



Reactivation of latent *Mycobacterium tuberculosis* infection with different outcomes after *in vitro* fertilization and embryo transfer: two case reports

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Background: Genital tuberculosis (TB) is a common form of extrapulmonary TB associated with female infertility and often exists without specific clinical manifestations. *In vitro* fertilization and embryo transfer (IVF-ET) has made it possible for women with latent TB to conceive. The pregnancy leads to an increased incidence of reactivation of latent TB. TB related maternal and neonatal complications has increased in recent years after IVF-ET. Chest X-ray is a routine screening procedure for active TB before IVF-ET. However, most women with latent TB do not exhibit pulmonary symptoms and usually negative results are reported. Therefore, screening for latent TB infection before IVF-ET is particularly important which holds benefits for both mother and child. In contrast, no consensus was reached regarding screening latent TB before IVF-ET. The current study presents two cases of latent TB infection before IVF-ET and discuss the different outcomes due to the screening of latent TB before IVF-ET.

Case Description: Two women without a history of TB, aged 32 and 33 years, underwent IVF-ET due to infertility. Both women had granulomatous inflammation detected on endometrial biopsy. A diagnosis of TB was considered, but tests for acid-fast bacilli and TB DNA were negative. One woman received IVF-ET and conceived. She was diagnosed with pulmonary TB with hematogenous dissemination at 10 weeks gestation, miscarried during antituberculosis treatment and recovered after a antituberculosis therapy. The other woman tested positive for TB by an interferon-gamma release assay (IGRA). Embryo transfer was postponed until she had completed antituberculosis therapy.

Conclusions: Women undergoing IVF-ET are at a high risk of reactivation of latent TB infection. Clinicians should screen patients for signs of TB before performing IVF-ET. Specific tests such as tuberculin skin test (TST) or IGRA can be used to identify latent TB before embryo transfer in patients with suspected TB.

Keywords: Interferon-gamma release assay (IGRA); *in vitro* fertilization and embryo transfer (IVF-ET); *Mycobacterium tuberculosis*; tuberculosis; case report

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Introduction

Background

Tuberculosis (TB) is a global infectious disease that is a major public health burden. According to a report by the World Health Organization, the global incidence of TB was 127 per 100,000 in 2021 (1). TB caused by *Mycobacterium tuberculosis* infection primarily causes lung infection. Most individuals with *Mycobacterium tuberculosis* infection experience no clinical signs or symptoms. These individuals have latent *Mycobacterium tuberculosis* infection, which is defined as a state of persistent bacterial viability, immune control, and no signs of active TB (2). It is difficult to diagnose TB infection directly. Therefore, latent *Mycobacterium tuberculosis* infection is diagnosed by a positive tuberculin skin test (TST) and/or interferon-gamma release assay (IGRA) based on the cellular immune response to *Mycobacterium tuberculosis* antigens (3). Latent *Mycobacterium tuberculosis* infection can progress to active TB, especially in the presence of predisposing factors, such as pregnancy (4). TB may affect any body part, including the female reproductive organs, known as genital tuberculosis (GTB). GTB affects the function of the fallopian tubes, ovaries, and endometrium, which may lead to infertility (5). Owing to the lack of specific clinical manifestations of TB, GTB may be misdiagnosed or may remain undiagnosed.

Highlight box

Key findings

- We report two cases of latent TB infection before IVF-ET and discuss the different outcomes due to the screening of latent TB before IVF-ET.

What is known and what is new?

- IVF-ET is contraindicated in women with active TB and chest X-ray is a routine screening procedure for active TB before IVF-ET. However, most women with latent TB do not exhibit pulmonary symptoms and usually negative results are reported.
- Screening for latent TB infection before IVF-ET is particularly important which holds benefits for both mother and child.

What is the implication, and what should change now?

- It is particularly important to diagnose latent TB infection before women undergo IVF-ET. Specific tests, such as IGRA, can be used to identify latent TB infection in women at high risk of TB.

Rationale and knowledge gap

In vitro fertilization and embryo transfer (IVF-ET) is an effective treatment for infertile couples. Women with GTB used to rarely conceive before the advent of IVF-ET. However, TB-related maternal and neonatal complications have increased in recent years after IVF-ET treatment (6). Several case reports of TB during pregnancy after IVF-ET have described severe adverse outcomes, including abortion, fetal malformation, and maternal death (7-10). IVF-ET is contraindicated in women with active TB and chest X-ray is a routine screening procedure for active TB before IVF-ET. However, most women with latent TB do not exhibit pulmonary symptoms and usually negative results are reported. Many reviews about management of latent tuberculosis have inclined to testing and treatment when potential benefits of treatment outweigh potential risks (2,11). However, there is lack of professional guidelines and studies regarding latent TB screening and preventive anti-tuberculous treatment in women seeking fertility treatment.

Objective

Previous reported cases pay more attention to management of latent TB reactivation after IVF-ET instead of underscoring the timely detection and treatment for latent TB infection before IVF-ET (7-10). Here, we report two cases of latent TB infection before IVF-ET and discuss the different outcomes due to the screening of latent TB before IVF-ET (*Figure 1*). We present the cases in accordance with the CARE reporting checklist (available at <https://gpm.amegroups.com/article/view/10.21037/gpm-22-28/rc>).

Case presentation

This study was approved by the institutional review board of West China Second Hospital of Sichuan University. All procedures performed in this study were in accordance with the ethical standards of the institutional and national research committees and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patients for publication of this case report. A copy of the written consent is available for review by the editorial office of this journal.

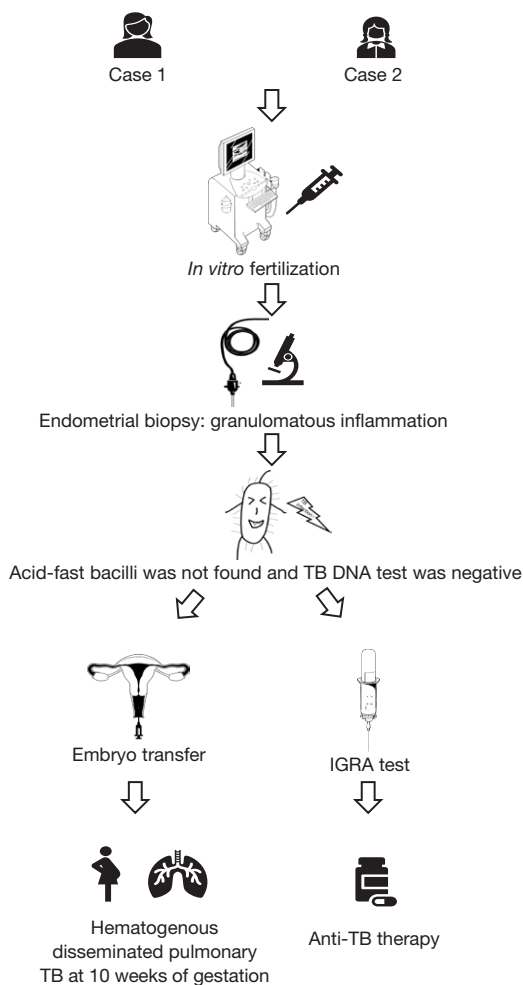


Figure 1 Flowchart of treatment of these two cases. TB, tuberculosis; IGRA, interferon-gamma release assay.

Case 1

A 32-year-old pregnant Chinese woman was hospitalized at 10 weeks gestation due to a 10-day history of a cough and a 3-day history of fever and dyspnea. She had a history of infertility caused by bilateral fallopian tube blockage and decreased ovarian reserve and conceived after IVF-ET treatment in another hospital on December 4, 2021. She had no prior history of pulmonary TB, and her chest X-ray was negative for signs of TB before IVF-ET. Eleven oocytes were harvested using a minimal ovarian stimulation protocol, and two of them were fertilized. Hysteroscopy and endometrial biopsy were performed before embryo transfer. The endometrial histopathology revealed granulomatous inflammation, but both acid-fast bacilli and TB DNA tests

were negative. Frozen embryo transfer was performed, and the pregnancy was subsequently confirmed. On January 25, 2022, the patient experienced a cough, accompanied by dizziness and fatigue at 10 weeks of pregnancy. Three days later, she developed chills and shortness of breath. Her highest recorded body temperature was 40.4 °C. She was admitted to our hospital and was treated for 3 days with antimicrobial therapy (Mepem every 8 hour). However, her condition did not improve, and her shortness of breath worsened. Chest computed tomography (CT) showed reduced transparency and dense ground-glass opacities and diffuse miliary nodules in both lungs. She was then transferred to the intensive care unit, and non-invasive mechanical ventilation was performed on February 2, 2022. She experienced a miscarriage on February 4, 2022. Alveolar lavage fluid was collected for microbiological testing. The diagnosis of pulmonary TB was confirmed by the presence of MTB in alveolar lavage fluid and 188 sequences of the MTB complex group being identified by metagenomic next-generation sequencing. Hematogenous dissemination of pulmonary TB was diagnosed on February 7, 2022. A standard anti-tuberculosis regimen (2HREZ/10HRE) was begun with an initial 2-month intensive phase of four drugs (rifampicin at 450 mg once daily, isoniazid at 300 mg once daily, pyrazinamide at 750 mg twice daily, and ethambutol at 750 mg once daily) followed by a 10-month consolidation course of three drugs (rifampicin at 450 mg once daily, isoniazid at 300 mg once daily and ethambutol at 750 mg once daily) without severe adverse effect. Diammonium glycyrrhizinate (150 mg three times daily) was administered to alleviate anti-tuberculosis drug induced liver injury. On March 28, 2022 almost 2 months after anti-tuberculosis, the CT revealed that the lung lesions were absorbed significantly. Continuous clinical and radiological improvement was observed during the follow up.

Case 2

A 33-year-old woman with a 10-year history of primary infertility came to our reproductive medical center for IVF-ET treatment on August, 2021. The patient had regular menstruation, and her husband's semen analysis was normal. Transvaginal ultrasound showed an antral follicle count of 5 and an anti-Mullerian hormone level of 0.6 ng/mL. She had no history of TB and her chest X-ray was negative for signs of TB before IVF-ET treatment. Ovarian stimulation was performed using a gonadotropin-releasing hormone antagonist protocol. Three oocytes were collected, and

all were fertilized. Hysteroscopy and endometrial biopsy were performed and revealed granulomatous inflammation with non-caseous necrosis on October, 2021. However, acid-fast bacilli were not found, and the TB DNA test was negative. Although TB was suspected, the histopathology was atypical, and microbiological evidence was absent. A multidisciplinary team meeting was organized and blood-based IGRA test was recommended. The IGRA result was positive for TB. Latent endometrial tuberculosis was considered in combination with endometrial biopsy results. Therefore, the frozen embryo transfer procedure was postponed. A 6-month anti-tuberculosis regimen was administered with rifampicin at 450 mg once daily, isoniazid at 300 mg once daily, pyrazinamide at 1,500 mg once daily, and ethambutol at 750 mg once daily during the first 2 months, followed by a 4-month course of two drugs (rifampicin at 450 mg once daily and isoniazid at 300 mg once daily). She was compliant on all medications and experienced no adverse effects. IGRA was negative after six months of anti-tuberculosis therapy.

Discussion

Key findings

In this study, we reported two cases with endometrial histopathology, using samples collected via hysteroscopy, showing granulomatous inflammation, which suggested the possibility of endometrial *Mycobacterium tuberculosis* infection. In contrast, negative test results for acid-fast bacilli and TB DNA did not support a diagnosis of TB. In Case 1, embryo transfer was performed, but the patient experienced hematogenous dissemination of pulmonary TB. In Case 2, an IGRA was performed and was positive for TB. Considering the high risk of TB. Embryo transfer was postponed until she had completed antituberculosis therapy.

Strengths and limitations

The greatest strength of this study was the similar background of the two cases which made the outcomes comparable. However, there are several limitations of this study. Firstly, only two cases were included, more clinical data would be needed for further study. Secondly, up to now, frozen embryo transfer procedure is not yet provided after anti-tuberculosis treatment in case 2, so that the pregnancy outcome is not available.

Comparison with similar researches

Hematogenous dissemination of pulmonary TB was diagnosed in case 1. Similar result was obtained in a recent report of seven cases suggesting TB reactivation, mostly as miliary TB and TB meningitis, is severe in pregnant women after IVF-ET and deleterious to pregnancy outcomes (9). However, it is difficult to diagnose TB during pregnancy. First, symptoms of pregnancy, such as weakness, weight changes, and shortness of breath, overlap with those of TB. There are no specific symptoms of pregnancy complicated by TB. Second, the diagnosis of TB may be delayed due to a reluctance to perform chest X-rays and CT scans in pregnant women (12). Therefore, screening TB before IVF-ET appears to be particularly important. Several case reports and case series referring to reactivation of TB after IVF-ET have been reported previously, but no screening strategies were proposed (7-10). Comparing with those cases, our study focusing more on different outcomes due to the screening of latent TB before IVF-ET.

Explanations of findings

Disseminated TB is a fatal disease resulting from the hematogenous dissemination of TB. Pregnant women have a high risk of hematogenous dissemination of TB because pregnancy and delivery can reactivate latent TB (12). In Case 1, the activation and dissemination of TB may have been associated with latent *Mycobacterium tuberculosis* infection. The increased levels of estrogen, progesterone, and human chorionic gonadotropin during pregnancy can inhibit T-lymphocyte proliferation and lead to an increased incidence of *Mycobacterium tuberculosis* infection (13). High estrogen levels can also promote the proliferation of *Mycobacterium tuberculosis* (10). Moreover, increased levels of adrenocortical hormones, which enhance vascular permeability, increase the risk of hematogenous dissemination (10,11). All these changes during pregnancy are conducive to the acquisition and reactivation of TB. Large doses of steroid hormones and gonadotropins are used in women undergoing IVF-ET, resulting in a significantly higher level of estrogen and progesterone than the natural physiological level. Furthermore, an increasing number of immunosuppressive drugs, which suppress normal immune function and facilitate the reactivation of latent *Mycobacterium tuberculosis* infection, are being used to improve the success rate of IVF-ET. Both cases are lack

of typical histopathological and microbiological features. This may be because of the natural characteristics of the endometrium. The endometrium is shed every month due to menstruation, leading to inadequate granuloma formation, and acid-fast bacilli are rarely found (14).

Implications and actions needed

Women undergoing IVF-ET are at an increased risk of progression or reactivation of latent *Mycobacterium tuberculosis* infection leading to active TB and possible transmission of infection to others. Identifying individuals at a high risk of TB activation before IVF-ET is essential. Chest X-ray is a routine screening procedure before IVF-ET. However, many women with latent TB have normal chest X-ray findings and no prior history of TB (15). Therefore, when IVF-ET is performed in clinical practice, attention should be paid to patients with latent TB, even in the absence of typical histopathological and microbiological features. At present, there is no international guideline about screening for latent *Mycobacterium tuberculosis* infection before IVF-ET. We recommend performing TST, IGRA, or both for latent *Mycobacterium tuberculosis* infection in addition to a chest X-ray in women at high risk of TB. TST is a traditional tool to diagnosis latent TB but with some known limitations, for example it is affected by previous vaccination with bacillus Calmette Guerin. IGRAs have been used to detect latent TB in recent years and have the same or better sensitivity and higher specificity than the TST, which has limited specificity due to cross-reactivity with the BCG vaccine (16). Untreated individuals with positive IGRA results have a 10.8-fold higher rate of progression to active TB (17). While, IGRAs are not readily available in many countries with a high TB burden.

For high-risk TB individuals, timely identification of latent TB infection and preventive antituberculosis treatment are also important measures for the prevention and control of TB. Prophylactic antituberculosis therapy is needed in individuals with human immunodeficiency virus infection and those receiving tumor immunosuppressive therapy, necrosis factor alpha inhibitors, or glucocorticoids (14). However, the preventive treatment of latent TB is a clinical dilemma for infertile patients undergoing IVF-ET due to the possible side effects of antituberculosis therapy and the delay in pregnancy. Further studies are required to determine whether prophylactic anti-tuberculous therapy is warranted for infertile patients before undergoing IVF-ET.

Conclusions

Women undergoing IVF-ET are at an increased risk of activation and hematogenous dissemination of latent *Mycobacterium tuberculosis* infection. Therefore, it is particularly important to diagnose latent *Mycobacterium tuberculosis* infection before women undergo IVF-ET. Specific tests, such as TST and IGRA, can be used to identify latent *Mycobacterium tuberculosis* infection in women at high risk of TB. More clinical data would be needed to clarify whether to receive antituberculosis therapy without affecting IVF treatment to avoid reactivation of latent TB.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at <https://gpm.amegroups.com/article/view/10.21037/gpm-22-28/rc>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://gpm.amegroups.com/article/view/10.21037/gpm-22-28/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the institutional review board of West China Second Hospital of Sichuan University. All procedures performed in this study were in accordance with the ethical standards of the institutional and national research committees and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patients for publication of this case report. A copy of the written consent is available for review by the editorial office of this journal.

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