

Review Article Female genital tuberculosis

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ARTICLE INFO

Article history: Received 13-08-2022 Accepted 24-08-2022 Available online 08-11-2022

Keywords: Genital tuberculosis Extra-pulmonary tuberculosis Infertility Fallopian tube

ABSTRACT

Female genital tuberculosis (FGTB) is a common health problem in developing countries. It frequently causes pelvic inflammatory disease, menstrual abnormalities and infertility. It represents 15-20% of extrapulmonary tuberculosis. It is mostly secondary infection acquired from hematogenous spread from extra-genital source such as pulmonary or abdominal tuberculosis. The fallopian tube is affected in almost all the cases followed by endometrium and cervix. It occurs in the most economically productive age of 15-45 years causing infertility in 44-74% of individuals affected. The clinical diagnosis of genital TB requires a high index of suspicion. Infertility and menstrual irregularities are the commonest presentation. Diagnosis requires a multi-modality approach involving clinical, radiological, bacteriological, molecular and histopathological methods. Treatment requires the combination of four drugs (Rifampicin, Isoniazid, ethambutol and pyrazinamide) for a minimum of six months duration. In case of drug resistant tuberculosis reserve drugs are used for the extended period.

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1. Introduction

Globally tuberculosis is the leading cause of death from a single infectious agent (above HIV/ AIDS) and one of the top 10 causes of death. Reported death among HIV-negative people due to tuberculosis in 2017 was estimated to be 1.3 million (range, 1.2–1.4 million) and accumulate 300 000 more deaths from TB among HIV-positive people.¹

Though tuberculosis affects all ages but more than 90% of adults aged ≥ 15 years. Among tuberculosis diseased persons 9% were people living with HIV (72% in Africa) and two-thirds were in eight countries: India (27%), China (9%), Indonesia (8%), the Philippines (6%), Pakistan (5%), Nigeria (4%), Bangladesh (4%) and South Africa (3%).¹ The maximum number of cases and death occur more in males(64%) but the disease also affects

females (36%) in a significant amount.¹ Fourteen percent of the 6.4 million incident cases that were notified in 2017 were extrapulmonary, ranging from 8% in the WHO Western Pacific Region to 24% in the WHO Eastern Mediterranean Region.¹ However, it was said that extrapulmonary tuberculosis remained underreported.

Female genital tuberculosis (FGTB) is the form of extrapulmonary tuberculosis and includes 5% of all female pelvic infections.² Developing countries are more severely infected leading to pelvic inflammatory disease and it is the important cause of significant morbidity and sequelae leading to infertility.³ Prompt diagnosis and proper treatment are the keys to the prevention of infertility and other sequelae due to FGTB.

2. Epidemiology

The precise incidence of FGTB is difficult to estimate because of under-reporting. The reason for under-reporting

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https://doi.org/10.18231/j.ijogr.2022.086

is the asymptomatic nature of the disease, vague symptoms, and unable to make the proper diagnosis in absence of highly sensitive diagnostic tests along with other comorbidities such as HIV, diabetes, and other bacteriological infections.^{4,5} Genital tuberculosis represents 15–20% of extrapulmonary tuberculosis.⁶ The reported incidence of FGTB varies from region to region and greatly according to socioeconomic and public health conditions. It usually parallels the incidence of pulmonary and abdominal TB.⁷

In Swedish study⁸ reported incidence of FGTB was only 0.002% while in the USA⁹ it was reported <1%. While in Malaysia FGTB was diagnosed in only 12 patients during the 17 years.¹⁰ Saudi Arabia reported incidence was 4.2% of a total of 945 infertile women studied and where infertility was due to a tubal factor.¹¹ Turkey reported involvement of 5.7% of female genitourinary system involvement in 2009.¹²

Incidence of genital tuberculosis has been estimated to range from 1 to 19 percent in different studies from India.

In developing countries, FGTB affects females in the 20-30 years of age group⁴ while in western countries, FGTB is usually diagnosed in premenopausal women over the age of 40 years.¹³ In postmenopausal women, FGTB is rare and responsible for only approximately 1% of postmenopausal bleeding.¹⁴

3. Mode of Transmission

Transmission of Mycobacterium Tuberculosis (MTb) in humans can occur in various ways. Inhalation of droplets aerosols from the coughs or sneezes of people with active pulmonary or laryngeal tuberculosis is the commonest route. Consumption of dairy products infected with Mycobacterium bovis from infected cattle may also lead to tuberculosis. With the more frequent use of pasteurized milk Mycobacterium bovis infection has become quite rare.

Other uncommon routes of transmission of Mtb include congenital transmission, sexual transmission, accidental inoculation, vaccination, and therapeutic instillation. The accepted form of congenital and/or neonatal transmission combines transplacental transmission via blood or lymphatics from active tuberculosis in the mother or aspiration or ingestion of Mtb infected amniotic fluid during childbirth.¹⁵

Vaccination with live BCG vaccine of HIV infected and immunosuppressed persons has caused local and disseminated BCG M. bovis strain TB.¹⁶

Intravesical instillation of BCG is frequently used as an adjuvant treatment for transitional cell carcinoma of the urinary bladder. This may also cause TB of the bladder, epididymis, prostate, and kidney.¹⁵ Even tuberculosis of the spine can occur following intravesical instillation of BCG.¹⁷

The sexual mode of transmission of TB can also occur. Tubercular penile ulcers were found to have a similar strain of endometrial TB which his wife was harboring.¹⁸ Cervical tuberculosis may occur due to the deposition of infected semen by an infected male partner.¹⁹

4. Risk Factors

Risk factors for the development of tuberculosis include immunosuppressive states like HIV and diabetes, chronic liver and renal diseases, malnutrition, and alcoholism. Poor housing, homelessness, pneumoconiosis, genetics, vitamin deficiency, immunosuppressive drug intake, and renal transplantation is also been implicated as the risk factor for the development of tuberculosis. A person on renal dialysis for the treatment of chronic renal failure also has more chances of developing tuberculosis.^{15,20}

Smoking is an independent risk factor causing approximately a twofold increase not only in active TB disease but also in latent TB infection and mortality.²¹ Few of the modifiable socioeconomic risk factors, including indoor air pollution, living in a poor housing condition with a low number of windows per room, and socioeconomic position of the household, can be powerful predictors of tuberculosis infection and disease.²² Moreover, people who have had one episode of tuberculosis in the past have more chances of developing TB again than compared who had not to have an episode of tuberculosis and thus further exacerbating the vicious cycle of poverty and tuberculosis.²³

5. Pathogenesis

Mycobacterium tuberculosis (rarely Mycobacterium bovis and/or atypical mycobacteria) is the aetiological agent.⁵ There is evidence that suggests that some individuals are resistant to latent M. tuberculosis infection despite longterm and intense exposure. This may be due to innate immunity and they are term as 'resisters'.²⁴

Primary infection occurs through inhalational or through ingestion. M.tuberculosis multiply locally in the lung, tonsil, or intestine (ileum or caecum) leading to the complex immunological response in the body leading to the eradication of bacilli or the formation of primary Ghons focus (granuloma). Rarely are primary tuberculosis lesion can be found on the cervix, vagina, or vulva in a woman.²⁵ Primary tuberculosis complex consists of Ghons focus along with lymphangitis and local lymphadenitis. The primary tuberculosis complex has three fates.¹⁵

1. Localized progressive primary tuberculosis: Local spread to the surrounding tissue and adjacent organs lead to pulmonary tuberculosis (pneumonia or cavities), pleural effusion, and intestinal tuberculosis (ileocaecal tuberculosis). Sputum and tissue biopsies are positive for Mtb by GeneXpert or by culture. After treatment, it goes into a latent phase and may undergo reactivation in the future.

- 2. Hematogenous and lymphatic spread: Widespread dissemination of Mtb lead to the disseminated kochs thus extrapulmonary form of tuberculosis occur. Biopsies, fine needle aspirates urine, pleural fluid, and CSF are usually positive for Mtb by GeneXpert or by culture. After treatment, it goes into a latent phase and may undergo reactivation in the future.
- 3. **Containment of Infection:** In the majority of cases (90-95%) due to an acquired immunity there occurs the containment of the Mtb leads to latent tuberculosis or it is eliminated from the body. According to one estimates 1.7 billion peoples have latent tuberculosis infection and have no signs or symptoms of the disease. They are not infectious. But there are chances of latent tuberculosis becoming active and becoming infectious in near future because of reactivation of the bacilli. Latent tuberculosis may reactivate in 5-15% of people and thus progress to become active tuberculosis.²⁶

5.1. Route of infection to female genitalia

The route of infection to genital tuberculosis in females is usually hematogenous or lymphatic spread from pulmonary tuberculosis or direct spread from the adjacent organ like intestinal tuberculosis/peritoneal tuberculosis. For tuberculosis of the cervix, vagina, and vulva sexual transmission is also been reported.¹⁵

5.2. Fallopian tube tuberculosis

Inflammation of the fallopian tube also known as salpingitis. Fallopian tubes are involved most frequently (95-100%) in FGTB²⁷ and are involved bilaterally in most cases. One can diagnose only one infected fallopian tube but the microscopic lesion can be seen in another tube also.²⁸ Initially, the ampullary portion got involved and at times shows extensive lesions leading to swollen fimbrial process and the ostia remain open or closed.²⁸

5.3. Endometrial tuberculosis

The endometrium is affected by tuberculosis in 50-60 percent of FGTB.²⁷ Transmission occurs through a hematogenous, lymphatic, or contagious route. Tuberculosis causes large ulcer formation in the later stage lately leading to architectural distortion of the uterine cavity. The predominant histological features of tuberculous endometritis are epithelioid cell granuloma. The granuloma may be scanty in distribution and tend to be small and central. Caseation is unusual.²⁹ Histopathological findings indicating chronic inflammation or lesions such as proliferative solid epithelioid granulomas, dense polymorphonuclear cells, lymphocytic infiltrations, giant or beaded cells, enlarged lymphoid cells, and accumulation of plasma and spindle cells are also suggestive of tuberculosis.³⁰

5.4. Ovarian tuberculosis

Involvement of ovaries is seen in 20-30% of cases of FGTB.^{27,28} It involves because of hematogenous or direct spread. Perioophoritis develop from the direct spread leading to peri-ovarian adhesions and tubercle formation. Oophoritis occurs due to hematogenous spread in which infection occurs in the stroma.²⁸ Grossly anatomical relationship between the ovary and fimbriae get obliterated.³¹ Typical granuloma formation can be seen in ovarian tuberculosis.

5.5. Tuberculosis of the vulva, vagina, and cervix

Tuberculosis may affect the vulva, vagina, and cervix by coitus of a partner with genitourinary tuberculosis or by the secondary spread of tuberculosis from other sites. Pulmonary tuberculosis is the most common primary source of infection is pulmonary tuberculosis. Fallopian and endometrial tuberculosis may also disseminate to lower genital tuberculosis.²⁹

The cervix is involved in about five percent of cases of genital TB.^{5,27} Usual lesions are ulcerative or proliferative although in rare cases military or interstitial tuberculosis also be seen. Tuberculous cervicitis may be confused with malignancy making the histopathological examination necessary.

Tuberculosis rarely involves the vagina and vulva i.e. 1% of cases.³² On histopathologic examination, it contains multiple granulomas or tubercles with central caseation necrosis, epithelioid histiocytes, and multinucleated Langerhans giant cells.³¹ Sometimes there may be associated vesicovaginal fistulas.³³

5.6. Clinical features

FGTB may remain silent and present with no symptoms. It may require a high index of suspicion to diagnose genital tuberculosis in asymptomatic patients.

5.6.1. Infertility

Worldwide incidence of infertility in genital tuberculosis varies from 44 to 74% however in India it is reported to be 58%.³⁴ Primary or secondary infertility is the commonest presentation of FGTB. It can be due to tubal, endometrial, or ovarian factors.

Tubal factors: Tubal blockage and destruction is the cause of infertility. Due to distorted fallopian tube ovum transport become hampered. A damaged, scarred, or obstructed fallopian tube prevents the sperm from reaching the ovary to fertilize the egg.

Endometrial factors: Involvement of the endometrium is seen in 50–60% of genital tuberculosis patients. FGTB may cause intrauterine adhesions and obliteration either partially or completely. A study from India showed that impaired sub-endometrial blood flow due to latent genital tuberculosis in apparently unexplained infertility could be one of the causes of repeated In Vitro Fertilization failure.³⁵ This study also emphasizes that infertility may not always require frank FGTB but may also be due to subclinical endometrial mycobacterial infection.

Ovarian factors: Animal studies had showed the antigonadotrophic effect of Mycobacterium Tuberculosis.³⁶ Human studies also showed that patients with genital tuberculosis required more exogenous gonadotropins as compared to patients with tubal factor infertility.³⁵

5.6.2. Menstrual irregularities

All types of menstrual irregularities can be seen in FGTB. Menstrual irregularities can be seen in nongenital tuberculosis also. Apart from tuberculosis, any disease that can cause significant weight loss and is associated with systemic inflammatory response and cachexia can cause amenorrhea.³⁷ Non-genital tuberculosis can lead to hypomenorrhea and secondary amenorrhea may be resulting from dysfunction attributed to the hypothalamus, pituitary, and premature ovarian failure.³⁸ Involvement of the endometrium is usually the cause of menstrual abnormalities in FGTB. Menstrual irregularities are seen in the form of oligomenorrhoea, hypomenorrhea, amenorrhoea, menorrhagia, dysmenorrhea, and metrorrhagia. In one of the studies from India, oligomenorrhoea was found to be the most common menstrual disorder present in histopathologically confirmed cases of FGTB.³⁹ In post-menopausal women, it may present as vaginal bleeding and it ought to be differentiated from uterine malignancy.

5.6.3. Abdominal pain

Chronic abdominal pain or pelvic pain which is noncharacteristic, dull aching, chronic, and localized to the lower abdomen is also seen frequently³ and occasionally may present as acute abdomen due to pelvic inflammatory disease or twisted pelvic organs. Pain may be severe presenting as acute abdomen or swelling of the abdomen. Sometimes episodes of secondary infection may lead to acute lower abdominal pain. With the progression of FGTB, pelvic pain becomes more severe and is usually aggravated by coitus, exercise, and menses.⁷

5.6.4. Vaginal discharge

Abnormal or persistent vaginal discharge occurs when tuberculosis affects the cervix or vagina. Discharge can be watery, blood-stained, and at times purulent when the lesion got a secondary bacterial infection.^{40,41}

5.6.5. Other symptoms

The patient may present with poor general health over months and years, weight loss, fatigue, low-grade fever, and vague lower abdominal pain. Though cervical tuberculosis is rare it may present with post-coital bleeding and coital discomfort.⁴² From time to time patients may give a history of recurrent pelvic inflammatory disease that has shown no response to anti-bacterial therapy.²⁸

5.7. Physical signs

Around 10% of patients may present with no signs and they are normal on physical examinations.⁵

Abdominal examination: Ascitis can be seen causing abdominal distension. At times the doughy feeling of the abdomen can be seen due to tubercle formation on the intestine and peritoneum.²⁸ Ovarian tuberculosis may present with a tubo-ovarian mass causing an abdominal lump. It also causes tenderness in the adnexa and suprapubic region. It should be differentiated from ovarian cancer.⁴³

Pelvic examination:²⁸ It can be normal on examination. Tubo-ovarian mass can be found along with the thickened tube. Adnexal mass with an enlarged uterus can be seen with pyometra present. Fullness or tenderness of the pouch of douglas can be seen due to fluid.

Per speculum examination: TB cervix though rare may present with papillary growth and ulcers mimicking cervical cancer and other granulomatous lesions.¹⁵ TB vagina though rare can present with lumps, swelling, hypertrophic lesions, pigmented growths, ulcers, discharging sinuses, elephantiasis, and esthiomene,⁴⁴ vulval lymphedema,⁴⁵ grossly hypertrophic lesions, or a non-healing ulcer mimicking malignancy making a biopsy and histopathological examination essential to confirm the diagnosis.¹⁵

6. Diagnosis

Genital tuberculosis is a paucibacillary disease and thus it is not possible to detect Mtb in all cases of genital tuberculosis. An early and exact diagnosis is needed for the fruitful treatment of genital tuberculosis. It is dependent on suspicion, confirmation, and suggestion.¹ The gold standard test for the diagnosis of tuberculosis is the identification of Mtb from the clinical sample like sputum, body fluid, and or tissues.¹ Imaging help in the identification of the diseased site and thus image-guided aspiration of abscess or biopsy for the microbiological and molecular confirmation.^{15,46} The diagnostic capacity and resources. Ideally, all clinical samples sent for microbiological examination should be sent for culture and molecular analysis.⁴⁷

6.1. Chest X-Ray

All patients suspected of having EPTB should have a clinical assessment for pulmonary TB in line with Revised National Tuberculosis Control for India and World Health Organization guidance for investigating suspected pulmonary TB(48,49). Chest X-ray should be done to evaluate the associated pulmonary tuberculosis and/ or for the evidence of old healed pulmonary Koch's.

6.2. Mantoux/Tuberculin test (TST)

Positive TST has limited utility in a high endemic regions of tuberculosis and the places where the BCG vaccination is routinely practiced.⁴⁸ Positive tests just indicate infection but not disease and it can be falsely positive in BCG vaccination, treated cases of tuberculosis, and non-TB mycobacterial infection. A false negative test can be seen in an immunocompromised state.

6.3. Urine Lipoarabinomannan(LAM)

LAM is a heat-stable glycolipid of the outer cell wall of Mycobacterium which is released by metabolically active bacilli. Kidney filtered the LAM making it detectable in urine. The lateral flow urine lipoarabinomannan (LF-LAM) assay is a commercially available point-of-care test for active tuberculosis (Alere Determine TB LAM Ag; Alere).⁴⁹ According to WHO LF-LAM may be used to assist in the diagnosis of TB in HIV-positive adult inpatients with signs and symptoms of TB (pulmonary and/or extrapulmonary) who have a CD4 cell count less than or equal to 100 cells/ μ L, or HIV positive patients who are seriously ill regardless of CD4 count or with unknown CD4 count⁵⁰ and it should not be used for the screening of TB. The usefulness of this assay for diagnosing FGTB has not yet been evaluated.

6.4. Endometrial biopsy (Currete and Aspiration)

It is obtained in the pre-menstrual phase either by aspiration or by biopsy of the endometrium. It can also be obtained by dilatation of the cervix followed by curettage of the endometrium.³ One part of the aspirate/biopsy should be sent for the histopathological examination and the other part should be sent for microbiological and/or molecular test.

Histopathology will reveal granuloma formation with or without Langerhans cell demonstration. Multiple biopsies are often needed to increase the pickup rate. Differential diagnoses of granuloma include fungal infections, syphilis, leprosy, rheumatoid arthritis, systemic lupus erythematous, pneumoconiosis, and sarcoidosis.⁴⁸ Biopsy from the cervix is needed to differentiate tubercular lesions from carcinoma.

Mycobacterial Isolation: Isolation of Mtb is needed for the definitive diagnosis of TB. Microscopy and culture are the conventional methods of diagnosis of TB. Microscopy for AFB is a rapid test for diagnosis but with variable sensitivity. Acid-fast (Ziehl-Neelsen (ZN), Kinyon) staining or fluorescent (auramine, rhodamine) staining is a more frequent method. For ZN staining to yield a positive result, a sample should contain 5,000-10,000 bacilli/ml.⁵¹ Culture for mycobacterium is more sensitive and requires 10-100 bacilli/ml of tissue/fluid samle for the diagnostic yield. Culture of clinical specimens for Mtb is the goldstandard diagnostic test for the diagnosis of active TB with a sensitivity of 65% and specificity of 100%.¹ The standard culture method includes solid media (Lowenstein-Jensen (LJ) medium and Dorset egg medium) and liquid media (Dubios medium and Krishner medium). Standard culture methods are time-consuming as it usually takes 2-20 weeks for the result. Conventional methods have been replaced with been phased out in most countries and have been replaced with automated liquid Mycobacteria Growth Indicator Tube (MGIT) culture using the BACTEC MGIT 960 System (Becton Dickinson-BD) 213, which is based on modified Middlebrook 7H9 broth, and positive results can be available within ~2 weeks.¹⁵ The advantage of using these methods is the drug sensitivity test that can be performed in this method.

GeneXpert MTB/RIF or Xpert MTB.Rif: It is a commercially available cartridge-based nucleic acid amplification test (CBNAAT) diagnostic test for the Mycobacterium tuberculosis complex. It took only 2 hours for the confirmation of the result. It uses polymerase chain reaction (PCR) to test specimens (Biopsy and fluid) for genetic material specific to Mtb and simultaneously detects a gene that confers resistance to rifampicin, rpoB (Blakemore, 2010). It is manufactured by Cepheid, Sunnyvale, California, USA.⁵² Due to the paucibacillary nature of the FGTB, the size and quality of the specimens may affect the sensitivity of the test. In 2016, a new version of Xpert MTB/RIF, Xpert MTB/RIF Ultra, was introduced with a lower limit of detection. This new test has a sensitivity for M tuberculosis detection similar to culture assays (which are known to be highly sensitive). This WHO-endorsed test has the advantages of requiring fewer resources and yielding faster results has been used in South Africa. But this test does have a lower specificity for detection of M tuberculosis, and so interpretation of so-called trace-positive results remains a challenge.²⁰ Xpert XDR, which allows for the detection of resistance to isoniazid, injectable agents, and fluoroquinolones was also shown to be effective in a large validation study and is expected to become commercially available soon.²⁰ A positive CBNAAT is useful but a negative test does not always rule out TB. Sharma et al⁵³ observed 35 percent sensitivity and 100 percent specificity in the detection of FGTB with GeneXpert.

6.5. Hysterosalpingography

It is performed for the visualization of the uterine cavity and fallopian tube by injecting radio-opaque dye preferably water soluble in the uterine cavity. Hysterosalpingography should not be performed in suspected cases of genital tuberculosis as it may flare up the subclinical infection. It is routinely performed for the investigation of infertility for the unsuspected cases of genital tuberculosis. Certain lesions are described that are suggestive of tuberculosis in the fallopian tube and uterus include.

Fallopian tube: Tubal occlusion is the commonest finding seen on HSG occurring commonly at the junction of isthmus and ampulla.^{54–56} Characteristic findings described fallopian tube are

- 1. Rigid pipe stem tube appearance: Encasement of the fallopian tube in connective tissue leading to the loss of normal tortuosity appearing as a rigid pipe.⁵⁴
- 2. Salpingitis isthmica nodosa (SIN): Tubercular granuloma undergoing caseous ulceration leading to mucosal irregularity causing ragged contour of the lumen of the tubes and diverticular outpouchings (salpingitis isthmica nodosa). SIN is delineated by nodular thickening of the isthmic and ampullary portions along with a collection of contrast in the fallopian tube wall causing the appearance of multiple small diverticuli.⁵⁴
- 3. Hydrosalpinx: Edematous thickening and dilatation of the tubal wall. Twisting of the hydrosalpinx may result in the floral hydrosalpinx.⁵⁴
- 4. Rosary beaded appearance: Alternate area of constriction with tubal dilation because of the scarring of the tubes giving rise to the rosary bead appearance of the tubes characteristic of TB.^{54,55}
- Cotton wool plug appearance: Dissemination of contrast in an irregular manner at the tubal termination produces a cotton-wool plug appearance.⁵⁴
- 6. Golf club appearance: Sacculation of both tubes in the distal portion with an associated hydrosalpinx giving a Golf club-like appearance.
- 7. Tobacco pouch appearance: It occurs because of the eversion of the fimbria secondary to adhesions, with a patent orifice producing the tobacco pouch appearance.^{54,57}
- 8. Sawtoothed appearance: When the tubal lumen is filled with putty-like caseous material the fallopian tube outline on HSG is irregular with pockets giving a sawtoothed appearance.⁵⁴
- 9. Leopard skin appearance: When the ampulla is partially filled with radio-opaque contrast causing multiple granulomatous lesions in the lumen of the tube giving a speckled 'leopard spot' appearance.^{15,54}
- 10. Cobblestone appearance: Caused by intraluminal scarring and adhesions.^{15,54}
- 11. Peritubular halo: Peritubular adhesions lead to thickening of the tubal leading to a cloudy sign on HSG. This is a non-specific feature of tubal tuberculosis.

Endometrial tuberculosis: It is characterized by synechiae, a distorted uterine contour, and venous and lymphatic intravasation on HSG. These findings are non-specific. Generally, synechiae and intrauterine adhesions in tuberculosis are irregular, angulated, and stellate-shaped with well-demarcated borders.⁵⁸ Characteristic findings described in relation to the uterus are

- 1. Psudounicornuate uterus: Unilateral scarring may lead to the obliteration of the uterine cavity on one side giving rise to a unicornuate-like appearance which should be differentiated from the true unicornuate uterus which shows characteristically smooth contour, a more horizontally oriented long axis, and normal fallopian tube.^{58,59}
- 2. T-shaped uterus: Scarring of the uterine cavity may lead triangular uterine cavity into a T-shaped cavity.
- 3. Dwarfed uterus: HSG shows a very small and deformed uterine cavity because of severe scarring and fibrosis.^{58,59}
- 4. Trifoliate-shaped uterus. It is formed because of synechiae formation at the uterine borders and partial obliteration in the uterine fundus.⁵⁹
- 5. Netter syndrome: Glove finger appearance occurs on HSG in Netter syndrome. Netter syndrome occurs because of the destruction of endometrium and myometrium followed by fibrosis and complete obliteration of the uterine cavity.

6.6. Laparoscopy and hysteroscopy

It is done to assess the anatomical abnormality and localization of urogenital tubercular lesions and to obtain a tissue sample for the molecular, microbiological, and histological assessment.¹⁵

Hysteroscopy may show normal uterine cavity in genital tuberculosis in the early stage of uterine tuberculosis or when there is no involvement of endometrium. Abnormal findings on hysteroscopy seen in endometrial tuberculosis include intrauterine synechiae, granulomas, and poor ability to distend making the diagnosis of Asherman Syndrome.^{28,60}

Laparoscopy helps in the inspection of ovaries, fallopian tubes, and peritoneal cavity for tubercular lesions and obtaining biopsies.^{5,15} Finding on laparoscopy may depend upon the stage of tuberculosis described as subacute and chronic stage.³ The subacute stage is characterized by the presence of whitish yellow and opaque miliary granulations with hyperemic areas over the fallopian tube and uterus. The chronic stage is characterized by nodular and patchy salpingitis, hydrosalpinx, caseosalpinx and adhesion bands between loops of the intestine and the omentum. Other abnormalities include granuloma, plaques, exudates, tuboovarian mass, and pelvic congestion.²⁸

6.7. Ultrasonography (USG)

There is no specific finding that can make a definitive diagnosis of genital tuberculosis.²⁸ But it has been routinely used to assess pelvic and abdominal problems. At times

normal USG findings are there in genital tuberculosis.⁶¹ Due to edema fallopian tubes are dilated with a thickened wall. Tubes may be folded and filled with clear fluid suggestive of hydrosalpinx, and when showing internal echoes are suggestive of pyosalpinx.⁵⁶ Tubo-ovarian masses with calcification and fluid in the pouch of Douglas can be seen on USG(5). Tubercular endometritis in the acute stage shows thickened hypoechoic endometrium on USG while the chronic stage shows synechiae appearing as defects disrupting the continuity of the endometrial lining or as irregularities in the endometrium surrounded by cystic spaces.⁵⁶

6.8. Computed tomography (CT)

It may show ascites and abdominal and pelvic lesions with or without lymphadenopathy. Calcification can be seen more efficiently on CT and if it is seen favors the diagnosis of tuberculosis.

6.9. Magnetic resonance imaging (MRI)

Used more frequently for evaluating the abdominal and pelvic masses and found to be more useful for localizing soft tissue irregularities in genital tubercular patients. It is considered better than CT in abdominal masses and may avoid the need for laparotomy.^{28,62}

6.10. Serodiagnosis

World Health Organization (WHO) has strongly recommended that commercial serodiagnostic tests should not be used for the diagnosis of pulmonary and extrapulmonary TB⁶³ because of the imprecise and inconsistent findings. Interferon Gama release assay (IGRA) is also not recommended by WHO for the diagnosis of active TB disease.

6.11. Positron-emission tomography (PET) scan

It shows unilateral or bilateral tubo-ovarian masses with increased fluorodeoxyglucose (FDG) uptake by TB lesion.⁶² Though PET-CT scanning is nonspecific for tumor as well as infectious and inflammatory conditions.⁶⁴ Its specificity is a major concern. It is useful for identifying the site of biopsy, and stages of the infection, and detects disease in previously unknown sites.⁶⁵ It plays a major role in the diagnosis of active TB infection in areas where conventional microbiological methods are unavailable and it helps in monitoring response to therapy in cases such as multidrug-resistant TB or extrapulmonary TB.⁶⁶

7. Treatment

Medical: The latest WHO-recommended treatment guidelines for drug-sensitive TB and drug-resistant TB should be used.¹

Treatment for Drug Sensitive Tuberculosis: The WHO (2010) and Revised National Tuberculosis Control Program (RNTCP) of India^{67,68} for TB treatment guidelines recommend that patients newly diagnosed with TB should receive an intensive phase with isoniazid (H), Rifampicin (R), ethambutol (E) and pyrazinamide (Z) for two months followed by a continuation phase with HRE for four months. In a randomized controlled trial, six months of antitubercular treatment was found to be equally effective as nine months of therapy. There was found to be no difference in complete cure rate, recurrence rate, and pregnancy rate for either 6 months or 9 months of intermittent directly observed treatment short course anti-tuberculous.⁶⁹ WHO and RNTCP recommends all people diagnosed with tuberculosis should be offered daily treatment with fixeddose combinations.^{20,70}

Treatment for Drug-Resistant Tuberculosis (DRTB): All patients who failed to improve clinically radiologically after two months of conventional anti-tubercular treatment should be evaluated for DRTB. Drug-resistant genital tuberculosis is treated with reserve drugs for 18-24 months and the duration may be modified according to the patient's response to therapy. The findings from studies of shorter DR-TB regimens were limited to patients with pulmonary disease, and they cannot be assumed to be used directly with extrapulmonary TB. Thus, the shorter DR-TB regimen cannot be used in patients with extrapulmonary DR-TB.^{71,72}

Surgical: Surgery is not considered a main part of treatment for genital TB. It is used as complementary to chemotherapeutic treatment. Surgical treatment for TB is quite difficult and risky because more complications occur during laparoscopy, hysteroscopy, and a vaginal hysterectomy performed in females with genital tuberculosis.^{48,73,74} It occurs due to congestion, edema, and hyperemia in the acute stage of the disease and due to abdominal and pelvic adhesions and frozen pelvis in the chronic stage of genital tuberculosis.⁴ Surgical treatment is needed for the removal of the uterus, both tubes, and ovaries for persistent disease, tubercles, pyosalpinx, tuboovarian mass, and non-healing ulcers in DR TB despite medical treatment.⁴⁸ It is also done after the completion of treatment if pelvic mass persists or increases in size after six months of anti-tubercular treatment and if the endometrial tissue again become positive for tuberculosis on culture or histology after full treatment.³

8. Female Genital Tuberculosis and HIV Infection:

Anti-tubercular treatment should be given as per national /WHO protocol. Anti-retroviral treatment should be initiated within two weeks of the beginning of anti-tubercular treatment if the CD4 count is below 50 cells/mm³ and for others within eight weeks of initiation of anti-tubercular treatment. The duration of treatment remains the same similar to a person without HIV coinfection.^{52,70}

9. Female Genital Tuberculosis and Pregnancy

The outcome of infertility in GT is not very good. A study done by Tripathy et al. showed a very low conception rate i.e. 19.2%, and the live birth was 7.2% in genital tuberculosis patients.⁷⁵ It also increases the chances of ectopic pregnancy. Reconstructive surgery of the fallopian patency restoration has been advised but the pregnancy remains rare. Cilia and mucosa destruction due to tuberculosis is the reason for infertility.²⁸ It is believed that genital TB that involves the peritoneal surface but not the mucosa does not impair reproductive function, in comparison to patients with mucosal involvement should be considered infertile, the reason may be due to scarring of the endometrium, which prevents implantation.⁹

In vitro fertilization in women with endometrial and tubal tuberculosis is considered a good method for pregnancy. Patients with endometrial tuberculosis showed reduced fertilization, implantation, and cumulative pregnancy rates.⁷⁶

10. Conclusion

A high index of suspicion is needed for the diagnosis of FGTB. Infertility and menstrual irregularities are the common presentations of the FGTB. At times FGTB remains asymptomatic. Most of the time females present at the advanced stage of tuberculosis when the adhesions and destruction of the fallopian tube and the uterus have already occurred. As the treatment is needed for a long time precise diagnosis is required using multi-modality diagnostic procedures. The serodiagnostic test should not be used to diagnose the FGTB.

11. Source of Funding

None.

12. Conflict of Interest

None.

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Cite this article: Singh SK, Gupta M, Yadav P. Female genital tuberculosis. *Indian J Obstet Gynecol Res* 2022;9(4):442-451.