycobacterium TB infection. It has high sensitivity and specificity, low cost, simple operation, and is not affected by Bacille Calmette-Guérin (BCG) vaccination (*32*). Due to its comparable performance to TST, it can be used as an alternative testing method for TST in areas with high HIV prevalence and widespread BCG vaccination (*33*).

3.2. Bacteriology examination

Bacteriology examination of mycobacterium TB includes smear method and culture method. The advantages of sputum smear examination are simplicity, speed, and ease of implementation. However, its sensitivity during pregnancy is relatively low, it is recommended to conduct more than three sputum tests to avoid missed diagnosis. Although the culture of mycobacterium TB is considered as the gold standard for the diagnosis of TB, its clinical application is limited by the long culture time.

3.3. Imaging examination

A retrospective study showed that 50% (14/28) of PWT patients did not undergo chest X-ray or CT examination at their first visit, which resulted in delayed diagnosis (*34*). According to the latest guidelines, X-ray and CT examinations are safe during pregnancy and lactation, with radiation levels much lower than those that have adverse effects on the fetus (*35*). Multi slice spiral CT can find small lesions that are difficult to be found by X-ray, which is of great significance for early diagnosis of TB. Among them, High resolution CT has irreplaceable advantages in diagnosing tuberculosis negative and active TB (*36*). With the development of MRI technology, the impact of respiration and heartbeat on imaging quality has been effectively eliminated, making it more sensitive in detecting caseous necrosis, liquefaction, active cavities, lymph node abnormalities, and pleural abnormalities (*37*). It is suitable for pulmonary tuberculosis patients who require long-term routine follow-up, especially children, women, and pregnant women. Compared to CT, due to the clearer display of anatomy and lesions in the brain, spine, and spinal cord, MRI is more suitable for the diagnosis of extrapulmonary tuberculosis (*38*).

Pelvic genital tuberculosis is an important cause of infertility in developing countries, and hysterosalpingography (HSG) is the initial evaluation method. HSG before IVF-ET can not only understand the morphology of the uterine cavity and the patency of the fallopian tubes, but may also detect granulomatous calcification, irregular or extensive scar formation of the endometrium, and even uterine cavity collapse and adhesions. Chavhan *et al.* reviewed 492 cases of HSG due to infertility and found 37 cases of pelvic genital tuberculosis (*39*). The research results of Eng *et al.* are similar, and found that the incidence of contrast medium reflux is high in patients with endometrial tuberculosis undergoing HSG (*40*). Although the diagnosis of pelvic genital tuberculosis depends on the presence of clear reproductive tract MTB, HSG is also a reliable diagnostic indicator.

3.4. Molecular biology diagnosis

The molecular biology examination of PWT mainly includes polymerase chain reaction (PCR), gene sequencing, Xpert MTB/RIF test, *etc.*, as it is not affected by drug resistance and cell phenotype, it has high specificity. With the rapid development and application of molecular biology technology, various PCR based techniques and gene roll up techniques can also be used for the diagnosis of tuberculosis, such as the restriction fragment length polymorphism genotyping method of the insertion sequence IS6110 of tuberculosis strains, to understand the drug resistance and molecular mechanisms of drug resistance of tuberculosis bacteria (*41*). Gene chip technology can quickly and specifically detect mutations in the rpoB, katG, and inhA genes of most Mycobacterium TB isolates, analyze drug-resistant genotypes of Mycobacterium TB, and guide clinical medication (*42*).

It is suggested that Xpert MTB/RIF test should be used as a routine method to screen whether pregnant women with infectious fever after IVF-ET are complicated with TB (*43*). The method is relatively fast and has higher sensitivity and specificity, which can provide reference for clinical diagnosis and selection of treatment plans for drug-resistant TB (*44*).

3.5. Other detection technologies

On the basis of routine bronchoscopy examination, transbronchial ultrasound guided percutaneous transbronchial biopsy can more accurately confirm the location of the lesion and improve the diagnostic accuracy of TB, but whether it can be applied in pregnancy still lacks authoritative clinical guidelines.

Immunohistochemical diagnosis technology and traditional pathological diagnosis technology can effectively improve the accuracy of pathological diagnosis of tuberculosis. However it is more difficult to perform lesion extraction in pregnancy.

4. Pregnancy assistance strategies for infertile women infected with TB

Early treatment of GTB can improve the reproductive prognosis of patients. Jindal *et al.* found that in women with asymptomatic endometrial TB, administering anti-tuberculosis treatment can increase the chance of natural conception (*45*). If the damage caused by TB is too great, usually only ART can be sought for conception. With the continuous improvement of the success rate of IVF-ET, the pregnancy rate of IVF-ET also increases for infertility caused by GTB. However, the overall embryo implantation rate and pregnancy rate are lower than those of non GTB, and the abortion rate is higher than that of non GTB (*46*). A study in India on repeated failure of IVF-ET caused by LTBI also shows that, the pregnancy rate of LTBI patients is significantly lower than that of non tuberculous infertility patients, and the natural abortion rate is higher (*15*). GTB can lead to abnormal energy metabolism, increased amino acid synthesis, and significantly reduced glucose production in the endometrium, which can lead to embryo implantation failure (*47*). In addition, changes in the immune response of tuberculosis patients can activate antiphospholipid antibodies, leading to the activation of antiphospholipid antibodies and the formation of microthrombosis, leading to embryo implantation failure (*15*).

The low success rate of IVF-ET is believed to be related to untreated GTB. A large study involving over 10000 infertile patients receiving IVF-ET treatment showed that the clinical pregnancy rates (31.7% *vs.* 38.1%) and live birth rates (23.8% *vs.* 30.6%) after IVF-ET in untreated past PWT patients were significantly lower than those receiving treatment (*48*). Combined anti-tuberculosis treatment can significantly improve ovarian reserve function and endometrial receptivity, and the number of retrieved oocytes is also increased (*15*).

The process of assisted pregnancy treatment may trigger tuberculosis lesions or complicated with non genital active tuberculosis. The systemic blood transmission of maternal tuberculosis infection after vaginal oocyte recovery has been reported (*49*). In addition, reports of transplacental fetal transmission have once again raised concerns, with consequences including late abortion, premature delivery and congenital tuberculosis (*50*). Given the increasing adoption of IVF-ET as the gold standard treatment for tubal infertility, it is expected that a large proportion of women with GTB will receive IVF-ET under tuberculosis pretreatment. The coexistence of primary tubal infertility and untreated tuberculosis does exist the risk of tuberculosis transmission, which may cause fatal consequences for mothers and children. Therefore, infertility experts must be vigilant about the harm of GTB before undergoing ART, and carry out appropriate pre-treatment to achieve ideal pregnancy outcomes.

5. Treatment of tuberculosis during pregnancy

The key to improving the prognosis of pregnant women with tuberculosis lies in early diagnosis and treatment. The treatment of tuberculosis in pregnancy is a multi-disciplinary problem, which requires the joint participation of obstetricians, infectious physicians, neonatal pediatrics and public health units. The treatment of pregnant women with tuberculosis should generally refer to the treatment principles of non pregnant tuberculosis. The American College of Obstetricians and Gynecologists (ACOG), the American Academy of Pediatrics (AAP), and Centers for Disease Control and Prevention (CDC) recommend that all women at high risk of TB should be screened for symptoms and physical examination at the beginning of prenatal care, including

cough, expectoration, fever, night sweats, weight loss, *etc*. If the patient has signs or symptoms related to TB, and TB infection develops into active tuberculosis risk factors screening is positive, TB testing should be carried out as soon as possible. The diagnostic process for pregnant patients is shown in Figure 2. Once diagnosed as PWT, treatment should be carried out immediately to control the progress of TB and treatment should be targeted and personalized.

Isoniazid (INH), rifampicin (RIF), ethambutol (EMB) and pyrazinamide (PZA) are four first-line drugs for the treatment of TB, which are classified as Class C drugs in pregnancy by the Federal Drug Administration (FDA). INH can pass through the placenta, but even if taken in the early stages of pregnancy, it will not cause deformities. RIF may have a small risk of teratogenesis (*51,52*). A study of 204 pregnancy cases showed that 4.4% of pregnant women found abnormalities related to the use of RIF, including hydrocephalus, anencephaly, and limb defects, higher than the 1.8% reported in other studies (*53*). However, in a large-scale latent tuberculosis infection trial using INH + RIF or INH, 125 pregnant women did not show any unexpected fetal loss rate or congenital abnormalities (*54*). Given decades of experience using rifampicin and limited data on potential teratogenicity, most experts believe that using rifampicin during pregnancy is appropriate.

5.1. Treatment of active TB

Although tuberculosis drugs are all defined as Class C drugs by FDA, considering the adverse maternal and infant outcomes of untreated active tuberculosis, the benefits of treatment outweigh the potential risks of drugs. Compared with the second and third trimesters of pregnancy, if active tuberculosis is treated in the first trimester of pregnancy, it can almost eliminate the increased risk of premature delivery, low birth weight and perinatal death, and maternal complications are also reduced (*55*). Reasonable anti tuberculosis treatment has a relatively small impact on the growth and development of infants and young children, which is beneficial for the clinical cure of patients in the middle and late stages of pregnancy (*56*). A prospective cohort study showed that the treatment success rate of PWT without HIV infection was comparable to that of non pregnant women (*57*). Therefore, it is recommended that active TB during pregnancy should be actively treated.

WHO recommends that INH, RIF, EMB and PZA should be used together every day for 2 months, and then INH, RIF and EMB should be used every day for 4 months (2HREZ+4HRE). This plan can cure 90% of cases, have good drug compliance, and improve maternal and perinatal outcomes (*4,58*). However, CDC recommends that pregnant women with active TB should first choose INH, RIF and EMB for 2 months, and then INH and RIF for 7 months (HREx2+HRx7), because the impact of PZA on the fetus is still unclear (*59*). During treatment, pyridoxine and vitamin K should be supplemented as INH may increase maternal liver toxicity, and regular liver function testing should be conducted. Obstetricians and gynaecologists can cooperate with disease experts, including infectious disease experts, tuberculosis medical consultants and health departments, to ensure timely and accurate diagnosis and treatment, while strengthening the link with nursing to strengthen patients' treatment compliance.

In addition to medication treatment, PWT patients should also be advised to have a balanced diet. Medical personnel should pay attention to their mental health, regularly follow up, and timely implement psychological intervention measures for mentally unhealthy individuals to alleviate their tension, anxiety, and depression, which is beneficial for patients' recovery and return to normal

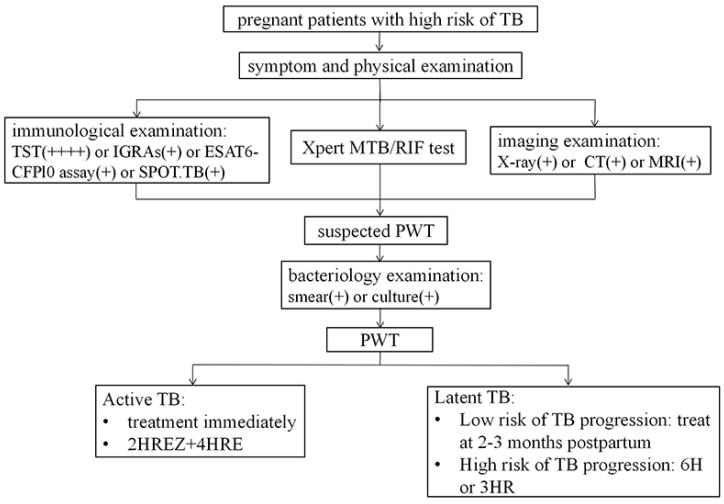

Figure 2. Diagnosis process of PWT. First, evaluate the symptom and physical of pregnant patients with high risk of PWT. Second, if there are abnormal signs, perform immunological, Xpert MTB/RIF test or imaging examination. If any one is positive, it is a suspected PWT patient, and further bacteriology examination is required. Once diagnosed with PWT, individualized treatment should be carried out accordingly.

life. And infection control management is also crucial, and screening of staff and family members is necessary.

5.2. Treatment of LTBI

The treatment of pregnant women with latent tuberculosis infection during pregnancy is still controversial. To avoid using unnecessary medications during pregnancy, CDC recommends delaying treatment until 2-3 months postpartum unless there is a clear risk of disease progression (*59*). When the risk of LTBI progression is high, as shown in Table 1, it is recommended to use INH treatment for 6 months or RIF+INH treatment for 3 months (*60*). A study evaluated the results of 125 cases of LTBI during pregnancy who received RIF + INH or RIF monotherapy for prevention and treatment. The abortion rates were 13% (4/31) and 14% (8/56), respectively, and the incidence of congenital abnormalities was 0% (0/20) and 5% (2/41), respectively. This indicates that the RIF+INH regimen can also be used for LTBI prevention and treatment (*54*).

Before the standardized treatment of tuberculosis in pregnancy, the basic diseases such as liver disease should be excluded first, and the liver function and other related indicators should be monitored during the treatment period to avoid liver injury (*61*). At the same time, plasma endotoxin, C-reactive protein and procalcitonin are regularly tested to identify whether tuberculosis patients are complicated with pulmonary bacterial infection, guide clinical rational drug use and timely adjust treatment (*62*). The recently released CDC guidelines review data on the preferred and alternative treatment options for LTBI during pregnancy, and evidence suggests that a 6-9 month course of INH treatment remains the recommended option for pregnant women, as there is currently no supporting data on the use of rifampicin during pregnancy (*59*). There is limited research data on LTBI treatment for pregnant women, and there is currently a lack of sufficient evidence on the safety, tolerability, and long-term treatment outcomes of LTBI treatment during pregnancy.

5.3. Timing of Termination of PWT

TB is not an indication for terminating pregnancy, but it is recommended to terminate pregnancy in the following situations (*63*). *i*) Severe pulmonary TB is accompanied by decreased lung function and cannot tolerate continued pregnancy and childbirth. *ii*) Active pulmonary tuberculosis requires timely anti-tuberculosis treatment, considering the adverse effects of drugs on the fetus that are difficult to avoid. *iii*) Those who cannot continue pregnancy due to other systemic diseases. *iv*) Pregnancy of AIDS patients complicated with tuberculosis. *v*) Indications for obstetric termination of pregnancy. The termination of pregnancy is generally within 3 months of pregnancy. If the pregnancy has exceeded 3 months, with the informed consent of family members and pregnant women, appropriate anti-tuberculosis drug treatment can be chosen to maintain pregnancy.

6. Conclusion and prospects

PWT is not uncommon in clinical practice. In view of its poor reproductive prognosis, it is recommended that infertile women receive screening for tuberculosis before IVF-ET. Once tuberculosis is suspected after pregnancy, relevant examinations should be conducted to confirm the diagnosis and avoid delaying treatment due to symptoms similar to those of early pregnancy. Once pregnancy is diagnosed with active tuberculosis, start anti-tuberculosis treatment as soon as possible, and form a safe and effective anti-tuberculosis treatment plan during pregnancy to reduce the abortion rate and death rate. In addition to drug therapy, medical personnel should pay more attention to the mental health of patients. The treatment of PWT requires multidisciplinary joint management, joint development of anti-tuberculosis treatment plans, monitoring of treatment effectiveness and pregnancy outcomes.

The training and management of medical staff should be strengthened to make use of more advanced molecular biological diagnostic technology for early diagnosis and early treatment of PWT. At the same time, the informed understanding of tuberculosis of patients in the first and second trimesters should be strengthened, and the whole process management should be standardized jointly by doctors and patients, so as to achieve good outcomes for mothers and children of patients with gestational tuberculosis during the whole pregnancy.

Acknowledgements

This work was supported by grants from a grant from Zhejiang Province Traditional Chinese Medicine Technology (grant no. 2023ZL769 to WL Cao).

Funding: None.

Conflict of Interest: The authors have no conflicts of interest to disclose.

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Received February 3, 2024; Revised April 2, 2024; Accepted April 8, 2024.

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Released online in J-STAGE as advance publication April 17, 2024.