FEMALE GENITAL TUBERCULOSIS
India contributes 23% of all tuberculosis (TB) cases in the world. Non-adherence to treatment results in disease relapse, and may develop resistance to anti-TB drugs. Drug-resistant TB poses a major threat to the control of TB in India. The Directly Observed Short course Strategy (DOTS) using a thrice weekly regimen for six months has been the backbone of country’s TB programmes for last two decades.

- **29 March 2016**
  A study showed that anti-tubercular therapy (ATT) significantly improved ovarian function and ovarian stromal in women with female genital tuberculosis (FGTB).

- **18 October 2016**
  According to new study, a high rate of glycemic disorders was seen among patients with tuberculosis and heterogeneity among the diabetic tuberculosis (TB) population.

- **08 November 2016**
  Xpert MTB/RIF assay is a significantly more sensitive and specific test as compared to other conventional tests for diagnosis of tuberculosis.

- **06 February 2017**
  **Rifampicin worsens hypertension in CKD patients**

- **07 February 2017**
  New short-course regimen for multi-drug resistance tuberculosis | Lancet Respiratory Medicine

Illustrated above is Just an example of how much is happening in the field of tuberculosis at a very rapid pace .. new information – every few months, every other month and now ... every other day!!

We are sure that there is more to know and i congratulate president Dr Sheela CN and her team for bringing out this special issue on Tuberculosis with contributions from our members and wish everyone who is reading this – the best of learning!

31st March 2017
Bangalore

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**Dr Hema Divakar**
Consultant and Medical Director
Divakars Speciality Hospital
FOGSI ambassador to FIGO
President FOGSI 2013

31st March 2017
PREFACE

Female genital tuberculosis is a burning issue especially in infertile women around the globe and is an important public health issue in our country. Coexisting HIV infection, MDR tuberculosis, incomplete treatment, morbidity and mortality associated with this disease are of great concern for the clinicians.

Thus we felt the need for a simple monograph on female genital tuberculosis the idea of which was conceived a couple of months ago, and the work is able to see the light of this day because of the quick and effective response to our request by the contributors of the various chapters. The concept of this BSOG Focus we honestly owe to the concept of FOGSI Focus, our parent organization

This is an attempt to put all the aspects of female genital tuberculosis as required for a practicing gynaecologist for suspecting, diagnosing and managing the various forms of genital TB.

We are grateful to our own Dr Hema Divakar, Ex FOGSI president and FOGSI Ambassador to FIGO for writing a foreword for this monograph whose gesture has tremendously increased the weight of this work. We sincerely thank all the contributors of the various chapters who also happen to be in the managing committee of BSOG. We also would like to thank all the people who supported this venture and contributed directly or indirectly to make this dream a reality.

Dr C N Sheela          Dr K Srinivas

EDITORS
PRESIDENT’S MESSAGE

Dear Friends,

Tuberculosis is one of India’s major public health problems and has the world’s largest tuberculosis epidemic. Genital tuberculosis which is more commonly encountered now is a cause of infertility in a significant proportion of women in our country. Being a silent invader, it is hard to diagnose unless a very high degree of suspicion is maintained. It leaves the tubes damaged, and often the endometrium too. Prognosis for fertility is poor even after ATT and ART (assisted reproduction). It affects mainly the women between 20-40 years of age, often robbing these young women of their motherhood, which is most distressful. Confusing array of clinical presentation, diagnostic tests and their interpretation adds to the difficulty in decision making with respect to management.

It was therefore my wish to bring out this comprehensive review on Genital Tuberculosis to update ourselves regarding how best to utilize our clinical acumen as well as the diagnostic modalities, understanding and ensuring correct interpretation, leading to timely and adequate treatment. This will hopefully restrict the damage and preserve fertility in these affected women. It was also an initiative to encourage our team members. Hope this will be useful for all practicing gynecologists.

I immensely thank Dr Srivivas who joined hands in editing this article. I sincerely thank all the contributors for their excellent articles. I am grateful to my team, senior members and past presidents who have encouraged me in bringing out this article. My sincere thanks to Ms Suchitra, Office Secretary, for all the help.

This publication is dedicated to all the young women who have been robbed of their motherhood by this dreaded disease—Genital Tuberculosis

Dr. Sheela C N
President, 2016-17

HON. SECRETARY’S MESSAGE

Dear Friends

I am happy to be a part of the BSOG focus which is another new activity to showcase and encourage the office bearers of this society. The focus is on genital TB in women because according to the recent study by the Indian journal of medical research survey the incidence has increased from 19% in 2011 to 30% in 2015 and it is a matter of great concern because most of them are asymptomatic and by the time it is diagnosed the damage is already done affecting fertility and morbidity immensely. Therefore diagnosis, early and adequate treatment prevents complications and improves outcome.

BSOG focus presents chapters on different aspects of female genital TB with emphasis on early diagnosis and prompt adequate treatment to prevent adverse outcome.

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Hon.Secretary, 2016-17
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“Global actions and investments fall far short of those needed to end the global TB epidemic”


This summarizes the scenario regarding tuberculosis (TB) worldwide. The TB epidemic is larger than previously estimated, though the number of TB deaths and the TB incidence rate continue to fall globally and in India. In 2015, there were an estimated 10.4 million new TB cases worldwide, of which 56% were among men, 34% among women and 10% among children. People living with HIV accounted for 11% of all new TB cases. Six countries accounted for 60% of the new cases and India was one amongst them.

In 2015, there were an estimated 480,000 new cases of multidrug-resistant TB (MDR-TB) and an additional 100,000 people with rifampicin-resistant TB (RR-TB) who were also newly eligible for MDR-TB treatment. India, China and the Russian Federation accounted for 45% of the combined total of cases. There were an estimated 1.4 million TB deaths in 2015, and an additional 0.4 million deaths resulting from TB disease among people living with HIV. Although the number of TB deaths fell by 22% between 2000 and 2015, TB remained one of the top 10 causes of death worldwide in 2015.

India has been engaged in Tuberculosis control activities for more than 50 years. Yet TB continues to be India’s severest health crisis. TB kills an estimated 480,000 Indians every year and more than 1,400 every day. This tragic loss of life, continued suffering, poverty need to end with concerted efforts from all of us.

The National Strategic Plan (NSP) for TB elimination 2017-2025 in India by Government of India has been devised with a vision and goal -

**VISION:** TB-Free India with zero deaths, disease and poverty due to tuberculosis

**GOAL:** To achieve a rapid decline in burden of TB, morbidity and mortality while working towards elimination of TB in India by 2025.

Although pulmonary TB is the primary and the most common presentation of tuberculosis in India, extra pulmonary TB is being increasingly encountered and accounts for about 15-20% of all cases of tuberculosis and more than 50% in HIV positive individuals. Reportedly about 9 per cent of all extra-pulmonary tuberculosis are genital tract TB. Female Genital Tuberculosis, FGTB, is a chronic disease, with very few specific symptoms, often asymptomatic. It is an important cause of significant morbidity, short- and long-term sequelae especially infertility. Incidence varies from 1 to 19 % in India. Prevalence of FGTB in women with infertility was 26% and incidence of infertility in FGTB, 42 %. Several authors have reported that genital tuberculosis as an important causative factor in women with tubal factor infertility not only in endemic but also in non-endemic areas. And also that genital TB is a leading cause for infertility in women seeking assisted conception.

The diagnosis is often a challenge, sensitivity of detection of acid-fast bacilli on microscopy or culture on endometrial
biopsy or histopathological detection of epithelioid granuloma being low. Though PCR for detection of mycobacterial DNA is a rapid, sensitive test, because of risk of false positivity as well as negativity, cannot be used alone to decide on treatment 7,8. This suggests the urgent need for an accurate method for diagnosis of female genital tuberculosis.

Most women with genital tuberculosis have poor prognosis for fertility in spite of ATT 8. Recent evidence suggests that ATT improves ovarian function 9. Therefore high index of suspicion, early diagnosis, timely and adequate treatment may limit the long term sequel including infertility.

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Chapter 2

AETIOPATHOGENESIS OF FEMALE GENITAL TUBERCULOSIS

Dr Thejavathy G V

INTRODUCTION

Genital tuberculosis in females is found in 0.75 to 1% of gynaecological admissions in India with considerable variation from place to place. Tuberculosis (TB) can affect any organ in the body (exceptions being skeletal muscle, cardiac muscles, pancreas) can exist without any clinical manifestation and can recur.

The disease is almost always secondary to primary pulmonary TB, responsible for 5% of all female pelvic infections and occurs in 10% cases of pulmonary tuberculosis. Female genital tuberculosis (FGTB) is typically understood as a disease of young women, especially in developing countries, with 80-90% of cases diagnosed in patients 20–40 years old, often during workup for infertility. The disease has been reported in postmenopausal females as well.

TB was recognized as a clinical entity as far back as 1000 BC. However, it was not until 1744 that Morgagni, following a postmortem examination of a 20-year-old woman who died of TB and whose uterus and fallopian tubes were found to be filled with caseous material, described the first case of genital TB. The word *tuberculosis* was first used in 1834, although Koch discovered the organism only in 1882.

INCIDENCE

The most common form of extrapulmonary TB is genitourinary disease, accounting for 27% (range, 14 to 41%) worldwide. In India the incidence of genital tuberculosis is about 19%. It is estimated that 1% of infertile women, aged between 20-40 years in United States and 3-16% in India suffer from genital TB.

ETIOPATHOGENESIS

Tuberculosis is a chronic infection, caused by different species of *Mycobacterium tuberculosis* complex, such as *M. tuberculosis*, *M. canettii*, *M. africanum*, *M. bovis*, *M. microti*, *M. pinnipedii*, and *M. caprae*. Commonly, *Mycobacterium tuberculosis*, *bovis*, and *africanum* are infectious. While *M. tuberculosis* is the major cause of TB in humans, *M. africanum* sometimes causes pulmonary TB in humans in Africa. Predisposing factors for TB include factors reducing personal immunity like poverty, overcrowding with improper ventilation, inadequate access to health care, malnutrition, diabetes mellitus, smoking, alcohol and drug abuse, end stage renal disease, cancer treatment, hemodialysis patients and patient with HIV infection. Illness occurs either from direct bacterial invasion to any organ in the body or by abnormal immune reactions secondary to mycobacterial products. Tubercle bacilli can remain dormant in tissues and persist for many years. Along with the type of mycobacterial species, duration of exposure, size and infectivity of the strain are also responsible for the difference in infectivity.

Sources of genitourinary tuberculosis

At the time of primary TB, the disseminated microorganisms through the blood stream to different organ systems remain dormant in latent foci. In 5-15% of infected patients, these dormant foci break down (liquefaction necrosis and cavitation) causing dispersion of tubercle bacilli. This secondary disease, or reactivation TB, occurs as a consequence of a decreased cellular immunity.
Genitourinary TB is usually caused by reactivation of these dormant organisms, usually within the first two years following the primary infection by *M. tuberculosis* (90-95%) and very rarely (5-10%) by *M. bovis*, where the source of infection is the gastrointestinal tract.\(^1\)

**Mode of spread:**

Genital TB is almost always secondary to TB elsewhere in the body—usually pulmonary and sometimes renal, gastrointestinal, bone, or joint; occasionally it is part of a generalized miliary disease process. The bacilli reach the genital tract by three principal routes.

The mode of spread is usually hematogenous or lymphatic and occasionally occurs by way of direct contiguity with an intra abdominal or peritoneal focus. The focus in the lung often heals, and the lesion may lie dormant in the genital tract for years, only to reactivate at a later time.\(^6\)

1) *The hematogenous route*: From any of the primary sites pelvic organs are involved by hematogenous route in 90% of cases. Bacillemia may persist for 6 weeks or longer, if the disease is not recognized and treated promptly with antituberculous drugs. The fallopian tube forms a most favorable nidus for tubercle bacilli, with the earliest lesion found in the mucosa. There is almost uniform initial pelvic involvement of the tubes, with subsequent dissemination to other genital organs and the peritoneum. Tuberculous peritonitis is commonly seen with genital tract involvement and may also be associated with rupture of a caseous abdominal lymph node or, less frequently, with spread from an intestinal focus.\(^7\)

2) *Descending direct spread or by lymphatic spread*: Here involvement occurs directly or by lymphatics from infected organs such as bowel, mesentery

   Lymphatic spread, occurs when the primary lesion is in the abdominal cavity. In some countries in which people drink raw milk (unpasteurized), infection which spreads by way of the alimentary tract and caused by the bovine tubercle bacillus is still reported.\(^6\)

3) *Direct extension to the genital tract organs from tuberculous abdominal viscera*, such as the bladder, rectum, appendix, and intestines, has been described. Some researchers believe that this spread is along the peritoneal surface. However, peritoneal involvement can also be the result of spillage of infected material from the fallopian tubes; thus, the primary process is not always clear.

   Once the genital tract is colonized, granulomata containing viable tubercle bacilli form within various pelvic organs. After the development of tubercular hypersensitivity, these generally become clinically silent and intervals of 1–10 years or even longer may pass before infection in this location is reactivated or becomes clinically manifest, if symptoms occur at all.\(^8\,^9\)

4) *Ascending infection*: Vulval, vaginal and cervical lesion may occur by this route. This can happen two ways. Although rare, sexual transport has been reported, as 3.9% men with genitourinary tuberculosis harbour bacilli in semen. It can also occur in a child sitting on infected sputum.\(^4\)

There are reports of primary cervical and vulvar disease in which sexual partners have been thought to be the source of infection. This type of disease may also occur in a woman who has TB of another organ and who excretes tubercle bacilli in her stool, urine, or sputum. When these excretions come into contact with the external genitalia, TB of the vulva or vagina may result, particularly if the skin is abraded or broken.\(^10\)

The fallopian tubes are involved in 90–100 % cases with congestion, military tubercles, hydrosalpinx, pyosalpinx and tubo-ovarian masses. Endometrium is involved in 50–80 % cases with caseation and ulceration causing intrauterine adhesions (Asherman's syndrome) and myometrium in 2.5%. Ovaries are involved in 20–30 % cases with tubo-ovarian masses. Cervical TB may be seen in 5–15 % cases of genital TB and may masquerade cervical cancer necessitating biopsy for confirmation of diagnosis with granulomatous lesion. Tuberculosis of vagina and vulva is rare (1–2%) with a hypertrophic lesion or a nonhealing ulcer mimicking malignancy needing biopsy and histopathological examination.
to confirm the diagnosis. Rarely TB of the vagina can cause involvement of Bartholin’s glands, vesicovaginal and rectovaginal fistula formation. Peritoneal TB can be a disseminated form of TB with tubercles all over the peritoneum, intestines and omentum and may cause ascites and abdominal mass. It may masquerade as ovarian cancer as even CA 125 levels are raised. Varying grades of pelvic and abdominal adhesions including perihepatic adhesions (Fitz-Hugh–Curtis syndrome) are common in genital and peritoneal tuberculosis11.

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Chapter 3

CLINICAL FEATURES OF GENITAL TUBERCULOSIS

Dr Nagarathnamma R, Dr Asha Kiran T R

Tuberculosis has affected mankind from very ancient times. Galen described tuberculosis as “ulceration of the lungs, thorax or throat, accompanied by cough, fever and consumption of body by pus.

Genital tract TB is a chronic disease that often presents with low grade symptomatology and very few specific complaints. Clinical diagnosis requires high index of suspicion. The following history should arouse strong suspicion of genital TB

- Women with family history of tuberculosis (20%)
- Past history of tuberculosis (30-50%)
- Chronic pelvic pain associated with infertility
- Secondary amenorrhoea alone or associated with infertility
- Women with adnexal lump
- Unexplained infertility more than 5 years duration
- Puberty menorrhagia not responding to usual treatment
- Primary amenorrhoea
- Chronic PID in adolescent
- Poor general health persisting over months or years.

These cases should be investigated thoroughly for genital tuberculosis


SYMPTOMS

Approximately 11% of patients are asymptomatic

- General
  Low grade fever with evening rise in temperature, loss of appetite , loss of weight

- Infertility (43 to 74%).
  According to most of the studies infertility is the most common initial symptom. Is caused due to the damage of the fallopian tubes both anatomical and functional, endometrial damage causing Asherman’s syndrome. Rarely can be due to anovulation due to poor ovarian reserve and volume.

- Pain abdomen
  Lower abdominal pain or chronic pelvic pain is present in approximately 25-50% of patients. Pain can be
  1. Pain abdomen (42.5% of cases) which is not severe. Peritoneal, gastrointestinal, urinary and tubercular salpingitis can cause pain abdomen.
  2. Chronic pelvic pain (25 to 40%), due to chronic pelvic inflammation. Can present with repeated pelvic inflammatory disease. Tuberculosis accounts for 6% of all PIDs.
  3. Dysmenorrhoea (12 to 30%): patients present with congestive dysmenorrhoea due to chronic pelvic inflammation.
4. Dyspareunia-5-12%
5. Pain may be aggrevated by HSG and D & C
6. Rupture of TO mass can cause acute abdomen

- **Menstrual disturbances**
  Abnormal uterine bleeding has been reported in 10-40%
  1. HMB is seen in 19% cases.
  2. Polymenorrhoea
     Are seen in earlier stages of infection where there is pelvic congestion secondary to pelvic inflammation
  3. Hypomenorrhoea- 54%
  4. Amenorrhoea (10%)
     Are due to chronic endometrial inflammation, atrophy and synechiea (asherman’s syndrome) formation
  5. Puberty menorrhagia(4%)
  6. Post menopausal bleeding-2%

Other symptoms less frequently seen are

- **Discharge per vagina** is due to pelvic inflammation.
- **Mass per abdomen**
- **Recurrent PID not responding to treatment**
- **TO mass**: Genital TB can mimic ovarian ca. They present as adenexal mass with ascites
- **Ulcers in vulva and vagina**
- **Symptoms associated with urinary and bowel fistulae**

**SYMPTOMS RELATED TO OTHER SYSTEMS**

- **Gastrointestinal:**
  Altered bowel habits, the patient can have either constipation or diarrhea(typically seen is alternate constipation and diarrhea), Pain abdomen.
- **Urinary**
  Tuberculosis should be suspected if there is a urinary tract infection with sterile pyuria and not responding to antibiotics.

**SIGNS**

**Physical examination may be normal in up to 50% cases**

**General examination:** signs which can be found are

1. Poorly nourished
2. Fever
3. Cervical lymph node enlargement
4. Signs of pulmonary tuberculosis

**Abdomen**
1. On palpation abdomen feels doughy suggestive of peritoneal tuberculosis.
2. Distension of abdomen: due to ascitis. Sometimes there is encysted ascitis due to adhesions, characterized by a mass which is tympanic on percussion (due to the bowel loops adherent on the mass).

**Pelvic examination**
1. Mobility of uterus restricted due to adhesions(frozen pelvis)
2. Cervical movements may be tender
3. Adnexal masses(tuboovarian mass, hydrosalpinx)- 23%- Usually less tender- Virgin with bilateral TO mass with h/o any form of TB should rouse a strong suspicion
4. Enlarged uterus due to pyometra
5. Fullness or tenderness in pouch of douglas

Tubercular peritonitis seen in combination with genital tract TB is of two types- plastic variety and serous variety. Plastic variety is characterised by “doughy” abdomen with matting of intestines resulting in partial intestinal obstruction.

The serous variety is seen with ascites, signs of peritoneal inflammation, fever, abdominal pain, weight loss and anorexia.

Lower genital tract tuberculosis is rare. May present with
1. Hypertrophic/ulcerative lesions in cervix, vagina, vulva
2. Labial mass
3. Fistula: vesical, rectovaginal, tubovesical, uterocutaneous etc

TUBERCULOSIS OF CERVIX: Rare (5%), generally as a lymphatic spread from lung primaries. Ulcerative, papillomatous, schirrous and miliary forms are seen. Simulate carcinoma due to friability. Respond well to short course of antitubercular chemotherapy.

DIFFERENTIAL DIAGNOSIS:

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Early diagnosis is crucial for timely treatment and prevention of fibrosis and long term sequel especially infertility. A detailed history, general examination to identify signs of TB at any other site, chest, abdominal and pelvic examination helps in the diagnosis.

In a suspected case of tuberculosis, the purpose of various investigations is to directly isolate the organism, or indirectly look at the effects on the tissues, organs by haematological, histopathological or microbiological methods.

All tests are not required for every case. Following are the various investigations that can be done.

1. Blood and urine examination
2. Chest X ray
3. Mantoux Test and Interferon Gamma Release Assays (IGRA)
4. Mycobacterial smear and Culture
5. Histopathology
6. PCR
7. Identification by Accuprobe
8. FAST plaque TB

**Routine Blood tests**

Routine laboratory studies are of little value as they are nonspecific. Anemia and leukocytosis with a tendency to lymphocytosis (1) and a raised ESR may be seen.

**Chest X ray**

May be of value in excluding concurrent pulmonary TB, which is rare, but signs of previous TB may be present.

**Tuberculin Skin Test (TST)**

The test is based on the fact that infection with *M. tuberculosis* produces sensitivity to certain antigenic components of the organism that are contained in culture extracts called *tuberculin*. The typical Mantoux² method is by injecting 0.1 mL of PPD (purified protein derivative) intracutaneously into the dorsal or volar surface of the forearm. A discrete wheal should be produced. The test is read between 48 and 72 hours after the injection.

A reaction of \( \geq 5 \text{ mm} \) is classified as positive in patients with human immunodeficiency virus (HIV) infection or those with risk factors for HIV infection, in patients who have had recent close contact with infectious TB, and in those who have chest radiographs consistent with old healed TB. A reaction of \( \geq 10 \text{ mm} \) is classified as positive in persons who do not meet the aforementioned criteria but who have other risk factors for TB. A reaction of \( \geq 15 \text{ mm} \) is classified as positive in all other groups of patients.

Mantoux test has limited clinical utility in the diagnosis as a positive test is only indicative of exposure to tubercle bacilli in the past and has poor sensitivity and specificity. A false-positive result may be caused by non-tuberculous mycobacteria or previous BCG vaccination. False negative may be seen in recent TB / recent viral infections/ vaccinations, very young age and incorrect technique and interpretation.
Interferon gamma release assay (IGRA) Quantiferon TB gold test

In vitro laboratory diagnostic test using heparinised whole blood from sensitised persons. Cannot differentiate TB disease from latent infection. It is rapid and not affected by BCG vaccination. TST and IGRA are not recommended for the diagnosis of Tb by Govt of India as advantages are not proved in high burden settings like India.

Mycobacterial smear and Culture

Traditionally, the laboratory diagnosis of TB depends on demonstration of the causative organism, mycobacterium tuberculosis, by acid-fast staining and/or growth of the organism on Lowenstein-Jensen (LJ) medium

Substantial number of TB lesions of the genital tract are paucibacillary and hence demonstration of the Mycobacterium is not possible in all cases. Endometrial biopsy/curettage /aspiration in the premenstrual phase is the most commonly used test for the diagnosis of genital tuberculosis. Menstrual blood within 12hrs is also used for the purpose. In addition, biopsy from TO masses, peritoneal fluid/biopsy, cervical/ vaginal secretions may also be subjected to smear and cultures for diagnosis.

It is important to remember to send the specimen in normal saline for the smear and culture tests and in formalin for the histopathological examination.

Staining methods

- Ziehl-Neelsen (Z-N) staining -Conventional staining method
- Fluorescent staining-
  - Fluorochrome - Auramine-rhodamine
    - Higher sensitivity; faster screening
    - ST: 22-78%

Microscopic examination of acid-fast bacilli (AFB) requires the presence of at least 10, 000 organisms/ml in the sample to be positive. Sensitivity is low.

Bineeta Kashyap et al  in a recent study, attempted to identify endometrial TB in endometrial biopsies taken from women evaluated for infertility by comparison of various staining techniques. They reported sensitivities of ZN, Gabbet, fluorescent and H and E staining were 33, 33, 66, and 66% respectively while their specificities were 100, 100, 98, and 100% respectively. They concluded that, combination of fluorescent staining techniques along with one of the acid fast staining techniques or histopathology achieves sufficient sensitivity and specificity for the diagnosis of female genital tuberculosis.

Culture for Mycobacterium tuberculosis

Culture methods are still the gold standard in the detection of genital TB
- Solid media- Conventional media include the Lowenstein-Jensen Media, Pettragnini, Dorset egg media, Tarshis, Loeffler, Pawlowsky egg based media.
- Liquid media are the Middlebrook’s, Dubos’, Beck’s, Sula’s, and Sauton’s

Sensitivity is low(30-35%) and needs atleast 2 weeks and upto 8weeks for isolation.

The radiometric culture system- BACTEC 460 is more sensitive (80-90%) and results are faster(5-10 days). Useful in drug susceptibility testing and MDR TB. Other rapid diagnostic tests are MGIT and specific gene probes,(DNA and RNA probes)

ENDOMETRIAL HISTOLOGY

Endometrial tissue is obtained at D&C/hysteroscopy directed biopsy. The histologic examination of endometrial tissues removed by biopsy or curettage, especially from the cornual area, affords a rapid method of diagnosing genital TB.
The optimal time for sampling is at the end of the menstrual cycle or within 12 hours after the onset of menstrual flow to allow the endometrial granulomata maximal time to develop. Tubercles are present in the superficial layers of endometrium and are shed during menstruation.

Demonstration of granuloma with or without Langerhans giant cells on histopathology is diagnostic of genital TB. A negative biopsy however does not rule out genital TB.

**Molecular test - POLYMERASE CHAIN REACTION**

PCR is a *rapid*, sensitive and specific molecular biological method for detecting mycobacterial DNA in both pulmonary and extra-pulmonary samples from suspected TB patients.

**Sensitivity** is so high that it can detect even <10 microorganisms in clinical specimens to achieve a positive report and this is an important feature since genital TB is paucibacillary. **Results are available within 1-2 days.** False negative result may be due to contamination and false positive is possible as it cannot distinguish between live and killed bacilli. Hence cannot be used alone to start or stop ATT.

Sharma N et al found it, the method of choice for rapid diagnosis and management of TB. Evaluating PCR, culture & histopathology in the diagnosis of female genital tuberculosis R.B.P. Thangappah et al\(^8\) reported a sensitivity of 57% for PCR compared to 10.7% for histopathology and 7.14% for culture. They found that AFB smear was positive in 8.3%, culture in 5.6%, histopathology in 6.9% and PCR in 36%. They concluded that conventional methods had low sensitivity and PCR was useful in early diagnosis.

However, Arpitha VJ et al\(^7\) who studied the correlation between polymerase chain reaction positivity and laparoscopic findings, reported that PCR appears to be a rapid and highly sensitive diagnostic modality. But by itself it can neither confirm nor exclude genital TB. Endometrial TB-PCR and Laparoscopy are complementary tests and together can effectively confirm an early clinical diagnosis of GTB.

Gunjan Shrivastava et al\(^8\) also reported that the conventional methods of diagnosis like microscopy and culture are less sensitive when compared with PCR. PCR also helped in early diagnosis of infection. However simultaneously, false negative results were an important limitation and PCR negative samples were found to be positive by culture methods. Deoxyribose nucleic acid PCR alone is not reliable for TB due to false positive or negative result. They suggested that both culture and PCR were important diagnostic methods.

Radhika et al\(^9\) comparing the diagnostic accuracy of PCR and BACTEC with Lowenstein-Jensen culture and histopathology, concluded that BACTEC had a sensitivity of 40% with a specificity of 90% while PCR showed a sensitivity and specificity of 62.5% and 54%, respectively, as compared to conventional methods (L-J culture or histopathology). Addition of PCR to BACTEC improved sensitivity from 40% to 52%. They concluded that combination of BACTEC and PCR had an improved detection as compared to conventional tests with an advantage of early results.

Several recent studies\(^10,11\) have concluded that the molecular test, Xpert MTB/RIF assay is potentially a useful tool for the diagnosis of TB and is a sensitive method for rapid diagnosis of Tuberculosis, especially in smear negative cases and in EPTB. Ruvandhi Nathavitharana and Madhukar Pai\(^12\) in CME Journal,(GP CLINICS, Let’s talk TB(supplement) Second edition, 2016) have reported that both ISTC, (International Standard for TB Care) and STIC (Standard of TB Care in India) now recommend the Xpert MTB/RIF assay for both PTB and EPTB as this allows for rapid detection of MTB DNA. It is automated, very easy to use and produces results in 2 hours. Thus, Xpert MTB/RIF should now be considered a central test in the workup of EPTB and should be used along with microscopy, liquid cultures and histopathology.

**Accuprobe:** Gen-probe’s culture identification tests.

- Definitive identification of common mycobacteria.

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**Chapter 4 Laboratory diagnosis of female genital tuberculosis**

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• It is based on hybridisation of nucleic acids.
• Involves 4 steps: sample preparation, hybridization, selection of hybrid and detection of hybrid

**FAST plaque TB:**

• Mycobacteriphage detection system.
• M smegmatis lytic cycle: 90 minutes
• Not expensive, safe.
• Viable bacillie, intact phage receptor
• Affected by effective ATT- monitor treatment success.
• Phage inhibitory substances.
• Analytical ST 100-300 bacilli/ml.

Other supportive tests needs to be done whenever indicated, which may strengthen the diagnosis of tuberculosis

a. Sputum for AFB
b. Sputum culture
c. Lymph node biopsy
d. Spine X ray

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Chapter 5

IMAGING IN FGTB

DR. K SRINIVAS, DR. MANJULA N V

Tuberculosis of the female genital system is one of the most difficult conditions to diagnose with certainty. Various imaging modalities are being used in specific situations for the diagnosis.

X-ray

1. About 75% of cases with active genital tuberculosis have a normal chest X-ray, so a normal chest X-ray cannot exclude the diagnosis of genital tuberculosis.
2. But never the less in genital TB, old healed lesions may be picked up by chest X ray
3. X ray of the spine may show tuberculosis of the spine, cold abscess in the paravertebral area.
4. During the evaluation of infertility certain findings in HSG may support the diagnosis of genital tuberculosis
5. HSG is a good and simple imaging technique and can identify the lesions in more than 70% of cases. The fallopian tube is affected in almost all patients with active genital tuberculosis.
   a. Non specific findings like hydrosalpinx
   b. Multiple constrictions along the whole length of the tube giving a beaded appearance
   c. Most common finding of tubal occlusion either at the isthmus or ampulla
   d. Multiple occlusions and scarring making the tube rigid and giving a pipestem appearance
   e. Cobblestone appearance
   f. Leopard skin appearance
   g. Tubal calcifications
   h. Golf club appearance- Bilateral distal isthmic obstruction
   i. Healing process may produce dense tissue with scar around tubes with decreased tubes motility and makes them fixed - peritubal adhesions
   j. Caseous ulceration of the mucosa of the tube gives it an irregular contour and diverticular outpouching surround the ampulla giving it a tufted appearance
   k. Same process in the isthmic region gives the typical appearance of salpingitis isthmica nodosa (SIN)

Other than the changes in the tubes, uterine changes that may be appreciated in HSG are.

a. Endometritis, Intrauterine adhesions and asymmetrical cavity- All non specific.
b. collar-stud abscess- Specific
c. Tuberculosis T-shaped uterus- TB's scar cause triangular uterine cavity and make T-shape or septate appearance
d. Pseudunicornuate uterus- Unilateral obliteration followed by unilateral scar in uterine cavity
e. Small uterine cavity with irregular contour and resembling septate appearance
f. Complete obstruction of uterine cavity with glove's finger appearance
g. Due to progressive endometrial lesion contrast medium may passed through lymphatic and venous systems- Dye extravasation to vascular channels

Pelvic node calcification also may be detected
The diagnostic criteria established by Klein et al are very useful for TB diagnosis

1. There is calcified lymph node or irregular calcifications in adnexal area.
2. Obstruction of the fallopian tube in the zone of transition between the isthmus and ampulla.
3. Multiple constrictions along the course of the fallopian tube.
4. Endometrial adhesions and/or deformity or obliteration of the endometrial cavity in the absence of a history of curettage or abortion could be detected.

<table>
<thead>
<tr>
<th>Pipe stem appearance</th>
<th>Septate appearance with small cavity</th>
<th>Salpingitis isthmica nodosa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Golf club appearance</td>
<td>Glove’s finger appearance</td>
<td>Dye extravasation to vessels</td>
</tr>
</tbody>
</table>

**Ultrasound scan**

- Adnexal mass in an adolescent girl (Not sexually active) especially with ascitis
- Small uterus
- Atrophic endometrium/ calcifications in the endometrium
- Encysted ascitis
- Saline salpingogram/ sonohysterogram showing adhesions, tubal block etc.,

**CT and MRI and PET scan**

Peritoneal tuberculosis and tubo-ovarian lesions have usually minimal findings at CT and frequently misdiagnosed with peritoneal carcinomatosis. MRI is useful for the diagnosis of tubo-ovarian lesions. Regular pattern of small nodularities along the peritoneum at MRI are helpful findings.

All the advanced modalities are useful in diagnosing and evaluating TO mass

In spite of significant technological advances in imaging noted with ultrasonography, CT and MRI; hystrosalpingography remains the gold standard in evaluating the internal architecture of the female genital tract and fallopian tubes.
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CHAPTER 6

ROLE OF ENDOSCOPY IN FGTB

Dr Vidya V Bhat

Endoscopy in the armamentarium of a gynaecologist has become an indispensable tool for any condition. It is useful both as a diagnostic tool and also as a therapeutic tool. Most often evaluation of cases of infertility, chronic pelvic pain, Abnormal uterine bleeding etc., may involve the use of endoscopic techniques and tuberculosis may be an incidental diagnosis.

LAPAROSCOPIC FINDINGS

Diagnostic laparoscopy is currently the principle modality of diagnosing genital TB because many of the common findings can be seen during the procedure.

In addition, questionable lesions may be biopsied in an attempt to obtain a histopathologic diagnosis.

Tubal findings include hydronephrosis, beading, tobacco pouch or Maltese cross appearance, and calcification, pyosalpinx, occlusion (by chromopertubation), Cornual block, Peritubal adhesions, Rigid tubes, Fimbrial phimosis, Granulomas,tubercules, delayed spill, Shortened tubes, Sacculations/beaded tubes are suggestive of GTB.

Ovary - ovarian tubercules, tubo-ovarian mass, Periovarian adhesions, Associated PCO.

Perihepatic adhesions (Fitz-Hugh-Curtis syndrome), ascites, and caseous or granulomatous nodules.

Associated endometriosis, Bowel and omental adhesions and Isolated tubercles.

- High coloured copious peritoneal fluid (tending to become encysted)
- Periuteritis (non glistening uterine surface), with lepra patches or a thrush appearance
- Blue Uterus on injecting methylene blue
- Perisalpingitis, salpingitis Isthmica Nodosa, beaded tubes, rosary appearance,
- Tubercles, micro & macro caseation (on tube, pouch of Douglas, posterior part of broad ligament)
- Flimsy adhesions in right iliac fossa, pouch of Douglas, left iliac fossa, and the liver area.
- Fibrosis in posterior part of broad ligament, mimicking endometriosis because of breaking of fibrosis typically by ante-verteing the uterus
- Smaller than normal size fibrous uterus
- Synechiae observed by vaginal assistant during elevation of the uterus

Fitz-Hugh–Curtis syndrome is one of the presentation of genital tuberculosis. Liver capsule inflammation leading to the creation of adhesions. The condition is named after the two physicians, Thomas Fitz-Hugh, Jr and Arthur Hale Curtis who first reported this condition in 1934 and 1930 respectively.

Right upper quadrant showing dense adhesions of the liver to the anterior abdominal wall (Fitz-Hugh-Cutis syndrome)
Hydrosalpinx is a distally blocked fallopian tube filled with serous or clear fluid. The blocked tube may become substantially distended giving the tube a characteristic sausage-like or retort-like shape. The condition is often bilateral and the affected tubes may reach several centimeters in diameter. The blocked tubes cause infertility. Tubal tuberculosis is the commonest variety of genital tuberculosis.

The most common finding is pelvic adhesions, followed by tubal pathology (i.e. hydrosalpinx, pyosalpinx) or occlusion (by chromopertubation), peritoneal, fallopian tube, or ovarian tubercules, perihepatic adhesions (Fitz-Hugh-Curtis syndrome), tubo-ovarian mass, ascites, and caseous or granulomatous nodules opportunity to complete more definitive TB testing (i.e. biopsy, culture, and/or peritoneal fluid ADA levels).

HYSTEROSCOPY FINDINGS IN GENITAL TUBERCULOSIS

Hysteroscopy is the gold standard for diagnosing uterine adhesions, distortion of the uterine cavity, and tubal Ostia,

Hysteroscopy is used to evaluate the uterine cavity and tubal ostia and allows for operative treatment in the event uterine pathology is identified. Preferably the procedure needs to be done by an expert under laparoscopic guidance to avoid complications. Distending the cavity may be difficult.

CERVIX - Cervical stenosis, Irregular and ulcerated endocervical canal, Fleshy and hyperplastic cervical erosion not bleeding on touch, and placed anteriorly.

UTERINE CAVITY - Irregular uterine cavity, Intrauterine adhesions, or (ASHERMAN SYNDROME), Synechiae and fibrosis in the uterine cavity, especially precipitated after a curettage. Treatment of intrauterine adhesions, from any etiology, for the purpose of improving fertility outcomes usually involves hysteroscopic adhesiolysis. Small shrunken cavity may be found Unfortunately, the prognosis of Asherman syndrome secondary to TB is much worse because of the extensive endometrial damage that occurs.
ENDOMETRIUM - Scanty endometrium, Endometrial calcification, Caseation/ tubercles, Hyperplasia of endometrium with scanty periods (not bleeding to touch with hysteroscope).

OSTIA - Periosteal fibrosis, Caseous material coming out of ostia, Ostia not visualized, Microcaseation, Non-breathing tubal ostium, focusing as a blocked tube.

Hysteroscopic biopsy of sinister part of endometrium gives more positive histopathological results.

When surgery is advocated, the patient should be given chemotherapy for at least 1–2 weeks preoperatively for following procedures

Hysteroscopic adhesiolysis, second look hysteroscopy,

Laprosopic salpingectomy, adhesiolysis.

REFERENCES


**Chapter 7**

**MEDICAL AND SURGICAL TREATMENT OF FGTB**  
**Dr Shubha Rama Rao**

*Mainstay Of Treatment Is Multiple Drugs Therapy In Adequate Doses For Adequate Duration Of Treatment.*

Short course chemotherapy for 6 to 9mths is as effective. In the olden days ATT was given for 18-24mths, the compliance was poor and there were many side effects.

**DOTS** (Directly observed treatment short course), intermittent observed 6month therapy was found equally effective to 9 month therapy, in a study by Central TB Division, Ministry of Health, GOI, and is recommended for patients. However it is not necessary in developed countries and for women who can afford and are compliant in the underdeveloped countries. DOTS is favoured by WHO to prevent MDR and for better results.

The patient is categorised and given treatment as per the Revised National TB Control Programme (2013). Genital TB is classified under Category I being seriously ill extrapulmonary disease.

<table>
<thead>
<tr>
<th>TB diagnostic category</th>
<th>TB patients</th>
<th>TB treatment regimens</th>
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| I                      | New smear positive patients  
New smear negative Pulmonary TB with extensive parenchymal involvement  
Severe concomitant HIV disease  
Severe forms of extra pulmonary TB (including FGTB) | Initial Phase (Daily or thrice a week)  
• 2 HRZE  
• Dose  
• INH 600mg  
• Rifampicin 450 (600mg if >50Kg)  
• Pyrazinamide 1500Mg  
• Ethambutol 1200 mg for 2 months | Continuation Phase (Daily or thrice a week)  
• 4 HR  
• INH 600mg  
• Rifampicin 450 (600mg if >50Kg)  
• For 4 months |
| II                     | Previously treated sputum smear positive pulmonary TB  
Relapse (Including FGTB)  
Treatment after default (Includes FGTB)  
Treatment failure (FGTB included) | 2 HRZES/IHRZE  
Dose HRZE as in category I  
Inj Streptomycin 0.75G daily or thrice weekly (DOTS) for 2 months followed by 1 month of RHZE |
|                        | 5 HRE  
INH 600mg  
Rifampicin 450 (600mg if >50Kg)  
Ethambutol 1200 mg for 5 months |

In the DOTS centre a full 6month course pack is booked for individual patients with fixed drug combipacks. (H-INH, R-Rifampicin, Z-Pyrazinamide, E-Ethambutol S-Streptomycin)
Regimes

HRZE thrice a week (intensive) x 2 mths under direct observation followed by RH three times weekly x 4 mths.

Three times weekly dosing therapy can be given as DOTS, provided every dose has to be directly observed, and patient is not HIV positive or living in HIV prevalent setting.

Alternatively 2 mth intensive RHZE daily followed by alternate day RH combination for 4 mths can be given.

In case of relapse or failure (Category 2) Treatment includes 2 mths IM of Inj Streptomycin thrice wkly with Intensive phase - RHZE daily for 2 mths, followed by RHZE thrice a week for 1 month, followed by Continuation phase - RHE thrice a week for 5 months.

Non DOTS treatment

Intensive phase - Daily RHZE for 2 mths

Continuation phase - RH daily for 4 mths.

Combi packs are available for patients not opting for DOTS treatment. It is important to emphasise the need to take ATT very regularly. Consumption of good and nutritious food is important to improve general health and immunity of the body. As multiple drugs are used patients should be warned about possible side effects and asked to report immediately.

INH is to be taken after breakfast. It can cause peripheral neuropathy which can be avoided by prescribing pyridoxine. Rifampicin is a hepatic enzyme inducer and can interact with many other drugs. Hence due precautions have to be taken while prescribing other drugs especially Oral contraceptives. (the efficacy reduces as the metabolism is altered)

INH, Rifampicin and pyrazinamide can cause hepatitis. Ethambutol can cause optic neuritis. Streptomycin causes auditory and vestibular toxicity and may need modification of ATT. Liver function tests should be done at the start of therapy especially for patients on rifampicin and repeated whenever patient has vomiting or right upper quadrant pain. Drugs should be stopped if the enzymes are elevated and reintroduced when they normalise.

Monitoring response to treatment.

The response to therapy should be assessed by

- Improvement in the constitutional symptoms and general health.
- Change in the size of pelvic mass, ascites by clinical and USG assessment.
- Change in the ESR.

Endometrial biopsy done 3 monthly

Decision to changeover to second line therapy and need for surgical intervention can be made on assessment of clinical response to treatment.

Surgical treatment

Need for surgical intervention is limited as the medical therapy is highly effective in the treatment of FGTB. Indications for surgical intervention are as follows

- Diagnosis is in doubt
- Drainage of large residual pelvic or tubo-ovarian abscesses, pyosalpinx.
- Persistent symptoms of fever, pain, ascites.
- Presence of fistulae.
- Fertility evaluation after treatment.

Surgical intervention required may be laparoscopy, laparotomy or hysteroscopy. The chances of complications such
as haemorrhage, injury to bowel, bladder and other pelvic structures during surgery are higher due to the presence of dense adhesions, matted bowel loops. The uterus and adenexae may be buried underneath the dense adhesions making the access very difficult. In such cases biopsy must be taken from representative areas and the abdomen closed, instead of a difficult pelvic clearance which may carry the risk of fistula/sinus formation, followed by complete medical treatment.

In younger women, ovarian conservation should be attempted. In cases of advanced TB the prognosis for fertility is poor. The risk of ectopic pregnancy increases should these women conceive.

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4. Overview
Chapter 8

INFERTILITY AND FGTB

Dr Shobha N Gudi

FGTB can lead to serious damage to the reproductive organs leading to infertility and subsequent sterility. A recent study suggests that GTB is responsible for 1% of all gynecological admissions in India and 17.4% in infertility clinics. The prevalence of GTB in India is reported to be 18%–19% among infertile women, and is very variable, reported as 39% by Parikh et al in 1996. However, in another study in 2001 by Tripathi and Tripathy, it is reported as only 3%. This is partly because of the spectrum of clinical presentation from latent to active to florid disseminated disease. Patients present with a variety of symptoms, the most common presentation being subfertility or menstrual irregularity.

Causes for infertility

a. Ovulation issues- anovulation, tubo-ovarian masses, Decreased Ovarian reserve and volume
b. Tuboperitoneal: Adhesions. Motility problems, mucosal blocks, tubal block at various sites, hydrosalpinx, kinking, salpingitis isthmica nodosa, etc.,
c. Endometrial: adhesions, atrophy, implantation problems, cornual lesions

Factors responsible for infertility

• Inflammation
• Fibrosis
• Atrophy
• Toxins
• Mechanical obstruction
• Inflammatory mediators

Aim of the Investigations

• Confirmation of diagnosis
• Activity of the disease assessment
• Site of involvement
• Assessment of damage and its extent
• Formulating the best option to improve fertility

The diagnosis is made by detection of acid-fast bacilli on microscopy or culture on endometrial biopsy or on histopathological detection of epithelioid granuloma on biopsy. Polymerase chain reaction may be false positive and alone is not sufficient to make the diagnosis. Laparoscopy and hysteroscopy can diagnose genital tuberculosis by various findings.

Management of genital tuberculosis in infertile women

So far, evidence is lacking in support of treatment of FGTB in infertile women. Results of fertility outcome in treated cases is not significantly better than for women who were found to be DNA PCR positive but were not treated with
ATT. An overview is therefore necessary, to establish some practice guidelines. After arriving at a diagnosis all cases should be treated with a full course of ATT as incomplete treatment has a high risk of developing drug-resistant TB.

Management of causes for infertility:

Management decision in these cases is difficult as these adhesions can be a result of bacterial infection or a previous surgical trauma. However, in India, since the possibility of Koch’s is high and isolation of MTB is fraught with difficulty, a course of ATT for 6–8 months should be considered, especially if there is no previous history of pelvic infection, vaginitis, or surgical interference. The bacterium may still be viable within the fibrotic lesion and may get activated at a later time when patient immunity is low.

Iatrogenic REACTIVATION in infertile women

Immuno compromise is the most important cause of reactivation of dormant bacterium as seen in HIV positive individuals. Reactivation can also be initiated during surgical manipulation and has been observed post laparoscopy, hysteroscopy, hysterosalpingography, and pelvic surgery. High-steroid levels and an increased vascularity during ovarian stimulation are thought to be the triggering factors in the infertile population going through in vitro fertilization (IVF). Empirical use of steroids and immunotherapies is common in infertile patients with recurrent implantation failure and recurrent pregnancy loss, and these too increase the risk factor for reactivation.

Interventional procedures

- Hysteroscopic adhesiolysis
- Laparoscopic assessment, but usually surgical procedures to be avoided as they are associated with the risk of complications including fistulae
- Cornual blocks may be treated with cannulation
- ART may be the only option for these women.

ART in FGTB

Most women with genital TB present with infertility and have poor prognosis for fertility in spite of ATT. The conception rate is low (19.2 %) with live birth rate being still low (7 %) in Tripathy and Tripathy series. Parikh et al. found IVF with ET to be the only hope for some of these women whose endometrium was not damaged with pregnancy rate of 16.6 % per transfer. Jindal observed IVF–ET to be most successful out of all ART modalities in genital TB patients with 17.3 % conception rate in contrast to only 4.3 % with fertility enhancing surgery. Dam et al. found latent genital TB responsible for repeated IVF failure in young Indian patients in Kolkata presenting with unexplained infertility with apparently normal pelvis and non-endometrial tubal factors. If after ATT their tubes are still damaged but their endometrium is receptive (no adhesions or mild adhesions which can be hysteroscopically resected), IVF–ET is recommended. However, if they have endometrial TB causing damage to the endometrium with shrunken small uterine cavity with Asherman’s syndrome, adoption or gestational surrogacy is advised to them.

Conclusion: FGTB is an endemic problem in India especially in the infertile population. Early diagnosis and appropriate treatment can result in successful pregnancies. In advanced stages, careful individualization, counseling and multidisciplinary approach will yield better results. ART should be offered to a select few after ensuring the quiescent nature of disease as hormonal treatment of ART can result in disease reactivation and is highly counterproductive.

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Chapter 9

TUBERCULOSIS IN PREGNANCY

Dr Shashikala Karanth, Dr Sheela C N

Introduction

Pregnancy happening in association with tuberculosis is relatively infrequent when compared with infertility being associated with this disease.

Despite tuberculosis being a global problem, maternal tuberculosis remains an unrecognised and underestimated tragedy, especially in south Asian countries. The exact incidence of tuberculosis in pregnancy, though not readily available, is expected to be as high as in the general population, with possibly higher incidence in developing countries like India. India accounts for 30% of the burden of all cause in the world. Exact incidence of tuberculosis in pregnancy is not available in the Indian context too because of poor reporting system. Tuberculosis associated with HIV infection and drug-resistant tuberculosis present special challenges in pregnancy because of teratogenic effects of second-line antituberculosis agents.

Effect of pregnancy on Tuberculosis

Pregnancy is not known to cause progression of the disease except in women with quick succession of pregnancies which can reactivate latent TB. Drug compliance is the determining factor for this. Pregnancy was found to have no adverse or beneficial effect on the course of TB according to sputum conversion rate, stabilisation of the disease and relapse rate. Coexisting HIV infection is known to augment the progression of TB and worsens the immune suppression.

Effect of TB on pregnancy

Tuberculosis and pregnancy are two different types of stresses experienced by women, it may affect her both mentally and physically. It has been best described as a double edged sword, one being the effect of TB on pregnancy and the pattern of growth of the newborn while the other is the effect of pregnancy on the progression of TB. TB has multiple implications on maternal health. Prolonged debility, lack of social support, complications of TB, nutritional deficiency and need for prolonged anti TB medications put an enormous pressure on maternal physical and mental health.

The effects of TB on pregnancy depend on various factors such as the severity of the disease, site and extent of TB, HIV co-infection, and gestation at diagnosis and treatment initiation, nutritional status of the mother, presence of concomitant disease, immune status, and patient compliance.

The pulmonary and extra pulmonary forms of TB effect pregnant in the same way as the non-pregnant women.

Obstetric complications that have been reported in these women include a higher rate of spontaneous abortion, small for date uterus, and suboptimal weight gain in pregnancy. Others include preterm labour, low birth weight and increased neonatal mortality. Late diagnosis is an independent factor, which may increase obstetric morbidity about fourfold, while the risk of preterm labour may be increased nine folds due to delay in initiating ATT to late pregnancy (Early initiation has no such effects). However recent studies have reported that no unusual increase in preterm labour or other adverse pregnancy outcome happens in treated cases of TB.

Poor nutritional status, hypopro-teinemia, anaemia and associated medical conditions add to maternal morbidity and mortality. If pregnant women were compliant to anti TB treatment this can be reduced.
Diagnosis of TB

Diagnosis of tuberculosis in pregnancy can be extremely challenging, even to an astute clinician because of its insidious onset, protean manifestation, nonspecific nature of symptoms, and overlapping presentation with other infectious diseases. All common symptoms of TB like loss of appetite, tiredness, fatigue, shortness of breath and sweating, may mimic common symptoms due to the pregnancy itself. The weight loss associated with the disease may also be temporarily masked by the normal weight gain in pregnancy. Even in symptomatic patients, often diagnosis gets delayed because of reluctance of clinicians to perform radiological investigation in pregnant women and relative difficulties in accessing health care facilities especially in rural areas because of multiple social, economic and cultural barriers.

Management of TB

The management of tuberculosis in pregnancy is a multidisciplinary approach, with the team comprising the obstetrician, communicable disease specialty personnel, neonatologists, counselling unit, and public health officials. Though most of the cases could be pulmonary Kochs, extrapulmonary TB too occurs frequently and the treatment regime depends on this too. Treatment is achieved through the use of Directly Observed Therapy, Short Course (DOTS). This therapy entails the use of combination therapy for at least 6 months. This combination includes isoniazide and rifampicin compulsorily, supported by ethambutol and pyrazinamide. These drugs are considered safe for use in pregnancy and have no proven teratogenic effects. Pyridoxin 10 mg/day should always be given with isoniazid. The dosage and duration of therapy are not modified due to pregnancy. The women should be monitored for compliance and toxicity of the drugs. Hepatotoxicity of isoniazid remains a major concern especially during peripartum period. Drug susceptible TB and good drug adherence will cure 90% of TB cases.

Post partum management.

Management of neonate born to mother with tuberculosis

Congenital infection by vertical transmission of TB is described by transplacental transmission through umbilical veins to the foetal liver and lungs; or aspiration and swallowing of infected amniotic fluid in utero or intrapartum causing primary infection of foetal lungs and gut. Transplacental infection occurs late in pregnancy and aspiration from amniotic fluid occurs in the perinatal period. Mothers who have completed antitubercular treatment (ATT) before delivery or have received ATT for at least two weeks duration before delivery are less likely to transmit the disease to the newborn.

Aim is to ensure TB free survival of the newborn. If congenital tuberculosis is diagnosed, standard ATT must be started. INH prophylaxis is recommended for 3-6 months in the neonate if the mother has received treatment for <2 weeks or sputum smear positive. BCG vaccine is recommended at birth or after completion of prophylaxis. WHO recommends 6 months of prophylaxis, testing for Mantoux after 2 weeks and if negative BCG vaccine. IAP recommends a minimum of 3 months of prophylaxis to all neonates, till mother is sputum negative.

Breast feeding

Breastfeeding should be continued in these neonates and isolation is recommended only if mother is sputum positive, has multidrug resistant tuberculosis or non-adherent to treatment. Expressed breast milk feeding is an alternative, with personal hygiene. Barrier nursing using face mask and appropriate cough hygiene has been advised for the mothers who are breastfeeding. First line ATT is secreted in milk in small quantity and causes no adverse effects. WHO recommends feeding under all circumstances, however, reducing close contact with the baby.

Contraception

Rifampicin is known to reduce the efficacy of oral contraceptive pills by stimulating 450 which increases their metabolism. Therefore OC pills with higher dose of estrogens or an alternative method must be used to prevent contraceptive failures.

Pregnancy in MDR- TB patients

Pregnancy is not a contraindication for treatment of active drug-resistant TB, but poses great risk to the lives of both
the mother and fetus. Pregnant patients should be carefully evaluated, taking into consideration the gestational age and severity of drug-resistant TB. The risks and benefits of treatment should be carefully considered, with the primary goal of smear conversion to protect the health of the mother and child, both before and after birth. However, since the majority of teratogenic effects occur in the first trimester, treatment may be delayed until the second trimester when the patient is very stable with minimum disease. Delaying treatment carries a risk as TB can advance quickly in a pregnant patient.

A decision to start treatment in the first trimester or to postpone until after the first trimester should be agreed to by at least the patient and the doctor, after analysis of the risks and benefits. When the condition of the mother is so poor that a pregnancy would carry a significant risk to her life, a medical abortion may be indicated. The decision is based primarily on clinical judgment of the severity of the disease, the effective treatment and care options available, and assessment of the risk/benefits with the mother. Detailed counselling is necessary regarding potential maternal–foetal hazards and scope for therapeutic abortion. Teratogenicity has been described with aminoglycosides, capreomycin and Ethionamide and patients taking these agents should be advised to take measures to avoid pregnancy. Despite limited data on safety and long-term use of fluorquinolones (cycloserine, para-aminosalicylic acid (PAS) and amoxicillin/ clavulanate) in pregnancy, they are considered the drug of choice for MDR-TB treatment during pregnancy.

If the injectable agents, ethionamide/prothionamide, or other drugs were withheld because of the pregnancy, they can be added back postpartum to make a more complete regimen

**TB in pregnancy and HIV infection**

HIV infection and TB during pregnancy are considered a ‘deadly combination’ and are independent risk factors for maternal mortality. HIV co-infection affects approximately 4–5% of all TB incidence cases in India. TB-HIV co-infection is a significant non-obstetric cause of maternal mortality primarily in resource-limited countries. Immunological changes during pregnancy may predispose to the susceptibility of new infection and the activation of latent TB infection. Whether this increased risk of TB in HIV-infected women is further increased by being pregnant, remains unknown.

Active tuberculosis disease in HIV-infected pregnant women increases the risk of maternal mortality by nearly 300%. Neonatal mortality is considerably high among TB-HIV co-infected women compared to HIV-uninfected pregnant women. Its management during pregnancy demands special expertise, judicial sequential combination of anti-TB drugs and anti-retroviral drugs.

Among HIV-infected Indian women, studies found a high incidence of post-partum TB and co-infection with TB has substantially increases the post-partum maternal death and death of their infants. Studies also has been reported that maternal TB, mostly detected after delivery, is associated with increased mother-to-child transmission of HIV. Therefore, prevention of TB among HIV-infected mothers should be a high priority for communities with significant HIV/TB burden. This raised a serious concern regarding the strategy of screening and managing latent TB during pregnancy in the context of India, and other South Asian countries, where isoniazid prophylaxis is not advocated at present in latent TB. It has been suggested that active screening and targeted use of isoniazid preventive therapy among HIV-infected women in India should be considered to prevent post-partum maternal TB in HIV patients.

Management of tuberculosis/HIV co-infection in pregnancy is complicated. It remains unknown whether pregnancy affects the metabolism of ATT or whether ART interacts with ATT differently during pregnancy. Treatment regimens for active or latent TB in patients with HIV infection are similar to those used in HIV-negative patients, but dose adjustments may be necessary. The most significant differences involve the avoidance of rifampin in patients who are on protease inhibitors. Rifabutin may be used in place of rifampin in such patients.

Perinatal mortality, intrauterine growth restriction, and low birth weight are higher among women with tuberculosis/ HIV coinfection as compared with HIV or tuberculosis monoinfection. Infants of HIV-positive women who developed tuberculosis in the first year were more likely to die and to be HIV-infected than infants born to mothers with HIV alone.

In settings with high burden of TB and HIV, successful implementation of PMTCT programmes in HIV-infected women, with earlier initiation of ART, is critical to reduce maternal and infant morbidity and mortality. In addition,
preventing TB deaths among HIV-infected women requires intensified scale-up of TB prevention, diagnosis and treatment interventions within maternal health and TB programmes. Basic antenatal TB screening should routinely be included in high burden TB/HIV settings, and the high risk of TB in the postpartum period should also be considered in TB screening guidelines. The use of improved molecular diagnostics, including Xpert MTB/RIF, may reduce diagnostic delays and result in more rapid initiation of antituberculosis treatment. A high degree of clinical awareness is essential to diagnose TB in pregnancy and the postpartum period. Improved recording and reporting of maternal TB and treatment outcomes during pregnancy will contribute to better estimates of disease burden, and inform much needed guidelines to improve TB case finding and outcomes amongst women and their infants.

Conclusion
The wide array of opinion of Medical practitioners on tuberculosis in pregnancy simply reflects the Public Health significance of the condition. Improving knowledge of tuberculosis and MDR-TB amongst antenatal care providers, more proactive screening for tuberculosis and MDR-TB, and availability and optimum use of new accurate rapid tuberculosis diagnostic tests must be coupled with accurate recording, collection, and reporting of disease-specific demographic and epidemiological data will help to reduce the morbidity and mortality related to tuberculosis in pregnancy.

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Chapter 10

CHALLENGES IN MANAGEMENT OF FGTB

Dr. Aruna Muralidhar

INTRODUCTION

Clinicians have been grappling with Tuberculosis for decades now due to its unique features such as chronicity with low grade symptomatology and very few specific complaints. Presenting symptoms of genital tuberculosis particularly are generally varied; infertility being the most frequent clinical presentation (43-74%). Other clinical presentations include oligomenorrhea (54%), amenorrhea (14%), menorrhagia (19%), abdominal pain (42.5%), dyspareunia (5-12%) and dysmenorrhea (12-30%).

Challenges continue to exist at the Policy making level and at the clinical level. Despite various national programmes; identification, proper treatment and follow up are a monumental task.

At the clinical level, the diagnostic dilemma arises because of the varied clinical presentation of the disease confounded by diverse results on imaging, laparoscopy, histopathology and a mixed bag of bacteriological and serological tests, each of which has its limitation in diagnostic sensitivity and specificity.

Francis stated that the incidence of genital TB varies not only with the prevalence of extragenital TB in the community but also with the physician’s interest in searching for the disease!

CHALLENGES IN DIAGNOSIS

The clinical diagnosis of genital TB requires a high index of suspicion. About 20% of patients with genital TB give a history of TB in their immediate family. Patients with genital TB will give a history of prior diagnosis or treatment of extragenital TB approximately 30–50% of the time.

Examination

35–50% of patients have an entirely normal examination. Most studies reveal that physical examination can be normal in up to 50% of cases of female genital TB. When abnormal findings are present, they usually consist of adnexal masses or signs of ascitis.

Tuberculous tuboovarian masses are less tender than those due to pyogenic infection, although secondary infection and acute exacerbation may produce sharp pain and tenderness. Other pelvic lesions, such as fibromyomas, ovarian cysts, and adenomyosis, as well as cervical cancer, may coexist with genital TB. The presence of active extragenital foci of TB, as a rule, is rare when the genital lesion is discovered. In Minimal TB, there may not be any physical findings whereas in advanced TB, tuboovarian masses may be present.

Investigations

Diagnosis is based on a positive tuberculin skin test (TST), a delayed hypersensitivity reaction to the purified protein derivative of MTB or a T-cell response to MTB-specific antigens and NAA tests.

There are limitations with various investigations used in diagnosis.
Sputum smear microscopy has a lack of sensitivity especially in HIV co-infection and extrapulmonary TB, and is unable to detect drug resistance. Culture has the disadvantage of slow turnaround time (13-21 days) but is still the gold standard. In comparison to solid LF media culture, liquid systems are more sensitive for detecting mycobacteria and may increase the case yield by 10% over solid media. Liquid systems are, however, more prone to contamination by other microorganisms. Several manufacturers have recently marketed tools that can automatically detect M. tuberculosis growth in the laboratory, such as the Bactec “Mycobacterial Growth Indicator Tube 960” (MGIT 960; Becton-Dickinson, Sparks, MD, USA) and the MB/Bact Alert 10 3D (Biomérieux, Durham, NC, USA). Unfortunately, these automatized incubators are expensive, they do not give rapid mycobacterial species’ identification, and they do not identify contaminated or mixed cultures. Conversely, cultures on solid media provide all of this information with a simple observation of colonies.

The current guideline recommends that all specimens cultured on liquid media also be inoculated on solid media to ensure purity and sufficient strength for the diagnosis.

Nucleic acid amplification (NAA) tests are a reliable way to increase the specificity of diagnosis, but the sensitivity is too poor to rule out disease, especially in smear-negative (paucibacillary) disease where clinical diagnosis is equivocal and where the clinical need is greatest. NAAT tests have the disadvantages of high cost, and limitation of being negative in smear negative cases.

Gene Xpert is a rapid PCR test which is both reliable and sensitive in diagnosing both paucibacillary and active TB. The test costs about Rs. 2000 under the IPAC. It also detects Rifampicin- resistance which is a marker of MDR/XDR-TB. However, even this test has the problems of suboptimal sensitivity, cross-contamination of samples, limited shelf-life of the diagnostic cartridges, some operating temperature and humidity restrictions, requirement for electricity supply, unknown long-term robustness, and the need for annual servicing and calibration of each machine. In a large population in developing countries, the introduction of this test may not be cost-effective and may in fact divert funds to diagnosis rather than effective treatment. Development of multiplex-PCR may help in detecting M.bovis which is quite prevalent. Since M.bovis is pyrazinamide- resistant, initial treatment can be modified.

Patients of MDR and XDR-TB are diagnosed very late; due to which resistance to a large number of drugs develops, making treatment difficult. Main reason for late diagnosis is lack of mycobacteriology laboratories in the neighbourhood which can perform culture and susceptibility testing with reliability. The challenge is, establishing quality assured laboratories for diagnosis and monitoring of MDR-TB. We must have a wide network of such laboratories all over the country. It also requires trained manpower and specialized equipment which are also not available presently at many laboratories.

CHALLENGES IN TREATMENT

Optimal management of TB with the current drug regimens require a long treatment time to achieve cure. This generally happens as a few of the subpopulations may display phenotypic drug-resistance in response to altered environmental signals. The most effective of the TB drugs at killing actively replicating tubercle bacilli is Isoniazid, while Rifampicin, an inhibitor of RNA synthesis, is active against both replicating and non-replicating bacteria. Pyrazinamide, acts by inhibiting energy metabolism across the cell membrane, is a pro-drug requiring acidic conditions. The combination of Rifampicin and Pyrazinamide has helped in reducing the longer term of treatment to 6-9 months currently.

Surgery should be considered for a patient with bacilli resistant, or probably resistant, to all except two or three relatively weak drugs. Unfortunately many such patients will have too extensive disease and/or too poor lung function for surgery to be possible. If the patient has a large localized cavity with little other disease, reasonable lung function and only two or three (weak) drugs available, surgery should be seriously considered.

Although, the WHO introduced DOTS programme has been implemented, multi-drug resistant TB has become a huge problem.

Strains resistant to at least INH and RMP are referred to as “multi-drug resistant” (MDR-TB). Recently strains that are resistant to INH, RMP, fluoroquinolones and at least one second line injectable drug (capreomycin, kanamycin,
or amikacin) are defined as “Extremely drug resistant” (XDR-TB).

Treatment of MDR TB must rely on second line drugs which are less effective and more toxic than first line therapy, as well as up to 110-fold more expensive overall. The mortality rate in a recent outbreak of XDR approached 100% a XDR TB has thus come to worldwide attention as a major therapeutic challenge and potential threat to public health.

The most important predictors of drug-resistant TB are

- A previous episode of TB treatment
- Persistent or progressive clinical and/or radiographic findings while on TB therapy
- Residence in or travel to a region with high prevalence of drug-resistant TB
- Exposure to an individual with known or suspected infectious drug-resistant TB

**Special situations**

Challenges are posed in patients with co-infection with HIV as well. Interactions of rifampin, non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) with cytochrome P450 3A4, create a significant therapeutic obstacle in the treatment of these patients. The anti-retrovirals and isoniazid can both cause peripheral neuropathy, and their toxicity is enhanced when used together. Rifabutin may have to be considered instead of rifampicin in these cases

Improving TB treatment focuses on achieving several goals:

- Shortening the duration of treatment for active TB to improve compliance, lessen the burden on public health infrastructure, and reduce the occurrence of MDR-TB.
- Developing safe, tolerable drugs with novel mechanisms of action that will therefore be effective against resistant disease (MDR-TB and XDR-TB).
- Developing TB drugs that lack liver cytochrome P450 enzyme induction and inhibition, to avoid drug-drug interactions, especially with ART, and facilitate treatment of patients co-infected with M. Tb and HIV.
- Developing safe and effective drugs to shorten the treatment of latent TB, thus making it possible to address the problem of the biologic reservoir of M. Tb.

It may be a real challenge for investigators to design a drug that should fulfil the above criteria.

**FERTILITY AND TB**

Achieving pregnancy is a real challenge for the infertility expert in patients with genital tuberculosis. Even after treatment with ATT, overall conception rates are very poor (varies between 10-20%) and depend on the endometrial involvement. In general, IVF- ET is the better option rather than surgical correction of anatomical distortions of the uterus and tubes and ovulation induction. The risk of ectopic pregnancy and miscarriage are high in those who conceive. Prior to the development of extensive fibrosis and adhesions of the endometrium, presence of M. Tb in the basal endometrium may lead to impairment of endometrial and sub-endometrial blood flow. The use of PCR and Doppler parameters to assess endometrial receptivity may help in prognosticating the IVF cycle.

**CHALLENGES IN FOLLOW UP**

The duration of treatment and the ATT regime depends on various factors including the degree of disease, the culture results and HIV co-infection. The major determinant of complete cure and non-development of MDR-TB is the adherence to the regime over the entire course. Monitoring must include a vigil for ATT- induced hepatoneurotoxicity. Also Patient response to treatment should be monitored by doing endometrial curettage 6 and 12 months after the initiation of treatment. Patients need to be followed closely for an indefinite period. Recurrence or
dissemination to other organs is rare but occasionally occurs. Chest radiographs, urine cultures for M. tuberculosis, and uterine curettage should be repeated at the end of the treatment course, with a repeat curettage or endometrial biopsy every 6–12 months.

Conclusion

Global increase in multidrug resistant Global TB rapid resistance testing to assure appropriate initial treatment for the patient, and to initiate TB control activities like contact investigation, treatment of close contacts, decisions about isolation etc. Currently, the high priorities seem to be more sensitive tests for TB (esp. in children, HIV-positive, patients with extrapulmonary only disease), rapid resistance tests, and simpler tests with lower risk of cross-contamination. Also, adherence to the regimen and various modifications in ATT regimen seem to be of utmost importance to reduce MDR-TB.

Finally, in the words of Dr. R.C. Jain, Vice Chairman of National Tuberculosis Association of India

‘To defeat TB, we require both rigour and persistent efforts. We should develop a strong political will for TB control. Researches have to be done to find out an ideal diagnostic test, develop new drugs and vaccine, and an alternate and less expensive strategy than DOTS with same or better effectiveness. Programme achievements and successes have to be sustained and maintained for decades to have an effect on epidemiology of TB. Complacency has no role in TB Control.’

The irony is that the disease of antiquity has been the most difficult to conquer and is posing challenges at every step of its revelation.

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<td>No specific clinical manifestations make the situation difficult to suspect in a given scenario and hence a high index of suspicion is required in certain cases</td>
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<td>3.</td>
<td>Diagnosis is really challenging and the earlier diagnostic techniques are out of recommendation and latest ones are less specific with very high sensitivity and thus false positive diagnosis happens more often</td>
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<td>Combination chemotherapy success is challenged by the organism by multidrug resistance (MDR)</td>
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<td>Damages caused are so devastating that future fertility of the woman becomes highly compromised</td>
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<td>Special situations like association with HIV infection, with pregnancy, other atypical strains, co existing morbidities, side effects of drugs make the situation more complex</td>
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<td>Imaging modalities may give some strength to the clinical suspicion but not diagnostic of the condition</td>
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<td>Endoscopy could be the best available modality for near perfect diagnosis which may be proved by a biopsy which can be obtained during the endoscopic procedure itself.</td>
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<td>World TB day being celebrated globally on the 24th of March and the revision of strategies by the various organizations show the research work going on this one of the oldest infection known to mankind.</td>
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<td>10.</td>
<td>Social, familial, ethical issues continue to haunt the clinician in addition to the clinical challenges faced with a case of female genital tuberculosis</td>
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