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Review Article

A Review of Literature on Female Genital Tuberculosis

Salma Yonus Alkhyrallah[1], Maathir Fahad Al-Harbi[1], Majd Abdulrahman Almuqati[1], Samah Himayda[2] and Rawabi Qadhi[3,4,5]*

[1]*Medical Student, Faculty of Medicine, Umm Al-Qura University, Makkah, Saudi Arabia*

[2]*Department of Gynaecology and Obstetrics, Faculty of Medicine, Umm Al-Qura University, Makkah, Saudi Arabia*

[3]*Department of Pharmacology and Toxicology, Faculty of Medicine, Umm Al-Qura University, Makkah, Saudi Arabia*

[4]*Saudi Toxicology Society, Makkah, Saudi Arabia*

[5]*King Abdullah Medical City in Holy Capital (KAMC) Research Center, Makkah, Saudi Arabia*

***Corresponding Author:** Rawabi Qadhi, Department of Pharmacology and Toxicology, Faculty of Medicine, Umm Al-Qura University, Makkah, Saudi Arabia.

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Abstract

In 2015 about 10.4 million people developed tuberculosis (TB) and caused nearly 500,000 women deaths. The tubercle bacillus causes tuberculous infection. When it invades the body, genital tract infection can occur secondary to tuberculosis in another site (primarily, the lungs). TB infection of the women genital organs can result in infertility, dyspareunia, menstrual irregularities and chronic pelvic inflammatory disease. 20 - 30% of patients are affected by adhesions, caseation, adnexal cyst, or mass formation. However, 11% of women are asymptomatic. Several tools are used to diagnose tuberculosis, such as histological examination, and the gold standard for diagnosis is the isolation of the causative organism from the biopsy. Although laparoscopy has little diagnostic value, it was done in some cases, especially to differentiate between pelvic tuberculosis and Female Genital Tuberculosis. This happens in cases where a biopsy is not done. However, laparoscopy helped visualize pelvic organs and exclude other causes. There have been new diagnostic tools such as ELISA and PCR that may help in the earlier detection of tuberculosis. PCR is a good tool for detecting organisms. Recently, a multiplex real-time PCR assay was developed to detect over 20 mycobacterial species, the most efficient diagnostic tool for uterine tuberculosis. This review aims to evaluate the efficacy of PCR technique, culture, and histopathological examination in diagnosing Genital Tuberculosis in female infertility through an electronic literature search for relevant studies identified using keywords on the MEDLINE database. Multiple drug therapy is the mainstay in treating tuberculosis, including Female Genital Tuberculosis, and surgery may be required in advanced cases.

Keywords: *Genital Tract Infection; Asherman's Syndrome; Hysteroscopy; Infertility; Tuberculosis; PCR*

Abbreviations

AFB: Acid Fast Bacillus; AIDS: Acquired Immunodeficiency Syndrome; ATT: Anti-TB Treatment; CBC: Complete Blood Count; ELISA: Enzyme-Linked Immunosorbent Assay; ESR: Erythrocyte Sedimentation Rate; FGTB: Female Genital Tuberculosis; HIV: Human Immunodeficiency Virus; HPE: Histopathological Examination; HSG: Hysterosalpingography; PCR: Polymerase Chain Reaction; PID: Pelvic Inflammatory Disease; TB: Tuberculosis; USG: Ultrasonography

Introduction

Tuberculosis (TB) as a result of effective diagnosis and treatment, the number of deaths among TB patients is not as common as before in spite of the fact that it is a widely spread disease. Over 10 million people had TB in 2015, and 60% were from South East Asia and Western Pacific Regions. About 60 percent of TB cases and deaths occur among males, but the disease burden is high among women also [1].

In 2015 nearly 500,000 women died from TB, and among them, 28 percent had human immunodeficiency virus (HIV) co-infection. Genital TB in females is well recognized as an important etiological factor for infertility in countries with a high prevalence of TB. Genital TB usually occurs secondary to TB in other sites (primarily, the lungs). The spread is generally through hematogenous or lymphatic routes [1].

TB infection of the female genital organs can leads to infertility, dyspareunia, menstrual irregularities, and chronic pelvic inflammatory disease (PID). Drug therapy for female genital TB (FGTB) is similar to the standard treatment regimens used for pulmonary TB. In patients with infertility, the conception rate is not very encouraging after anti-TB treatment (ATT). Here we review the epidemiology, clinical presentations, recent advances in diagnosis and treatment of FGTB [2].

Aim of the Study

This study aims to check how useful multiplex PCR (m-PCR) is in detecting uterine TB in women with infertility.

Materials and Methods

This review was performed through an electronic literature search for relevant studies identified using keywords on the MEDLINE database, inclusive: Genital tract infection, Asherman's Syndrome, hysteroscopy, infertility, Tuberculosis, PCR. Similar keywords were used to peruse and identify relevant articles on Google Scholar. The articles were chosen based on defined inclusion criteria.

Results and Discussion

Clinical presentation of female genital tract tuberculosis

The causative organism of TB is tubercle bacillus. When body is invaded by this organism, genital tuberculosis is one of the manifestations and they are usually secondary to another primary site of infection. The most common site is the lungs [3]. Women with genital TB usually have several symptoms besides sterility. However, pelvic organs tend to be normal during clinical examination [3]. Female patients with genital TB present with a wide range of symptoms depending on the site of involvement.

Interestingly, there is 11% of asymptomatic women. Infertility is the major concern in genital TB. Endometrium is involved in 50 - 80% of cases with caseation and ulceration causing intrauterine adhesions (Asherman's syndrome) [2]. Signs and symptoms of female genital TB are summarized in table 1 [1,2].

Symptoms	Signs
No symptoms (11%)	No sign (10%)
General systemic symptoms	Raised temperature
Pyrexia	Lymphadenopathy
Anorexia	Crackles on chest auscultation (PTB)
Weight loss Feeling unwell, Malaise	Vague or definite abdominal or pelvic lump

Menstrual irregularity	Ascites
Puberty menorrhagia Heavy menstrual bleeding (in early stage)	Doughy feel of abdomen
(Primary and secondary) Dysmenorrhea	Soft tender enlarged uterus (pyometra) Tenderness and induration in the fornices
Infertility (primary and secondary)	Lump in adnexa
Abdominal or pelvic mass	Fullness and tenderness in the pouch of Douglas
Abdominal and pelvic pain Acute abdomen	Douglas ulcers or growth
Vaginal discharge	Ulcers on external genitalia Genital fistula
Urinary incontinence or feacal incontinence	

Table 1: *Symptoms and signs in female genital tuberculosis.*

Diagnosis and lab work

Clinical professionals should suspect TB in their differential diagnosis of any pelvic mass. This is crucial, especially in countries with a high prevalence of TB [4]. Some criteria are necessary to diagnose primary genital TB; these criteria are (1) the genital infection should be the primary in the body and (2) the same stage should present in the regional lymph nodes as the genital organs. Auerbach stated that no such cases were ever described in the literature [5].

There are several tools for diagnosis. For example, histological examination is used to diagnose cervical and vulvovaginal TB. This occurs through biopsy specimens. The gold standard for diagnosis is isolating the causative organism from the biopsy. However, the presence of typical granulomata is enough to make the diagnosis. Because at some stages, the culture no longer benefits as in the third stage. Furthermore, acid-fast bacilli stain might be unyielding.

New diagnostic tools, for example, enzyme-linked immunosorbent assay (ELISA) and polymerase chain reaction (PCR), have an essential role in the earlier detection of TB. In addition, simultaneous HIV testing should be performed, especially in regions with a high prevalence of HIV. Moreover, health professionals should have a higher index of suspicion of genital TB in areas where HIV and TB are common [5,6].

It is known that infertility is a consequence of female genital TB. So, for pregnancy to occur, female genital TB must be detected in an early stage. This is significant in preventing permanent, irreversible anatomical pathology resulting in sterility. In addition, this is very important to begin treatment immediately [7]. PCR is a good tool for detecting organisms, and recently a multiplex real-time PCR assay was developed to detect more than 20 mycobacterial species [8].

In a prospective study, endometrial curetting was inspected among 620 females with infertility. The authors used laparoscopy, hysteroscopy, histopathology, smear microscopy, mycobacterial culture in BACTEC MGIT 690, and in-house m-PCR. BCTEC MGIT 960 is an instrument that is a fully automated system that exploits the fluorescence of an oxygen sensor to determine the growth of mycobacteria in culture. The mean age of involved women was 29.75 ± 4.66 years. Most of them looked for medical care due to infertility (n = 596).

Among them, 455 (76.34%) presented with primary infertility, and the rest with secondary infertility. Among the study sample, 158 (25.48%) were diagnosed with uterine TB using at least one diagnostic method. Laparoscopy was positive in 46 (29.11%), hysteroscopy in 77 (48.73%), histopathology in 8 cases only (5.06%), acid bacilli smear in 4 cases (2.53%), and liquid culture in 24 (15.18%) women. It was positive among patients who underwent in-house m-PCR in 135 (85.44). Among them, 129 (95.55%) samples were positive for mycobacterium TB; on the other hand, 6 (4.44%) were positive for non-tuberculous mycobacterial DNA. Among the previous sample, 112 women received anti-TB treatment, and 23 succeeded in getting pregnant after completion of the treatment. It was concluded that m-PCR is the most efficient diagnostic tool for uterine TB than other methods [9].

On the other hand, laparoscopy and hysteroscopy are the most accurate tools to diagnose genital TB. This is very useful for tubal, ovarian, and peritoneal diseases. In addition, the test can be combined with hysteroscopy. Those two imaging techniques for diagnosing FGTB are hysterosalpingography (HSG) and ultrasonography (USG). HSG is used to evaluate the internal structure of the female genital tract, while USG allows simultaneous ovarian and uterine evaluation [10].

Complications

Genital TB spreads to the uterus and endometrium through the hematogenic route, lymphatic or infectious in about 50 - 80% of patients. There are no visible lesions at the beginning; nevertheless, ulcers are found later, and in advanced stages, uterine dysfunction occurs due to synechiae. Lesions occur in several forms, such as multiple ulcers, necrosis, or hemorrhagic, and endometrium damage. Asherman's syndrome progresses as secondary amenorrhea and infertility. Patients are also affected with adhesions, caseation, adnexal cyst, or mass formation. This occurs in about 20 - 30% of women. In advanced cases, ovaries are impaired and reserve, which often leads to ovarian destruction. In addition, acute abdominal pain could present a tubo-ovarian cyst that resembles appendicitis or abscess [2].

The pelvic and abdominal peritoneum may have many tubercles, ascites, and masses that look like ovarian cancer. In 5% of cases, the cervix can be implicated, secondary to tubal or endometrial TB. But this can rarely be the primary disease transmitted by a partner or infected semen [2]. Vaginal and vulva involvement is uncommon and extends from the cervix or endometrium. Sometimes they are predominant due to transmission by a partner or infected semen. Biopsy and histopathology could be required in cases of hypertrophic ulcer or granuloma development in the vulva or vagina [2].

However, a rare complication of pelvic inflammatory disease is Fitz-Hugh-Curtis syndrome, which develops acute perihepatitis [8].

Pathogenesis

As we mentioned before that genital TB is secondary to another primary site in the body which is most common in the lungs. However, it could be renal, gastrointestinal, bone, or joint source. It is usually a part of a generalized miliary disease process. There is a lifelong reactivation risk if eradication is not complete of bacilli. This is common in conjunction with diseases or drugs that lower T-cell immunity, such as Hodgkin's lymphoma and Acquired immunodeficiency syndrome (AIDS). The spread to genital organs occurs in the lymphatic or hematogenous through direct contiguity with an intraabdominal or peritoneal source. This focus source in the lung usually heals, and the lesion may become dormant in the genital tract for years to be activated later [5].

It is claimed by several pathologists that there is no primary infection in female genital organs. Also, TB foci may present in the body for years without detection. This, in turn, spreads to genital lesions and heal without leaving any trace evidence on clinical examination [5].

As mentioned earlier that the causative organism is *Mycobacterium tuberculosis*. On microscopic examination, typical caseation epithelioid granulomas might not appear as well as epithelioid cells and specialized giant Langerhans cells. This is due to the shedding of the endometrium during menstruation [5].

TB of the uterine cervix may appear as papillary or vegetative growth with or without ulceration which resembles invasive cervical cancer. Moreover, suppuration and ulceration may affect inguinal lymph nodes [11].

Risk factors

Risk factors for genital TB include poverty, overcrowding, low health care services, diabetes, illicit drug use, poor ventilation, and many diseases as kidney disease and HIV. Genital TB is a consequence of lung infection or any other organ, usually by lymphatic or hematogenous spread. However, it sometimes occurs through adjacent organ spread such as bowel or lymph node. Also, it can be transmitted during sex from an active genitourinary TB partner or infected semen [5].

Genital TB is very high in low-income countries. Especially with the rise of HIV infections which are associated with genital TB. About 9% of all extrapulmonary TB cases occur in the genital tract as genital tract TB [11].

Role of endoscopy in FGTB

In some cases, direct hysteroscopy of the uterine cavity reveals a normal cavity, especially in the early stages with bilateral tubal Ostia. However, when findings are there, the endometrium is pale, and the cavity is obliterated either entirely or partially. This is due to adhesions of varying grades that often involve the ostia. The cavity is sometimes shrunken. In a study that used hysteroscopy for genital TB, it was observed that there is increase in complications of the procedure as severe bleeding, perforation and flare-up of genital TB. Nevertheless, hysteroscopy in patients with genital TB should be performed by an experienced clinician under supervision. This is necessary to avoid incorrect passage formation and injury to pelvic organs [1].

Patients usually undergo laboratory tests of complete blood count (CBC), erythrocyte sedimentation rate (ESR), Mantoux test, chest x-ray for the presence of TB, baseline abdominal ultrasound, and examination of pelvic organs. In addition, laparoscopy reveals the conditions of fallopian tubes, tubal patency, ovaries, and any masses. HSG was performed for cases of TB having infertility and for cases in which laparoscopy was challenging to perform [9].

During surgery, histological examination was done to investigate the presence of TB granulomatous lesions. Specimens were obtained using biopsy during laparotomy or curettage. After the biopsy, two samples are sent to the lab. The first one is preserved in 10% formalin for histopathologic analysis and the second in normal saline for culture [9].

Although laparoscopy has little diagnostic value, it was done in some cases significantly to differentiate between pelvic TB and FGTB. This occurs in cases where a biopsy is not done. In addition, however, laparoscopy was helpful to visualize pelvic organs and exclude other causes [12].

In another study, laparoscopy was suggestive in 59.7% of cases, acid-fast bacillus (AFB) smear was positive in 8.3%, culture was positive in 5.6%. AFB smear is a microscopic examination of a person's sputum or other stained specimens to detect acid-fast bacteria. It is a rapid test that provides presumptive results within one to two days. It is valuable in helping to make decisions about treatment while waiting for cultural results. Histopathological examination (HPE) was positive in 6.9%, and PCR was positive in 36.7%. FGTB was suspected in 28 cases of 49 total based on diagnostic criteria. The sensitivity of PCR, HPE, and culture were 57.1%, 10.7%, and 7.14%, respectively. Culture and HPE showed mild agreement with diagnostic criteria using Kappa measurement analysis. On the other hand, PCR showed moderate agreement. There were two false-positive cases by PCR, and they were ruled out. The PCR results were negative in 12 cases of 28 cases. PCR using TCR4 primers had higher sensitivity than IS6110 primers (46.4% against 25%) in clinically detecting suspected FGTP [10].

Treatment

The mainstay in treating TB is a multiple drug therapy in adequate doses and for sufficient duration. For example, in the olden days before rifampicin, the anti-tuberculous therapy (ATT) was given for patients with FGTB for 18 - 24 months with significant side effects and poor compliance. On the other hand, short-course chemotherapy for 6 - 9 months is effective for the medical treatment of FGTB [13].

American Thoracic Society [14] and British Thoracic Society and NICE (National Institute of Clinical Excellence) Guidelines (2006) [15] suggest that the first best treatment should be the 'standard recommended regimen' using a per-day dosing schedule using combination tablets and does not consider DOTS (Directly Observed Treatments) necessary in the management of most cases of TB in low-income countries who can comply with treatment. WHO favored DOTS to prevent MDR (Multi-Drug Resistance) and for better treatment. Recently, WHO has removed category three and recommended daily therapy of rifampicin (R), isoniazid (H), pyrazinamide (Z), and ethambutol (E) for two months followed by daily four-month therapy of rifampicin (R) and isoniazid (H). Alternatively, two months intensive phase of RHZE can be daily followed by an alternate-day combination phase (RH) of four months. 3 weekly dosing throughout therapy (2RHZE, 4HR) can be given as DOTS. Every dose should be directly observed, and the patient should not be a HIV positive or living in an HIV prevalent setting [16].

Conclusion

Genital tuberculosis (GTB) is one of the major causes of severe tubal disease leading to infertility. Unlike pulmonary tuberculosis, the clinical diagnosis of GTB is difficult because, in most cases, the disease is either asymptomatic or has varied clinical presentation. Therefore, routine laboratory values are not so effective in the diagnosis. A definite diagnosis cannot be made from characteristic features in hysterosalpingogram (HSG) or laparoscopy. Because of the paucibacillary nature of GTB, diagnosis by mycobacterial culture and histopathological examination (HPE) has limitations and a low detection rate. This study aimed to evaluate the efficacy of PCR technique, culture, and histopathological examination in diagnosing GTB in female infertility.

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Conflict of Interest

Authors have no conflict of interest to declare.

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