

Emerging progress on diagnosis and treatment of female genital tuberculosis

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Abstract

Female genital tuberculosis (FGTB) is an infection caused by *Mycobacterium tuberculosis* and usually occurs secondary to pulmonary tuberculosis (TB) through the blood circulation, lymph circulation, or direct spreading from abdominal TB. FGTB is an uncommon type of TB that can destroy genital organs, and lead to menstrual disorders and infertility. The diagnosis of FGTB is often made by detection of acid-fast bacilli under microscopy, culture with endometrial biopsy, or histopathological examination of epithelioid granuloma on a biopsy. A multidrug anti-TB regimen is the major management of FGTB, including rifampicin, isoniazid, pyrazinamide, and ethambutol, while surgery is proposed in more deteriorated cases. However, the conception rate in infertile women with FGTB is still low, even after multidrug anti-TB therapy. Additionally, the risk of complications, such as ectopic pregnancy or miscarriage, remains high. In this review, we summarize the characteristics of FGTB, present current epidemiological data, and focus on its early diagnosis and effective management.

Keywords

Female genital tuberculosis, infertility, reproduction, multidrug resistance, epithelioid granuloma, endometrial biopsy

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Introduction

Tuberculosis (TB) remains a major public health problem worldwide. Although TB has shown a declining trend in mortality during past years owing to advanced diagnosis and treatment, more than 10 million

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people develop active TB each year with 1.33 million deaths.¹ Approximately one quarter of women who die from TB are found to be co-infected with human immunodeficiency virus (HIV).² Female genital tuberculosis (FGTB) is a major etiological factor for infertility, especially in regions with a high prevalence of TB. The main consequences following FGTB infection include infertility, menstrual disorder, and chronic pelvic inflammation,³ which may be prevented by timely diagnosis and effective treatment. More novel and convenient diagnostic tools for detection of TB are becoming increasingly available, such as bacterial cultures and polymerase chain reaction (PCR)-based diagnostics.⁴ However, suspicion of TB by clinicians remains the most important tool for diagnosis. We review the current progress on epidemiology, clinical presentations, diagnosis, and treatment of FGTB.

Epidemiology

Human tubercle bacillus is the most common causative organism for TB and it is spread predominantly via the air. People with active pulmonary TB can release infectious aerosol droplets, with a diameter ranging from 0.5 to 5 μm , via coughing, sneezing, spitting, or even speaking. A single sneeze releases up to 40,000 droplets. Statistical data have shown that one third of the world's population has been infected with *Mycobacterium tuberculosis*, and of concern, new infections occur at a rate of one per second.⁵ The incidence rate of TB is highest in countries or areas that usually have a poor economic environment and low gross domestic products, such as Africa, Latin America, and Asia. The majority of new TB cases worldwide are reported in developing countries according to a survey by the World Health Organization.^{1,5}

FGTB is a common form of extra-pulmonary TB and responsible for 27% of

cases of extra-pulmonary TB. However, FGTB is often underestimated because most patients are asymptomatic and are only diagnosed during evaluation for infertility.⁶ Additionally, underreporting of cases, vague symptomatology, and a lack of reliable diagnostics with high sensitivity have led to an undefined incidence rate of FGTB.⁷

Pathogenesis

FGTB can be hematogenously transmitted from the lungs or by the lymphatic circulation or adjacent organs, such as the bowels or lymph nodes. FGTB can also spread sexually through male semen with active TB.⁸ Studies have shown that people with low immunity, malnutrition, diabetes, excessive smoking, alcohol/drug abuse, renal hemodialysis, or HIV infection are susceptible populations for TB.⁸ FGTB usually occurs secondary to pulmonary TB or extra-pulmonary TB, which includes the gastrointestinal tract, kidney, skeletal system, and meningeal TB. Primary FGTB occurs in women whose male partners have active genitourinary TB, such as tuberculosis epididymitis, and transmits through infected semen.⁹ FGTB can also directly spread from nearby abdominal organs, such as the intestines or abdominal lymph nodes.^{6,7} Patients with fallopian tube TB account for 90% of the total FGTB cases, and show congestion, tubercles, hydrosalpinx, pyosalpinx and tubo-ovarian masses.¹⁰ Patients with endometrial TB account for 50% of the total FGTB cases, and show intrauterine adhesion, caseation, and ulceration.¹⁰ Patients with ovarian TB account for 10% of the total FGTB cases and show tubo-ovarian masses.¹¹ Patients with cervical TB account for 5% to 15% of the total FGTB cases and show granulomatous lesions.¹² Vaginal and vulval TB cases are rare and only account for 1% to 2% of the total FGTB cases, and often have hypertrophic lesions or a non-healing ulcer.^{13,14} Notably,

FGTB is rarely associated with other gynecological pathologies, such as ovarian cancer, genital prolapse, or a fibroid uterus.

Diagnosis

Tubercle bacilli was discovered in 1882 and isolation of bacilli in samples of urine and sputum in 1883 greatly contributed to the diagnosis and management of TB.¹⁵ Easily diagnosing *M. tuberculosis* in all cases is not possible owing to the paucibacillary nature of FGTB. Physicians should be aware of TB in women with chronic pelvic inflammatory disease, chronic vaginal discharge, or long-term infertility.⁸ Various approaches have been used to diagnose FGTB, such as family history tracing, a gynecological examination, and a general physical examination for evidence of any lymph node, skeletal, pulmonary, or abdominal TB.^{16,17} Additionally, a history of HIV positivity is also important for diagnosing FGTB.²

There are still many diagnostic problems, although various techniques have been well developed in diagnosis of FGTB, which requires extensive clinical examinations with sensitive observation and systematic investigations.¹⁸ An example of this situation is that the possibility of FGTB should be taken into consideration in women who suffer from undetermined infertility or chronic pelvic inflammatory disease and who do not respond to regular antibiotic treatment.¹⁹ The main risk factors leading to FGTB are close exposure to patients with pulmonary TB, medical history of TB infection, travel to an epidemic high-risk area, and HIV infection.² Currently, there is still no single diagnostic test that can be used to verify the diagnosis of FGTB. Therefore, integrated analysis of clinical suspicion, exhaustive history taking, a comprehensive physical examination, *M. tuberculosis* tests, and various visible imaging methodologies are imperative for diagnosing FGTB.²⁰

To decrease the morbidity and mortality induced by TB, rapid and accurate diagnosis is urgently required.²¹ Therefore, a sensitive and specific method for diagnosing FGTB using biopsies from female genital organs would be helpful to detect this disease. PCR has been used as a novel strategy for diagnosing using body fluids or biopsies.²² Compared with the conventional method, primers used for PCR and the source of biopsies are used to determine the sensitivity and specificity.²³ Notably, PCR as a stand-alone diagnostic test for endometrial TB is not appropriate for confirming diagnosis and initiating anti-tuberculosis treatment. Addition of laparoscopy and hysteroscopy can significantly improve the diagnostic yield for FGTB.²⁴ Another automated nucleic acid amplification test, GeneXpert MTB/RIF (Cepheid, Sunnyvale, CA, USA), has been approved for detecting TB, especially in regions with high rates of TB-HIV co-infection or multidrug-resistant TB. This is because of its rapidity, sensitivity, and specificity as described by the World Health Organization in 2020.²⁵ For the diagnosis of FGTB, GeneXpert appears to be highly specific, but less sensitive. Therefore, GeneXpert might be useful for ruling out FGTB. However, when this test is negative, it is not a proper test to rule out FGTB.²⁶

These findings suggest that patients who are suspected of having FGTB with unknown infertility, abnormal discharge, menstrual dysfunction, chronic pelvic pain, or a family/past TB history should be carefully diagnosed using various diagnostic tests (Table 1). Tissue from the endometrium in the premenstrual phase should be sampled and used.²⁷

Treatment

Patients with FGTB receive similar medical therapy to patients with pulmonary TB. This treatment is a four-drug regimen for

Table 1. Various tests used to diagnose FG TB.

Tests used to diagnose FG TB	Results/symptoms	Diagnosis	Treatment
Acid-fast bacilli test			
Microscopy	(+)	FGTB	Anti-TB
Culture	(+)	FGTB	Anti-TB
Cartridge-based nucleic acid amplification test	(+)	FGTB	Anti-TB
GeneXpert	(+)	FGTB	Anti-TB
Histopathology examination	Epithelioid granuloma	FGTB	Anti-TB
PCR-positive, suspicion from a history of TB, or symptoms			
Laparoscopy	(+)	FGTB	Anti-TB
	Undefined	Suspected FG TB	Anti-TB
	(-)	No FG TB	No
Radiology	Adnexal mass	Suspected FG TB	Anti-TB
PCR-negative and all other tests are negative	(-)	No FG TB	No

FGTB, female genital tuberculosis; TB, tuberculosis; PCR, polymerase chain reaction.

6 months as follows: initial 2-month treatment of daily rifampin, isoniazid, pyrazinamide, and ethambutol, followed by 4-month treatment of daily isoniazid, rifampin, and ethambutol.^{25,27} Generally, bacilli in urine can be barely detected after the 2-week above-mentioned treatment. When this first-line treatment fails, (e.g., in patients with HIV co-infection or multidrug-resistant TB), a second-line treatment is adopted. Patients with HIV co-infection are recommended to have a minimum 9-month standard regimen to decrease the risk of relapse.¹ Patients with multidrug-resistant TB require additional antibiotic treatment and the regimen is as follows: initial 6 to 9-month treatment of daily kanamycin, levofloxacin, ethionamide, cycloserine, pyrazinamide, and ethambutol, followed by 18-month treatment of daily levofloxacin, ethionamide, cycloserine, and ethambutol.⁵ Additionally, patients with FG TB should be carefully monitored for any abnormal liver function during the whole medical therapy because long-term use of the four-drug regimen might lead to side effects, such as serious hepatotoxicity.²⁸ Moreover, frequent drug

replacement or irregular drug intake can cause multidrug-resistant TB or recurrence.²⁹

Surgical treatment was adopted before wide clinical use of chemotherapeutic drugs.⁶ Currently, clinical application of surgical treatment is limited, except in patients with a persistent pelvic mass, recurrent pelvic pain, or excessive bleeding.³⁰ In patients with multidrug-resistant TB and pyosalpinx, tubercles, or a tubo-ovarian mass, surgery is suggested, including removal of the ovaries, uterus, and/or fallopian tubes. However, the consequent complications make surgical treatment of TB patients risky and difficult.^{31,32} An example of these problems is that patients with FG TB show severe complications, including increased excessive bleeding, bladder injury, and peritonitis during a laparoscopic operation. Patients with FG TB who receive vaginal hysterectomy show excessive bleeding, bowel injury, and a high fever post-operation. However, confined surgery for the purpose of drainage of a persistent pelvic or tubo-ovarian abscess besides medical treatment could be performed as suggested by the American Thoracic Society.³⁰

FGTB and infertility

The fallopian tubes are affected in almost all FGTB cases, while an impaired endometrium has been found in half of FGTB cases.³³ Infertile women with genital TB account for a large number of the total infertile women worldwide and there is an exceedingly uneven regional distribution (e.g., <1% in the US vs. 18% in India).⁵ In contrast, the incidence rate of infertility in FGTB cases ranges from 10% to 85%.³⁴ To date, hysterosalpingography and hysteroscopy are the two most important tools to assess anatomical abnormalities of the genital tract in infertile women with suspected FGTB.^{16,35} Chavan et al.³⁶ comprehensively described the features observed under hysterosalpingography in patients with FGTB and infertility.

FGTB can induce salpingo-peritonitis, which causes adhesions and tubo-ovarian mass formation, and hydrosalpinx with or without obstruction. This leads to unilateral or bilateral tubal blockage and loss of tubal function, further affecting fertilization and embryonic implantation.^{33,37} FGTB can also cause defective ovarian function.³⁸ Patients with FGTB usually have an endocrine disorder, chronic anovulation, oocyte defect, poor quality of embryos, lower progesterone secretion, implantation failure, a lower pregnancy rate, and a higher abortion rate. Additionally, FGTB damages endometrial receptivity, and promotes endometrial vascularization, atrophy, and synechiae.³⁵

Patients with FGTB who receive comprehensive treatment still suffer from an extremely low rate of pregnancy, as shown in a study with a 19.2% conception rate and a 7.2% birth rate.³⁹ Therefore, assisted reproductive technology (ART), such as *in vitro* fertilization and embryo transfer, remains the best choice for treating female infertility associated with tubal tuberculosis.⁴⁰ However, patients with endometrial TB show significantly reduced fertilization,

implantation, and cumulative pregnancies.⁴⁰ A study reported the success rate of ART, in which the conception rate varied from 9% to 28%, and only <30% of the conceptions were normally delivered.³⁵ Furthermore, the rate of ectopic pregnancy was up to 10%, which indicated poor results even with ART.³⁵ ART results are even worse in patients with FGTB and synechiae of the uterine cavity. Even latent FGTB has been shown to be a main cause of repeat *in vitro* fertilization failure due to poor implantation.³³

Prevention

Reducing exposure to *M. tuberculosis* is the primary strategy to prevent TB.⁴¹ Patients with pulmonary TB should perform respiratory hygiene at home and in public areas and receive formal treatment. For genital TB, safe and healthy sexual activities can reduce the risk of acquiring genital TB infection. Additionally, Bacille Calmette–Guérin vaccination has been adopted as a preventive step, especially in high-prevalence areas of TB, such as India. Although Bacille Calmette–Guérin immunization shows positive effects in preventing progress of serious TB, its protective response is widely distinct among the population.⁴²

Conclusion and future prospects

TB is a major factor that induces female reproductive and genital morbidity.^{5,7,29} Of concern, the amount of the population from endemic areas of TB who are immigrating into developed countries is increasing. TB, especially genital TB, remains silent and undetectable in most patients. A TB test in high prevalence regions usually lacks sufficient specificity and sensitivity, with 80% and 55%, respectively. Therefore, alternative methods with advanced specificity and sensitivity are imminently required. Additionally, the

incidence rate of genital TB has risen during recent years, which is partially attributed to an HIV pandemic.^{2,37} Therefore, a high suspicion of tuberculosis in female patients with an abnormal genital appearance should be taken into consideration, especially those women from areas that are prevalent for both HIV and TB.

In recent years, development of new drugs has been carried out. To resist *M. tuberculosis* and reduce the treatment span, the World Health Organization has suggested bedaquiline and delamanid as an injection-free regimen for all types of TB, including multidrug-resistant TB. Additionally, the World Health Organization has recommended terminating clinical application of the category-II regimen. Generally, the 2HRZE/4HRE regimen (daily therapy of rifampicin, isoniazid, pyrazinamide, and ethambutol for 2 months followed by daily therapy of rifampicin, isoniazid, and ethambutol for 4 months) is provided to rifampicin- or isoniazid-sensitive patients with TB.³⁵ The 6LfxRZE regimen (daily use of levofloxacin, rifampicin, pyrazinamide, and ethambutol for 6 months) is applied to isoniazid-resistant patients. Bedaquiline, levofloxacin (or moxifloxacin), linezolid, cycloserine, and clofazimine are proposed for patients with multidrug resistance or extensive drug resistance.⁴³ With advancement of novel biotechniques, such as stem cell transplantation and nanomaterials, regenerative ovaries, the fallopian tubes, or the endometrium have been tested to treat permanent injuries.

Declaration of conflicting interest

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