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NEWSLETTER

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CONTENTS

NEWSLETTER Obstetric Medicine

From the Editor's Desk

Dear Members,

We all come across pregnant women with tuberculosis and it poses difficulties in many ways. Many of the symptoms associated with extra pulmonary tuberculosis like malaise, nausea, loss of appetite and weakness are often mistaken as normal manifestations of pregnancy and hence we need to have a high index of suspicion for tuberculosis in pregnancy, especially for extra pulmonary tuberculosis. Reluctance in ordering a Chest X-ray often results in delay in diagnosis of pulmonary tuberculosis too. This issue of our newsletter includes an overview of tuberculosis in pregnancy, genital tuberculosis and laboratory diagnosis of tuberculosis which is the same as that of outside pregnancy.

It is needless to mention the relevance of this special issue on pregnancy and tuberculosis! I am sure you will have some questions unanswered and some comments and we hope to hear from you in the form of letters to the Editor. The theme for the next issue of our newsletter would be **'Thrombophilias in Pregnancy'.** Please do send in your articles and contribute to the next issue of our newsletter. You can submit interesting case reports, original articles, review articles and letters to the Editor with comments on previous articles. Your article will be reviewed by the editorial board before acceptance for publication. You can send in your articles to obsmedindia@gmail.com with a copy to the Editor, drharikishan@gmail.com. I also request you to encourage your colleagues and friends to join the Society of Obstetric Medicine, India (SOMI).

Let me also to take this opportunity to invite you all on behalf of SOMI, to the Obstetric Medicine Conference to be held on October 4th and 5th in Hyderabad. Looking forward to your presence at the conference and contributions to the newsletter.

Dr. Hari Kishan Boorugu
Editor

NEWSLETTER Obstetric Medicine

Tuberculosis in Pregnancy

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Introduction

Tuberculosis (TB) is believed to be nearly as old as human history. About one-third of the world's population (estimated to be about 1.75 billion) is infected with tubercule bacillus (1) and as much as 75% of individuals with TB are within the economically reproductive age group of 15 to 54 years (2). Progress made in the diagnosis, treatment and control of tuberculosis has been substantially undermined by the HIV-1 epidemic, the growing challenge of drug resistance, and other increasingly important epidemiological factors that contribute to fuel the tuberculosis epidemic (3).

Twenty-two countries account for 80% of worldwide tuberculosis burden and the five countries that rank first to fifth in the world in terms of total numbers of incident cases in 2009, were India, China, South Africa, Nigeria and Indonesia (4). India also leads in the total number of drug resistant cases and, along with China, contributes to about 50% of the worldwide burden of MDR tuberculosis (5).

There has been a resurgence of tuberculosis in India over the last few years. Large scale population migration from rural areas to urban slums, poverty, overcrowding, poor sanitation, malnutrition, and the appearance of drug resistant strains of Mycobacterium has led to the upsurge of the disease. In addition, with the spread of HIV infection the incidence of tuberculosis has increased concomitantly (6). (FA)

Mycobacterium tuberculosis infection occurs most frequently during the childbearing years and worldwide, TB is the number one infectious cause of death among women, killing more than 1 million women each year. TB currently is responsible for more deaths annually than all other causes of maternal morbidity combined (7). In communities in which TB is endemic, pregnant women are at high risk, especially for infection with resistant organisms.

Etiopathogenesis

Mycobacterium tuberculosis was first identified by the German scientist Robert Koch in 1882.

Mycobacterium tuberculosis is an obligate intracellular pathogen that can infect several animal species, although human beings are the principal host. It is an aerobic, acid-fast, non-motile, non-encapsulated, non-spore forming bacillus and is one of five members of the Mycobacterium tuberculosis complex, others being *M. bovis, M. ulcerans, M. africanum,* and *M. microti.* Other Mycobacterium species that may infect humans include *Mycobacterium leprae, M. avium, M. intracellulare,* and *M. scrofulaceum.*

Almost all tuberculosis infections are caused by inhalation of infectious particles aerosolized by coughing, sneezing, talking, or manipulation of infected tissue. Other modalities of transmission may, however, include ingestion of unpasteurized milk and direct implantation through skin abrasion or the conjunctiva.

Pathophysiology

Tuberculosis can affect almost every organ in the body but in more than 80 percent cases it involves the lungs (8). Aerosolized tuberculosis particles with sizes ranging between 1 and 5 microns are carried to the terminal air spaces of high-airflow areas, where multiplication of the bacilli occurs. Following phagocytosis by pulmonary macrophages, a granulomatous reaction may be initiated, in conjunction with the regional lymph nodes, thereby forming the Ghon's focus. The bacilli remain in a state of dormancy within the Ghon's focus, from where they may later become reactivated.

An estimated 2 billion people worldwide have latent *M tuberculosis* infection (9). With advances in technology, our understanding of pathogenesis and protective immune responses to infection with *M tuberculosis* is constantly growing. *M tuberculosis* has evolved elaborate survival mechanisms in human beings that allow it to remain in a clinically latent state, although the mechanisms of persistence remain incompletely defined. The high rates of clinical tuberculosis in people infected with HIV and in those with various inherited defects of the interferon-γ signaling pathway indirectly suggest a key role for the adaptive immune responses after antigen recognition by specific T cells (10,11).

Tuberculosis in Pregnancy

Views as to whether the incidence of tuberculosis is increased by pregnancy have varied over time. The Hippocratic view that pregnancy was beneficial to tuberculosis was generally held until the 19th century(12).

By the early 20th century opinion had swung to pregnancy having a deleterious effect on tuberculosis, so much so that abortion was recommended (13).

The exact incidence of tuberculosis in pregnancy is not readily available in many countries due to a lot of confounding factors. It is, however, expected that the incidence of tuberculosis among pregnant women would be as high as in the general population, with possibly higher incidence in developing countries (14, 15). In India, the disease is responsible for killing more women of reproductive age than all the combined causes of maternal mortality and gives rise to nearly one-third of the female infertility in the country.

Effect of Pregnancy on Tuberculosis

Pregnancy has neither a beneficial nor a detrimental effect on the course of TB, including sputum conversion rate, stabilization of the disease and relapse rate (16), as long as it is diagnosed and treated appropriately without delay (17). It is the anatomical extent of the disease, the radiographic pattern and the susceptibility of the individual woman to TB, rather than pregnancy itself, which determines the course and prognosis of the disease in pregnancy.

Researchers like Hedvall (18) and Schaefer (15) also demonstrated no net benefit or adverse effect of pregnancy on the progression of TB. Frequent, consecutive pregnancies may, however, have a negative effect, as they may promote recrudescence or reactivation of latent tuberculosis. It is, however, important to note that the diagnosis of tuberculosis in pregnancy may be more challenging, as the symptoms may initially be ascribed to the pregnancy. The weight loss associated with the disease may also be temporarily masked by the normal weight gain in pregnancy.

Effects of Tuberculosis on Pregnancy

The presentation of tuberculosis in pregnant women is similar to that in non-pregnant women (19) but diagnosis may be delayed by the non-specific nature of early symptoms and the frequency of malaise and fatigue in pregnancy. The most common site in pregnancy is pulmonary but 5-10% of patients may have extra pulmonary disease.

SITE	CLINICAL FEATURES
Pulmonary TB 90% have pulmonary involvement (44)	■ Asymptomatic. ■ Persistent cough – the most common symptom. Initially dry and non-productive but may later become productive with haemoptysis in some cases. ■ Breathlessness – a late feature. ■ Chest pain – relatively uncommon. Dull, ill localized. ■ Localised wheeze
Lymph Nodes Most common site of extra pulmonary disease	■ Gradual painless enlargement of lymph nodes (> 4 weeks), fluctuant swelling, superficial ulceration and sinus formation with discharge
CNS TB Responsible for 5% of extra pulmonary disease. Associated with significant morbidity and mortality	■ Headache, vomiting and altered behaviour. ■ Focal neurological signs ■ Decreased level of consciousness after a few weeks or months.
Bones and Joints	■ Low backache – often mistaken for a physiological change associated with pregnancy ■ Isolated lesion of the joint or mono arthritis ■ Local tenderness over spine, loin or psoas abscess.
Gastrointestinal TB	■ Unexplained, non-specific pain abdomen ■ Acute abdomen in some cases ■ Associated with weight loss, anorexia, altered bowel habits.
Other sites	■ Genitourinary, miliary, skin and pericardial TB are very rare in pregnancy.

The effects of TB on pregnancy may be influenced by many factors, including the severity of the disease, how advanced the pregnancy has gone at the time of diagnosis, the presence of extra pulmonary spread, and HIV coinfection and the treatment instituted. The worst prognosis is recorded in women in whom a diagnosis of advanced disease is made in the puerperium as well as those with HIV co-infection. Failure to comply with treatment also worsens the prognosis (20). If anti-tuberculosis treatment (ATT) is started early in pregnancy, the outcome is same as that in non-pregnant patients, whereas late diagnosis and care is associated with 4-fold increase in obstetric morbidity and 9-fold increase in pre-term labour (21). Poor nutritional states, hypo-proteinaemia, anaemia and associated medical conditions add to maternal morbidity and mortality.

Studies have revealed that pulmonary TB, if associated with late diagnosis, increases the obstetric morbidity in the form of pre-eclampsia or acute respiratory failure. A higher incidence of postpartum hemorrhage and difficult labour has also been noted in mothers with TB compared with control subjects (22, 23, 24). Extra pulmonary TB has no direct effect on the course of pregnancy, pre-eclampsia or mode of delivery but is associated with maternal morbidity in the form of recurrent admission rates and disability as well as increased mortality in cases of TB of the central nervous system and other complications (25). Other obstetric complications that have been reported in these women include a higher rate of spontaneous abortion, fetal growth restriction, and suboptimal weight gain in pregnancy (26).

Diagnosis of Tuberculosis in Pregnancy

Careful history taking and assessment of risk factors plays a crucial role in reaching a diagnosis of TB in pregnancy. High index of suspicion is required as most of the symptoms may be nonspecific in pregnancy (31). These include, night sweats, evening rise of temperature, progressive loss of weight, chronic cough for more than 3 weeks duration and hemoptysis. Laboratory diagnosis of TB is discussed in detail in a separate article.

Risk factors for TB
■ Close contact with infectious cases ■ Belonging to ethnic minority community ■ Living in or travelling to places where TB is still very common ■ Low immunity due to HIV, Diabetes or other medical disorders ■ Poor socioeconomic status, drug abuse, migrant worker, alcoholism ■ Overcrowding, including living in hostels.

INVESTIGATION	INTERPRETAION
Mantoux test	Reaction is classified by the diameter of induration perpendicular to the long axis of the forearm. ■ 0-4mm – negative. No action required ■ 5-10mm – doubtfully positive ■ 10-15mm – reactive in high risk cases ■ >15mm – positive in all cases
Chest X-ray ■ Radiation exposure of <0.01mGy- safe	■ Patch or nodular shadows in the upper zones ■ Loss of volume and fibrosis with or without cavitation ■ Primary focus in latent TB
Other imagining ■ CT/MRI of spine, abdomen, brain etc to be done with caution after appropriate counselling	■ Depends upon the site of the lesion
Smear/ Culture sensitivity ■ Gold standard	■ Gram positive acid-fast bacilli seen May be negative in paucibacillary cases
Interferon-gamma release assays ■ Immunological test such as QuantiFERON Gold or T-SPOT. TB	■ QuantiFERON TB Gold in-Tube assay reports a value of ≥35 IU as a positive test ■ T-SPOT.TB reports a value of ≥6 spots as a positive value

In India, under the revised national tuberculosis control programme (RNTCP), sputum examination done as per an algorithm is the preferred method for diagnosis of pulmonary TB (32). A chest X-ray (performed after shielding the abdomen) is done if all the 3 sputum smears are negative and symptoms persist despite giving antibiotics for 1-2 weeks. The presence of suggestive radiographic abnormalities and a medical officer's decision to treat with ATT labels the patient as a "smear-negative' TB case. A pregnant woman with extra-pulmonary TB has constitutional and organ-affection symptoms. Routine haematology and Mantoux test (not commonly advocated in programme) along with investigations specific for the site are carried out for the establishment of specific diagnosis. Co-existence of HIV infection should specially lead to a thorough search for any extra-pulmonary tuberculous focus.

Treatment of Tuberculosis

"Untreated tuberculosis represents a far greater hazard to a pregnant woman and her fetus than does treatment of the disease" (33).

The management of tuberculosis in pregnancy is a multidisciplinary approach, with the team comprising the obstetrician, chest physician, communicable disease specialty personnel, neonatologists, and public health officials.

The aims of treatment are to:

- Achieve cure without relapse
- Prevent progression of the disease or occurrence of complications
- Stop transmission to other individuals, health care professionals or newborns and
- Prevent emergence of drug resistance.

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, depending on the combination of antituberculous agents that are available. This combination includes Isoniazid and Rifampicin compulsorily, supported by Ethambutol and Pyrazinamide (34, 35). This cures about 90 percent of cases. The use of these first-line antituberculous drugs in pregnancy are considered safe for the mother and the baby by the WHO (36).

ISONIAZID – INH is safe during pregnancy even in the first trimester, though it can cross the placenta (38, 39). The women must, however, be followed up because of the possibility of INH-induced hepatotoxicity. Pyridoxine supplementation (50mg OD) is recommended for all pregnant women taking INH to reduce the risk of peripheral neuropathy.
DOSE: 3 – 5 mg/kg

RIFAMPICIN – This is also believed to be safe in pregnancy, though in an unknown proportion of cases, there may be an increased risk of hemorrhagic disorders in the newborn while some other researchers reported the possibility of limb deformity but none of these are in excess of what is obtained in the normal population. Rifampicin is an enzyme inducer and may also cause hepatitis and cutaneous hypersensitivity (39).
DOSE : 10 – 20 mg/kg

ETHAMBUTOL – It is safe in the standard doses, however, retrobulbar neuritis is a rare but serious complication which may need discontinuation of the drug. Studies have now shown that there is no interference with the ophthalmological development of the fetus (39,40).
DOSE : 15 mg/kg

PYRAZINAMIDE – Used with caution in pregnancy even though many international organizations now recommend its use, including the International Union Against Tuberculosis And Lung diseases (IUATLD), British Thoracic Society, the World Health Organisation as well as the Revised National Tuberculosis Control Programme of India. There are no reports of significant adverse events from the use of this drug in the treatment of TB in pregnant women [48]. Its use is particularly indicated in women with tuberculous meningitis in pregnancy, HIV coinfection, and suspected INH resistance (39, 41).
DOSE : 20 – 30 mg/kg

STREPTOMYCIN – The drug has been proven to be potentially teratogenic throughout pregnancy. It causes fetal malformations and eighth-nerve paralysis, with deficits ranging from mild hearing loss to bilateral deafness. It causes marked vestibular abnormalities in the fetus. Thus, its use is contraindicated in pregnancy (42, 43).
DOSE : 12 – 15 mg/kg

SECOND LINE DRUGS – Kanamycin, Amikacin, Capreomycin, Ofloxacin, Ciprofloxacin, Ethionamide, Prothionamide, Cycloserine, Para-aminosalicyclic acid.

Safety profile in pregnancy has not been ascertained and should generally be avoided unless necessary for maternal wellbeing. These drugs are nephrotoxic and ototoxic. Their inadvertent use does not require termination of pregnancy or invasive diagnostic procedures, but hearing tests should be performed after birth (39).

REVISED NATIONAL TUBERCULOSIS CONTROL PROGRAM

- Launched in 1997
- Applies DOTS strategy
  (An observer ensures patient receives the right drugs at the right dose, at the right interval, for the right duration)
- Aims to achieve at least 85% cure rate and 70% case detection rate
- Since the inception of RNTCP –
  - TB mortality reduced from over 42/100,000 in 1990 to 23/100,000 population in 2010
  - TB prevalence reduced from 568/100,000 in 1990 to 249/100,000 population by 2010 (37)

WHO RECOMMENDED DOTS STRATEGY AS THE MOST EFFECTIVE TOOL OF RNTCP

Categories of Treatment

CATEGORY	TYPE OF PATIENT	REGIMEN
Category I	■ New sputum smear +ve ■ Seriously ill new sputum smear-ve ■ Seriously ill new extrapulmonary	2 H3 R3 Z3 E3 (intensive phase of 2 months) + 4 H3 R3 (continuation phase of 4 months)
Category II	■ Sputum smear +ve relapse ■ Sputum smear +ve failure ■ Sputum smear +ve Rx after default	2 H3 R3 Z3 E3 S3 + 1 H3 R3 Z3 E3 + 5 H3 R3 E3
Category III	■ New sputum smear -ve, not seriously ill ■ New extrapulmonary, not seriously ill	2 H3 R3 Z3 + 4 H3 R3
H – Isoniazid, R – Rifampicin, Z – Pyrazinamide, E – Ethambutol		

Supportive measures during ATT administration include:

- An intake of Pyridoxine with Isoniazid during the entire period of therapy to prevent peripheral neuropathy (as being practiced under the RNTCP).
- Prophylactic vitamin K administration to baby at birth for preventing hemorrhagic disease of the newborn.
- Segregation of the mother from neonate if she has active and infectious disease (especially MDR-TB) and is either not likely to receive ATT due to maternal non-compliance or has received it only for less than 2 weeks prior to delivery.
- Substitution of either protease inhibitors with another class of anti-retroviral drugs or rifampicin with Rifabutin in case of their co-administration.
- Cautious addition of drugs in case multiple therapies need to be given during the co-existence of various diseases.
- Examination of the contacts of the pregnant woman's household.
- Necessary procedural interventions like pleural, pericardial or ascitic tapping, intercostal chest drainage tube etc.

Multi Drug Resistant Tuberculosis (MDR-TB)

MDR tuberculosis is caused by *M. tuberculosis* that is resistant to at least Isoniazid and Rifampicin, and extensively drug-resistant tuberculosis (XDR) is caused by MDR tuberculosis strains that are also resistant to any fluoroquinolone and one of three injectable aminoglycosides (Capreomycin, Kanamycin, and Amikacin) (6).

Pregnant women with MDR-TB have a less favorable prognosis. Safety of the second line anti-tubercular drugs in pregnancy has not been established. Therapeutic abortion has been proposed as an option of management for these women (45). Another option is to delay initiating treatment to the second trimester where possible (46). Management of these cases should thus be individualized.

The World Health Organization (WHO) released new guidelines in August 2011 on the management of drug-resistant tuberculosis to offer the latest approaches for better control of the disease.

Principles underlying the treatment of multi-drug resistant tuberculosis adapted from WHO guidelines (47).

Number of Drugs

- Treatment regimens should consist of at least four drugs with either certain or almost certain effectiveness. Often more than four drugs are started if the susceptibility pattern is unknown or questionable.

Reliability of Drug Sensitivity Testing (DST)

- In general, susceptibility testing for Isoniazid, Rifampicin, the fluoroquinolones, and the injectable drugs is fairly reliable. For other drugs this is less reliable and basing individualized treatments on DST for these drugs should be avoided.

Treatment administration

- Each dose of an MDR regimen should be given by directly observed therapy throughout the treatment.

Monitoring treatment response

- To assess treatment response, smears and cultures should be done monthly until smear and culture conversion (two negative smears and cultures taken 30 days apart). Thereafter smears should be monitored at least monthly and cultures quarterly.

Duration of intensive phase

- The intensive phase of treatment for MDR tuberculosis is defined by the duration of treatment with the injectable drug. This should be given for a minimum of 6 months and for at least 4 months after the patient first becomes and remains smear or culture negative.

Total duration of therapy

- Treatment for MDR tuberculosis should be given for a minimum of 18 months after culture conversion, but extension to 24 months might be indicated in patients with chronic disease with extensive pulmonary damage.

Tuberculosis and Lactation

Breastfeeding is the healthiest way to feed a baby and though the antituberculous drugs are secreted into the breast milk, the amounts are too small to produce toxicity to the newborn. The American Academy of Pediatrics recommends that women with tuberculosis who have been treated appropriately for two weeks or more and who are not considered contagious may breastfeed (48), while the RNTCP recommends breastfeeding of neonates regardless of the mother's TB status (49). The use of Isoniazid, Rifampicin, Ethambutol, Pyrazinamide, Streptomycin, Kanamycin and Cycloserine has been considered safe for breastfeeding, but safety of PAS is unproven. The effect of these drugs gets minimized, if the mother breastfeeds before taking the drugs and substitutes the next feed with formula preparation. Even though the chances of toxicity in the newborn are minimal, they should be monitored for jaundice, which may suggest drug-induced hepatitis, and joint pains resulting from drug-induced hyperuricaemia. Breastfeeding may be discouraged in women who are yet to commence treatment at the time of delivery and those who are still actively excreting the bacillus while coughing. It may also be discouraged as part of a prevention of mother to child transmission in HIV coinfection and women with tuberculosis of the lactiferous ducts or glands (14).

Congenital Tuberculosis

Congenital tuberculosis is rare and may be as a result of haematogenous spread through the umbilical vein to the fetal liver or by ingestion and aspiration of infected amniotic fluid (27). A primary focus subsequently

develops in the liver, with involvement of the peri-portal lymph nodes. The tubercle bacilli infect the lungs secondarily, unlike in adults where over 80% of the primary infections occur in the lungs (8). The risk to neonate of getting TB infection shortly after the birth is greater than true congenital TB.

Clinically, tuberculosis in the newborn infant simulates other congenital infections such as syphilis or cytomegalovirus or bacterial sepsis. Congenital tuberculosis should be suspected if aggressive broad spectrum antibiotics are ineffective and tests for other congenital infections are negative, particularly if the mother is known to have tuberculosis and especially if recently diagnosed. The most common presentation is hepatosplenomegaly, respiratory distress, fever, and lymphadenopathy (28, 29). Infants usually develop symptoms in the 2nd or 3rd weeks but they may also manifest it at birth (28). Virtually all infants have an abnormal chest radiograph, with nearly half having a miliary pattern.

Cantwell et al Modified Criteria for the Diagnosis of Congenital TB (30)

Tuberculosis lesion in infants accompanied with one of the followings:

1) Lesion during the first week of life
2) A primary hepatic complex or caseating granuloma
3) Documented tuberculosis infection of placenta or endometrium
4) Exclusion of postnatal transmission through contact tracing.

If possible, the placenta should be examined and cultured for tubercle bacilli. The tuberculin skin test result is unhelpful since it is always negative initially and can take 1–3 months to become positive. Diagnosis rests on clinical suspicion and demonstration of acid fast bacilli in tissue or fluids, particularly on the culture of *M. tuberculosis*. Early morning gastric washings that are positive for acid fast bacilli on microscopy should be regarded as indicative of tuberculosis, although false positives can occur.

The overall mortality for congenital TB is 38% in the untreated and 22% in the treated (30).

Follow-up of the Newborn

In the absence of evidence of congenital tuberculosis, Isoniazid (10mg/kg/day) should be commenced at birth and continued for six months. Clinical or radiological features of active tuberculosis and a positive tuberculin skin test are indications for a full course of anti tuberculous treatment. The tuberculin skin test and chest X-rays are done at 6 weeks, 12 weeks, and 6 months. The baby is vaccinated with BCG at 6 months if these tests are negative. The baby is, however, changed to multiple drug therapy if any of these tests turn positive during the period of monitoring.

Tuberculosis and HIV Co-infection

Over 50% of the maternal mortality occurring in mothers with TB in pregnancy is due to co-infection with HIV (50). As much as 1.1 million people were diagnosed with the co-infection in 2009 alone (2). Moreover, treatment is complicated by the challenges of adherence, polypharmacy and the overlapping side effect profiles of anti tuberculosis and antiretroviral drugs (51,52). The spectrum of antiretroviral drugs available for use in pregnancy is limited. The risk of toxicity from the use of Didanosine and Stavudine is significantly increased in pregnancy. Rifampicin may cause a reduction in the serum concentration of Efavirenz and Nevirapine. To circumvent this problem, Rifabutin, another Rifamycin that is as effective as Rifampicin in the treatment of tuberculosis may be used, as the drug has less effect on the CYP3A system that metabolizes Nevirapine.

Prevention and Control

Prevention plays a crucial role in tuberculosis. TB is mainly a disease of poverty and overcrowding. Improved living condition is, therefore, encouraged with good ventilation, while overcrowding should be avoided. Improvement in nutritional status is another important aspect of the prevention. Primary prevention of HIV/AIDS is another major step in the prevention of tuberculosis in pregnancy. Screening of all pregnant women living with HIV for active tuberculosis is recommended even in the absence of overt clinical signs of the disease.

The BCG vaccine confers active immunity from childhood diseases. Non immune women travelling to tuberculosis endemic countries should also be vaccinated. It must, however, be noted that the vaccine is contraindicated in pregnancy (53).

Conclusion

Tuberculosis in pregnancy is more likely to be seen in areas with a higher incidence of TB. It is the commonest infectious cause of maternal morbidity in India. A high index of suspicion is needed to diagnose tuberculosis in pregnancy. The tuberculin skin testing is a valuable screening test and its sensitivity is not affected by pregnancy. Chest X-ray with shielding is essential and safe in all TB suspects. Pregnancy does not affect the course of TB; however, delay in treatment or untreated TB increases maternal and fetal morbidities and can be transmitted to the newborn. First-line anti tuberculous drugs can be used safely in pregnancy and while breastfeeding. Co-infection with HIV increases maternal mortality rates.

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NEWSLETTER Obstetric Medicine

Genital Tuberculosis

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Tuberculosis (TB) is the second leading cause of death worldwide amongst communicable diseases and is second only to HIV/AIDS. In 2012, an estimated 8.6 million people developed TB and 1.3 million died from the disease, including 3,20,000 deaths among HIV-positive people. India has the highest TB burden in the world, accounting for nearly one-fourth of the global incidence. Over 95% of TB deaths occur in low- and middle-income countries, and it is among the top three causes of death for women aged 15 to 44. HIV and TB form a lethal combination, each speeding the other's progress (1).

In countries with comprehensive diagnostic and reporting systems, extrapulmonary TB accounts for 20–25% of reported cases. Approximately 30% of cases of extrapulmonary TB involve the urogenital tract. The prevalence of genital TB among infertile women varies from <1% in the USA to nearly 18% in India (2). The true incidence of genital TB is not known as many cases remain undiagnosed owing to its subtle presentation. The genital tract is vulnerable to this disease after puberty and most cases occur during the childbearing period. Postmenopausal women account for 7–11% of cases of genital TB (3).

Aetiopathogenesis

Genital TB is almost always secondary to TB elsewhere in the body, usually pulmonary TB and occasionally is part of a generalized miliary disease process. *Mycobacterium tuberculosis* accounts for 90–95% of cases of genital TB. *Mycobacterium bovis* may be the causal agent (5–10%), especially when the organisms are acquired from the gastrointestinal tract. Generally the *M. tuberculosis* gains access through the respiratory passage (droplet infection) and then disseminates to different organs via lymphatic drainage and blood circulation. Direct extension to the genital tract from tuberculous abdominal viscera, such as the bladder, rectum, appendix, and intestines, and ascending infection after sexual intercourse can also occur.

Genital organs commonly involved include the fallopian tubes (95–100%) endometrium (50–60%) and ovaries (20–30%). The cervix (5–15%), vulva/ vagina (1%) and the myometrium (2.5%) may also be involved (3). Haematogenous spread of TB bacilli to the tubes results in endosalpingitis while direct spread results in exosalpingitis with tubercles on the surface. The endometrial involvement is most extensive in the fundus and decreases toward the cervix. Ovarian TB may manifest as perioophoritis in which the ovary is surrounded by adhesions and studded with tubercles or oophoritis in which infection from a haematogenous source produces a caseating granuloma within the parenchyma. Tuberculous peritonitis is seen in combination with genital tract TB approximately 45% of the time and is thought to be responsible for the often extensive adhesions seen in these patients (4).

Clinical Features

Approximately 11% of patients are asymptomatic and pelvic TB is often found serendipitously during an infertility workup (4). About 20% of patients with genital TB give a history of TB in their immediate family and 50% might have had TB elsewhere in the body.

The common presenting symptoms of genital TB include infertility (43-74%), oligomenorrhoea/amenorrhoea (68%), menorrhagia (19%), abdominal pain (42.5%), dyspareunia (5-12%) and dysmenorrhoea (12-30%) (3). Causative factors for infertility are salpingitis, ovulatory dysfunction, endometritis and extensive adhesions. Uterine synechiae are an important cause of secondary amenorrhoea. Menorrhagia can follow when TB causes tubo-ovarian masses. Non-genital TB can also be responsible for menstrual disturbances although the exact mechanism is unknown. Rifampicin has also been shown to induce menstrual disturbances (5). Tuberculous lesions of the cervix and vagina can present with postcoital bleeding and abnormal discharge. In the postmenopausal woman, genital TB presents with postmenopausal bleeding, persistent leucorrhoea and pyometra (3). Symptoms associated with fistula formation are less common.

Physical examination is normal in majority of the patients (3). Abnormal findings when present usually consist of adnexal masses or ascites. The cervix may appear normal or inflamed, and may resemble invasive carcinoma, both grossly and with the colposcope. Cervical, vaginal and vulvar lesions usually present as isolated, chronic ulcers. Sinuses discharging caseous material and pus, and rarely hypertrophic, irregular warty growths resembling

elephantiasis may be found on the vulva. Enlarged uterus with pyometra and fistulae are encountered less frequently.

The serous variety of tuberculous peritonitis is characterized by ascites, signs of peritoneal inflammation, fever, abdominal pain, weight loss, and anorexia. The plastic variety is less common and is characterized by tender abdominal masses and an abdomen doughy to palpation. Pelvic TB can mimic peritoneal carcinomatosis secondary to ovarian or primary peritoneal cancer and present with pelvic and/or omental mass, ascites, and elevated CA-125.

Diagnosis (details of laboratory investigations are discussed elsewhere)

Routine laboratory studies are of little value; most patients have a normal white blood cell count with differential counts, although there is a tendency to lymphocytosis. Anaemia is sometimes seen, and haematuria or abacteriuric pyuria if there is concomitant urinary tract involvement. Extrapulmonary TB is more common in HIV-positive patients and testing for HIV is recommended for all patients with genital TB (3).

Characteristics of pelvic TB commonly found on ultrasound include adnexal mass, tubal disease, ascites and omental and/or cul-de-sac nodularity. The wet type of tuberculous peritonitis is characterized by incompletely septated ascites, particulate ascites, loculated fluid, a thickened peritoneum or omentum, and an adnexal mass, mimicking ovarian cancer; the dry type is characterized primarily by adnexal masses, adhesions, and loculated fluid, mimicking tuboovarian complexes. The parallel violin string appearance, although rare, may possibly be typical of tuberculous peritonitis (6).

Tubal findings on hysterosalpingography (HSG) include occlusion, hydrosalpinx, irregular tubal outline, multiple constrictions (beaded appearance), scarring (rigid pipe appearance) and calcifications. Occlusion occurs most commonly at the junction between the isthmus and ampulla. The uterine cavity is shrivelled and deformed (pseudo-unicornuate or T-shaped or asymmetrically small) and characterized by synechiae and venous or lymphatic intravasation. Fistulous tracts between the genital tract and other pelvic organs may also be identified. In known cases, or in circumstances in which genital TB is highly suspected, HSG should be avoided because of the risk of reactivation (3, 7).

Endoscopic procedures can demonstrate adhesions or granulomas and can be used to collect samples for culture and histological analyses. Up to 45% of female patients with genital TB have a macroscopically normal uterus. The most common finding of TB affecting the endometrium is adhesions that may be firm and agglutinated occluding the ostia. The most common finding at laparoscopy 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 (8).

The cytopathologic examination of the cervix may reveal multinucleated giant cells, histiocytes, and epithelioid cells arranged in clusters, simulating the appearance of the granulomata. The granulomatous lesions in an endometrial biopsy are usually best recognized on cycle days 24–26 or within 12 hours of the onset of menses.

Differential Diagnosis

In the presence of ascites and/or peritonitis, other conditions presenting similarly such as pelvic inflammatory disease, hepatitis, cholecystitis, appendicitis and ovarian cancer should be considered and excluded. Other granulomatous lesions such as sarcoidosis, brucellosis, schistosomiasis, etc. also need to be ruled out (4).

Complications

Despite effective therapeutic regimens for genital TB, sterility remains a major complication. The damage to the fallopian tubes can be extensive and irreparable if genital TB is not diagnosed and treated early in its course. A rare but potentially serious complication of female genital TB is congenital TB which has considerable neonatal morbidity and mortality if untreated (4).

Treatment

It is essential that physicians and microbiologists experienced in TB management are involved in the

treatment of genital TB (3). Treatment is directed towards the eradication of the infection by means of specific chemotherapeutics. Combined therapy enhances compliance and reduces the risk of secondary drug resistance.

1. 2HRZE/4HR regimen: A 6-month regimen consisting of isoniazid (INH), rifampin (RIF), pyrazinamide (PZA) and ethambutol (EMB) / streptomycin (SM) for 2 months, followed by INH and RIF for 4 months is the preferred treatment for patients with a fully susceptible organism who adhere to treatment. In the presence of HIV infection, the clinical course should be closely monitored, and treatment should be prolonged if the course is determined to be slow or suboptimal.
2. A 9-month regimen of INH and RIF is acceptable in patients who cannot tolerate PZA. EMB or SM should be included until the drug susceptibility studies are available, unless there is little possibility for drug resistance.

DRUG	RECOMMENDED DOSE			
	Daily		3 Times per Week	
	Dose and Range (mg/kg)	Maximum Dose (mg)	Dose and Range (mg/kg)	Maximum Dose (mg)
INH	5 (4 – 6)	300	10 (8 – 12)	900
RIF	10 (8 – 12)	600	10 (8 – 12)	600
PZA	25 (20 – 30)	–	35 (30 – 40)	–
EMB	15 (15 – 20)	–	30 (25 – 35)	–
SM*	15 (12 – 18)	–	15 (12 – 18)	1000
*Patients aged over 60 years and weighing less than 50 kg may not tolerate doses above 500 to 750 mg daily (9)				

The major determinant of the outcome of treatment is patient adherence to the drug regimen. Consideration should be given to treating all patients with directly observed therapy (DOT). In general, over 95% of patients treated for TB for the first time, using a combined drug regimen, undergo successful treatment if they complete the prescribed drug course. Most patients become noninfectious very rapidly, usually within 2 weeks. Relapse after treatment is seen in 0–3% of cases.

Rifampicin induces pathways that metabolize other drugs, thereby reducing the concentration and effect of those drugs. To maintain a therapeutic effect, dosages of the other drugs may need to be increased, such as use of a contraceptive pill containing high dose (50 mcg) of oestrogen or choosing an alternative method of contraception. Dosage adjustments of other medications have to be made in consultation with a physician to counter the effect of these drug interactions. With the exception of streptomycin (which is ototoxic to the fetus), the first line anti-TB drugs are safe for use in pregnancy.

All anti-tuberculous drugs can cause adverse reactions; these are seen in about 10% of patients and are common in HIV-positive patients. INH and RIF both are associated with hepatitis, cutaneous hypersensitivity and haemolytic anaemia. INH may cause peripheral neuropathy. PZA causes anorexia, nausea, hepatitis, arthralgia and hyperuricaemia. EMB is associated with retrobulbar neuritis, hepatitis and peripheral neuropathy (3).

Resistance to two first-line drugs like INH and RIF is called multidrug resistant TB, and when in addition to these drugs, the disease is also resistant to fluroquinolone and second-line injectable drugs, the disease is called extended drug resistant TB. This is important with respect to TB with pregnancy where many of the second-line drugs are teratogenic and need to be prescribed

with great caution and the outcome of the treatment with the best of regimens is suboptimal.

Indications for surgical intervention include persistent or recurrent pelvic masses after 6 months of adequate therapy, persistent or recurrent symptoms such as pelvic pain and abnormal bleeding, non-healing fistula, multi-drug resistant disease and concomitant genital tract neoplasia or other pathology. The patient should be given chemotherapy for at least 1–2 weeks preoperatively. Surgery should be performed midcycle in premenopausal patients and chemotherapy should be continued for 6–12 months postoperatively. The operation of choice is total abdominal hysterectomy with bilateral salpingo-oophorectomy followed by hormone replacement therapy. Adhesiolysis may be performed for chronic pelvic pain. When TB is first diagnosed postoperatively after histologic examination, antituberculous treatment is given immediately and continued for 6–12 months (3, 4).

Successful pregnancy is extremely rare even after complete treatment of genital TB, the conception rate being 19.2% and birth rate 7.2%. Provided that the tuberculous process has not destroyed the uterine lining, in vitro fertilization (IVF) following successful anti-bacterial treatment is the only rational method of treating infertility associated with pelvic tuberculosis. Conception rate varies from 9 to 28%, live birth rate from 4.2 to 30.7% and ectopic pregnancy rate from 3.3 to 10%. The prognosis of Asherman's syndrome secondary to TB is much worse because of the extensive endometrial damage that occurs and surrogacy may be the only option for these women (3, 4).

Summary

Genital tuberculosis may be asymptomatic and can go unrecognized or masquerade as other gynaecological conditions. This disease is an important cause of infertility, menstrual disturbances, chronic pelvic pain, and maternal and neonatal morbidity when associated with pregnancy. Failure to consider the possibility of TB may result in unnecessary and ineffective diagnostic and therapeutic interventions. Infertility for which no obvious cause can be found, chronic pelvic inflammatory disease refractory to standard antibiotic therapy, or adnexal disease with ascites in a virgin should alert the clinician to a possibility of genital TB. Although most patients are treated successfully by medical treatment, the damage to the fallopian tubes (and endometrium if involved) is often permanent with poor conception rates and unfavourable pregnancy outcomes despite the use of artificial reproductive techniques.

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NEWSLETTER Obstetric Medicine

Laboratory Diagnosis of Tuberculosis

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Unlike pulmonary tuberculosis (TB), it is often difficult to diagnose extra pulmonary TB and one needs to have a high index of suspicion! Many new tests are available today to help diagnose TB but we need to interpret them correctly and know which are reliable and accurate.

Confirmatory Tests for TB

To date, culture remains the gold standard for diagnosing TB. Tuberculosis can be diagnosed with certainty by microbiological confirmation (by demonstrating acid fast bacilli in smear or culture) and/or by histopathology. Characteristic histopathological findings include caseating granulomatous inflammation.

Which specimen can be used for testing?
Pulmonary TB – sputum / broncho-alveolar lavage for microbiology
Extra pulmonary TB – sterile fluid (CSF, Ascitic fluid etc) or tissue specimen for TB culture and tissue specimen for histopathology

TYPE OF TB	TB CULTURE /SMEAR	HISTOPATHOLOGY
Central nervous system	CSF, tissue from tuberculoma, meningeal tissue	Tissue from tuberculoma, meningeal tissue
TB lympahdenitis	Lymph node tissue	Lymph node tissue
Pericardial TB	Pericardial fluid/pericardial tissue	Pericardial tissue
Tuberculous peritonitis	Ascitic fluid/peritoneal tissue	Peritoneal or omental tissue
Gastro intestinal TB	Tissue obtained by endoscopy/colonoscopy or surgical specimen from the gut	Tissue obtained by endoscopy/colonoscopy or surgical specimen from the gut
Musculoskeletal TB	Synovial fluid, synovial tissue, bone biopsy	synovial tissue, bone biopsy
Genital TB	Endometrial tissue, tissue from involved fallopian tube, ovarian mass etc	Specimen from diseased part of genital tract

Diagnostic Microbiology

1. Acid fast staining: conventional Ziehl-Neelson method or more rapid flurochrome methods(using auramine O or auramine rhodamine dyes and flurescence microscopy)(1).
2. Culture methods:
   a. Lowenstein-Jenson medium – solid medium (growth in 6-8 weeks)
   b. Automated liquid broth culture systems (growth in 1-3 Weeks) – eg Bactec liquid medium
   c. MODS (Microscopic observation drug susceptibility) – This a method wherein drug free and drug coated liquid media are inoculated with patient's specimen and cultures are examined microscopically for growth. This is a rapid and inexpensive method and turn-around time for drug susceptibility is much less but it has biosafety concerns and labour intensive (2).

Comparative sensitivities of MODS, automated mycobacterial culture and Lowenstein-Jensen culture on 3760 sputum samples in Peru were 98, 89, and 84 percent, respectively. Median time to culture positivity was 7, 13, and 26 days, respectively.

Molecular Methods

Nucleic acid amplification test (NAAT) : It is a test wherein mycobacterial DNA is amplified by using nucleic acid probe. As few as 1-10 organisms/ml can give a positive result (3). Sputum or other tissue specimens can be tested by NAAT. Accuracy of test depends on the type of specimen and the nucleic acid probe used. This is

an expensive test, technically demanding but result is available in one or two days and has good specificity if specimen contamination is avoided and is expected to have high sensitivity. There is not much data on accuracy of TB PCR of endometrial tissue in diagnosing endometrial TB.

GeneXpert MTB/RIF

It is a type of NAAT which is used to detect mycobacterium tuberculosis and also Rifampicin resistance at the same time (1). WHO has approved this test for sputum testing. It has good sensitivity and specificity. In a study, it identified 98% of sputum smear positive tuberculosis and 76% of sputum smear negative/culture positive patients. This assay is simple to perform, requires minimal training but expensive. Report can be obtained the same day. The same technique can be used for specimens other than sputum (in diagnosis of extra pulmonary TB). Among 547 patients with suspected extrapulmonary TB in India and 1068 patients in Europe, the sensitivity and specificity of the Xpert assay were 81 and 99 percent, respectively.

Role of Serology

ELISA tests for TB (IgM and IgG antibodies in serum for TB) are widely used in TB diagnostic work-up, especially in infertility work-up. They are not of any value in diagnosing TB and should not be used! WHO issued a strong negative recommendation against the use of TB antibody testing (4).

Mantoux and IGRA (interferon gamma release assay) tests

Used in diagnosis of latent TB and not active TB (5).

MANTOUX/TST (tuberculin skin testing)

Can be false positive and false negative. False positive test may be seen in the setting of non tuberculous mycobacterial infection and prior to BCG vaccination. False negative test may occur in patients with waning immunity or improper injection of tuberculin protein or inaccurate interpretation of the induration.

IGRA

To put it simply, it is a glorified Mantoux test. IGRAs measure T cell release of interferon (IFN)-gamma following stimulation by antigens unique to Mycobacterium tuberculosis. It is used to diagnose latent TB i.e., past history of TB infection and not active disease. Positive IGRA is not an indication for treatment in high prevalence countries like India except a few conditions where we may decide to treat latent TB. (eg – if patient needs immunosuppressive therapy associated with risk of reactivation of TB). Quantiferon gold is a commonly available IGRA test in our country. It scores over Mantoux test –

1. Patient does not need to come back unlike in TST where patient's induration needs to be examined after 48-72 hours.
2. It does not turn positive because of prior BCG vaccination or in non tuberculous mycobacteria

Adenosine Deaminase (ADA):

ADA is associated with lymphocytic proliferation and used widely in the diagnosis of tuberculosis. A meta analysis published in 2003 revealed a wide range of sensitivity and specificity of pleural fluid ADA in diagnosis of pleural TB, 47-100% and 50-100% respectively. A recent meta analysis to assess usefulness of ascitic fluid ADA in the diagnosis of TB revealed a overall sensitivity and specificity of 93 and 94% respectively. In the diagnosis of TB meningitis, studies on efficacy of CSF ADA yielded a wide range of sensitivity and specificity (44-100% and 70-100% respectively). In conclusion, ADA can be used in the diagnosis of TB as an adjunct to other clinical and diagnostic markers (6).

Pathogen Associated Molecular Pattern (PAMP) and Gene Polymorphisms

Occasionally we come across this test being conducted on endometrial tissue as part of infertility work up. Some obstetricians diagnose endometrial TB based on presence of specific PAMP and gene polymorphisms for TB on endometrial tissue and initiate anti tuberculous therapy. There is hardly any literature and data on utility of this test in diagnosis of TB and this test is not recommended.

Radiology in Diagnosis of Tuberculosis

Chest X-ray is a simple, inexpensive, widely available tool in diagnosis of pulmonary tuberculosis. It gives important clues to diagnosis, though it does not confirm the diagnosis.

Computerised tomography (CT) or MRI can be used in

work-up of both pulmonary and extra pulmonary TB. These findings may not be confirmative of TB but will provide information which helps in deciding the best of site of obtaining a specimen surgically or a guided biopsy (U/S or CT). This specimen can be further subjected to histopathological or microbiological confirmation.

Other Preliminary Investigations

CBP, ESR, liver function tests (LFT), serum creatinine need to be done in all patients with suspected tuberculosis. LFT needs to be done 2-4 weeks after initiation of anti-tuberculous therapy to look for development of hepatotoxicity. Ethambutol dose needs to be adjusted in patients with renal impairment. ESR is non specific but can be used while following up of patients for response to therapy.

TEST	COMMENT
AFB smear and culture	Confirmatory. Poor sensitivity in extra pulmonary TB which is often a paucibacillary disease. Culture takes a few weeks.
Histopathology	Often confirmatory. Needs tissue which needs an invasive procedure
NAAT- TB PCR	Quick result, expensive , needs expertise Good specificity if contamination is avoided Associated with false positive and false negative tests.
NAAT- GeneXpetMTB/RIF	Approved by WHO. Quick result, provides information on Rifampicin resistance simultaneously. Easy to perform, has good sensitivity and specificity
Mantoux/TST	Diagnosis of latent TB False positive and false negatives possible
IGRA/Quantiferon gold	Diagnosis of latent TB
TB serology (IgM, IgG)	DO NOT USE THESE TESTS
ADA	Useful in pleural, CSF and ascitic fluid TB but not conclusive

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NEWSLETTER

Obstetric Medicine

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- To establish a forum for exchange and interchange of views and for enhancing fellowship among its members and to come out with evidence-based guidelines for management of medical disorders complicating pregnancy.
- To assist in the establishment of Obstetric Medicine as an important sub-specialty to advance clinical and scientific knowledge of medical illness complicating pregnancy.
- To promote research and training in Obstetric Medicine.
- To foster collaboration with other regional and international societies interested in Obstetric Medicine.
- To carry out all such activities as would contribute to the promotion of Obstetric Medicine.
- To promote formation of patient forums.

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