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Genital Tuberculosis in Females : AOGD Good Clinical Practice Guidelines for Diagnosis and Management#

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Abstract

Tuberculosis (TB) caused by the bacterial pathogen mycobacterium tuberculosis (MTB) is one of the oldest and hardiest diseases known to mankind. The primary site of infection is the lung, spread to other organs can be haematogenous or through lymphatics. 15–20% of all TB cases are extra-pulmonary TB (EPTB). In females, genital TB infection (FGTB) first strikes the fallopian tubes, followed by the endometrium and ovaries with devastating effects. Symptomatology is varied and vague with the commonest presentation being infertility and menstrual irregularity. Diagnosis is difficult due to the pauci-bacillary status and requirement for tissue biopsy. Increase in empirical treatment has contributed to the increase in drug resistance. The aim of these good clinical practice guidelines is to encourage a uniform, evidence-based practice for suspecting, diagnosing and managing female genital tuberculosis in an Indian setting.

Keywords: Anti-tubercular treatment; Female Genital Tuberculosis; Infertility; Latent Tuberculosis; Mycobacterium Tuberculosis.

Key Message

1. Genital Tuberculosis is an important cause of infertility.
2. Asymptomatic GTB is a tissue diagnosis so should be termed 'Subclinical GTB (SGTB)'
3. Diagnosis and treatment of SGTB should be based on a combination of tests.
4. ATT does not reverse existing damage, may not improve outcome of fertility treatment.
5. NTM/MOTT cannot be treated with ATT.

Aim: The aim of these good clinical practice guidelines is to encourage a uniform, evidence-based practice for suspecting, diagnosing and managing female genital tuberculosis.

Standardised case definitions for TB: World Health Organization criteria.

1. *Active disease:* a) Bacteriologically confirmed TB and b) Presumptively treated TB
2. *Latent infection:* The presence of immune responses to MTB antigens (IGRA or TST positive) without clinical evidence of active TB

Summary of Recommendation

A. Definition

1. Genital Tuberculosis is a result of infection by Mycobacterium Tuberculosis (MTB).
2. The disease exists in clinical (symptomatic with actively replicating bacteria) or Sub-clinical state (asymptomatic with presence

of dormant MTB).

3. Disease progression in an individual depends on their immune competence.
4. MTB attacks the fallopian tubes in 90% cases followed by the endometrium leading to gross damage in the absence of specific symptoms.
5. Clinical/Active GTB refers to bacteriologically confirmed disease- HPE, Culture, AFB detected on staining.
6. Latent TB is diagnosed by a positive TST or IGRA in an asymptomatic individual as per CDC recommendations and is not a tissue diagnosis.
7. Since asymptomatic GTB is a tissue diagnosis, it is recommended that the term 'Subclinical GTB (SGTB') should replace LGTB.
8. SGTB is an important cause of infertility in India.

B. *Evaluation*

- Confirmatory specific tests for diagnosis of active GTB are culture of endometrial/ target tissue, HPE, AFB staining.
- Diagnosis of sub-clinical GTB is difficult because of the pauci-bacillary status and lack of specific symptoms.
- Diagnosis of sub-clinical GTB should be based on a combination of tests rather than one single test - NAAT, Koch's culture, AFB staining and Endoscopy.
- NAAT (DNA PCR) pick up cases with low bacterial load. Both dead and living MTB are estimated.
- The traditional non-automated DNA PCR tests have a false positive rate of 20%.
- The test remains positive for a long time so should not be used in previously treated patients to check disease clearance or make a diagnosis of recurrence.
- Gene Xpert is an automated DNA PCR test with a high negative predictive value. Identifies rifampicin resistance. Recommended to reduce false positives.
- IGRA identifies host reaction to primary exposure. IGRA's could contribute supplementary information as part of the diagnostic work-up. (ECDC guidance document).
- Endoscopic evaluation – signs of tubercular infection can be visualized on endoscopy. Definitive signs include caseation. Other evidence eg. hydrosalpinx, pelvic or IU adhesions can be suggestive but not diagnostic as other pelvic infections can mimic the picture. Hence NAAT and Culture are required to clinch the diagnosis. IGRA may help in confirming primary exposure.

There is an urgent need for accurate tests to diagnose SGTB and treat persons with high risk of reactivation and avoid unnecessary treatment.

C. *Management*

1. A decision on management of SGTB based on a combination of tests is more prudent.
2. For active TB i.e culture positive, HPE diagnosis or AFB stain positive, ATT should be advised for 6 months (Index TB Guidelines). Culture should be repeated after 3 months of treatment. Drug sensitivity initially (if possible) or in the event of a repeat positive culture should be carried out.
3. Unexplained Infertility patients with EB positive for DNA PCR (traditional) but negative Koch's culture and IGRA, treatment should be withheld, as it may be a false positive. A repeat IGRA may be done after 3 months to look for conversion. A repeat endometrial tissue sample for gene X-pert can be obtained by curettage under GA.
4. If the patient becomes pregnant IGRA may be repeated at 8-12 weeks of pregnancy as activation of MTB may occur during pregnancy when immunity is altered.
5. In patients of UI if both IGRA and EB for NAAT is positive full course of ATT should be offered. Neither of the tests should be repeated, as they remain positive even after treatment. Repeat treatment on the basis of a positive EB for NAAT is not advised.
6. In patients with TF, Asherman's or frozen pelvis ATT may be offered even when tissue diagnosis is negative. Decision on advising ATT in such a situation rests with the treating physician. ATT does not reverse the damage that has occurred. ATT in these cases may not improve the outcome of fertility treatment.
7. ATT can lead to liver toxicity. Baseline

LFT needs to be done. Monitoring of LFT every 4–6weeks is important if patient is symptomatic or in patients > 35 years old, daily alcohol consumption, abnormal baseline LFTs or a history of hepatic disease. Patient should be apprised to look out for other side effects eg. joint pains, visual symptoms, s/o peripheral neuropathy. (Guidelines for management of adverse effects of ATT)

8. NTM/MOTT cannot be treated with ATT. Clarithromycin and azithromycin are used for treatment. Ofloxacin and ciprofloxacin also seem to be effective.

Introduction

Tuberculosis (TB) is caused by the bacterial pathogen mycobacterium tuberculosis (MTB). It is one of the oldest and hardiest diseases known to mankind. World health organization global tuberculosis report (2013) states that there were 8.6 million incident TB cases globally and India contributed 26% to this global scenario. Epidemiological data indicates that 15–20% of all TB cases are extra-pulmonary TB (EPTB) this figure increases to 50% in HIV (human immunodeficiency virus) infected individuals. Approximately 10% of infected individuals develop active tuberculosis at a later stage of their life, 5% in the first 2 years after infection and 0.1% per year thereafter. *Risk of progression is highest within the first 2 years of exposure. Impaired immunity such as HIV infection increases the risk to 10% per year and ~50% per lifetime.* The remaining infected individuals have asymptomatic or latent tuberculosis (LTB) and do not spread infection to others [1].

Tuberculosis can affect any organ in the body through haematogenous or lymphatic spread from its primary site of infection - the lung. In females, genital TB infection (FGTB) first strikes the fallopian tubes (90%), followed by the endometrium (50%-60%) and ovaries (10–30%), cervical involvement is seen in 5–15% patients (Schafer), vaginal and vulval disease is rare about 1%. Symptomatology is varied with the commonest presentation being infertility and menstrual irregularity (Table 1). One percent of all gynaecological admissions in India and 17.4% in infertility clinics are for GTB [2]. The prevalence of FGTB amongst infertile women in India has been reported to be 18–19% [3].

Host Response to MTB: MTB triggers a complex immune response which develops 4–6 weeks after primary infection. Macrophages have the ability to ingest and kill MTB bacilli however they may persist within the macrophages because of immune escape mechanism [4]. The classic tubercular granuloma contains macrophages surrounded by T & B lymphocytes & fibroblasts. The outcome of infection i.e primary active infection or development of adequate immunity, is determined by the balance between host immunity and bacillary multiplication. Reactivation & development of post-primary TB can occur many years after latency.

Latent Tuberculosis Infection (LTBI): *Latency is a clinical term* suggesting exposure to infection in the absence of any clinical symptoms. Persons with LTBI are asymptomatic, have a negative chest radiograph & are not infectious. Diagnosis is based on a positive tuberculin skin test (TST) or interferon gamma release assay (IGRA). MTB remains viable in people with latent infections and reduced immunity can lead to reactivation. Latent infection has been described as a dynamic process of bacterial persistence & immunologic control. It has been suggested that TB infection should be viewed as a continuous spectrum extending from **sterilizing immunity**, to **subclinical active disease, to fulminant active disease** [5]. This dynamic equilibrium between host and parasite appear to be genetically controlled [6].

Dormancy: *Dormancy is a stable non-replicative state* of the bacterium where bacteria have reduced metabolic activity, including transcription and translation. *It can occur during antibiotic therapy if the bacterium develops a resistant cell wall* preventing penetration of the drug. Dormant bacteria can be resuscitated into a metabolically active growing population by exogenous factors.

Table 1: Symptoms related to genital tuberculosis

Systemic	Infertility	Menstrual	Others
Weight loss	Primary	Amenorrhea	Abdominal swelling
Fatigue	Secondary	Menorrhagia	Post-coital bleeding
Low grade fever		Metrorrhagia	Vaginal discharge
		Oligomenorrhea	Pelvic pain
			Dyspareunia

Reactivation of MTBI and GTB- Risk factors:

9. Immuno-compromise is the most important cause of reactivation. Increased susceptibility in HIV individuals and patients administered biological agents (TNF alpha antagonists) for treatment of arthritis.
10. Surgical manipulation- reactivation has been observed after laparoscopy, hysteroscopy, hysterosalpingography and pelvic surgery.
11. High steroid levels and increased vascularity during ovarian stimulation are thought to be triggering factors in women going through in-vitro fertilization.
12. Use of steroids and immune therapies – common in patients with recurrent implantation failure and recurrent pregnancy loss.

For resource-limited and other middle-income countries where burden of disease is high WHO recommends treatment of LTBI for people living with HIV and children below 5 years who are household or close contacts of people with TB [1]. Given the adaptive ability of the mycobacterium indiscriminate use of ATT has an immense potential to promote drug resistance. In India levels of multidrug-resistance are lower than 2.2% (1.9–2.6) among new cases and as high 15% among retreatment cases [7].

Diagnosis of female Genital TB (FGTB): poses a unique challenge because of an asymptomatic presentation, non-specific signs and symptoms, pauci-bacillary status and poor sensitivity of available tests. We have suggested an algorithm for diagnosis of FGTB (Fig. 1).

Tests for GTB

Specific Tests

- AFB staining
- Culture methods
- Histopathology
- Immunological test
- Molecular tests - Nucleic Acid Amplification Tests (NAAT).

Non-Specific

- Imaging methods.
- Endoscopy

Specific Tests

AFB staining: Ziehl-Neelsen (ZN) staining for acid fast bacilli (AFB) requires 10^4–10^6 bacilli/ml for diagnosis and is not species specific. Detection rate is 10%.

Histopathology: A caseous granuloma with giant epithelioid cells is suggestive of TB. Ideal time for endometrial sampling is late secretory phase of menstrual cycle. Multiple site biopsy is advisable. It is important to rule out pregnancy before taking a pre-menstrual biopsy.

Limitations

1. Similar lesions may be found in other conditions like leprosy, rheumatoid arthritis, systemic lupus erythematous, pneumoconiosis, sarcoidosis, fungal infections and syphilis.
2. In the fallopian tube in early disease there may be non-caseating granulomas while in the ovary, vagina and vulva caseation is rare. TB of the cervix may mimic cervical malignancy.
3. Endometrial shedding leads to inadequate granuloma formation.
4. Bacteriologically mute lesions may be present.

Tissue Culture: Culture remains the gold standard for confirmation and is required for isolating bacteria for drug-susceptibility testing and genotyping. 10–100 bacilli/ml of sample are required and it takes 2–6 weeks for the growth of Mycobacterium in culture. Traditionally Lowenstein-Jensen culture has been used, addition of the BACTEC MGIT™ (mycobacteria growth indicator tube) system has shortened the time to diagnosis to 2 weeks. Observation is continued for 6 weeks before a negative result is reported. BACTEC MGIT is a rapid liquid culture method that utilizes fluorescence technology. It senses oxygen reduction in the culture media, which is then centrifuged and stained with ZN stain to identify MTB. The advantages of liquid culture are its sensitivity, identification of *Mycobacterium* species and ability to perform phenotypic drug susceptibility tests (DSTs) and genotyping for further molecular epidemiology studies. The radiometric culture BACTEC has a sensitivity of 80–90% whereas the LJ medium has a sensitivity of only 30–35% for endometrial sample.

Immunological Tests: TST and IGRA detect an immune response to antigens and consequently do

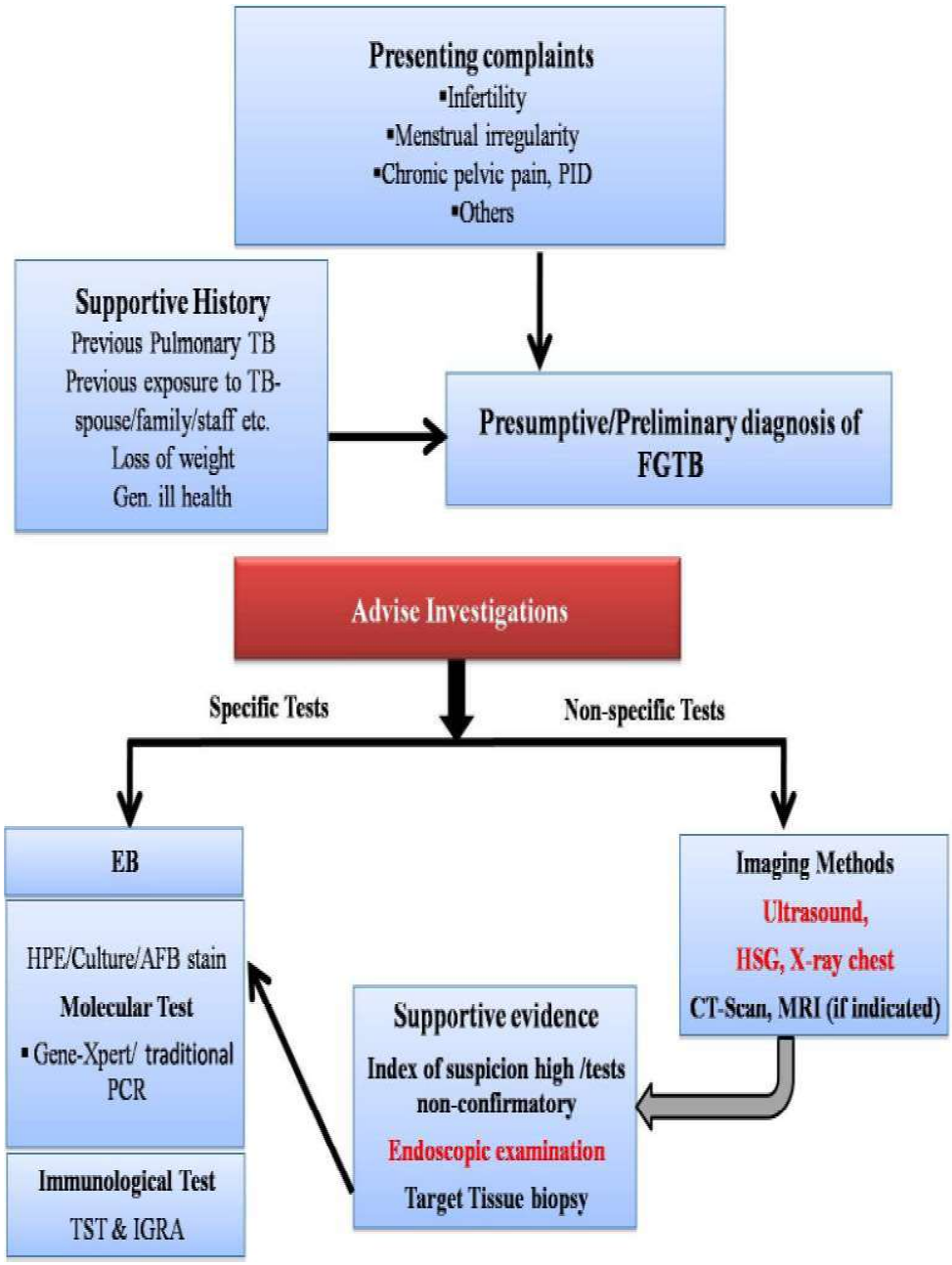

Fig. 1: Diagnostic algorithm for female genital tuberculosis (FGTB). PID (pelvic inflammatory disease); EB (endometrial biopsy); HPE (histopathology examinations); AFB (acid-fast bacilli); PCR (polymerase chain reaction); TST (tuberculin skin test); IGRA (interferon gamma release assay); HSG (hysterosalpingography); CT (computed tomography); MRI (magnetic resonance imaging).

not allow a direct measure of persistent infection (ECDC).

TST: 0.1 ml of tuberculin purified protein derivative (PPD) is injected intra-dermally and read after 48–72 hrs. A positive test reads >10mm but has a low specificity and is not useful in BCG-vaccinated or TB treated populations. False positives are seen in infection with non- tuberculosis mycobacteria and false negative in cutaneous anergy, overwheming TB infection, recent tuberculosis and immune-compromised state.

IGRA's: measure Interferon-gamma (IFN-γ) release in response to the RD1-encoded (genomic region of difference) immunodominant antigens ESAT-6 (early secretory antigenic target-6), CFP-10 (culture filtrate protein 10) and the TB7.7 antigens.

IGRA's cannot distinguish between active TB and LTBI but results are not confounded by BCG vaccination and exposure to NTM. Two commercial IGRAs are available, the QuantiFERON-TB Gold In-Tube assay (QFT-GIT) (Cellestis Ltd., Australia) and the T-SPOT-TB (Oxford Immunotec, UK). Indeterminate results reflect technical factors (e.g. inappropriate storage of blood) or an individual with impaired immune response and a repeat test is recommended. IGRAs are ideal for serial testing and can be repeated any number of times without sensitization and boosting.

The ECDC guidance document suggests that- IGRA's should not replace standard diagnostic methods for active TB. In certain clinical situations (e.g. patients with EPTB, or culture negative patients) IGRAs could contribute supplementary information as part of the diagnostic work-up. A negative IGRA does not rule out active TB. The high negative predictive value (NPV) for progression (99.8%) of IGRAs indicates that *at the time of testing and in the context of an overall risk assessment, progression to active TB in healthy immunocompetent individuals with negative IGRAs is very unlikely in the next 2 years.*

Nucleic acid amplification tests (NAAT): are used to amplify DNA and RNA segments with high specificity for rapid identification of microorganisms. Turnaround time is 48-72 hrs. False positives may occur due to laboratory contamination. A major disadvantage is the inability to detect difference between viable and nonviable organisms. *The test can therefore remain positive for long periods in patients taking anti-TB medications or those who have completed treatment. It should not be used for detection of LGTB1 in patients treated for pulmonary or extra-pulmonary Koch's previously.* False negative results may occur because of the inefficient extraction of the DNA due to low mycobacterial numbers, or the presence of PCR inhibitors. Commercial DNA-PCR tests available are Ampiclor, MTD-2.

Gene-Xpert: The Xpert MTB/RIF (Xpert) assay (Cepheid Inc., Sunnyvale, CA, USA) is a cartridge-based, semi-automated, rapid molecular assay, which permits rapid TB diagnosis through detection of the DNA of MTB and simultaneous identification of a majority of the mutations that confer rifampicin resistance (which is highly predictive of multi-drug resistant TB [MDR-TB]. The entire process is carried out in a closed automated system except for addition of the specimen into the cartridge thus reducing contamination. *WHO now recommends gene Xpert over conventional tests for diagnosis of TB in EPTB as it has pooled specificity of >98.7%, Senstivity - 58.2%, PPV- 66.7% and NPV 97.7% for extrapulmonary specimens.* It can increase detection of MTB in EPTB by 2–3 times as compared to conventional techniques.

Limitation

1. Affected by humidity and heat.
2. Detects non-viable bacteria.

Single tube nested reverse transcription polymerase chain reaction (STN RT-PCR): detects only live organism in the clinical specimen as well as phenotypic drug susceptibility testing. It needs to be *transported in ice to the laboratory within 2 hrs* to prevent degradation of RNA since the average half-life of bacterial mRNA is three minutes.

Of the NAATs only the line probe assay and Xpert MTB/RIF have been endorsed by the World Health Organization for use in low- to middle-income countries.

Role of whole genome sequencing: This may overcome the shortcomings of the NAAT's.

WGS may identify the organism 1-3 days after a liquid culture flags positive.

Comparison of diagnostic tests: There is a significant difference in sensitivities of different tests 33.79% for ZN smear, 48.9% for LJ culture, 55.8% for BACTEC culture, 74.4 % for PCR test.

Diagnostic value of IGRAs has been evaluated for FGTB in two studies.

a) Lui et al. (2016) reported a sensitivity, specificity, PPV, NPV, positive likelihood ratio, and negative likelihood ratio of 94%, 70%, 75%, 92%, 3.09, and 0.09, respectively. T-SPOT.TB appeared valuable for FGTB diagnosis in endemic settings with high sensitivity and NPV [8].

b). Mahajan et al. (2016) evaluated diagnostic accuracy of IGRA in combination with NAAT and culture in GTB [9]. ***They concluded that the high NPV of IGRA could be valuable in ruling out GTB. However, for a confirmatory diagnosis, a combination of tests should be carried out. Importantly EB for DNA PCR was negative in 7 of their cases with positive cultures emphasizing the importance of doing culture.***

Studies evaluating NAAT

a). Shrivastav et al. (2014) comparing PCR technique, AFB culture and staining, [10] found PCR to be most sensitive. Some PCR negative

samples were found to be culture positive.

b). Radhika et al. (2016) comparing diagnostic accuracy of standard tests in infertility, menstrual abnormalities and pelvic inflammatory disease [11] concluded that combination of BACTEC and PCR improved detection.

Studies evaluating Gene Xpert for GTB

Sharma et al.(2014) [12] evaluated 1376 samples with 95 endometrial biopsies in treatment naïve patients. For endometrial samples the specificity was 100%, sensitivity 33 %PPV 100% and NPV 96% Addition of composite reference standard improved sensitivity to 50%.

Non - Specific Investigations for GTB

Imaging: Findings suggestive of GTB on imaging are listed on Table 2.

Table 2: Radiological and ultrasound findings in GTB

Investigation	Findings
X-ray- HSG	*Fallopian tubes first to be affected in TB may appear as:*
	• Beaded - ragged outlines with multiple strictures.
	• Rigid with small terminal sacculations of the ampullary end.
	• Occluded-at corneal or distal end. Distal occlusion has the appearance of a sperm head or tobacco pouch.
	• Gross hydrosalpinx may be seen.
	Uterus and endometrium:
	• Uterine cavity may appear shrivelled, deformed with ragged margins.
	• There may be filling defects.
	• Intrauterine adhesions.
	• Lymphatic extravasation of the dye.
	• Uterine cavity may give maltese cross appearance in case of severe damage.
	• Fistulous tracts between the genital tract and other pelvic organs may be identified.
X-ray abdomen	Calcified pelvic and abdominal lymph nodes.
Ultrasound	*Variable:* ranging from normal findings to:
	Thin endometrium.
	Heterogeneous appearance of endometrium.
	Endometrial fluid.
	Endometrial calcifications.
	Endometrial bands.
	Subendometrial calcifications.
	Intrauterine synechie: Disruption in the continuity of the endometrium or as irregularities in the endometrium surrounded by cystic spaces.
	Tubo-ovarian mass.
	Hydrosalphinx-cog wheel sign.
	Inhomogeneous enlarged ovaries.
	Follicles with echogenic rims.
	Adnexa appears fixed.
	Free and loculated peritoneal fluid.
	On Doppler : Impaired endometrial midcycle vascularity.
	On Sonohysterography : Intrauterine adhesions appear as linear echogenic bridges in the fluid filled endometrial cavity.
	Poor distensibility of the cavity.
CT Scan	Adnexal mass mixed (solid & cystic) with multilocular caseous necrotic enhancement,
	High density ascites.
	Thickened and enhanced peritoneum.
	Lymphadenopathy.
MRI	To masses.
	Lymphadenopathy.
	Intestinal thickening.

Chest Radiograph: Old healed or active infection is usually present in 10-50% GTB.

Endoscopy: remains the gold standard for evaluation of pelvic infection allowing for diagnosis and intervention at the same sitting.

Laparoscopy: findings depend on degree of damage caused by MTB. Unfortunately, these features may also result from gonococcal/pyogenic bacilli infection. Table 3 lists findings on endoscopy. ATT does not improve fibrotic lesions.

Rajaram et al. (2016) conducted a prospective study to estimate prevalence of GTB in patients with chronic pelvic pain correlating laparoscopic findings with microbiological and histological diagnosis [13]. Prevalence of GTB was 36%, concordance of results between laparoscopy and specific diagnostic tests, showed a substantial agreement (kappa value = .716) for PCR. *PCR failed to detect two cases that were positive by culture and histology.*

Baxi et al. (2011) correlating endoscopy findings with EB DNA PCR found that sensitivity and specificity of endoscopic evaluation was 85.71 and 22.8% respectively [14]. Presence of periovarian

Table 3: Endoscopic findings in FGTB

Procedure	Findings
Laparoscopy	Normal
	Subacute stage,
	Congestion, edema and adhesions in pelvic organs with multiple fluid-filled pockets.
	Chronic stage
	Adhesions –
	Pelvic, Peri-tubal, Bowel/Omental adhesions,
	Supra-hepatic adhesions.
	Fallopian tube-
	Hydrosalpinx, Pyosalpinx, Haematosalpinx, Caseo-salpinx.
	Cornual block, Beading, Rigid tubes,
	Fimbrial phimosis, TO mass.
	Peritoneal –
	Straw coloured fluid in Pouch of Douglas
	Tubercles on the peritoneal surface
	Miliary tubercles, white yellow and opaque plaques over the fallopian tubes and uterus.
	Uterus showing intravasation of dye.
	Oophoritis
	Caseous deposits
	Frozen pelvis
Hysteroscopy	Normal appearance
	Bald endometrium
	Spotted endometrium
	Endometrial caseation
	Endometrial calcification
	Endometrial tubercles
	Irregular appearance of uterine cavity
	Intrauterine adhesions
	Distorted ostia
	Periosteal fibrosis
	Caseous material coming out of the ostia
	Poor distensibility of uterine cavity
	Irregular appearance of endocervical canal
	Cervical stenosis/adhesions

adhesions, cornual block, tubal beading, tubercles, intrauterine adhesions, and ostial fibrosis had a very strong association with positive TB PCR.

Hysteroscopy: cyclic endometrial shedding delays appearance of major endometrial changes**.** Table 3 details hysteroscopic findings. The overall incidence of positive TB PCR with hysteroscopic finding was reported to be between 32.18% and 39% [14].

Management

Management of GTB in general gynaecological patients: does not pose a problem if patients are symptomatic and have suggestive clinical features. The larger problem is ensuring appropriate investigation of women for GTB if signs and symptoms are vague eg. AUB, prolonged vaginal discharge, unexplained infertility etc. An algorithm to aid clinicians in the management of FGTB (Figure 2) is suggested.

Management of GTB in Infertile women: is important as delay in treatment may lead to irreversible damage and sterility. *In order to avoid development of MDR-TB empirical treatment or treatment on basis of sole PCR positive should be avoided.* Kriplani *et al.* conducted a prospective randomized study on 100 women with primary or secondary infertility [15]. Women with positive endometrial DNA-PCR, patent tubes on laparoscopy, and all other tests being negative for genital TB were randomized into two groups. Group 1 received ATT for 6 months while Group 2 was not given ATT. The pregnancy rate in both groups did not show any difference (p = 0.422). Their study did not validate ATT for positive DNA-PCR. They also provided evidence that repeating PCR at 6 months and at 12 months has no role and ATT should not be repeatedly given to the patient on the basis of repeat DNA-PCR alone. An ICMR study (to be published) has arrived at a similar conclusion regarding treatment of GTB on basis of EB PCR from MTB.

In endemic areas, all cases of Koch's should be treated with a full course of ATT for 6 months. Treatment for 6 or 9 months has a similar rate of relapse (WHO guidelines). Side-effects of ATT include dermatological, gastro-intestinal, neurological effects and arthralgia. Termination of therapy is reported in 23% patients during the intensive phase (WHO update). *Baseline LFT needs to be done.* Monitoring of LFT every 4-6 weeks is important in patients who are symptomatic, > 35 years, daily alcohol consumption, abnormal baseline LFTs or have h/o hepatic disease.

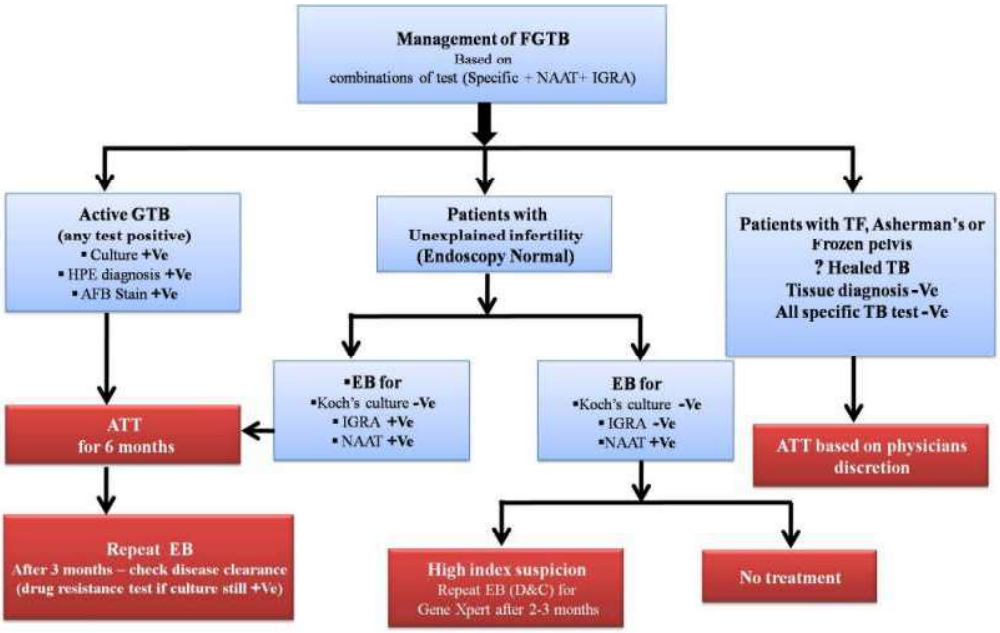

Fig. 2: Management algorithm for female genital tuberculosis (FGTB). EB (endometrial biopsy); HPE (histopathology examinations); AFB (acid-fast bacilli); IGRA (interferon gamma release assay); NAAT (nucleic acid amplification test); ATT (antitubercular treatment); D & C (dilatation and curettage).

Table 4: Adverse effects of ATT

System	Most common adverse effect	Management
Dermatologic Adverse Effects	Cutaneous "flushing" reactions	Mild rash: Symptomatic management / antihistaminics
	Hypersensitivity reactions	Severe-Stop all drugs, identify causative drug by restarting each drug at a lower dose every 4 days
Gastrointestinal Adverse Effects	Nausea/vomiting	Symptomatic management
	Diarrhea	Symptomatic
	Hepatotoxicity	Hepatotoxicity:
		Asymptomatic- SGOT, SGPT <3-5*- continue ATT & monitor
		SGOT, SGPT>3-5* withhold INH till transaminases return to normal
		Elevated bilirubin with normal transaminases: continue ATT. Levels usually return to normal
		Symptomatic Patient
		Rpt LFT
		LFT normal- continue ATT, monitor closely
		LFT abnormal - stop ATT till symptoms resolve and LFT transaminases decrease to < 2x normal
Miscellaneous Adverse Effects	Arthalgias (joint pain)	NSAID's
	Influenza syndrome	Symptomatic
	Neurotoxicity (nervous system)	Pyridoxine 50 mg once a day
	Optic neuritis (vision)	Discontinue drug

Patient need to be apprised of other side effects eg. joint pains, visual symptoms, s/o peripheral neuropathy. In case of severe reactions drugs should be withheld till symptoms improve. Guidelines for management of adverse effects of ATT are given in Table 4.

1. Active GTB: HP diagnosis, MTB Growth on culture

Management: Full course of ATT for 6months. Wherever, possible drug sensitivity should be carried out. Repeat culture after completing 3 months of treatment (2 months active phase and 1 month of maintenance).

2. Sub-clinical GTB: FGTB can lead to serious damage to reproductive organs leading to increased morbidity, infertility and subsequent sterility. Since *infertility is labelled as a symptom the term Subclinical GTB* instead of LGTB should be used. *LTBI diagnosis is based solely on a positive IGRA or TST without symptoms and signs (X-ray) of disease, limiting the ability to detect subclinical disease.*

Patients with unexplained infertility.

a). Normal Endoscopy, EB Koch's culture negative, EB NAAT positive

This could be a false positive. Treatment not advised in the absence of any other signs or symptoms. If index of suspicion is high a repeat EB for DNA PCR using gene Xpert can be done. A supplementary *Negative IGRA is helpful.*

b). Endoscopy normal, IGRA positive. EB NAAT positive, Koch's culture negative. Treatment may be offered to the patient since this could be an early pauci- bacilliary stage of the infection or even a dormant phase which could get re-activated during infertility treatment.

Management: A full course of treatment for 6months is recommended.

c). Only IGRA is positive:

This indicates exposure to MTBI it does not indicate GTB in the absence of tissue diagnosis. In endemic countries *EPTB guidelines do not recommend treatment* of LTBI in high burden areas. If the physician elects to treat on clinical suspicion, then a full course of ATT is advisable in endemic areas rather than a single /dual agent to avoid risk of MDR-TB.

3. Patients with Tubal &/or Uterine factor infertility

Healed/ contained GTB: Pelvic adhesions on laparoscopy &/or Intra-uterine adhesions with negative Tissue culture, NAAT, AFB stain can be classified as healed TBI. The healing process involves fibrosis, the Mycobacterium being sealed within.

Management: Management decision in these cases is difficult as these adhesions can be a result of bacterial infection or a previous surgical trauma. In India since the possibility of Koch's is high, a full course of ATT should be considered especially if there is no previous history of pelvic infection, vaginitis or surgical interference. Isolation of MTB from tissue samples may be difficult. The fibrotic lesion may house viable bacteria which could get reactivated during phases of lowered body immunity. IGRA may be of help in confirming exposure to infection.

Studies suggest that the diagnosis of EPTB especially GTB should be based on a combination of tests. Drugs used for ATT have serious side-effects especially drug induced hepato-toxicity and should preferably be started after adequate confirmatory tests. Indiscriminate use of ATT can also lead to drug resistance with serious consequences. Counselling and a full discussion with patients before giving ATT are of paramount importance, given the increasingly litigative nature of society. *There is an urgent need for accurate tests to diagnose SGTB and treat persons with high risk of reactivation and avoid unnecessary treatment.*

NTM/MOTT

Mycobacteria other than *M. tuberculosis* complex and *M. leprosy* are known as Non-Tuberculous Mycobacteria (NTM) and are known by various acronyms. The incidence of NTM infections is increasing worldwide. They are known to cause a TH1 response. The macrolides clarithromycin and azithromycin have become the cornerstones of therapy for MAC. Ofloxacin and ciprofloxacin are also effective.

Conclusion

Diagnosis of FGTB is difficult due to the pauci-bacillary status and requirement for tissue biopsy. A decision on management of FGTB based on a combination of tests is more prudent. Increase in empirical treatment and indiscriminate use of ATT has contributed to the increase in drug resistance with serious consequences. There is an urgent need for more accurate diagnosis of GTB to avoid unnecessary treatment.

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