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Review Article

Advances in diagnosis and Management of female Genital Tuberculosis-A Comprehensive Review

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Abstract

The burden of disease with Mycobacterium Tuberculosis causing tuberculosis (TB) is high worldwide, with main concentration in developing countries leading to high rates of morbidity and mortality. Mycobacterium Tuberculosis Bacteria reach the genital tract by haematogenous spread along with dissemination from foci outside the genitalia with lungs being the common primary focus. Genital tract TB (GTB) in females is of utmost importance for physicians dealing with artificial reproductive technology (ART), when silent FGTB becomes a major cause of failure of implantation in developing countries. It is a chronic disease with low grade symptoms, the fallopian tubes are affected in almost all cases of GTB, along with endometrial involvement leading to infertility in these women, For diagnosis, there is need for a combination of investigations to label the patient having Female GTB (FGTB). Multidrug anti TB treatment (ATT) remains the mainstay of management, with surgery being required in advanced cases. In view of rapidly developing resistance to the primary group of drugs one should be cautious before one starts the therapy and ensure patient compliance, monitor for symptoms like hepatitis and not start just with a positive polymerase chain reaction (PCR) in view of lot of false positives. One needs to individualize treatment after assessing the patient in toto since unnecessary ATT has lead to the development of multidrug resistant TB which is very difficult to tolerate with its side effects. Conception rates are low among infertile patients presenting with FGTB despite multidrug therapy for TB, with risk of ectopic pregnancy and abortion rates being high. Greater research is needed in view of the changing trends, both in the prevalence like newer cases getting reported from Bandung, Indonesia, Iran, Tunisia along with appropriate methods for diagnosing FGTB.

Keywords: GTB; ATT; Infertility; PCR; Ectopic Pregnancy

Introduction

Tuberculosis remains a worldwide public health problem although a decreasing trend in mortality has been observed with effective therapy. Roughly 10. 4million people developed TB in 2015, of which >than 60% of cases were seen in South East Asia and Western Pacific regions [1]. In 2015 nearly 500, 000women died of TB, although 60% of TB cases and deaths occur among males, and 28%of women had human immunodeficiency virus (HIV) coinfection [1]. Genital TB in females has been identified to be an important cause for infertility in countries having high prevalence of TB. It occurs usually as a result of TB in other sites, primarily in lungs. Spread occurs through haematogenous or lymphatic routes [2]. TB of the female genital organs may result in infertility, dyspareunia, menstrual irregularities and chronic pelvic inflammatory disease (PID). Drug therapy for female genital TB (FGTB) is akin to that used in pulmonary TB (the standard treatment regimens). Despite treatment in infertility patients conception rate is not encouraging [2].

Methods

Thus, we decided to update on the advancements made in the diagnosis and management of female genital tuberculosis. For this we used the search engines Pubmed, Web of Science and google Scholar from 1970-2019 using the MeSH terms Female genital tuberculosis; diagnosis, Polymerase Chain reaction (PCR), Culture methods, Imaging including hysterosalpingography (HSG), Ul-

trasonography (USG), Acid fast bacilli (AFB) staining, Laporoscopy, ART for conception along with treatment strategies.

Results

We came across 2638 articles out of which we selected 90 for this review after ruling out duplicate articles and animal studies. No meta-analysis was done.

Epidemiology and pathogenesis

Genitourinary TB is a common form of extrapulmonary TB (EPTB) all over the world (27%), of which genital TB accounts for 9% of all EPTB cases. Yet the burden of genital TB is mostly underestimated. Sharma 2015 reported the incidence of -16% among infertility patients [3]. Although higher rates reported from tertiary referral hospitals in India may be secondary to referrals from different parts of the country for the diagnosis along with management of complicated case. A study where women with infertility who were taken for IVF in North India showed a prevalence of genital TB in tubal factor infertility to be as high as 48.5%. Survey conducted by Indian Council of Medical Research (ICMR) demonstrated that the prevalence of female genital TB in India had increased from 19% in 2011 to 30% in 2015. A multicentric ICMR study team is working on developing a national algorithm for diagnosis and management of FGTB [4]. Different reports on TB among women with infertility and conception rates both spontaneous and assisted are high lighted in ref [5-7]. Of these most studies are from India, occasional ones from Pakistan and Yemen.

Genital TB is mostly secondary to pulmonary TB or extrapulmonary foci like kidneys, meninges, skeletal system and GIT. TB bacilli infect the genital tract by 4 routes i) haematogenous route (with lungs as the common primary focus), ii) descending direct spread. iii) lymphatic spread iv) and rarely as primary infection of the genitalia through sexual transmission [5]. Genital organs affected by Mycobacterium tuberculosis with decreasing frequency are fallopian tubes (95-100%), uterine endometrium (50-60%), ovaries (20-30%), cervix (5-15%), uterine myometrium (2.5%) and vagina/vulva rarely [8]. Morphology of the infected genital organs varies widely. Usually the ampullary regions of the fallopian tubes demonstrate the earliest changes and the fimbria processes become swollen later. Pathological changes in TB endometritis like ulceration, caseous necrosis and hemorrhage are seen in advanced endometrial TB. In later stages adhesion might occur between ovaries and adjacent pelvic organs =>adnexal mass formation. Intrauterine adhesions once occur can=>partial obliteration of uterine cavity. Cervix, vulva and vagina are rarely affected [8].

Clinical presentations of FGTB

Mycobacterium tuberculosis affecting the fallopian tubes =>infertility. It might occur in any age group, but usually women of the reproductive age group (15-45yrs) get mostly affected [9]. Disease being asymptomatic remains silent with only presentation being infertility. Occassionally menstrual irregularities like oligomenorrhea, hypoomenorrhea, amenorrhea, menorrhagia, dysmenorrhea, metorrhagia, pelvic pain and abnormal discharge are the presenting symptoms. In post menopausal women FGTB presents with symptoms mimicking endometrial malignancy like post menopausal bleeding, persistent leucorrhea and pyometra [5]. FGTB may simulate or coexist with other gynaecological and abdominal pathologies like genital Carcinoma, acute appendicitis, ovarian cysts, PID or ectopic pregnancy [10-12].

Diagnosis of FGT

Discovery of tubercle bacilli in 1882 and isolation of bacilli in samples of urine and sputum contributed largely to both diagnosis and management of GTB [13]. Despite these techniques dilemma still exists regarding FG TB diagnosis. Thus a thorough systematic clinical examination with high degree of suspicion and use of intensive investigations are required [14]. One should consider possibility of FGTB in patients with chronic PID, not responding to standard antibiotic treatment, unexplained infertility, or in women with irregular menstrual cycle or postmenopausal bleeding and persistent vaginal discharhge (once genital neoplasias have been excluded) [15]. Risk factors are contact with a smear positive pulmonary TB infection, resident in or recent travel to endemic areas, low socioeconomic background, people living with HIV and drug abuse. There is no single diagnostic test available to confirm the diagnosis of FGTB. High degree of clinical suspicion, elaborate history taking, systemic examinations, battery of tests to document Mycobacterium tuberculosis along with imaging methodologies for characteristic structural changes as needed to diagnose it [16].

Investigations

As per the WHO definition of EPTB should be made on the basis of 'one culture positive specimen, or positive histology or strong clinical evidence consistent with active EPTB [1]. A general examination to exclude a TB focus elsewhere in the body Xray chest, tuberculin skin test (TST), ESR and complete blood count should be done at baseline. It has been documented that 10-75% of patients with genital TB may have an abnormal X ray [17]. Yet a negative chest Xray [doesn't rule out the possibility of genital TB. TST has limited utility in populations with with high,TB burden and where

Bacillus Calmette –Guerin(BCG) vaccination is followed as a routine.

False positive (non mycobacterial, previous vaccination with BCG) and false negative reactions (patients on steroid therapy, coexisting HIV infection, recent TB infection, chronic liver failure and people with typhoid fever, typhus, brucellosis, leprosy, pertussis) can also occur when TST was positive in 42. 6%of patients of GTB as per Abdeluaub., *et al* [15]. While sensitivity and specificity of TSTTS is 55 and 80%, respectively in women with laparoscopically was positive in diagnosed GTBas per Raut., *et al* [18].

Imaging techniques

Hysterosalpingography

GTB is associated with characteristic structural changes in the organs involved and HSG presents as a useful tool in visualizing the abnormalities. Tubal TB presentation differs from nonspecific changes like tubal dilatation, tubal occlusion, irregular contour, diverticular outpouching (salpingitis isthmitis nodosa), hydrosalpinx to specific patterns like cotton wool plug, pipe stem tube, golf club tube, cobblestone tube, beaded tube', leopard skin tube', tubal occlusion and adhesions in the peritubal region that might present as a straight spill, corkscrew appearance and peritubal halo [19]. One should suspect TB strongly in the presence of synechiae, tubal occlusion in the transition zone between the isthmus and ampulla [20], multiple constrictions, calcified lymph nodes, irregular linear or nodular calcifications in the adnexal area [21].

The uterine changes due to TB may be seen as specific features like 'collar stud abscess', T shaped uterus and pseudounicornuate uterus or nonspecific features such as synechiae formation, uterine contour distortion, obliteration of the uterine cavity, venous and lymphatic intravasation [22]. Chronic infection may => excessive destruction of the endometrium and myometrium => complete narrowing of the uterine cavity, known as Netter Syndrome. On HSG, it appears like a gloved finger consisting of cervical canal and small part of the uterus [23]. Cervical TB is rare since the stratified epithelium of ectocervix is naturally resistant to bacterial penetration because of which cervical. TB is mostly secondary to fallopian tube TB and that of endometrium [24]. Cervical involvement is seen on HSG as irregularity in contours and diverticular outpouching with feathery appearance, cervical distortion with a feathery appearance, cervical, cervical distortion and serrated endocervical canal [21,24]. Since Cervical TB, mostly will be misdiagnosed as cervical cancer need for ruling out the latter needs to be ruled out immediately, for appropriate management [25].

Ultrasonography

Fallopian tubes might appear dilated, thickened and may be filled with clear fluid called hydrosalpinx or thick caseous material known as pyosalpinx [19]. The endometrium gets affected in 60-90%of cases og FGTB, and the uterine enlargement may be due to filling by caseous material [26]. The endometrium may appear heterogenous with hyperechoic areas which represent foci of calcification or fibrosis, intrauterine adhesions along with a distorted uterine cavity [19]. Variation of finding like a normal USG to abnormalities like thin or thickened endometrium cornual obstruction, alteration in the endometrial vascularity during midcycle, tubal fluid, free and loculated peritoneal fluid, heterogenous enlargement of ovaries and adnexal fixation. Findings with greater specificity are oligemic myometrial cysts, follicles with echogenic rims and presence of endometrial fluid along wuth a hydrisalpinx [27]. Computed tomography and MRI are used in FGTB in the presence of an abdominal or pelvic mass [28].

Laporoscopy

Though Laporoscopy is invasive, it helps in visual inspection of ovaries, fallopian tubes, peritoneal cavity and biopsy of the tubercular leasions. Advantage of combined laparo-hysteroscopy are besides ruling out endometrial involvement one can also proceed with lysis of synaechiae or encometrial priming with oestrogen [29]. Laparoscopic findings that suggest FGTB vary from normal appearance to tubercles on the surface, ovarian mass, hydrosalpinx and rigid tubes [30]. As per Baxi., *et al*. sensitivity, specificity and negative prediction value of endoscopic evaluations were 85. 7, 22. 2, and 77% respectively when compared to PCR [30].

Histopathological examination

HPE of the specimens show typical features of TB infection in the form of granulomatous caseous lesions. Demonstration of typical caseous granulomas with giant epitheloid cells is suggestive of TB, however these lesions can also appear in fungal infections, syphilis, leprosy, rheumatoid arthritis, systemic lupus erythematosus, pneumococcosis, sarcoidosis [30]. In 110 FGTB patients Mondal., *et al*. [31] reported HPE reports that varied from small-medium epitheloid cells granulomas in different stages of caseation and rare detection of acid fast bacilli (AFB). Feature s of chronic salpingitis include occasional non caseating granulomas in the early stage and single and/or multiple confluent epitheloid granulomas in the lamina propria in the later stage [31]. Caseation and AFB may be observed in the tissue sections of FT's. In ovarian TB, caseation is rare and granulomas are usually observed in the cortical

areas of the ovaries [32]. epithelioid granulomas might be present in cervical TB and caseation and AFB is a rare finding in vaginal and vulval TB [31]. To maximize yield in HPE specimens should be collected from multiple sites since the infecting organisms are scarce in genital TB [33], sampling site may not be infected or the infected site due to cyclical shedding => inadequate granuloma formation in endometrium. Ideal time of endometrial sampling is the late secretory phase of the menstrual cycle [17], that is favourable to identify the classic giant cells and tubercles. For diagnostic tests for menstrual blood, menstrual blood can be collected from the vagina on the 1st day of menstruation [34].

Bacteriology and evaluation

Definitive diagnosis of TB requires the isolation of TB bacilli. Convention methods for diagnosis of TB include microscopy and culture. Microscopy for AFB is a rapid test for diagnosis but with a variable sensitivity [35]. Usually Ziehl Staining (ZN), Kinyon, the acid fast stain, or fluorescent (auramine, rhodamine) staining is used. For ZN staining the yield for a positive result, a sample needs to contains 10^4-10^6 bacilli/ml. Culture for Mycobacterium tuberculosis is more sensitive and needs 10-100 bacilli/ml of tissue /fluid sample for the diagnosis yield [8]. Bacteriologic examination of menstrual blood for smear and culture is recommended by some, but the sensitivity of these tests is very low [36]. For diagnostic tests on menstrual blood, menstrual fluid can be collected from the vagina on the 1st day of menstruation [36]. An acid fast staining of the endometrial curetting's is a rapid test and needs 10organisms/ml for a positive result [17].

Culture

Solid cultures are usually performed on the egg based Lowenstein –Jensen (LJ) medium or agar based Middle brook 7 H10 medium, and the liquid culture is performed using automated BACTEC Mycobacterium/Growth Indicator Tube 960 (based on modified Middle brook7H9 Bro th with an oxygen sensitive fluorescent detection technology [37]. Advantages of liquid culture include its sensitivity, identification of Mycobacterium species and ability to perform phenotypic drug susceptibility tests (DST's) and genotyping for further molecular epidemiology studies. 9-10 days are needed for the growth or positive results and at least 6weeks for being considered negative is the disadvantage of liquid cultures, and for LJ medium cultures, minimum time to positivity is weeks [32]. In 72 infertile women studied Tiangappah., *et al*. [33] showed that the AFB smear positivity and culture positivity were 8. 3 and 5. 2% respectively, when endometrial samples were tested. Positivity in LJ medium and BACTEC for premenstrual samples were 1. 83 and 8. 8 respectively [36].

Molecular methods

Molecular techniques for the detection of TB are increasingly tested and used currently. The nucleic acid amplification tests (NAAT) give results in a few hrs, PCR is a rapid Molecular method for identification of nucleic acid sequences specific to Mycobacterium tuberculosis and other mycobacteria in tissue samples of patients with FGTB. PCR assays can detect <10bacilli /ml including dead bacilli and has a testing time of8-12h [37]. PCR has>sensitivity than culture and HPE and specificity may be as high as 100% in detecting FGTB [12]. Just on basis of positive PCR. Bhanothu and Venkatesan gave a comprehensive overview on the PCR, multigene (MG)/Multiprimer (MP) -PCR. At present, conventional PCR, MG/MP-PCR and/or amplification refractory mutation system (ARMS) - MG/MP-PCR have emerged as scientific innovations and perform significant functions in medical research, mutation analysis and clinical investigations. Although MG-PCR and or ARMS-MG/MP-PCR are considered simple, reliable, monoisotopic, low cost, fast, accurate and relatively easy to perform, the authors suggested it needs to be critically evaluated using huge number of clinical samples occurring across the world before it can be accredited for clinical utilization for diagnosis of FGTB [38].

Treating doctors should not start ATT, just on the basis of a positive PCR in view of high false positivity and need to correlate with clinical evidence and laparoscopic findings [39].

Further Lu., *et al*. demonstrated that T. SPOT. TB (an interferon-γ release assay is an useful adjunct in FGTB diagnosis having a 86. 41% and 75. 45% sensitivity and specificity respectively [40].

Serology

WHO has banned use of serological tests in individuals suspected of any form of active TB, irrespective of HIV status [41]. In a retrospective study Goel., *et al*. compared different methods like HPE, smear microscopy, LJ culture, BACTEC Culture and PCR-DNA for diagnosing endometrial TB in females with infertility. They concluded that none of the available tests were sensitive enough for diagnosing all cases of genital TB, but conv entional methods like HPE and LJ culture still have important role in the diagnosis of endometrial TB in resource limited settings [36]. PCR has high specificity and sensitivity, faster turnaround time but limited by high false positive rates. Recently GENEXpert MTB/RIF assay has been endorsed by WHO for worldwide application that permits the simultaneous detection of M. tuberculosis and resistance to rifampicin. GENEXpert is a useful diagnostic test for all forms of EPTB and gives results in <2h [42]. More research is needed in role of GENEXpert in the diagnosis of EGTB.

Treatment

Treatment of FGTB is just like that of pulmonary TB. The regimens recommended for EPTB is mostly not based on evidence from multiple studies, like those of PTB and the duration of 6mths though is debatable is considered adequate [42], If organisms are sensitive in1st line drugs, six mths regimen is quite effective [42]. WHO recommendations for TB treatment were introduced in 2010 [43]. Patients newly diagnosed with TB should receive a regimen in which rifampicin (R) for mths:intensive phase with isoniazid (H), Ethambutol (E) and pyrazinamide (Z) For 2mths duration followed by continuous phase with HR for 4 mths [44]. Alternative to the daily regimen is that TB patients may receive a daily intensive phase followed by a thrice weekly combination phase [2HRZE/4 $(HR)_3$] For thrice weekly dosing throughout therapy. [2HRZE/4 $(HR)_3$] provided that each dose is directly observed. Retreatment TB patients who default from their 1st Treatment course may receive 2HRZES/1HRZE/5HRE. According to Standards for TB Care Guidelines for new TB patients, the initial phase should consist of 2 mths of HREZ, for four mths [45]. Usage of ATT for duration of six mths consisting of H, R, E, Z for2 mths followed by H and R for the subsequent 4mths for the management of patients with genital TB [6,46]. Very limited literature is available regarding RCT's that have evaluated the optimal drugs and the duration of treatment for genital TB [45]. Patients need to be monitored for side effects during the course of treatment. Monitoring liver function is absolutely essential in view of all 4 drugs may cause hepatitis [44].

Adherence to 1st line drugs is essential since irregular intake can => development of treatment failure, development of multidrug resistant TB along with recurrence of TB and subsequent complications, The bacteriological confirmation of response of treatment is often not possible due to the problems in obtaining follow up samples and lack of follow up guidelines for these patients.

Sharma., *et al*. evaluated 6 patients with multidrug resistant (MDR) FGTB. EB showed positive culture for AFB with R and H resistance in both primary MDR FGTB patients and in 2 secondary MDR FGTB patients who were sexually active. In secondary MDR FGTB patients, 3 pulmonary MDR patients had positive sputum AFB smear and culture, while the patients with MDR lymphadenitis and lymph node aspirates for AFB smear and culture positive with all showing resistance to R and H. Gene Xpert on EB or sputum was positive in 5 (83. 3%) patients. All patients were given category IV drugs using kanamycin (intramuscular), levofloxacin, pyrazinamide, cycloserine.

Ethionamide and ethambutol (or para amino alicyclic acid [PAS] for ethambutol resistant cases) for 6 mths intensive phase followed by oral levofloxacin, cycloserine, ethionamide and ethambutol for 18mth continuation phase. Three (50%) patients (one primary and 2 secondary) have completed therapy while other3 are in continuation phase. All patients were asymptomatic with one having 12 wks ongoing successful pregnancy. Thus they concluded MDR FGTB should be considered in women of FGTB with tubo-ovarian masses who are not responding to 1st line drugs. Gene Xpert can be used in early diagnosis of MDR FGTB [46].

Outcomes of Treatment in FGTB

Laparoscopic findings like tubercles, caseous tubercles and encysted ascites might disappear following ATT; however severe findings like adhesions may persist [47]. Post ATT hysteroscopy findings show significant differences in Grade 1 adhesions and Grade II-IIa adhesions. Spontaneous conception rate varies from 31-59% among Patients treated with ATT for FGTB with better rates in patients diagnosed and treated earlier. Outcomes of pregnancy might be live birth, spontaneous abortion or ectopic pregnancy [48]. ART is considered if patients fails to conceive spontaneously for increasing pregnancy rates. Tripathy., *et al.* conducted a prospective study in India for patients of FGTB and found a 19. 2% conception rate, with a much lower live birth rate (7. 2%) [9]. In PCR positive and PCR negative FGTB patients with infertility treatment with ATT along with ART gave an overall pregnancy rate of 60% in Jindal., *et al.* study [49].

Surgery is rarely used these days, the limited role remains in patients having recurrent pelvic pain, persistent pelvic mass or TB sinus and excessive bleeding. Further drainage of a tubo-ovarian abscess, pyosalpinx followed by ATT may improve treatment outcome, Sharma., *et al*. demonstrated complications while a laparoscopic procedure in FGTB patients when there was an inability to create a pneumoperitoneum, inability to visualize pelvis, excessive bleeding, injury to the bladder and peritonitis. Total abdominal hysterectomy (TAH) with bilateral salpingo-oophorectomy (BSO) is the treatment of choice with proper chemotherapy coverage [49]. Vaginal hysterectomy can be linked to complications like excessive bleeding, peritonitis, bowel injury along with flare up in the post operative period.

Prevention

Initial Prevention of TB include strategies to maximize the risk of exposure to mycobacteria. Thus education of patients with PTB to follow respiratory hygiene at home along with public places along with sticking to standard therapy. As far as genital TB is concerned using safe sexual practices might reduce the chances of acquiring genital infection. Countries like India having a high bur-

den of TB BCG immunization is used as a prevention strategy. BCG Vaccine is up to 80% effective in preventing the severe form of TB, but its protective effect varies widely in the population [50].

Conclusion

A major cause of infertility in India, the prevalence of genital TB is usually underestimated in view of its asymptomatic nature, along with diagnostic challenges. Large multicentric studies are needed to estimate the magnitude of FGTB and to identify the most sensitive test for diagnosis. Treating doctors need to be a part of the evaluation of infertility along with menstrual abnormalities. Most patients present in advanced stage with scarring, severe fibrosis and adhesions, thus treatment outcomes are poor with regards to infertility. Thus aim of early diagnosis and prope r treatment is essential to avoid complications and restore fertility. With increasing development of MDR TB one has to be cautious in starting ATT in patients having false positive PCR results. Newer reports are coming from Tunisia, Bandung, Indonesia, thus one has to be aware about this problem in all Developing countries along with developed countries where Indian migrants are there.

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