THE EUROPEAN SOCIETY OF MEDICINE
Medical Research Archives, Volume 12 Issue 7

REVIEW ARTICLE

CHALLENGES IN THE DIAGNOSIS OF FEMALE GENITAL TUBERCULOSIS

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OPEN ACCESS

PUBLISHED
31 July 2024

CITATION
Thangappah, RBP, 2024. Challenges in the diagnosis of female genital tuberculosis. Medical Research Archives, [online] 12(7). https://doi.org/10.18103/mra.v12i7.5469

DOI
https://doi.org/10.18103/mra.v12i7.5469

ISSN
2375-1924

ABSTRACT

Genital tuberculosis (GTB) is a difficult disease to diagnose. It is nearly always secondary to primary elsewhere in the body and after spread to the genital tract it remains dormant in the latent foci to get reactivated at a later date. During periods of immunosuppression or around the time of puberty when the vascularity of the genital organs increases, the dormant bacilli get reactivated and the clinical features develop 10-15 years after the primary infection. In GTB, significant damage is seen in the fallopian tubes and the endometrium. Clinical diagnosis of GTB is difficult, because it is a disease of absent or few symptoms which are non-specific. A high degree of suspicion aided by intensive investigations is important in the diagnosis of the disease. Except when there are typical features such as tubercles/caseation, laparoscopic findings may be non-specific and the early disease can be easily missed when the infection is still confined to the mucosa. Conventional methods of diagnosis such as HPE, AFB smear and culture have low pick up rates. Molecular studies including GeneXpert show good specificity but, the sensitivity is poor to rule out the disease. As on now, there is no single investigation modality with good sensitivity and specificity available to diagnose GTB. These diagnostic difficulties are encountered both in low resource as well as and in high resource countries.

Keywords: Female genital tuberculosis, infertility, laparoscopy, Mycobacterium tuberculosis, culture, molecular studies.

Introduction

Tuberculosis (TB) is one of the oldest diseases which has been shown to be in existence since the time of human civilization[1]. Paleo pathologic studies in ancient humans show that tuberculosis was present in the ancient Africans 70,000 years ago[2]. Tuberculosis was recognized as a clinical entity as far back as 1000 BC, when Ruffer noted Potts' disease associated with a psoas abscess in the remains of an Egyptian priest of Ammon of the twenty – first dynasty[3]. The first reported case of genital tuberculosis (GTB) was described in 1744 by an Anatomist. When he did a post-mortem examination on a 20 year old woman, he found the uterus to be filled with caseous material[4]. By Polymerase Chain Reaction (PCR) analysis, Mycobacterial DNA has been detected in the genital areas of Andean Mummies dating back to A.D. 140-1200[5]. Though extensive research and developments have taken place in the diagnosis and management, TB still remains a major health problem, especially in the low resource countries. It is nearly three decades, since WHO declared tuberculosis as a global public health emergency and urged all countries to take effective measures to control tuberculosis [6]. In spite of tuberculosis being a preventable and a curable disease, according to the WHO Global tuberculosis report 2023, 10.6 million new tuberculosis cases were reported globally in 2022, and 1.3 million people died of tuberculosis [7]. Among these cases, more than two thirds of global TB cases were contributed by eight countries with India contributing for 27% of cases. Indonesia, China, Philippines, Pakistan, Nigeria, Bangladesh and the Democratic Republic of the Congo are the other countries which show the highest burden. Because of the high morbidity and mortality associated with tuberculosis, the United Nations Sustainable Development Goals (SDGs) has set a target to end the TB epidemic by 2030. It focusses on reducing the TB incidence rate (new and relapse cases per 100 000 population per year) by 80%, by the year 2030 [8].

Prevalence and Pathogenesis:

Tuberculosis occurs in two forms namely pulmonary and extra-pulmonary tuberculosis (EPTB). The occurrence of tuberculosis at sites other than the lung is defined as EPTB. In general population, 15-20% of all cases of tuberculosis are due to EPTB, whereas, among the HIV positive individuals, nearly 50% of all cases are EPTB[9,10]. EPTB is seen more often in children, young adults and in those with weak immune system. HIV, malnutrition, diabetes, old age and long term use of cortisone /chemotherapy are important risk factors for the occurrence of EPTB. Nearly 27% of EPTB are due to Genitourinary TB, with genital TB alone contributing to 9 per cent of all EPTB cases[11]. Genital tuberculosis (GTB) is shown to be significantly associated with infertility. Indian studies have shown that 20 – 35% of women attending the infertility clinics suffer from GTB (12,13). When tubal factor is the underlying cause for infertility, the incidence of GTB is as high as 40-50%[14,15,16].

GTB is nearly always secondary to primary elsewhere in the body. The clinical features develop 10-15 years after the primary infection, unless it is an acute miliary spread. The tuberculous bacilli reach the genital tract by haematogenous spread, through lymphatics or by direct spread from adjacent structures such as bowel. Rarely lower genital tract infection can occur secondary to sexual transmission manifesting with cervical and vaginal ulcers. After reaching the genital tract it may initiate active infection and present with features of acute pelvic inflammatory disease (PID). But, this manifestation is very rare. The most common presentation is, after spread to the genital tract it remains dormant in latent foci to get reactivated at a later date. Patients who are infected but who have no clinical, bacteriological, or radiographic evidence of active TB are said to have latent TB infection (LTBI).

During periods of immunosuppression or when there is increased vascularity of the genital organs during early adolescence or in the early reproductive years, more bacilli could reach the genital tract or

the dormant bacilli in the fallopian tubes can get reactivated. This explains why genital tuberculosis occurs more frequently in young women. These reactivated bacilli are capable of multiplying once every 15-20 hours[17]. It has been estimated that, among the individuals with latent tuberculosis the lifetime risk of progressing to active TB averages to about 5–10%[18]. The fallopian tube is the most commonly affected pelvic organ followed by the endometrium. On reactivation in the fallopian tube, the infection spreads from the mucosa, through the tubal wall to the peritoneal surface. There is also spillage of TB bacilli into the peritoneal cavity through the tubal ostia. The endometrium is affected by the transluminal spread.

Diagnosis of GTB:

The diagnosis of GTB is challenging and is very difficult. The disease may remain silent or present with varied clinical symptoms. There are no definite signs to diagnose the disease. The awareness among the clinicians is also limited to suspect the condition to initiate investigations. Even if GTB is suspected on clinical grounds, one may have to resort to invasive procedures to obtain the required samples for investigations. As on now there is no single investigation modality with good sensitivity and specificity available to diagnose GTB. Not only in low resource countries, even in in resource-rich countries the same difficulties are encountered.

Clinical Manifestations:

GTB is commonly seen in young women. It is a disease of absent or few symptoms. If symptoms are produced, they are of low grade, non-specific and are similar to symptoms produced by other Gynaecological conditions. Therefore, one has to have a high index of suspicion to consider GTB in the differential diagnosis. In a considerable proportion of patients the disease remains asymptomatic without producing any signs and symptoms and the diagnosis is made incidentally during the evaluation of infertility or other gynaecological problems. One can see extensive burnt out disease with fibrosis and calcification yet not producing any symptoms. It has been estimated that the disease is incidentally discovered in nearly 11% of patients[19]. Very rarely there could be active disease of the genital organs due to the miliary spread. These patients present with typical signs and symptoms of tuberculosis such as fever, loss of weight, loss of appetite, anorexia, malaise and night sweats and genital manifestation with acute PID.

The most common presentation of GTB is infertility. GTB can exist in infertile women without any signs and symptoms. In these cases, the disease may be latent or may harbour a low grade infection. It has been suggested that latent tuberculosis should be considered in Indian patients presenting with unexplained infertility or in those with repeated In Vitro Fertilization (IVF) failures[20,21,22]. Studies have shown that 40- 56% of women suffering from GTB did not have any gynaecological symptoms other than infertility. There could also be associated symptoms such as menstrual disturbances, chronic lower abdominal pain and secondary amenorrhoea in infertile women.

The next common presentation of GTB is lower abdominal pain and pelvic pain, reported in 17% to 50% of cases. The pain is usually chronic, low grade, and not responding to standard antibiotics. Occasionally there could be acute exacerbations secondary to bacterial infection. There may also be associated dysmenorrhoea and dyspareunia[23]. The prevalence of menstrual disturbances in GTB varies from 20% to 50% in various studies. The most common menstrual disturbance observed is heavy menstrual bleeding (HMB), oligomenorrhoea and amenorrhoea[24,25]. In the study by Thangappah et al 27.7% women presented with menstrual disturbances and oligomenorrhoea was the predominant menstrual disturbance seen in 70.8% of them[22]. In TB endemic countries, in young sexually naïve girls, if the HMB is non-responsive to conventional therapy they should be evaluated for GTB. GTB can also occur in postmenopausal women. As there is no shedding of the endometrium this allows the granulomas to grow, manifesting with vaginal

discharge or postmenopausal bleeding. Cervical lesions presenting with chronic vaginal discharge and or post coital bleeding may harbour cervical tuberculosis and are often mistaken as cervical carcinoma. Besides the genital involvement, there could also be concurrent abdominal tuberculosis or tuberculosis of the urinary tract. These patients often present with unexplained abdominal pain, abdominal distension, altered bowel habits and recurrent urinary tract infection not responding to antibiotics. All of the above mentioned symptoms are also manifested by other gynaecological conditions. Therefore, based on the symptoms alone, the GTB can be easily missed unless one has a high degree of suspicion and initiate investigations for GTB.

A past history of tuberculosis or a history of contact with a family member suffering from tuberculosis should raise the suspicion of GTB in infertile women. In Sutherland's large series of 710 patients, 80% had a history of tuberculosis elsewhere in the body[26]. The reported past history of tuberculosis in women suffering from GTB varies from 36-74%[27,28,29]. In the study by Prasad et al, the primary source of tuberculosis was pulmonary in 42.8%, lymph nodes in 28.5% and bone in 28.5% of cases[29]. In some of the studies, past history of tuberculosis is low and this may be due to the gastrointestinal source of the infective organisms, failure to re-call the past history as they are forgotten or not willing to disclose as it is considered a taboo in some places[22,30].

Studies have shown that there is a significant association between past history of tuberculosis and current diagnosis of GTB shown by laparoscopy, culture and GeneXpert. These studies have emphasized that in all women presenting with infertility it is mandatory to elicit past history of tuberculosis and if present they should be actively investigated for GTB[31,32]. History of close contact with family members / neighbours suffering from tuberculosis is also an important risk factor to develop EPTB.

There are no specific signs to diagnose GTB and the examination finding may be normal in up to 50% of cases. If there is miliary spread with active disease involving the genital tract, the individual appears poorly nourished, presents with fever, loss of weight, there may be evidence of pulmonary tuberculosis, or cervical node enlargement. Pelvic examination finding may suggest acute PID. But, this presentation is rare. Presence of sacculated ascites, doughy feel of the abdomen, mass with a tympanic note (due to loops of bowel adherent to the mass) , restricted mobility of the uterus and large tubo-ovarian (T-O) masses are late manifestations of GTB. Tuberculous T-O masses are often less tender. Most often these cases are diagnosed as malignancy. As Ca125 level is increased in both the conditions, differentiating tuberculosis from ovarian malignancy is also difficult. GTB can mimic various Gynaecological conditions such as adenomyosis, endometriosis, PID and malignancy of the genital tract /can co-exist with them[33,34]. Therefore, based on the clinical signs and symptoms, the diagnosis of GTB is difficult, however, the suspicion of GTB by the clinicians remains the most important tool for diagnosis.

Diagnosis of latent tuberculosis:

When Mycobacterium tuberculosis bacilli (MTB) spreads from the primary sites to other areas, it can evade immunity and remain in the dormant stage for many years. In the dormant stage, the individual is healthy and the infection does not produce any signs and symptoms of active disease. This is called latent tuberculosis infection (LTBI). These TB-infected individuals, are at permanent risk for progression to active disease. The WHO End TB strategy focusses on prevention of active disease by interrupting the transmission of latent disease [35]. In the active phase of the disease, the MTB organisms can be isolated from the various affected sites. Whereas, in the dormant stage, latent tuberculosis can only be diagnosed indirectly by detecting the individuals immune response to the Mycobacterium tuberculosis complex (MTC) antigens. Though no gold standard test is available, the tuberculin skin test (TST) and the interferon

gamma release assay (IGRA) are currently used to diagnose LTBI. These tests are not useful to differentiate active disease from LTBI and these tests cannot be used to predict which individual with LTBI will progress to active tuberculosis. These tests are also not used for the diagnostic work up of adults suspected of having active TB[36].

The Tuberculin skin test (TST)

The tuberculin skin test (Mantoux test) evaluates the delayed type of hypersensitivity in vivo in response to purified protein derivative (PPD). The test involves giving an intradermal injection of 5 tuberculin units which contains a mixture of antigens; antigens of *M. tuberculosis*, *M. bovis*, BCG strains and several antigens of nontuberculous mycobacteria (NTM). After 48-72 hours, the extent of induration on the site of injection is measured. A positive TST is only indicative of exposure to tubercle bacilli in the past. Different threshold levels are available to consider the test to be positive[37]. The main limitation of TST is its low specificity, as a positive tuberculin test is not specific for MTB. Infection with various NTM may produce skin test responses to PPD similar to that of tuberculous infection resulting in false positive results. Interpretation of tuberculin test is also complicated by prior Bacille Calmette-Guérin (BCG) vaccination and a positive reaction may be produced in BCG vaccinated persons. The proportion of BCG-vaccinated people who have a positive tuberculin skin test has been shown to vary from 0% to 90%[38]. It has been shown that the effect of BCG vaccination on the specificity of TST depends on the strain of vaccine used, number of doses given and the number of years since vaccination. BCG vaccination given at birth may have limited impact on the interpretation of TST results later in life [39]. False negative results may also be seen in immune compromised individuals due to various reasons and due to incorrect technique and interpretation. The reported positivity of TST test in women diagnosed with GTB ranges from 21.7% to 90%[22,40]. In the study by Sethi et al TST was positive in 71.6% of patients diagnosed with GTB[41]. Raut et al have analyzed the usefulness of the Mantoux test in the diagnosis of GTB and reported that the Mantoux test had a sensitivity of 55% and a specificity of 80% in women with laparoscopically diagnosed tuberculosis. They concluded that Mantoux test has limited utility in diagnosing active GTB during childbearing age. However, the study recommended that, in infertile women with a positive Mantoux test, laparoscopy may be advocated early[42].

Interferon-gamma release assay (IGRA)

It is a whole blood assay which evaluates the cell-mediated immune response in vitro. In the commercially available QuantiFERON (QFT) and QuantiFERON TB Gold in tubes (QFT-GIT), the early secretory antigenic target (ESAT-6) and the 10-kDa culture filtrate protein (CFP-10) antigens are used. It has been shown that IGRA results are not affected by BCG vaccination or previous exposure to mycobacteria and shows higher specificity[43]. In the study by Tal et al, QuantiFERON-TB Gold serum assay was positive in 7.7% of patients who were at risk for latent tuberculosis and it was suggested that all at risk patients seeking infertility treatment should be screened for latent tuberculosis and if they are screen positive they should be evaluated further by specific investigations on the endometrium[44]. It has been shown that only 10% of patients who are diagnosed to have latent infection are capable of progressing to disease[45]. WHO has recommended that either TST or IGRA can be used to test for latent infection in high risk population or in those who has had close contact and if positive, latent infection to be treated. Treating latent infection would reduce the risk of TB infection progressing to established disease. The treatment of latent infection involves using either monotherapy for 6-9 months or shorter courses with multiple drugs. Therefore, it is important that before initiating the treatment for LTBI, the possibility of TB disease should be ruled out to avoid undertreating the disease[36].

Imaging Studies:

CHEST X – RAY

In all patients with suspected / diagnosed GTB, chest X-ray should be taken and evaluated by trained chest physician to locate small or healed lesions or presence of active pulmonary TB[46]. Most often, the chest X – ray is reported normal as the pulmonary lesions are arrested by the time genital tract involvement becomes evident. In Thangappah et al study, chest, X – ray showed evidence of healed lesions in only in 2.3% of cases[47]. A similar observation was made by Nagpal et al and Sethi et al where chest X– ray was abnormal only in 1% and 2.9% of cases respectively[48,41]. Therefore, a negative chest X – ray does not rule out the possibility of GTB.

ULTRASONOGRAM (USG):

In patients presenting with Gynaecological symptoms, USG of the abdomen and pelvis is carried out as part of the initial assessment. If there are associated abdominal symptoms other imaging studies with Computerized Tomography (CT), Magnetic Resonance Imaging (MRI) and Positron emission tomography (PET) are also carried out. Awareness of the USG, CT and MRI findings associated with GTB is important so that unnecessary surgical exploration can be avoided. In the early stage of the disease, the USG findings are apparently normal. However, in the late stage of the disease, hydrosalpinx and T-O masses are diagnosed on USG and these findings are not specific for the diagnosis of GTB[49]. However, in sexually naïve adolescent girls presenting with adnexal masses especially when there is associated ascites, GTB should be considered in the differential diagnosis. As a late sequelae of tuberculosis, the uterus shows irregular endometrial surface, there may be presence of endometrial fluid and calcification. On 3D imaging one may be able to appreciate obliterated endometrial cavity. If there is associated abdominal involvement, USG images may show loculated ascites, peritoneal thickening, deposits, lymph node enlargement with or without calcification. These are non-specific findings, but they suggest the possibility of GTB. Using 2D/3D images of the pelvis in confirmed cases of GTB, Khurana et al have described certain specific USG findings which are diagnostic of GTB; vertical course of the interstitial portion of the tube, oligemic myometrial cysts, obliterated endometrial cavity and follicles with echogenic rims. The authors concluded that if GTB cannot be confirmed by culture, these specific USG findings may be useful in the management decision[50].

CT AND MRI AND PET SCAN

CT and MR imaging studies in GTB have shown heterogenous T-O masses, dilated fallopian tubes with thickened wall, ascites, thickened peritoneum, omental masses, enlarged lymph nodes and heterogenous uterine enhancement. Most often these findings are interpreted as malignancy[51,52]. The CT findings of TB peritonitis are non – specific and mimic disseminated peritoneal malignancy, mesotheliomas and non – tuberculous peritonitis. However, certain features on CT may help in the diagnosis. The most common manifestation of abdominal tuberculosis is ascites of variable amount and due to the high protein and cellular content in the tuberculous exudates, the ascitic fluid usually measures higher than water density (25 – 45 HU). The presence of a slight and smooth peritoneal thickening is more suggestive of TB, while nodular irregular thickening is diagnostic of peritoneal carcinomatosis. TB lymphadenitis is a common manifestation of abdominal tuberculosis and reported in 55 – 60% of cases[53]. Contrast enhanced CT/ MRI of the pelvis may be more valuable in characterizing the lesions when a T-O mass is present. Sharma et al have suggested that PET scan can be helpful in cases of T-O masses to differentiate tuberculous T-O masses from ovarian cancers as tuberculosis demonstrates increased glucose uptake[54].

HYSTEROSALPINGOGRAM (HSG):

As a part of infertility workup, in order to ascertain the tubal patency, HSG is a frequently performed investigation and most often it is the HSG finding that alerts the clinician as to the possibility of GTB.

In the early and latent TB, the HSG findings may be apparently normal. In thangappah et al study, in 23.5% of cases, the HSG findings were normal in spite of the confirmed GTB[55]. Number of tubal and uterine features have been described on HSG in patients diagnosed with GTB. Tubal occlusion is the commonest finding reported in nearly 80% of patients with proved tuberculosis[55,56]. Tubal occlusion is a non-specific finding as it can be caused by infections such as chlamydia and gonococci. Most often, in GTB mid tubal obstruction occurs between the ampulla and isthmus. Distal blocks with hydrosalpinx are also a common feature in TB and are reported in 16 to 46% of cases with proved GTB[57]. However, this finding is also not specific for tuberculosis as it can develop following PID caused by other organisms, adhesions or obstruction of any cause[49]. The one characteristic feature of hydrosalpinx in tuberculosis is its everted patent fimbrial end producing a characteristic tobacco pouch appearance which can be well appreciated at the time of laparoscopy. When this finding is noted, the probability of TB should be suspected. Other findings that have been noted in the tubal area are rigid pipe stem tubes, alternate areas of constriction and dilatation giving a beaded appearance (rosary bead), and intraluminal scarring giving a cobblestone pattern. The presence of calcified lymph nodes, calcified areas in the course of fallopian tubes and in the endometrial cavity may also suggest the diagnosis of TB. However, calcified areas may also be due to urinary calculi, pelvic phleboliths and ovarian dermoid. The uterine cavity may show irregular filling defects due to intrauterine synechiae, deformed uterine cavity giving the appearance as T shaped uterus, pseudo-uni cornuate uterus and complete obliteration of the uterine cavity giving a gloved-finger appearance[49,58]. Venous and lymphatic intravasations are good indicators suggesting endometrial tuberculosis and are reported in 6- 20% of cases with GTB[59,60]. However, these findings are also not specific for tuberculosis and can be seen if HSG was done in the early menstrual cycles, shortly after endometrial instrumentation and any condition causing obstruction to flow such as intra – uterine adhesions and tubal obstruction of any aetiology[61]. Though some of the imaging findings such as distorted uterine cavity, calcified lymph nodes, beaded tubes and vascular intravasation may suggest TB, specific investigations are required to make a definitive diagnosis. The presence of HSG findings indicate that considerable tubal damage has already occurred and there may be a need for assisted reproductive techniques (ART) in women seeking fertility treatment. In the presence of these HSG changes, it is mandatory that prior to attempting ART, GTB should be investigated and treated.

Endoscopic procedures in the diagnosis of GTB

LAPAROSCOPY:

Laparoscopy is an important tool in the evaluation of infertility and in the diagnosis and management of various Gynecological conditions. Besides the diagnostic and therapeutic uses, it facilitates sample collection from inaccessible sites for various laboratory investigations. Three clinical forms of tuberculosis of the appendages have been described[48].

1. Early or latent TB where there are no tubal or peritoneal changes.
2. Acute infection showing miliary tubercles, swollen and reddened tubes
3. Chronic infection with terminal hydrosalpinx with retort shaped tubes, beaded tubes , T-O masses and intravasation of dye into the parametrial vessels

Even with laparoscopy GTB presents unique diagnostic challenges. In early and latent cases, there may not be any evidence of pelvic tuberculosis and subtle manifestations may be overlooked at laparoscopy. Vynck et al reported that, in proved cases of GTB by microbiological studies on the menstrual fluid, in 44.5% of cases, the pelvis was clear at laparoscopy. Similar findings were shown by Deshmukh et al, where 3 of the 45

histologically proved GTB did not show any evidence of TB at laparoscopy[62,63]. Therefore, during the early stages of infection, the diagnosis can be easily missed when the infection is still confined to the mucosa. Only in the presence of active infection with miliary spread, one can see tubercles on the surface but this is a very rare manifestation. Visual inspection at laparoscopy alone is insufficient to make a diagnosis of GTB and tissue sampling has to done to confirm the diagnosis. Advanced stages of GTB can present with findings such as thickened tubes, hydrosalpinx, and T-O masses, caseating nodules, encysted ascites, adhesions , beaded tubes , tubal blocks and granulomas[64,65]. These findings are seen in PID due to other causes also. T-O mass of gonococcal/pyogenic origin, pelvic endometriosis, and ovarian malignancy may closely mimic a T. O mass of tuberculous origin and in these situations laparoscopy is of value in confirming the diagnosis as well as facilitating tissue biopsy[66,67]. The Index TB guidelines on extrapulmonary tuberculosis recommends that the diagnosis of FGTB can be made based on the laparoscopic appearances which are typical for FGTB such as presence of tubercles, caseation or beaded tubes[46].

HYSTEROSCOPY:

Hysteroscopy is the gold standard method to evaluate the uterine cavity. As the endometrium is involved in nearly 50% of cases of GTB, hysteroscopy has been used for the evaluation of GTB. It has been shown that findings such as obliterated endometrial cavity, intrauterine adhesions with synechiae formation, pale thin endometrium and obliterated fibrosed tubal ostia are associated with GTB. However, the presence of these features only suggest that there is chronic infection and the diagnosis of endometrial tuberculosis should be supported by bacteriological/ histopathological /molecular studies of the endometrium. Study by Sarbhai et al have shown that, hysteroscopy is complementary to endometrial biopsy and cannot replace the bacteriological confirmation of diagnosis by endometrial biopsy[68]. Very rarely typical features of TB such as tubercles, micro caseation and calcification are reported in the endometrium. In the study by Mohakul et al, on 105 infertile women, TB-PCR was positive in 43.75 % and 48.5% of cases who showed peri-ostial fibrosis and intrauterine adhesions respectively on hysteroscopy. The study suggested that in the presence of intra-uterine and periosteal fibrosis, further evaluation should be carried out for the presence of genital tuberculosis[69]. Arpitha et al evaluated hysteroscopy in patients who showed positive PCR results on endometrium and the findings were normal on hysteroscopy in 73.9% of patients and abnormal findings such as fibrosed ostia, poorly vascularised endometrium, synechiae and cervical stenosis were seen in 26% of patients[70]. Hysteroscopy can be used as a diagnostic tool for endometrial sampling in diagnosing GTB. It is also useful for releasing the intrauterine adhesions as well as to evaluate the endometrial cavity after treating GTB. It can also give valuable information on prognosis for future reproductive function[71].

Microbiological Investigations

The laboratory diagnosis of TB depends on the demonstration of MTB, by acid-fast bacilli (AFB) staining and/or growth of the organism on culture media.

DETECTION OF AFB IN DIRECT SMEARS:

Direct microscopy will show whether AFB are present or absent in the smears. It gives preliminary confirmation of the diagnosis while waiting for the culture report and this may be of value in primary health care settings. It is inexpensive, simple, easy to perform and the results are available immediately. However, the test has a limited sensitivity and it requires a high bacterial load of 5,000-10,000 AFB /mL of specimen for detection. Endometrium being an extra-pulmonary site, the bacilli are few in number, therefore, AFB positivity is low in endometrial samples. Absence of AFB in the smears does not exclude the diagnosis of GTB. AFB positive smears should always be followed by culture as the test does not distinguish between

viable and non-viable organisms and it does not provide species identification. The test has limited specificity as NTM are also AFB positive. In AFB positive smears, besides culture, PCR may be useful in differentiating tuberculosis from NTM[72]. The reported incidence of AFB smear positivity in endometrial samples varies from 1.6% to 8.3% in various studies[73,74,75,47].

CULTURE:

Culture still remains the gold standard method in the detection of GTB. It is useful for species identification, testing for drug susceptibility and useful in monitoring the response to treatment. Culture is important to differentiate NTM from MTB. Lowenstein Jensen (LJ) medium or Middlebrook 7 H 10 or 7 H 11 medium are traditionally used for the culture of Mycobacteria. In these media, bacilli may take up to 8 weeks to show positive colonies. The bacillary count should be more than 1000/ml of specimen to show positive results. With improvements in media, colonies grow even when the count is 100 bacilli/ml of specimen. This is possible with the use of liquid based media radiometric growth detection such as BACTEC 460. With this method culture time is reduced to 2 weeks , there is increased recovery of organisms and the test has a high sensitivity The radiometric culture BACTEC has a sensitivity of 80 – 90%, whereas the LJ medium has a sensitivity of only 30 – 35%. This high sensitivity is particularly useful in cases of GTB, as traditional methods show poor recovery of MTB[76,77] In order to improve the recovery of MTB, culture is recommended in both solid and liquid media. Another automated advance available for the detection of tuberculosis is Mycobacteria Growth Indicator Tube technique (MGIT). It has been shown that the addition of MGIT 960 media to other investigations significantly improves the diagnosis of GTB[78]. However, these automated techniques are expensive and there is high risk of contamination[79]. The reported culture positivity in GTB varies from 3 to 12%[73,74,75,80,47].

Demonstration of the Mycobacterium by culture is not possible in all cases. The possible reasons for the low incidence of culture positivity in endometrial tissue could be due to paucibacillary nature of the endometrial site and a substantial number of TB lesions of the genital tract are bacteriologically mute[73]. Prolonged time interval between biopsy and bacteriological examination can also result in reduced culture positivity[81]. The presence of a bacteriostatic substance in the endometrial tissue may also inhibit the growth of the bacilli[82]. Similar negative results can be obtained when the patient has had previous anti tuberculous therapy (ATT). Most of the infertile women in India are started on empirical ATT, and this could contribute to low pick up rate of MTB by culture. In order to increase the microbiological yield, the optimal time for sampling is at the end of the menstrual cycle or within 12 hours following the onset of menses to allow maximum time for the endometrial granulomas to develop[83]. A non-invasive way of getting samples for culture / HPE / and PCR could be menstrual blood. Menstrual blood culture has higher pick up rate in early and latent cases. Studies have shown that the *hsp65* nested PCR of menstrual blood can be used as a non invasive screening test for rapid detection GTB[84].

Histopathological examination (HPE)

A definite diagnosis of GTB is possible by the histological demonstration of tuberculous granulomas in tissue samples. HPE is easy, quick, cheap and provides characteristic features of MTB. The typical and almost pathognomonic lesion of the tuberculous endometritis in regularly menstruating woman is the non-caseating granulomas composed of epithelioid cells, Langhans-type giant cells and peripheral lymphocytes. The granulomas are usually situated in the superficial part of the endometrium. In non-menstruating women due to amenorrhea or post post menopausal state, there is ample time for the lesions to progress to full blown caseous granuloma. In female genital tuberculosis, the fallopian tube is the initial site of involvement, affected in almost all cases, followed by secondary extension to the endometrium seen in 50 to 90%

of cases. It seems probable that tuberculous endometritis is almost 100% proof of tubal tuberculosis. Therefore, endometrial biopsy is widely used to collect the material for the diagnosis of GTB. The best time for examining the endometrium is in the premenstrual phase, at which time the tubercles reach their maximum growth. The portion of the endometrium most likely to show tubercles is in the region of the uterine cornua where the spread from the tube first occurs.

Though endometrial curettage is the commonest procedure to obtain endometrial tissues, studies have looked at endometrial aspiration for the diagnosis of GTB. Endometrial aspiration cytology has been claimed to be simple, inexpensive and less traumatic, can be repeated more than once and can be done in the out-patient departments (OPD)[85,86]. On histopathological studies the reported incidence of endometrial tuberculosis varies from 0% to 9.5%[73,87,88,75,22,89].

The HPE of the endometrium, though easy and quick, the sensitivity is again low. The low prevalence of MTB in endometrial biopsy may be due to various reasons. Due to the secondary nature of the genital tuberculosis, the infecting organisms are sparse in number, and during sampling the infected site can be easily missed. In as many as 50% of cases, the infection may be limited to the fallopian tubes especially in the early stages. Moreover, due to the cyclical shedding of the endometrium, granulomas do not have enough time to form, so, the endometrium may not show evidence of tuberculosis in all the cycles and when the endometrium is severely damaged no tissue will be available for HPE. When there is associated HIV co-infection it may not elicit adequate cell mediated immune response to produce changes in the endometrium. Tuberculous endometritis can also masquerade as a non – specific non – granulomatous endometritis. Studies have shown that evaluating with microbiological methods / PCR is of greater value in doubtful cases reported with non-specific endometritis[90,22]. Therefore, diagnosis based on a single sampling of endometrium may result in false negative results. Therefore, multiple sampling would be required. Granulomatous lesions are highly indicative of, but not exclusive to tuberculosis unless TB Bacilli are seen. Granulomatous lesions can also be produced by other conditions such as sarcoidosis and foreign body reaction; however, these conditions are rare in the endometrium. Therefore, when a granulomatous lesion is present it is probably tuberculosis especially in an endemic country. As both culture and histopathology are not completely dependable for the diagnosis of GTB, in settings where molecular diagnostic methods are unavailable, simultaneous use of both histological and bacteriological methods may increase the diagnostic rate and both the methods are complementary to each other.

Molecular Diagnostic Tests:

Currently, molecular diagnostic techniques are widely used for the diagnosis of GTB. The nucleic-acid amplification tests (NAAT) are rapid molecular methods which identify nucleic acid sequences which are specific to MTB. The test performance of NAA for tuberculosis shows that, in general NAA tests have high specificity and positive predictive value. However, they have a lower sensitivity and negative predictive value. Therefore, a positive test in a patient with high pre-test probability is confirmatory of tuberculosis. Whereas a negative test does not rule out the diagnosis of tuberculosis. If the test result is negative, but there is a strong clinical suspicion of tuberculosis , the search for TB should continue[91].

THE POLYMERASE CHAIN REACTION (PCR) TECHNIQUE:

The Real-Time PCR technique is capable of amplifying minute amounts of DNA, even a single copy of DNA into millions of identical copies of DNA sequence. The specific DNA sequence may be a gene, part of a gene or a stretch of nucleotides. It is a rapid test and the results are usually obtained within 6-12 hours. The test can detect even < 10 bacteria /ml of specimen. PCR based diagnosis of TB has been evaluated to be

useful and important in the detection of pulmonary as well as extra-pulmonary TB. PCR assays target various gene segments such as 64kDa protein encoding gene, the IS6110 element and mpt64. The advantages of PCR test are, it is a rapid test, it can differentiate tuberculous from non-tuberculous mycobacteria in smear positive disease, it can be done in pauci bacillary samples and can be applied to sterile fluids such as peritoneal fluid which have low bacterial load. There are certain limitations associated with the Real-Time PCR tests. It should be performed only in established laboratories that have adequate quality assurance to avoid false positive results and the test also involves high cost. There is also problem of false positivity due to contamination of specimens from the PCR laboratory. The other major limitation is that, the test cannot differentiate viable from non-viable organisms and the test can remain positive for a longer period of time in those who were treated for tuberculosis. False negative results can also occur due to the presence of inhibitors such as blood in the samples tested as well as due to the inadequate extraction of DNA due to low bacterial load[92].

In the last few decades, PCR technique has been found to be useful in confirming the diagnosis of GTB[93]. The reported positivity of PCR in endometrial samples varies from 22.5% to 57.3%[27,47,94,89,73,95,88]. There have been number of reports looking at the accuracy of various specific diagnostic tests in diagnosing GTB. As the Gold standard test culture lacks sensitivity in diagnosing GTB, authors have used various parameters such as simplified algorithm, laparoscopy and set of clinical criteria (past history of tuberculosis, Mx positivity, positive findings at USG, HSG and laparoscopy) to evaluate the diagnostic tests[28,73,47,96]. All the studies have shown that, sensitivity of PCR is higher than culture and histopathology and specificity may be as high as 100 % in detecting FGTB. Study by Rozati et al showed that the sensitivity of PCR was 96.6% and the specificity was 100% in diagnosing GTB. The authors concluded that when the clinical suspicion of tuberculosis is high, PCR is the best method of diagnosing GTB[94]. Bhanu et al showed that with PCR there is a seven fold increase in the sensitivity of detection of tuberculosis compared to the culture and is 14 fold more sensitive compared to the smear[73]. In the study by Thangappah et al, the sensitivity of PCR was 44.3 per cent and the specificity was 80.4 per cent in diagnosing GTB[47]. The recent report by Meenu et al also showed similar findings with a sensitivity of 50% and specificity of 92.5%[95].

Though the sensitivity of PCR is higher than culture and histopathology, it is not sufficient enough to be used as a single diagnostic test for the diagnosis of GTB. Studies have suggested that in order to achieve sufficient sensitivity and specificity for the diagnosis of GTB, PCR should be combined with the other available methods of diagnosis. Recent reports suggests that combining both rapid culture and newer molecular techniques will facilitate the accurate and timely diagnosis of FGTB[97]. Study by Radhika et al has shown that addition of PCR to BACTEC improved the sensitivity from 40% to 52% and concluded that combination of BACTEC and PCR had an improved detection rate compared to the conventional tests[98]. Bhanu et al study suggested that multiple sampling from different areas and repeat sampling from the patient will improve the sensitivity of PCR as a diagnostic tool[73]. Using multiplex PCR with more than one set of primers may improve the detection rate[97,99]. In Thangappah et al study, two sets of primers were used . The sensitivity of IS6110 was 25% and that of TRC4 was 46.4% in diagnosing GTB. By combining IS6110 and TRC4 together the sensitivity increased to 57.1% [47]. By using multiplex-PCR, it may be useful in detecting M. bovis which is also frequently seen[100].

The major concern in using PCR in the diagnosis of GTB is its false negative and false positive results. If the PCR test is negative, in view of the high false negative results, if there is a strong clinical suspicion of GTB, the search for tuberculosis should continue. It has been suggested that PCR positivity in isolation should not be considered as diagnostic of GTB and treatment initiated. A

positive PCR should be supported by other corroborative evidence such as clinical findings, laparoscopy and hysteroscopy which would improve the diagnosis[73,101,102]. Though false positive PCR results can occur by way of contamination, dead bacilli or previous infection, the possibility of early disease or latent infection which has been picked up by PCR cannot be ignored. The subtle clinical manifestation of GTB in the early stages may be overlooked at laparoscopy when outpouring of bacilli is already happening from the tube into the uterine and peritoneal cavity. In Thangappah et al study, in which laparoscopy was taken as one of the a major criteria to suspect TB, in 18 samples PCR was positive but the clinical suspicion was negative. Though it raises the possibility of false positive results, in 13 of them PCR was positive both in the endometrium and in the POD fluid as well as in two urine samples. Moreover, in this study, reliability of PCR was checked by repeat sampling on patients and retesting of the saved samples. This confirms that PCR in fact has picked up the true positives and the early disease. Therefore, in an endemic country with high prevalence of tuberculosis, when there is a strong clinical suspicion of GTB, a positive PCR test result should be given due importance and the woman should be treated[22]. However, currently the only molecular test recommended by the World Health Organization (WHO) for the detection of MTB and rifampicin (RIF) resistance in EPTB is the cartridge-based NAAT Xpert MTB/RIF assay (Xpert)[103].

THE CARTRIDGE-BASED NUCLEIC AMPLIFICATION (CBNAAT)/GENEXPERT MTB/ RIF TEST:

In recent years, newer nucleic acid amplification technologies are widely used due to the shorter time to get the results, and due to their sensitivity, and specificity. Gene Xpert is a DNA based test and it is capable of detecting 80–130 MTB bacilli /ml of the infected material and also detects rifampicin resistance within 2 hours[104,105]. The (CBNAAT)/Xpert RIF test is a PCR-based method and is being used for the diagnosis of EPTB. However, limited studies are available evaluating CBNAAT for the diagnosis of GTB. GeneXpert test involves a simple processing technique, wherein the, isolation of genomic material, PCR amplification and the detection are all integrated into a single test unit, the GeneXpert cartridge. This minimises the possibilities of cross contamination and false positive results associated with Real-time PCR tests. As in other diagnostic tests, there are limitations associated with the test. The major limitation is that the sensitivity is too poor to rule out the disease, especially when the clinical diagnosis is equivocal. The shelf-life of the diagnostic cartridges is limited, there are temperature and humidity restrictions in conducting the tests and the machine needs annual servicing and calibration. The cost of the test is also high for low resource countries[106]. Because of its rapid results, sensitivity, and specificity, GeneXpert MTB/RIF has been approved by WHO for detecting TB, especially in regions with high rates of TB-HIV co-infection or multidrug-resistant TB. However, for the diagnosis of FGTB, GeneXpert appears to be highly specific, but less sensitive[18].

In recent years various studies have evaluated the efficacy of GeneXpert in diagnosing GTB compared to other diagnostic modalities. The reported sensitivity is low ranging from 11.1% to 46.6%, whereas the specificity is high at 100%[107,89,87,108]. Tiwari et al evaluated Gene Xpert compared with other diagnostic modalities in diagnosing GTB in 176 infertile women. The study showed that the sensitivity of Gene Xpert was 11.11% whereas the specificity was 100%[107]. In the study by Sharma et al. Gene Xpert was positive in 18.56% with a sensitivity of 35.63%, and specificity of 100%. The authors concluded that when the GeneXpert test is positive, it is very useful in confirming the diagnosis whereas, when the test is negative it does not rule out tuberculosis[89]. In the study by Garg et al among the 81 endometrial samples studied in infertile women, histology was positive for tuberculosis in one case and none were positive by CBNAAT testing[87]. Compared with microscopy and culture, GeneXpert MTB/ RIF assay demonstrated improvement rate in detection

of FGTB by 55.55% in Farhana et al study[108]. The findings of all these studies indicate that when the GeneXpert test is positive, it is very useful in confirming the diagnosis of GTB, whereas, when the test is negative GTB cannot be ruled out. Similar to the Real Time PCR, the low sensitivity of GeneXpert may be attributed to the paucibacillary nature of the disease and to the presence of inhibitors in the endometrial samples.

LOOP-MEDIATED ISOTHERMAL AMPLIFICATION (LAMP)

LAMP is another WHO-approved NAAT for the diagnosis of TB, but, it does not identify RIF resistance. The test uses six sets of specific primers to identify IS6110 sequence in the MTBC. The results are available within one hour[109]. Sethi et al carried out LAMP assay on the endometrial samples for the evaluation of GTB and found that LAMP had a sensitivity of 66% and specificity of 93%. They also observed a high concordance of 63 per cent between PCR and LAMP[110].

Composite reference standard (CRS)

Because of the low sensitivity of the specific diagnostic tests, in order to improve the diagnostic accuracy, various composite reference standards are being used to diagnose GTB[111]. There are no consensus guidelines on recommendations and definition of a CRS for use in GTB. However, the WHO Country Office for India developed the Index TB guidelines for EPTB, which suggests that confirmation of FGTB requires either positive laparoscopic findings, positive AFB smear or culture or presence of granulomas in Gynaecological specimens. The Indian EPTB guidelines do not recommend treatment on the basis of non-WHO -recommended PCR tests alone and there should be corroborative evidence from other test results[46]. However, in high resource countries such as US, when a molecular test (WHO-recommended rapid diagnostic test such as GeneXpert) result is positive, treatment is offered. It is also emphasized that whenever possible microbiological confirmation is important which enables drug susceptibility testing and identifies Multidrug resistance[112].

Conclusion:

The prevalence of GTB is high in developing countries and is one of the major causes of infertility. But the diagnosis of this condition is difficult and challenging. Because of the silent nature or varied clinical presentation clinicians often fail to consider GTB in the differential diagnosis. It is the clinician's suspicion of GTB which plays a vital role in the diagnosis. Though laparoscopy may be of value in advanced disease, subtle clinical manifestations of early disease may be easily missed . As on now, there is no single diagnostic test which is sensitive enough for diagnosing GTB.

In order to prevent the devastating sequelae of GTB, the need of the hour is to identify latent tuberculosis as well as the early stage disease so that effective treatment can prevent the damage to the genital organs. In all infertile women with a past history or contact history of tuberculosis especially in those diagnosed with unexplained infertility, TST/IGRA may be performed to diagnose latent tuberculosis. If found positive, after ruling out active disease, preventive treatment may be considered and more research is needed in this area.

In women with or without infertility, when presenting with symptoms such as oligomenorrhoea, chronic vaginal discharge, chronic pelvic infection not responding to standard antibiotics, the possibility of GTB should be considered and investigated further with multiple diagnostic modalities. Same is true in young girls presenting with HMB, not responding to hormones or in those with adnexal masses in young age. In-spite of extensive investigations and integrated testing the disease can still be missed. Therefore, when the clinical suspicion is high, but the test results are negative, the search for the disease should continue.

Conflict of Interest:

The authors declares no conflicts of interest.

Acknowledgements:

None.

Funding Statement:

None.

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