Health Science Reports

WILEY

Health Science Reports
Open Access

ORIGINAL RESEARCH OPEN ACCESS

Clinical Characteristics of Miliary Pulmonary Tuberculosis in Pregnancy After In Vitro Fertilization-Embryo Transfer: A Retrospective Clinical Study

Litao Guo[1,2] | Xiaoling Wu[3] | Lin Cao[3]

[1]Department of Critical Care Medicine, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China | [2]Department of Critical Care Medicine, Qinghai Provincial People's Hospital, Xining, China | [3]Department of Critical Care Medicine, The Fifth People's Hospital of ShaanXi, Xi'an, China

Correspondence: Litao Guo (glt02@163.com)

Received: 7 October 2024 | **Revised:** 26 March 2025 | **Accepted:** 2 April 2025

Funding: The "Kunlun Talents. High-level Health Talents" Project in Qinghai Province (LitaoGuo,No.2023).

Keywords: female infertility | In Vitro fertilization-embryo transfer | lung infection | metagenomic next-generation sequencing | pregnancy | tuberculosis

ABSTRACT

Background and Aims: Miliary pulmonary tuberculosis (MPTB) is rare in patients treated with In Vitro fertilization-embryo transfer (IVF-ET), and can be life-threatening to pregnant women and fetuses. We aimed to describe the clinical characteristics of MPTB after IVF-ET and pregnancy outcomes to provide reference for early diagnosis and treatment.

Methods: Clinical data from patients who developed MPTB after IVF-ET from January 2018–December 2021 were retrospectively and statistically analyzed.

Results: Ultimately, 21 patients (mean age: 29.81 ± 3.79 years) were included. Three patients had a history of pulmonary or extrapulmonary tuberculosis (TB), and were cured or showed no suggestive TB activity before pregnancy. Patients presented with atypical early symptoms, fever (39.16 ± 0.74°C), and vaginal bleeding, and lung imaging changes. Patients became febrile 78.90 ± 26.04 days after IVF-ET; the time from fever to diagnosis was 17.76 ± 9.05 days. Patients were admitted 96.05 ± 25.33 days after IVF-ET. Sputum *Mycobacterium tuberculosis* smear and culture, purified protein derivative, TB polymerase chain reaction, and other routine TB examinations had low positivity rates; the erythrocyte sedimentation rate was generally within normal limits. Chest imaging during pregnancy is limited, further increasing the diagnosis time. Two critically ill patients were diagnosed by metagenomic next-generation sequencing. Seven patients had TB meningitis or encephalitis. Pregnancy was terminated in all but three patients. All patients received anti-TB therapy; however, two patients died during hospitalization (mean hospitalization: 58.29 ± 33.40 days).

Conclusions: Comprehensive TB screening before IVF-ET is necessary for infertile patients. MPTB develops after IVF-ET with atypical symptoms and poor pregnancy outcomes. Clinicians should use multiple methods to confirm TB diagnoses early on, without delaying chest imaging.

Importance

Miliary pulmonary tuberculosis (MPTB) is rare in patients treated with In Vitro fertilization-embryo transfer (IVF-ET), and can be life-threatening to pregnant women and fetuses. We aimed to describe the clinical characteristics of patients with MPTB after IVF-ET and their pregnancy outcomes to provide a reference for early diagnosis and treatment. We believe that our

Litao Guo and Xiaoling Wu contributed equally to this study.

study makes a significant contribution to the literature because our findings indicate that MPTB develops after IVF-ET with atypical symptoms and poor pregnancy outcomes. Therefore, infertile patients require comprehensive tuberculosis screening before IVF-ET. Moreover, clinicians should use multiple methods to confirm a tuberculosis diagnoses early on, without delaying chest imaging. Although our sample size was small, the number of cases included our study was greater than those previously reported on this topic. In addition, we analyzed the patients' occupations and the use of metagenomic next-generation sequencing detection technology to identify the pathogen early.

1 | Introduction

Tuberculosis (TB) is an infectious disease caused by M. tuberculosis, which seriously endangers human health [1]. The TB incidence is significantly higher in pregnant than nonpregnant women, as high as 57.0%, with rates increasing with maternal age and in women from high TB-incidence settings [2]. Pregnancy-associated TB progresses rapidly potentially leading to miscarriage and death, endangering pregnant women and their fetuses [3, 4] and possibly leading to the inability to become pregnant [3]. Therefore, pregnancy and childbirth are important triggers leading to TB recurrence in women [5]. Genital TB (GTB), including fallopian tube, ovary, pelvic peritoneum, and endometrium involvement, is the most common cause of female infertility [5, 6]. In Vitro fertilization-embryo transfer (IVF-ET) is the best treatment for tubal infertility [7]. Peak serum estrogen levels are significantly higher in patients who undergo IVF-ET compared with those in a normal pregnancy, possibly affecting cellular immunity and causing a TB recurrence. TB spreads through the circulatory system, forming miliary pulmonary tuberculosis (MPTB) and extrapulmonary tuberculosis (EPTB) [6, 8]. Because patients with TB during pregnancy exhibit nonspecific clinical symptoms such as fever and cough, chest X-rays (CXRs) and computed tomography (CT) are rarely performed, and TB diagnosis and treatment are often delayed [1, 3, 8]. The proportion can be as high as 40% [8]. Some patients are in critical condition with respiratory failure or acute respiratory distress syndrome (ARDS) when definitively diagnosed, resulting in adverse outcomes including fetal and maternal death [1, 8, 9].

China, a developing country with a high incidence and TB burden during pregnancy [10], has had an increased incidence of TB during pregnancy corresponding to increased IVF-ET use, posing a serious threat to the health of pregnant women and their fetuses [8, 11]. Hence, timely TB diagnosis and treatment during pregnancy is important. However, some difficulties and hysteresis in the clinical diagnosis of MPTB in patients who undergo IVF-ET remain [3, 6]. Currently, reports (mostly Chinese case reports) are limited, and the number of reported cases is small. Therefore, we aimed to describe the clinical characteristics of patients with MPTB who underwent IVF-ET and their pregnancy outcomes to provide a reference for TB diagnosis and treatment, thereby improving treatment success rates in patients with MPTB undergoing IVF-ET.

2 | Materials and Methods

2.1 | Research Design

This retrospective study retrospectively analyzed clinical data from patients with MPTB admitted to the Fifth People's Hospital of Shaanxi Province and First Affiliated Hospital of Xi'an Jiaotong University from January 2018 to December 2021.

2.2 | Ethical

Patients or delegated agent informed consent, and written consent was documented in the patient's medical records. To protect patient privacy, we concealed their basic information. All study procedures conformed to the tenants of the Declaration of Helsinki, and was approved by the Ethics Committee of The Fifth People's Hospital of ShaanXi, the principal site. (No. 2021-8).

2.3 | Inclusion and Exclusion Criteria

Inclusion criteria: We included patients with infertility treated with IVF-ET who were successfully impregnated and the diagnostic criteria for MPTB [12, 13]; Age 18–50 years. Exclusion criteria: We excluded patients with spontaneous conception with MPTB; pulmonary TB (PTB) or EPTB diagnosis before IVF-ET treatment with active TB; patients co-living with family members diagnosed with PTB or EPTB with active TB; length of hospital stay (LOS) < 24 h; and patients missing important data. Patients transferred between hospitals were considered the same patient. Case review and classification were expertly performed by Litao Guo and Xiaoling Wu.

3 | Research Methods

3.1 | Diagnosis

MPTB generally presents as miliary nodules in both lungs (also called miliary PTB) and is caused by focal M. tuberculosis dissemination into the lungs via the blood or lymph. MPTB appears as millet-seed sized tuberculous lesions (1–2 mm) on imaging [13]. Patient diagnosis was confirmed based on clinical manifestations, pulmonary imaging, and laboratory tests.

3.2 | Data Collection

Clinical data of patients who developed MPTB following IVF - ET between January 2018 and December 2021 were retrospectively collated and analyzed. Basic information (sex, age, weight, occupation, hypertension, diabetes, and comorbid diseases), TB history, TB testing and treatment(e.g., Sputum mycobacterium tuberculosis smears and cultures, T-spot, Xpert, PPD, PCR-TB, TB antibody and TBtreatment), admission time, LOS, prognosis, infertility causes, number of IVF-ETs, pregnancy outcomes, symptoms and signs (e.g., fever, chills, vaginal

bleeding, dyspnea), presence of TB meningitis, chest imaging findings after admission, and relevant laboratory test results were collected from all included patients. Lin Cao was in charge of data collection and management. Patient - related data were directly inputted into a database and stored on a dedicated computer. Only Litao Guo, Xiaoling Wu, and Lin Cao had access to the data; others were not permitted to access it.

3.3 | Statistical Analysis

The entirety of the collected data was collated with the use of Microsoft Excel. Data statistics and analyses were performed using SPSS software, version 20.0 (IBM Inc. Armonk, NY, USA). Continuous variables were presented as means ± standard deviations (x ± s) and counts as frequencies and percentages (%), and related items were collated in summary tables.

4 | Results

4.1 | Basic Characteristics of Patients

Twenty-one patients were included in the study. Ages ranged from 25 to 41 (mean: 29.81 ± 3.79) years; weights ranged from 42 to 65 (mean: 51.14 ± 6.35) kg. No patient had a history of rheumatic immune disease, hypertension, diabetes, or long-term drug or immunosuppressive agent use. However, one patient each had previous PTB, GTB, and joint TB, all of which were cured or inactive. Three patients' family members had a history of TB (Table 1). Furthermore, all patients were screened for TB before IVF-ET treatment and were negative (PPD, T-spot, PCR-TB, TB antibody, Gynecologic Ultrasound, et al.).

TABLE 1 | Basic characteristics of patients ($n = 21$).

Characteristic	$x \pm s/n$, %
Age, years	29.81 ± 3.79 (25–41)
Body weight, kg	51.14 ± 6.35 (42–65)
Body temperature,°C	39.16 ± 0.74 (37.5–40.0)
Occupation	
Farmers	17 (80.95)
Clerks	3 (14.29)
Nurse	1 (4.76)
Underlying disease	
Hypertension	0 (0.00)
Diabetes	0 (0.00)
History of TB	
PTB	1 (4.76)
GTB	1 (4.76)
Joint TB	1 (4.76)
Family Member TB History	3 (14.29)

Abbreviations: GTB, genital TB; TB, tuberculosis.

4.2 | Clinical Features and TB Diagnosis

Fever was present in all 21 patients; vaginal bleeding was present in 19 and considered an early symptom. Most fevers first appeared in the first and second trimesters (40–146 [mean: 78.90 ± 26.04] gestation days). The admission period ranged from 60 to 160 (mean: 96.05 ± 25.33) gestation days. The duration from fever onset to admission was 1–34 (mean: 17.14 ± 9.10) days. The time from onset to diagnosis was 1–34 (mean: 17.76 ± 9.05) days. Approximately one-third of the patients presented with chills, night sweats, and dyspnea. Three patients presented with critical illness manifestations, including septic shock and ARDS, and were admitted to the intensive care unit (ICU). Seven patients presented with TB meningitis or encephalitis, although none presented with impaired consciousness. No patient developed renal impairment after anti-TB treatment; however, 14 patients developed mild hepatic impairment (Table 2). CXRs and CT showed diffuse miliary infiltrates bilaterally, which were widely distributed and uniform in size, with some scans showing exudation and ground-glass opacity (Figure 1).

Regarding diagnostics, two patients had positive sputum *M. tuberculosis* smears, nine had positive sputum M. tuberculosis

TABLE 2 | Clinical features and imaging findings ($n = 21$).

Variables	$x \pm s/n$, %
Time from IVF-ET to admission, days	96.05 ± 25.33 (60–160)
Time from IVF-ET to first fever, days	78.90 ± 26.04 (40–146)
Time from fever to admission, days	17.14 ± 9.10 (1–34)
Time from fever to TB diagnosis, days	17.76 ± 9.05 (1–34)
Clinical manifestations	
Fever	21 (100.00)
Chills	7 (33.33)
Night sweat	6 (28.57)
Shortness of breath	15 (71.43)
Dyspnea	4 (19.05)
Cough	19 (90.48)
Disorders of consciousness	0 (0.00)
TB meningitis	7 (33.33)
Mechanical ventilation	3 (14.29)
Shock	3 (14.29)
Renal impairment	0 (0.00)
Hepatic impairment	14 (66.67)
Radiologic findings	
Multiple nodules	21 (100.00%)
Calcification	4 (19.05)
Pulmonary infiltrate	6 (28.57)

Abbreviations: IVF-ET, invitro fertilization-embryo transfer; TB, tuberculosis.

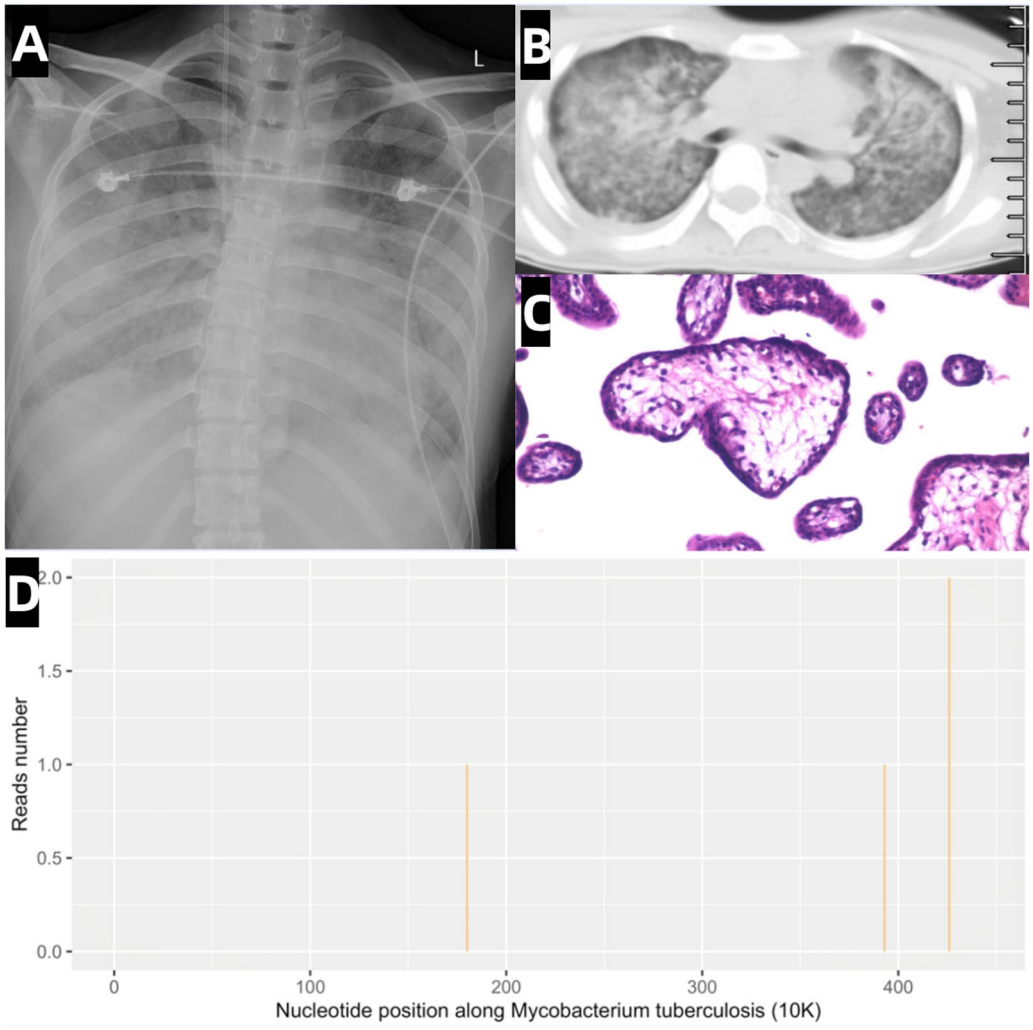

FIGURE 1 | A 26-year-old infertile woman presented with fever at 8 weeks + 4 days of gestation. (A) Posteroanterior chest radiograph showing miliary nodules and patchy blurred shadows in both lungs. (B) Chest CT showed miliary nodules with multiple patchy exudation and ground-glass opacity, in both lungswith uneven density. (C) Histopathological picture of placenta in uterine cavity after termination of pregnancy (HE 10×). (D) Nucleotide position along Mycobacterium tuberculosis (10 K). Mycobacterium tuberculosis 0.0051% coverage.

cultures, and eight tested positive for TB antibodies. The purified protein derivative (PPD) skin reaction and TB polymerase chain reaction (PCR) tests were negative in four and seven patients, respectively. T-cell linked immunospot (T-SPOT) and M. tuberculosis and rifampicin resistance (Xpert MTB/RIF) assays had positivity rates of 89.47% (17/19) and 52.94% (9/17), respectively. Three critically ill patients had negative sputum M. tuberculosis smears, sputum *M. tuberculosis* cultures, and T-SPOT and PPD tests. Two of these patients underwent metagenomic next-generation sequencing (mNGS), which suggested TB at three and four sequences, respectively (Figure 1). Erythrocyte sedimentation rate (ESR), neutrophil percentage, and C-reactive protein (CRP) levels were mildly elevated. White blood cell (WBC) counts ranged from 4.00 to 10.91 (mean: $7.04 \pm 2.52) \times 10^9$/L (mildly elevated) in four patients and were within normal range in the rest. Procalcitonin levels ranged from 0.10 to 8.89 (mean: 1.01 ± 2.14) ng/mL; three patients had mildly elevated levels and the rest were within normal range. Hemoglobin and plasma albumin levels decreased, and lymphocyte count (LYMPH) decreased significantly (Table 3).

4.3 | Pregnancy Presentation and Outcome

Infertility duration ranged from 2 to 10 (mean: 4.5 ± 2.31) years. Twenty-one patients were diagnosed with primary infertility due to unilateral or bilateral tubal obstruction or salpingography before IVF-ET. Nineteen patients underwent IVF-ET for the first time; one patient underwent IVF-ET twice and one patient four times. All patients had successful pregnancies after IVF-ET. Eighteen patients had their first pregnancy, one their second, and one their third. Fifteen and six women had singleton and twin pregnancies, respectively. Nineteen patients presented with vaginal bleeding for the first time 47–178 (mean: 97.58 ± 34.46) after IVF-ET; two patients had no vaginal bleeding. Except for three women who delivered normally (fetuses survived), the rest had spontaneous abortions (28.57%) or abortions due to inevitable spontaneous abortion or fetal death (57.14%) 75–209 (mean: 111.56 ± 33.12) days after IVF-ET. The time from the first vaginal bleeding to pregnancy termination ranged from 1 to 55 (mean: 19.18 ± 18.56) days. The time from fever onset to pregnancy termination ranged from 1 to 80 (mean 32.06 ± 19.17 days) Table 4.

TABLE 3 | Laboratory related test results.

Variables	$x \pm s/n$, %
Sputum mycobacterium tuberculosis smears	18
Positive	2 (11.11)
Negative	16 (88.89)
Sputum mycobacterium tuberculosis cultures	15
Positive	9 (60.00)
Negative	6 (40.00)
T-spot	20
Positive	18 (90.00)
Negative	2 (10.00)
Xpert	17
Positive	9 (52.94)
Negative	8 (47.06)
PPD	4
Negative	4 (100.00)
PCR-TB	7
Negative	7 (100.00)
TB antibody	18
Positive	8 (44.44)
Negative	10 (55.56)
ESR, mm/h	43.43 ± 23.79 (10–96)
WBC,*10^9/L	7.04 ± 2.52 (4.00–10.91)
NEUT,%	82.06 ± 11.21 (55.40–97.00)
HB,g/L	95.67 ± 12.72 (75–117)
LYMPH*109/L	0.83 ± 0.54 (0.30–2.40)
CPR, mg/L	46.23 ± 33.32 (4–122)
ALB,g/L	28.87 ± 4.34 (19.10–39.30)
PCT, ng/mL	1.01 ± 2.14 (0.10–8.89)

Abbreviations: ALB, albumin; CPR, C-reactive protein; ESR, erythrocyte sedimentation rate; HB, hemoglobin; LYMPH, lymphocyte count; NEUT, neutrophil; PCR, polymerase chain reaction; PCT, procalcitonin; PPD, purified protein derivative; TB, tuberculosis; T-spot, T-cell linked immunospot; WBC, white blood cell; Xpert, tests for Mycobacterium tuberculosis and rifampicin resistance.

TABLE 4 | Pregnancy-related conditions ($n = 21$).

Variables	$x \pm s/n$, %
No. of pregnancies	
1	18 (85.72)
2	2 (9.52)
3	1 (4.76)
No. of IVF	
1	19 (90.48)
2	1 (4.76)
4	1 (4.76)
Causes of infertility	
Oviduct obstruction	21 (100.00)
Assisted reproductive technology	
IVF-ET	21 (100.00)
IVF-ET outcomes	
Singleton	15 (71.43)
Twin	6 (28.57)
Vaginal bleeding	
Yes	19 (90.48)
No	2 (9.52)
Pregnancy outcomes	
Spontaneous abortion	6 (28.57)
Induced abortion	12 (57.14)
Parturition	3 (14.29)
Infertility duration, years	4.5 ± 2.31 (2–10)
Time from IVF-ET to vaginal bleeding, days	97.58 ± 34.46 (47–178)
Time from IVF-ET to pregnancy termination, days	111.56 ± 33.12 (75–209)
Time from IVF-ET to first fever, days	32.06 ± 19.17 (1–80)
Time from vaginal bleeding to pregnancy termination, days	19.18 ± 18.56 (1–55)

Abbreviations: IVF, invitro fertilization; IVF-ET, invitro fertilization-embryo transfer.

4.4 | Treatment and Prognosis

All patients received first-line anti-TB treatments as recommended by the World Health Organization (WHO) as well as symptomatic and supportive treatment. Three critically ill patients received comprehensive treatments such as treatment for shock and mechanical ventilation after ICU admission. Fourteen patients with liver function impairment showed no further liver function damage after their anti-TB treatment regimen was adjusted and hepatoprotective drug administration. Two critically ill patients died during hospitalization from ARDS and multiple organ dysfunction syndrome (MODS). One patient discontinued treatment and was discharged. Eighteen patients remained stable after treatment, and anti-TB treatment was continued after discharge. The LOS ranged from 8 to 129 (mean: 58.29 ± 33.40) days (Table 5).

TABLE 5 | The prognosis of patients ($n = 21$).

Variables	$x \pm s/n$, %
Hospital stay time, days	58.29 ± 33.40 (8–129)
Death	
In the hospital	2 (9.52)
By Day 28	2 (9.52)

5 | Discussion

TB prevalence is related to region, age, and occupation [14]. GTB prevalence among infertility patients also varies by country, with 6%–25% in India, 20% in Pakistan, 1% in the United States and Europe, and 0.72% in Portugal [15]. In Southeast Asia and Africa, the age of GTB onset is generally between 20 and 40 years, which may be related to marriage and childbearing policies in developing countries [15–17]. Our patients had an age of onset of MPTB between 25 and 41 years old (i.e., women within the legal marriage age of ≥ 20 years in China). We investigated the patients' occupations and farmers accounted for 80.95%. Surveys have shown that the TB incidence is higher in semi-urban and rural areas compared with urban areas, which is related to the level of economic development [18]. Compared with urban areas, rural areas have gaps in economic income, medical resources, and healthcare. However, the incidence of TB tends to be consistent with social progress, economic development, and increased personnel mobility. Because of the coronavirus disease 2019 pandemic, concerns about TB have diminished, and TB morbidity and mortality may increase in the near future [15], as well as the number of patients with infertility due to TB.

MPTB is a potentially fatal form of TB. Approximately 15%–30% of patients with PTB during pregnancy present with miliary PTB with hematogenous spread [19]. The incidence of MPTB in IVF-ET is higher than that in spontaneous pregnancies (41.38% vs. 24.44%) [20], possibly owing to a multitude of factors. First, GTB may be the cause of primary infertility in many patients, and 20% of primary infertility cases are reportedly caused by GTB, of which tubal TB accounts for the highest proportion [8, 21] and often presents with unilateral or bilateral tubal obstruction. These patients have an insidious condition, long incubation periods, and no other clinical manifestations except infertility [8]. Pregnancy can activate insidious GTB, causing dissemination to systemic organs including the lungs. The second potential factor is the use of glucocorticoids during maternal preparation for IVF to sensitize the ovaries to gonadotropin stimulation [20, 22] (estradiol levels increase after ovulation induction). Both hormones can suppress the immune system and reduce maternal immunity [20, 22], thus predisposing pregnant women to TB infection, recurrent TB, and the development of MPTB. Third, the increase in maternal estrogen during pregnancy can inhibit the immune function of maternal lymphocytes and facilitate M. tuberculosis reproduction and hematogenous dissemination [23]. Fourth, increased microvascular permeability in pregnant women allows M. tuberculosis to enter the blood and cause MPTB and EPTB [8, 20]. Our 21 patients presented with primary infertility due to unilateral or bilateral tubal obstruction on salpingography. GTB may lead to tubal obstruction, decreased endometrial receptivity, and ovarian dysfunction, resulting in infertility. However, the presentation of GTB is nonspecific, and its diagnosis depends on invasive procedures and pathological or etiological findings. Laparoscopy is not a routine method used for TB screening except in infertility patients [10]. Some researchers have performed laparoscopy in infertile patients, and the results showed that tubal obstruction and adhesions were consistent with TB [3]. Therefore, laparoscopy is still recommended before IVF-ET in patients with tubal infertility and high-risk factors [10]. No patient in our study underwent laparoscopy or further examination to exclude GTB. However, the clinical presentation after IVF-ET suggests that tubal obstruction may have been caused by insidious GTB.

Although IVF-ET has become a common treatment for infertile women, many women are not screened for TB before IVF-ET [24]. These screenings should also include TB, family, and TB treatment histories [15]. Patients with infertility and a history or family history of TB or family members with current TB should be considered high risk and undergo comprehensive TB screening before IVF-ET. Three of our included patients had a history of TB, including pulmonary, knee, and GTB. Three patients' family members had a history of TB. All patients were routinely screened for TB before IVF-ET and were negative; however, none were fully screened. Infertile patients should be comprehensively screened for TB, and GTB cannot be completely excluded even if the results are negative. Some scholars have suggested that prophylactic anti-TB therapy for latent TB infection (positive infection test without active TB) may benefit infertile women [25]. Furthermore, some researchers have proposed that laparoscopic salpingectomy before embryo transfer is the only definitive treatment for infertility caused by confirmed tubal TB, which is conducive to the success of embryo implantation and delivery [26].

The early clinical presentation of MPTB in patients with IVF-ET is not specific. Fever (39°–40°C), cough, shortness of breath, and vaginal bleeding are early symptoms in most patients, occurring in the first and second trimesters of pregnancy. Three of our patients presented with critical conditions such as respiratory failure and septic shock on admission and were admitted to the ICU. Patients' conditions can progress dramatically within a short period of time, with multiple organ dysfunction, such as respiratory failure or ARDS, and even death [8, 10], which is considered to be related to the immune status of such patients. Almost all of our patients had significantly low LYMPHs and albumin levels. Moreover, low immunity and poor nutritional status make it difficult for patients to fight the infection causing it to progress rapidly. Researchers reported on two patients who developed cerebral tuberculoma (MBT) after IVF-ET and concluded that IVF-ET may be a risk factor for MBT [23]. MBT is a rare TB granuloma of the central nervous system that presents as solitary or multiple granulomas that can involve any part of the brain and has a poor prognosis. MBT with TB meningitis accounts for approximately 10% of cases [23]. Seven patients were diagnosed with TB meningitis or encephalitis, although none presented with disturbance of consciousness and all excluded MBT. Routine improvement of cranial CT examinations in IVF-ET patients with TB is recommended for early definitive diagnosis.

Most of our patients had normal or mildly elevated infection indicators such as WBC count, procalcitonin and CRP levels, and ESR. Associated tests for early TB, such as the PPD skin reaction test, sputum smear and culture tests for M. tuberculosis, and TB PCR, were generally negative. The T-SPOT test positivity rate was much higher than that of the PPD test, possibly because patients with miliary PTB after IVF-ET are in a relatively anergic state [10]. The WHO also recommends Xpert MTB/RIF as the initial diagnostic test for sputum TB; however,

it is expensive and difficult to perform in primary hospitals. M. tuberculosis pathogen examination is the gold standard for TB diagnosis, although its positivity rate is low. Our etiological examination positivity rate was 52.94%, which was slightly lower than the 59% reported by the WHO [27]. Therefore, rapid detection has limitations, and etiological diagnosis is difficult. Medical staff and pregnant women must also consider fetal health, thereby limiting early CXR and CT examinations and increasing the difficulty of clinical diagnosis. Our patients had long durations from early symptom onset (e.g., fever) to admission and diagnosis, which averaged from 2 to 3 weeks. Our findings are similar to those of previous studies [3, 6, 20], suggesting that diagnosing the disease is difficult and delayed diagnosis is common [20]. Additionally, most patients ignore the early symptoms and present late, and medical staff have insufficient experience with patients with TB and IVF-ET. Most of our patients were admitted to the hospital following a TB diagnosis in the outpatient clinic; therefore, the time of admission and diagnosis were generally consistent. We included two critically ill patients who were definitively diagnosed by mNGS of bronchoalveolar lavage fluid after routine examinations for TB were negative and the number of *M. tuberculosis* sequences was three and four, respectively. These patients were diagnosed 6 days after admission which was a significantly shorter amount of time compared with the other patients. This included one patient we previously reported [8]. In terms of M. tuberculosis detection, mNGS is superior to conventional culture tests (odds ratio = 4; [95% confidence interval, 1.7–10.8]; $p < 0.01$) [28], as mNGS is less affected by anti-TB treatment and is more sensitive than culture tests (47.8% vs. 23.2%) [29]. Combining mNGS with traditional detection methods can improve the detection rate of M. tuberculosis (79.6%) [29] and facilitate early diagnosis and treatment. GTB permanently damages the female reproductive tract. Therefore, early diagnosis and treatment can prevent permanent damage and sequelae of the female genital tract and improve pregnancy and patient outcomes [15, 30].

Case reports demonstrate that although some patients experience impaired extrapulmonary organ function, most have a good prognosis [10, 20]. Although our patients were administered standardized anti-TB treatment after diagnosis, two critically ill patients still died of ARDS and MODS during hospitalization, with a mortality rate of 9.52%. A related study showed that advanced age, ARDS, consciousness disturbance, and high blood urea nitrogen levels are factors associated with poor prognosis in patients with miliary TB [20]. The two patients who died had 7–9 days from onset to spontaneous abortion and were soon diagnosed and treated with anti-TB therapy. However, both patients presented with life-threatening conditions such as ARDS and septic shock on admission and weighed 44 and 42 kg, respectively. Therefore, low body weight, shock, and rapid disease progression may be associated with poor prognosis.

TB during pregnancy is also associated with adverse fetal outcomes [10]. Eighteen patients in our study experienced spontaneous abortion, inevitable abortion, and fetal death 10–17 weeks after IVF-ET, consistent with previous reports [6]. The main causes were severe TB toxemia and M. tuberculosis dissemination through the blood infecting the placenta, causing chorioamnionitis and early vaginal bleeding, and ultimately leading to abortion and fetal death [8]. Even if the pregnancy continues, this often leads to premature birth, low birth weight, and intrauterine growth retardation. The neonate may also have rare congenital TB which has a poor prognosis [24, 31, 32]. TB can spread to the fetus through the placenta in pregnant women. Fetuses can also ingest infected amniotic fluid at birth or have direct contact with maternal genital infection with TB. Moreover, postpartum transmission may occur when the mother is not isolated from the infant immediately after delivery [31]. Three patients were discharged with stable treatment and delivered their babies despite their TB diagnosis; however, all the neonates were born prematurely. Because the patients were lost to follow-up, maternal- and fetal-specific conditions could not be determined.

This study had the following novel characteristics. First, data from 21 patients were retrospectively analyzed, and the number of cases was greater than those previously reported. In particular, we analyzed information on the patients' occupation, weight, infertility duration, number of IVF-ET sessions, and LYMPH. Second, two critically ill patients were treated to buy time for treatment by means of mNGS detection technology to identify the pathogen early and confirm the diagnosis, which has not been previously reported. Third, two patients died in our study, and the patients' characteristics and factors associated with poor prognosis were analyzed to provide a reference for the diagnosis and treatment of such patients.

This study had several limitations. First, although we included two centers, the number of patients from each center was inconsistent. Twenty patients were included from The Fifth People's Hospital of Shaanxi Province, a TB-specialized hospital. One patient was included from The First Affiliated Hospital of Xi'an Jiaotong University, a general hospital, which may have affected patient outcomes. However, almost all patients with MPTB with IVF-ET during the study period were included. Second, retrospective studies cannot intervene in advance; therefore, data from the included patients is inevitably incomplete. Although larger than those previously reported, the sample size was small and may have some impact on the results. However, MPTB with IVF-ET is rare; therefore, conducting prospective multicenter studies with large sample sizes is difficult. However, further prospective studies are required to confirm our findings, as our study aims to provide direction for future research.

6 | Practical Recommendations to Prevent These Poor Outcomes

MPTB is a potentially life - threatening form of TB. When IVF - ET is accompanied by MPTB, it often results in adverse pregnancy outcomes. Thus, the following practical recommendations are put forward to prevent such poor results: First, infertile patients about to undergo IVF - ET should receive comprehensive TB screening before treatment. This includes tests such as the PPD skin reaction test, sputum smear and culture for Mycobacterium tuberculosis, TB PCR, T - SPOT, Xpert MTB/RIF, and laparoscopy, among others. Second,

patients with IVF - ET complicated by MPTB present with atypical early symptoms and have low positivity rates in routine TB examinations. When patients show early symptoms like fever and vaginal bleeding, clinicians need to be vigilant and employ multiple methods for early detection of Mycobacterium tuberculosis infection, such as mNGS and chest imaging. Thirdly, for patients who continue their pregnancy and give birth despite having MPTB, the condition of the fetus and infant after delivery should be closely monitored. Fourthly, once TB is diagnosed, standardized anti - TB treatment should be initiated as early as possible. If the pregnancy cannot be maintained, it should be terminated at an early stage.

7 | Conclusion

Genital tuberculosis (GTB) is the most prevalent cause of female infertility and the primary factor leading to multi - drug resistant tuberculosis (MPTB) following In - Vitro fertilization and embryo transfer (IVF - ET). Patients undergoing IVF - ET who are concurrently affected by MPTB typically experience unfavorable pregnancy outcomes. Conducting comprehensive tuberculosis screening before IVF - ET is of utmost importance. Early diagnosis and treatment are capable of enhancing both adverse pregnancy outcomes and the overall condition of patients.

Author Contributions

Litao Guo: conceptualization, methodology, writing – original draft, writing – review and editing, formal analysis, software. **Xiaoling Wu:** data curation, project administration, writing – review and editing, conceptualization, investigation, validation. **Lin Cao:** writing – review and editing, data curation, formal analysis, project administration.

Acknowledgments

We thank the patients and their families and all staff in the department for their support. We thank Han Xia of Department of Scientific Affairs, Hugobiotech Co. Ltd. for the help of technical assistance in mNGS assay. The “Kunlun Talents. High-level Health Talents” Project in Qinghai Province (LitaoGuo,No.2023).

Ethics Statement

All study procedures conformed to the tenants of the Declaration of Helsinki, and was approved by the Ethics Committee of The Fifth People's Hospital of ShaanXi (No. 2021-8).

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

All authors have perused and given their approval to the final draft of the manuscript. The corresponding author, Litao Guo, possessed unrestricted access to all the data in this study and assumes full accountability for the integrity of the data as well as the accuracy of the data analysis. The authors confirm that the data underpinning the findings of this study can be accessed either within the article or from the corresponding author upon a reasonable request.

Transparency Statement

The lead author Litao Guo affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

References

1. R. Bouzeyen and B. Javid, “Therapeutic Vaccines for Tuberculosis: An Overview,” *Frontiers in Immunology* 13 (2022): 878471, https://doi.org/10.3389/fimmu.2022.878471.

2. A. J. Morton, A. Roddy Mitchell, R. E. Melville, et al., “Mycobacterium Tuberculosis Infection in Pregnancy: A Systematic Review,” *PLOS Global Public Health* 4 (2024): e0003578, https://doi.org/10.1371/journal.pgph.0003578.

3. X. Gai, H. Chi, W. Cao, et al., “Acute Miliary Tuberculosis in Pregnancy After In Vitro Fertilization and Embryo Transfer: A Report of Seven Cases,” *BMC Infectious Diseases* 21 (2021): 913, https://doi.org/10.1186/s12879-021-06564-z.

4. G. Sulis and M. Pai, “Tuberculosis in Pregnancy: A Treacherous Yet Neglected Issue,” *Journal of Obstetrics and Gynaecology Canada* 40 (2018): 1003–1005, https://doi.org/10.1016/j.jogc.2018.04.041.

5. A. Muneer, B. Macrae, S. Krishnamoorthy, and A. Zumla, “Urogenital Tuberculosis – Epidemiology, Pathogenesis and Clinical Features,” *Nature Reviews Urology* 16 (2019): 573–598, https://doi.org/10.1038/s41585-019-0228-9.

6. R. Ye, C. Wang, L. Zhao, X. Wu, Y. Gao, and H. Liu, “Characteristics of Miliary Tuberculosis in Pregnant Women After In Vitro Fertilisation and Embryo Transfer,” *International Journal of Tuberculosis and Lung Disease* 23 (2019): 136–139, https://doi.org/10.5588/ijtld.18.0223.

7. W. Dai, L. Ma, Y. Cao, D. Wu, T. Yu, and J. Zhai, “In Vitro Fertilization Outcome in Women With Endometrial Tuberculosis and Tubal Tuberculosis,” *Gynecological Endocrinology* 36 (2020): 819–823, https://doi.org/10.1080/09513590.2019.1702639.

8. H. Ma, J. Sun, L. Zhang, et al., “Disseminated Hematogenous Tuberculosis Following In Vitro Fertilization–Embryo Transfer: A Case Report,” *Infection and Drug Resistance* 14 (2021): 4903–4911, https://doi.org/10.2147/IDR.S332992.

9. M. Li, X. Yang, Q. Zhou, J. Wang, X. Wang, and L. Mao, “Acute Hematogenous Disseminated Pulmonary Tuberculosis and Tuberculous Meningitis Following In Vitro Fertilization and Embryo Transfer: A Case Report,” *IDCases* 38 (2024): e02096, https://doi.org/10.1016/j.idcr.2024.e02096.

10. S. Dong, R. Zhou, E. Peng, and R. He, “Analysis of Clinical Features and Risk Factors in Pregnant Women With Miliary Pulmonary Tuberculosis After In Vitro Fertilization Embryo Transfer,” *Frontiers in Cellular and Infection Microbiology* 12 (2022): 885865, https://doi.org/10.3389/fcimb.2022.885865.

11. World Health Organization. Global TB report, https://www.who.int/teams/global-tuberculosis-programme/tb-reports; 2020 [accessed 3 November 2020].

12. World Health Organization. WHO Consolidated Guidelines on Tuberculosis: Module 3: Diagnosis: Rapid Diagnostics for Tuberculosis Detection, 2021 Update, https://apps.who.int/iris/handle/10665/342331; 2021.

13. S. Vohra and H. S. Dhaliwal, *Miliary Tuberculosis* (StatPearls Publishing, 2022).

14. X. Y. Gai, H. B. Chi, L. Zeng, et al., “Untreated Prior Pulmonary Tuberculosis Adversely Affects Pregnancy Outcomes in Infertile Women Undergoing In Vitro Fertilization and Embryo Transfer: A Large Retrospective Cohort Study,” *Biomedical and Environmental Sciences: BES* 34 (2021): 130–138, https://doi.org/10.3967/bes2021.019.

15. J. B. Sharma, E. Sharma, S. Sharma, and S. Dharmendra, "Recent Advances in Diagnosis and Management of Female Genital Tuberculosis," *Journal of Obstetrics and Gynecology of India* 71 (2021): 476–487, https://doi.org/10.1007/s13224-021-01523-9.

16. J. B. Sharma, E. Sharma, S. Sharma, J. Singh, and N. Chopra, "Genital Tb-Diagnostic Algorithm and Treatment," *Indian Journal of Tuberculosis* 67 (2020): S111–S118, https://doi.org/10.1016/j.ijtb.2020.10.005.

17. C. Reis-de-Carvalho, J. Monteiro, and C. Calhaz-Jorge, "Genital Tuberculosis Role in Female Infertility in Portugal," *Archives of Gynecology and Obstetrics* 304 (2021): 809–814, https://doi.org/10.1007/s00404-020-05956-x.

18. P. Mijiti, L. Yuehua, X. Feng, et al., "Prevalence of Pulmonary Tuberculosis in Western China in 2010–11: A Population-Based, Cross-Sectional Survey," *Lancet Global Health* 4 (2016): e485–e494, https://doi.org/10.1016/S2214-109X(16)30074-2.

19. S. Sobhy, Z. Babiker, J. Zamora, K. Khan, and H. Kunst, "Maternal and Perinatal Mortality and Morbidity Associated With Tuberculosis During Pregnancy and the Postpartum Period: A Systematic Review and Meta-Analysis," *BJOG: An International Journal of Obstetrics & Gynaecology* 124 (2017): 727–733, https://doi.org/10.1111/1471-0528.14408.

20. K. Wang, D. Ren, Z. Qiu, and W. Li, "Clinical Analysis of Pregnancy Complicated With Miliary Tuberculosis," *Annals of Medicine* 54 (2022): 71–79, https://doi.org/10.1080/07853890.2021.2018485.

21. J. B. Sharma, A. Kriplani, E. Sharma, et al., "Multi Drug Resistant Female Genital Tuberculosis: A Preliminary Report," *European Journal of Obstetrics & Gynecology and Reproductive Biology* 210 (2017): 108–115, https://doi.org/10.1016/j.ejogrb.2016.12.009.

22. S. Liu, L. Shi, T. Wang, and J. Shi, "Effect of Low-Dose Dexamethasone on Patients With Elevated Early Follicular Phase Progesterone Level and Pregnancy Outcomes in IVF-ET Treatment: A Randomized Controlled Clinical Trial," *Clinical Endocrinology* 89 (2018): 771–778, https://doi.org/10.1111/cen.13824.

23. Z. Shi and Y. Sun, "Case Report: Multiple Brain Tuberculomas After In Vitro Fertilization, Embryo Transfer, and Abortion," *Frontiers in Neurology* 13 (2022): 971373, https://doi.org/10.3389/fneur.2022.971373.

24. G. Zhuang, L. Yang, L. Qu, W. Liu, and H. Zhu, "Congenital Tuberculosis in a Neonate Following In Vitro Fertilization-Embryo Transfer: A Case Report," *Frontiers in Pediatrics* 10 (2022): 985707, https://doi.org/10.3389/fped.2022.985707.

25. X. Gai, H. Chi, L. Zeng, et al., "Impact of Positive Interferon-Gamma Release Assay on IVF-ET Pregnancy Outcomes in Infertile Patients With Untreated Prior Tuberculosis: A Prospective Cohort Study," *Frontiers in Medicine* 8 (2021): 749410, https://doi.org/10.3389/fmed.2021.749410.

26. F. Ghaffari, S. Miralaie, Z. Chekini, and M. Faridi, "Pregnancy After Frozen Embryo Transfer in Mycobacterium Tuberculous Salpingitis: A Case Report and Literature Review," *International Journal of Reproductive Biomedicine* 18 (2020): 471–476, https://doi.org/10.18502/ijrm.v13i6.7288.

27. World Health Organization. Global Tuberculosis Report 2021, https://apps.who.int/iris/handle/10665/346387; 2021.

28. Q. Miao, Y. Ma, Q. Wang, et al., "Microbiological Diagnostic Performance of Metagenomic Next-Generation Sequencing When Applied to Clinical Practice," *Clinical Infectious Diseases* 67, no. S2 (2018): S231–S240, https://doi.org/10.1093/cid/ciy693.

29. X. Liu, Y. Chen, H. Ouyang, et al., "Tuberculosis Diagnosis by Metagenomic Next-Generation Sequencing on Bronchoalveolar Lavage Fluid: A Cross-Sectional Analysis," *International Journal of Infectious Diseases* 104 (2021): 50–57, https://doi.org/10.1016/j.ijid.2020.12.063.

30. N. Malhotra, U. B. Singh, V. Iyer, P. Gupta, and N. Chandhiok, "Role of Laparoscopy in the Diagnosis of Genital Tb in Infertile Females in the Era of Molecular Tests," *Journal of Minimally Invasive Gynecology* 27 (2020): 1538–1544, https://doi.org/10.1016/j.jmig.2020.01.005.

31. M. Cheng, T. Yuan, and Y. Liu, "A Woman With Disseminated Tuberculosis Experienced Preterm Delivery, Fallopian Tube Pregnancy, and Delivered Successfully Following In Vitro Fertilization: A Case Report," *BMC Pregnancy and Childbirth* 21 (2021): 27, https://doi.org/10.1186/s12884-020-03487-6.

32. A. Matsuda, N. Nishizaki, H. Abe, et al., "An Infant of 26 Weeks Gestation With Congenital Miliary Tuberculosis Complicated by Chronic Lung Disease Requiring Cpap was Diagnosed on Day 104 of Life: Congenital Tuberculosis was Confirmed by Detection of Calcified Ovaries in his Mother," *Paediatrics and International Child Health* 42 (2022): 72–77, https://doi.org/10.1080/20469047.2022.2076030.