Review Article

A Review Article on Genital Tuberculosis and it's Diagnosis

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Abstract

Tuberculosis is one of the top five fatal diseases mostly occur in reproductive age group. Infertility is the commonest symptoms in GTB cases. 90% cases of genital organ get infected by hematogenous spread. Big challenging problem is to be ruled out tuberculosis in asymptomatic patient in shortest possible time. Prevalence is high in either undeveloped or developing countries and less in developed countries. To be safe from tissue damaged in genitourinary organ and other complication it is essential to be ruled out in early stage. Culture and histopathological examination is said to be gold standard. There are many people who are physically and pathologically suspected but on the other hand confirmatory tests are usually fails to detect.

Keywords: Tuberculosis; Genital organ; Histopathology; Prevalence; Reproductive age

Introduction

Among all extra pulmonary tuberculosis Genital Tuberculosis (GTB) is supposed to cause severe tubal disease leads to infertility [1,2]. Tuberculosis is even now world biggest health related problem in which nearly one third of the world's population is affected and causing maximum number of deaths in adult. Most of the cases (90%) come from developing countries. In developing countries GTB incidence occurs 192 to 232 per 01 lakh population whereas death occurs 19 to 30 per 01 lakh population 4.25% to 50% of HIV patient have active TB often extra pulmonary at younger age 4.5%-47.9% of total TB cases comes from extra pulmonary tuberculosis. It commonly affects urogenital organs kidney, bladder, urethra, ovaries, fallopian tube, penis, lymph nodes, pleura and skeleton system. In case of developing countries GUTB is the second most, where as in case of developed countries it is the third most common organ associated with tuberculosis. In male GUTB is commonly found in 40-50 years age group and in female prevalence is twice. Genital organs are involved in 5%-30% of cases. Female genital tuberculosis is most occurring and major cause of infertility worldwide. According to WHO in 2014, 9.6 million people got ill because of TB with 1.5 million deaths worldwide. TB is one of the top 5 deaths causing disease of women at her reproductive stage. Female genital organs are easily infected causing untreatable damage to the fallopian tube causing infertility. From all form of extra pulmonary tuberculosis FGTB is very typical form about 27% worldwide. According to a recent study prevalence of FGTB having infertility was 26% and incidence of infertility with FGTB was 42% in New Delhi. Prevalence of TB in Bihar is very high. In India about 1000 people die every day due to it, even after availability of modern diagnostic and treatment. In HIV endemic area 75% of GUTB patient have HIV and worldwide 15% of TB patient have HIV 5%-13% pulmonary tuberculosis patient get GTB. Infact the actual figure is hard to determine because at least 11% of patient are asymptomatic and diagnosed accidently. In 2015 nearly 5 lakhs women died due to tuberculosis in which 28% had HIV. It is often spread through hematogenous or lymphatic route. Due to genital tuberculosis symptoms arise in female. These symptoms are irregular menstruation, chronic Pelvic Inflammatory Disease (PID), dyspareunia and infertility. Genital tuberculosis is the commonest form of extra pulmonary tuberculosis worldwide (27%) with 9% of all extra pulmonary tuberculosis. In India 3%-16% of GTB patient have infertility. According to the survey carried out by ICMR prevalence of FGTB increased form 19% (in 2011) to 30% (in 2015). Among all infertile female worldwide 5% to 10% have GTB. In developed countries it is 1% and in developing countries it is 13%. It affects persons in their reproductive stages. In India among infertile women 3% have GTB where as in women with infertility due to tubal factor it is 41%. Due to GTB genital organs get irreversible changes resulting infertility. In female fallopian tubes is the most common involving organ. In Australia GUTB incidence is lowest that is 0.69% where as in India it is highest which is 19% 55,120. In India between 1998 to 99, 50% of women get married in

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early age which is reduced to 44.5% during 2006 according to NFHS-III. In different states like Jharkhand which incidence of early marriage was 71%, in Bihar it was 65.2%. Worldwide GTB cases are 5%-10% among infertile women [5-7].

Literature Review

Transmission

Genital organ is mostly affected by FGTB are as follows fallopian tubes 90% to 100%, endometrium 50% to 80%, ovaries 20% to 30%, cervix 5% to 15% and vulva vagina rarely up to 1%. Transmission of disease occurs from infected person to healthy person during talk, cough, sneeze or spit and through air droplets by inhalation healthy person get infected. In female GTB infection spread from intra-abdominal site. Genital tuberculosis can also but rarely spread by sexual intercourse with infected partner. Transmission of disease to different genital organs about 90% occur by hematogenous spread from different sites where as some transmission also occur by descending mode about 7% in which transmission occur through peritoneum bowel and lymphatic mesenteric route where as 3% of transmission occur by ascending route in which transmission occur though visceral route, using infected sputum as a lubricant during sex, coitus with infected partner. In genital tuberculosis the transmission of disease to the genital organ is almost always secondary to pulmonary infection. MTB bacilli present in air reaches to the alveoli during inhalation and causing primary pulmonary tuberculosis. From pulmonary sites it is transmitted to the various organs by hematogenous spread. Among all genitourinary organs most common involve organ is kidney about 80% followed by epididymis 22%-55% of patient. Genital tb can also appear when latent form once again gets activated. Globus minor is the commonest site for hematogenous spread and it is the site from where disease usually starts to grow. TB can rarely infect genital organ directly without involvement of pulmonary organ. Sexual intercourse with infected partner can also spread tb. Morphological changes occur in genital organs after infection but in early stages they are morphologically normal. Earliest changes occur in ampulla region of fallopian tube. Cervix, vulva, and vagina are rarely affected. Due to low vitamin D level break down of host immunity occur leads to re-activation or re-infection of latent tuberculosis. Extra pulmonary tuberculosis occurs by the inhalation of contaminated air with tuberculosis bacilli. Lather on they form ghon focus. Latent form present in body can change in to active form due to pathogen and immune cell interaction. Immunocompetent MTB patient is always at high risk to developed tuberculosis (about 10% life time risk). Before 1950's TB occur due to *M. bovis* which causes TB in cattle and it infect human by consuming infected milk but now pasteurization prevent almost all these incidents [8-10].

Clinical features

Up to 11% of women having GTB may be asymptomatic. In developing countries 80% cases of GTB occurs in 20-40 years group. Due to involve of fallopian tube infertility is the commonest cause of genital tuberculosis. Due to paucibacillary nature it is very difficult to diagnose so a number of evidences are required and commonly diagnosed accidently during investigation for infertility. Common symptomatic symptoms are loss of weight, feeling bad, sweating at night, fever etc. Where as in acute stage fever, discharge from vagina and Pelvic Inflammatory Disease (PID) are common symptoms. ID tuberculosis leads to Fitz-Hugh Curtis syndrome. Other clinical symptoms are infertility, menstrual disturbance vaginal discharge after sex, pregnancy loss, abdominal distension and pain, tumour and chronic pelvic pain. In case of women with GTB at postmenopausal stage symptoms are bleeding, leucorrhoea and pyometra. In most of the cases of GTB cases symptoms like abdominal pain and pelvic examination are not present. Menorrhagia and intermenstrual bleeding is often considered as active TB. Genital tuberculosis of genital tuberculosis of female is basically known as silent and chronic disease because bacilli can remain in latent stage up to 20 years in body which is usually asymptomatic, atypical with low clinical symptoms and evidence.

Materials and Methods

Major problem of tuberculosis is its destruction nature which leads to fibrosis. So it is very important to rule out in its early stages to safe from organ damage. According to WHO diagnosis of EPTB can confirm only on the basis of culture or histology positive finding or strong clinical evidences. Almost all available tests are not enough to confirm the disease. Isolation and culture by laboratory investigation is gold standard for tuberculosis identification. Sterile urine with presence of pus cell can be considered as an involvement of genitourinary organ.

Microscopic examination

ZN stain or Aura mine stain it can identify AFB with sensitivity of 37.1% to 52.1%. EPS (Expressed Prostatic Secretion) can be collected for microscopic examination. To be ZN positive sample should have at least 10^4 to 10^6 bacilli per ml of sample. Endometrial curetting for ZN stain should have at least 10 organisms per ml to get positive result. In case of genital tuberculosis preferred sample should be semen or prostatic secretion similarly in case of urogenital tuberculosis urine sample should be preferred.

Histopathology

Endometrial biopsy traditionally considered the most accepted sample for culture but having low sensitivity in most studies. Granulomatous gaseous lesion with giant epithelioid cell on HPE suggestive of tuberculosis infection. Cervical tuberculosis is commonly misdiagnosed as carcinoma so earliest diagnosis is important. To get

maximum yield tissue from multiple sites should be collected. Endometrial sample should be collected at late secretory phase of menstruation cycle [11-15].

Culture techniques

It is considered as gold standard; its sensitivity is 10.7% to 80%. It takes 6 to 8 weeks. A sample should have 10-100 bacilli/ml of tissue/fluid to get positive yield. Menstrual blood for culture and smear has low sensitivity. Menstrual blood should be collected on the first day of menstruation. According to Thangappah, et al., positivity was 8.3% in case of AFB smear where as it is 5.2% in case of culture when endometrial sample is used. According to Goel, et al., positivity rate was 8.8% in bactec and 1.83% in LJ medium in case of premenstrual sample. Urine sample can be sent for culture but due to presence of *M. smegmatis* culture can be positive.

Solid culture: It requires 8 to 12 weeks. It is gold standard test. Some examples are LJ egg medium, middle brook 7H11 or 7H10, petragnani medium, TK medium is also used for drug susceptibility.

Liquid culture: It is rapid and automated required 1 to 7 weeks. Some examples are TREK/ESP, MB/Bact system, Bactec MGIT 960 (mycobacteria growth indicator tubes) and bactec 460 (gold standard).

Molecular techniques

PCR: Rapid and advance technology requires 1-2 days. Due to false negative and false positive result ATT should not be start. Its sensitivity is very high and can detect both dead and alive bacilli but sample should have at least per ml 10 or more bacilli. According to Jindal et al., high pregnancy rate can be achieved when infertility treatment did according to PCR result with ATT.

NAA: Nucleic Acid Amplification is rapid and has higher yield. It is widely used techniques. It gives results in 2 hr. Its sensitivity and specificity is 80% and 98%-99% respectively. It can detect tuberculosis DNA in 80.9% of GUTB suspected cases. Its sensitivity and specificity on urine sample from 94.3% to 95.6% and 85.7% to 94.3% respectively. But it cannot differentiate whether it is latent or active.

Gene xpert: It is very advance tool which provides report within 2 hrs and have low contamination risk. It is FDA approved culture based technique (gold standard) having specificity of 99%. It also provides rifampicin resistance.

T spot-TB test: It can diagnose both latent and active form it is also called ELISPOT It is based on T cell assay.

Quanti-FERON-TB Gold (QFN Gold): This technique is work on the principle of TB specific antigen known as RD1 based IFN-assay. This test measures immune reactivity component to MTB. ESAT-6 or CEP is MTB antigen, which sensitized T cells. These T cell stimulate IFN gamma. Presence of IFN gamma is suggestive of positive results within 24 hrs. These antigens are not present in BCG vaccine. It has sensitivity is 84%-95% and specificity 85%-99% respectively.

LAMP (Loop Mediated Isothermal Amplification): It is recent and advance based on nucleic acid amplification method under isothermal state [16,17].

Radiological examination

X-Ray: It has found that 10% to 75% of genital tuberculosis patient have abnormal X-ray.

HSG: Due to genital tuberculosis irreversible changes occur in genital organ which can be seen by HSG. Complication of synechiae, tubal obstruction in the transition zone between the isthmus and ampulla are strongly suggestive of tuberculosis.

USG: Dilated and thickened fallopian tubes are visualized under USG. Any abnormalities in genital organs are diagnosed by USG. It is less sensitive compare to IVU or CT. USG can also detect the abnormalities in epididymis.

Laparoscopy: It is a surgical technique in which diagnosis of different organs like ovary, fallopian tubes, peritoneal cavity can be done by visual inspection and also helpful to isolate tissue section for further investigation. It can detect the tuberculosis bacilli from normal appeared genital organs. Baxi, et al., its sensitivity and specificity were 85.7% and 22% respectively compare to PCR.

Intravenous program: IVU is used to diagnose renal tuberculosis. It can diagnose TB in its early stages by detecting changes in calyx.

CT: It can detail about the abnormalities in or outside of renal tract this is strong evidence of GUTB. CT is most sensitive to detect any calcification. CT and IVU are similar significance but USG is less sensitive as compare to CT and IVU.

Other investigations

Serological test: Banned by WHO.

ESR: Raised ESR is not a confirmatory test and not used as a diagnostic test but it is used as supporting evidence where microbiological evidence are lacking.

MT: It has limited significance false positive usually occur due to previous BCG vaccination or present of NTB (non-tuberculous mycobacterial) and false negative occur due to steroid medication, HIV co-infection and in case of recent TB infection etc. According to TST had found positive in 42.6% of GTB patient. According to in laparoscopically confirmed cases TST had sensitivity and specificity of 55% and 80% respectively. In MT stronger the reaction more suggestive of TB. Positive results not significant but used as supporting evidence. In this test tuberculin antigen is injecting subcutaneously and if leukocytosis, leucocyturia, lymphopenia and increase in body temperature occur after 24 hr and 48 hr then it is considered as positive.

Discussion

According to Goel, et al., histopathological examination, AFB smear microscopy, LJ culture method, bactec culture method and PCR DNA technique, none of this test was enough to diagnose all the cases of GTB, but any how HPE and LJ have important role in diagnosis of endometrial TB. Final diagnosis should be made upon good clinical history, careful gynecological examination and advance tools result like endometrial biopsy, imaging, and endoscopy with laparoscopy. Combining history taking, examination and investigation is accurate diagnosis of FGTB [18-20]. Tuberculosis of any form should be ruled out in shortest duration of time to escape from different types of complication like infertility, PID, tissue damage etc. It has also observed that living standard and personal hygiene is the main root cause of tuberculosis and other diseases (Figure 1).

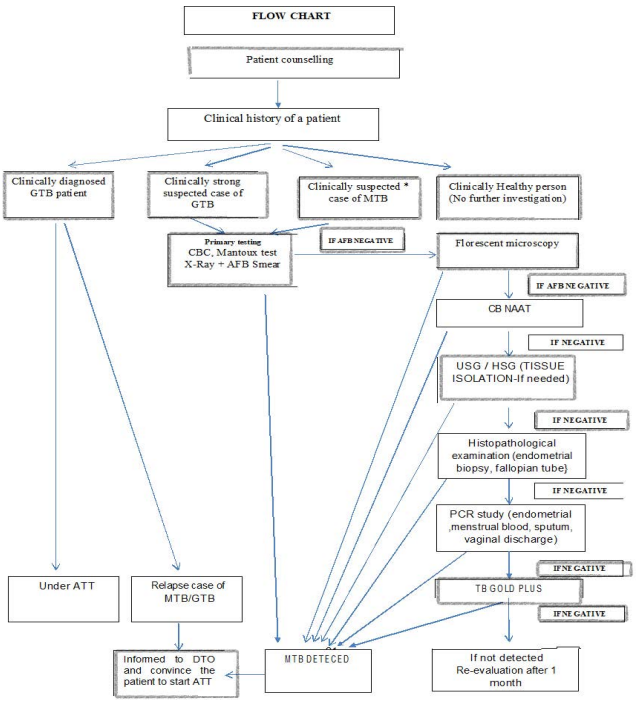

Figure 1: Flow chart of genital tuberculosis and it's diagnosis.

Conclusion

In developed countries where living standard and personal hygiene is well prevalence of tuberculosis is very low but in other hand in undeveloped countries and developing countries prevalence is high due to comparative lower living standard and personal hygiene status. At present there is not a single test which can diagnose tuberculosis in any stage. Even sometimes when all clinical symptoms are suggestive of tuberculosis but all investigations are negative. So most of the diagnosis has done on the basis of clinical history and many radiological and pathological investigations. Also we can't differentiate latent and active phases by any investigations. So further study should be carried out to develop technology which can rule out the disease in its initial stage with accuracy.

Conflict of Interest

No conflict of interest.

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