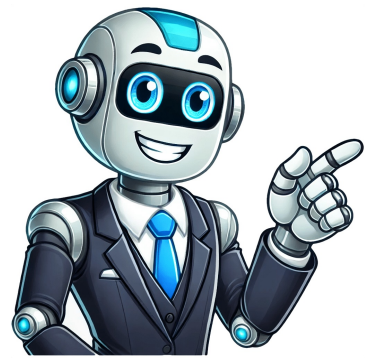


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Female genital tuberculosis (FGTB) is an important cause of significant morbidity, short- and long-term sequelae especially infertility whose incidence varies from 3 to 16% cases in India. Mycobacterium tuberculosis is the etiological agent for tuberculosis. The fallopian tubes are involved in 90–100% cases, endometrium is involved in 50–80% cases, ovaries are involved in 20–30% cases, and cervix is involved in 5–15% cases of genital TB. Tuberculosis of vagina and vulva is rare (1–2%). 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. Treatment is by giving daily therapy of rifampicin (R), isoniazid (H), pyrazinamide (Z) and ethambutol (E) for 2 months followed by daily 4 month therapy of rifampicin (R) and isoniazid (H). Alternatively 2 months intensive phase of RHZE can be daily followed by alternate day combination phase (RH) of 4 months. Three weekly dosing throughout therapy (RHZE thrice weekly for 2 months followed by RH thrice weekly for 4 months) can be given as directly observed treatment short-course. Surgery is rarely required only as drainage of abscesses. There is a role of in vitro fertilization and embryo transfer in women whose fallopian tubes are damaged but endometrium is healthy. Surrogacy or adoption is needed for women whose endometrium is also damaged. Keywords: Female genital tuberculosis, Endometrial biopsy, Acid-fast bacilli, Polymerase chain reaction, Laparoscopy, Hysteroscopy

Tuberculosis continues to be a major health problem throughout the world affecting about 9.4 million people annually with about two million deaths [1, 2]. Over 95% of new TB cases and 90% of deaths occur in developing countries with India and China together accounting for 40% of the world's TB burden. Co-infection with human immunodeficiency virus (HIV), more liberal migration from high risk to low risk areas due to globalization has been responsible for increased incidence all over the world. Multidrug resistant (MDR) and extreme-drug resistant TB (XDR), usually caused by poor case management, are a cause of serious concern [1, 2]. World Health Organization (WHO) in a drastic step declared TB a global emergency in 1993 and promoted a new effective TB control called Directly Observed Treatment Short-course (DOTS) strategy with 70% case detection rate and 85% successfully treatment rates [3]. The Revised National Tuberculosis Control Programme (RNTCP) of India incorporating DOTS strategy has achieved 100% geographical coverage with 71% case detection rate and 87% treatment success rate with a sevenfold decrease in death rate (from 29 to 4%) in the year of 2010 [4]. Apart from commonest and the most infectious pulmonary TB, extra pulmonary TB (EPTB) is being increasingly encountered throughout the world [5]. Female genital TB (FGTB) is an important cause of significant morbidity, short- and long-term sequelae especially infertility [5–8]. Timely diagnosis and prompt appropriate treatment may prevent infertility and other sequelae of the disease. The incidence of FGTB varies in different countries from 1% in infertility clinics of USA, 6.15–21.1% in South Africa and 1–19% in various parts of India [7, 9–13]. In infertility patients, incidence of FGTB varies from 3 to 16% in India with higher incidence being from apex institutes like All India Institute of Medical Sciences (AIIMS), New Delhi, where prevalence of FGTB in women of infertility was 26% and incidence of infertility in FGTB to be 42.5%, which may be due to referral of difficult and intractable cases to this apex hospital from all over India, especially from states like Bihar where prevalence of TB is very high [8, 13]. Similarly incidence of FGTB is also very high in women seeking assisted reproduction being 24.5% overall but as high as 48.5% with tubal factor infertility [14]. The FGTB is present in younger age (20–40 years) as compared to premenopausal age in developed countries [6, 8–15]. It may be due to younger age at marriage and child bearing in developing countries as compared to western world [8]. There has been fivefold increase in prevalence of TB in countries with high prevalence of HIV due to impaired immunity in them [16]. Mycobacterium tuberculosis is the etiological agent for tuberculosis. 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 [1–3, 5–8, 16]. Genital TB generally occurs secondary to pulmonary (commonest) or extra pulmonary TB like gastro-intestinal tract, kidneys, skeletal system, meninges and military TB [5–8] through hematogenous and lymphatic route. However, primary genital TB can rarely occur in women whose male partners have active genitourinary TB (i.e., tuberculosis epididymitis) by transmission through infected semen [5, 8]. The site of involvement in primary genital TB can be cervix, vagina or vulva [5, 8]. Direct contiguous spread from nearby abdominal organs like intestines or abdominal lymph nodes can also cause genital TB. The fallopian tubes are involved in 90–100% cases with congestion, military tubercles, hydrosalpinx, pyosalpinx and tubo-ovarian masses [5, 8]. Endometrium is involved in 50–80% cases with caseation and ulceration causing intrauterine adhesions (Asherman's syndrome) [17]. Ovaries are involved in 20–30% cases with tubo-ovarian masses [5, 8]. 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 [18]. 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 [19]. 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 in peritoneal TB with CT scan and MRI also giving similar picture and diagnosis may be made only on laparoscopy done for suspected ovarian cancer [20, 21]. Ascitic fluid tapping for bio-chemical analysis (elevated adenosine deaminase level in ascitic fluid in peritoneal TB) is useful in diagnosis [22]. Laparoscopic biopsy with frozen section evaluation has also been suggested to avoid laparotomy in such cases [21, 22]. Positron emission tomography with 18-F-fluorodeoxy glucose (FDG-PET) has been successfully used for the preoperative diagnosis of peritoneal tuberculosis and tuberculous tubo-ovarian masses [23, 24]. Varying grades of pelvic and abdominal adhesions including peripheatic adhesions (Fitz-Hugh-Curtis syndrome) are common in genital and peritoneal tuberculosis [25, 26]. Rarely genital TB may be associated with other gynecological pathologies like ovarian cancer, genital prolapse and fibroid uterus [5–8]. The clinical presentation of genital TB depends upon the site of involvement of genital organs and is shown in Table 1 [5, 8, 11, 27]. Up to 11% of women with genital TB may be asymptomatic [8, 13]. The age of presentation in 80% of women is 20–40 years group especially in developing countries. Infertility is the commonest presentation of genital TB due to the involvement of fallopian tubes (blocked and damaged tubes), endometrium (non-reception and damaged endometrium with Asherman's syndrome) and ovarian damage with poor ovarian reserve and volume [6–8, 17, 28]. Symptoms and signs in FGTB (A Symptoms in genital TB [5, 6, 8, 11, 27] Asymptomatic (up to 11%) General systemic symptoms Pyrexia with night sweats Loss of appetite Weight loss Poor general condition Menstrual dysfunction Puberty menorrhagia Menorrhagia Postmenopausal bleeding Oligomenorrhea Hypomenorrhea Amenorrhea (primary and secondary) Dysmenorrhea Infertility (primary and secondary) Abdominal lump Abdominal pain (may be flared up after HSG or D&C) Chronic pelvic pain (may be flared up after HSG or D&C) Acute abdomen (in rupture of tubo-ovarian abscess or flaring up of TB after HSG, D&C, coitus, exercise, menstruation) Abnormal vaginal discharge Unusual symptoms Vaginal/vulva/vulvovaginitis Labial swelling Rupture urinary incontinence Local inflammation BSGs in genital TB [5, 6, 8, 11–21] No physical sign (common) Systemic examination Fever Lymphadenopathy Lymph nodes TB Crepitations on chest examination (common) TB Tuberculous lesions in cervix, vagina or vulva (may be seen on speculum examination) Douchy feel on vaginal examination (abdominal TB), examination of external genitalia (vulva or vaginal TB), speculum examination (cervix TB), bimanual examination (endometrial or fallopian tube TB) help in the diagnosis of genital TB [5, 6, 8, 18]. All tests are not required for every single case of genital TB. The tests will depend upon the site of TB and its clinical presentation. The various tests are shown in Table 3 [29–33]. Investigations in genital TB [5–8, 15, 28–33] Blood tests Anemia, leucocytosis with lymphocytosis and raised ESR; nonspecific Serological tests like ELISA are not very sensitive and specific. Moderate rise in levels of CA 125 in genital TB Mantoux (tuberculin) test and interferon gamma release assays; poor sensitivity and specificity Chest X-ray For pulmonary TB Imaging methods Ultrasonography (USG) Computerized axial tomography (CT scan) Magnetic resonance imaging (MRI) [29]: useful for tubo-ovarian masses Positron emission tomography (PET scan) [42]: tubercular tubo-ovarian masses (Fig. 1) Hysterosalpingography (HSG) [30]: Endometrial TB can cause synechia formation, a distorted, obliterated or T-shaped cavity and venous and lymphatic intravasation Endometrial biopsy, curettage or aspirate Histopathology Demonstration of epithelioid granuloma Mycobacterial smear and culture Using Lowenstein-Jensen (LJ) medium or BACTEC 460 or mycobacteria growth inhibitor tube (MGIT) and specific gene probes can help in rapid identification and diagnosis [15] Polymerase chain reaction (PCR) Rapid (1–2 days), sensitive and specific method for detecting mycobacterial DNA (mpt 64 gene) with high pickup rate but can be false negative due to contamination or false positive as it can pick up even single mycobacterium tuberculosis and may not be able to differentiate between infection and disease [31, 32]. Hence ATT should not be started just on the basis of positive PCR unless there is some other evidence of FGTB on clinical examination or on investigations like the presence of tubercles or other signs of TB. History of TB or tuberculosis therapy (in the past or present) should be sought for ruling out the ATT as a mimicked form. HIV has high risk of HIV-related morbidity and mortality, while HIV is the most important factor for fueling TB epidemic in high HIV prevalence populations. In India, RNTCP and National AIDS Control Organization (NACO) have joined hands for better management of this dual epidemic. Possible options for antiretroviral therapy in TB patients include: Defer antiretroviral therapy until TB treatment is completed Defer antiretroviral therapy until the end of the initial phase of treatment and use ethambutol and isoniazid in the continuation phase Treat TB with a rifampicin-containing regimen and use efavirenz + 2 NRTIs (nucleoside reverse transcriptase inhibitors) Treat TB with a rifampicin-containing regimen and use 2 NRTIs and then change to a maximally suppressive HAART regimen on completion of TB treatment. The medical therapy, especially the modern short-course chemotherapy consisting of rifampicin and other drugs, is highly effective for the treatment of FGTB with rare need of surgery [8]. However, limited surgery like drainage from residual large pelvic or tubo-ovarian abscesses or pyosalpinx can be performed followed by ATT for better results as recommended by American Thoracic Society [8, 40]. There are much higher chances of complications during surgery in women with genital TB in hysteroscopy, laparoscopy, vaginal hysterectomy and laparotomy [35, 37, 42, 43]. There is excessive hemorrhage and nonavailability of surgical planes at time of laparotomy with higher risks of injury to the bowel and other pelvic and abdominal organs. In a case of abdomino-pelvic TB, bowel loops may be matted together with no plane between them and uterus and adnexa may be buried underneath the plastic adhesions and bowel loops and are inapproachable. Even trying to perform a diagnostic laparoscopy or laparotomy in such cases can cause injury to bowel necessitating a very difficult laparotomy and resection of injured bowel. It is better to take biopsies from the representative areas and close the abdomen without pelvic clearance in cases of laparotomy done for suspected pelvic tumors but found to be tubercular at laparotomy followed by full medical treatment. Sometimes even after a full 6-month course of ATT, women with genital TB with infertility do not conceive when laparoscopy and hysteroscopy may be repeated to see any remaining disease. Outcome for fertility in FGTB is only good when ATT is started in early disease. However, cases of advanced TB with extensive adhesions in pelvis and uterus are usually untreatable with very poor prognosis for fertility. Tuboplasty performed after ATT does not help much with chances of flare-up of the disease and risk of ectopic pregnancy, should the women conceive [10, 44]. 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 [10]. Parikh et al. [12] 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 attempt. Jindal [11] 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 4.4% with fertility enhancing surgery. Dam et al. [45] 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 [8, 46]. 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 [47]. There has been a renewed interest in research in TB at global level. New and improved BCG vaccines are being developed. New drugs, effective against strains that are resistant to conventional drugs and requiring a shorter treatment regimen, are being developed. Newer shorter (4–5 months) regime of ATT is being developed and studied [48]. By controlling TB, we can also get rid of bay and prevent early to late TB. The development of short-term and long-term sequelae of this menace [8]. FGTB prevalence varies in different parts of the world. In India, it is being more common in developing countries, especially Africa and Asia, and is also a secondary infection from lungs and other sites like abdomen. FGTB is responsible for up to 16% cases of infertility in developing countries, while infertility is seen in up to 40–50% cases of genital TB. The main symptoms are menstrual dysfunction, especially oligomenorrhea, amenorrhea, chronic pelvic pain and discharge. High index of suspicion is needed and has been awarded merits in early stages when it can be treated without causing significant damage to genital organs as repeated FGTB can cause permanent sterility through tubal damage and endometrial destruction (Asherman's syndrome) Diagnosis is by good history taking, thorough clinical examination and judicious use of investigations, especially endometrial sampling for AFB culture, PCR and histopathological testing. Laparoscopy and hysteroscopy may be helpful in early diagnosis and to see the severity of disease for prognostication for fertility Medical treatment using DOTS strategy under direct observation and using quality-assured drugs in appropriate dosage and for adequate time is the main stay of treatment. Prognosis for fertility is poor. However, for tubal disease in the absence of endometrial disease, ART especially IVF-ET, may give some results. In cases of endometrial disease with shrunken cavity, prognosis for fertility is very poor even with IVF ET. Surgical treatment is rarely required and should only be done in exceptional circumstances and should be in the form of limited surgery like laparoscopy, hysteroscopy and drainage of abscess as surgery in genital and peritoneal TB can be difficult and hazardous. Treatment of TB in HIV-positive woman is same as in HIV-negative woman in consultation with experts in the field. I am thankful to Prof. Alka Kriplani, Prof. S Kumar, faculty and residents of Obstetrics and Gynecology at AIIMS, New Delhi, and Dr. Sangeta Sharma (National Institute of Tuberculosis and Respiratory Diseases, New Delhi, for their help in preparing this manuscript. I am also thankful to Sona Dharmendra, Senior Research Fellow (AIIMS), Dr Asmita (SRF, AIIMS) and Mr. Pawan Kumar for their help in data, typing and writing of manuscript. MD, DNB, Professor, MFFP F&MS, FRCOG in Department of Obstetrics and Gynecology, All India Institute of Medical Sciences, New Delhi. Before that he has worked as Professor in Mauritius, Azad Medical College, New Delhi. He has over 360 publications and has 120 paper reviewed. He has published articles in various journals of national and international repute. He is currently editor in chief of Indian Obstetrics and Gynecology, Journal of Paediatrics and Obstetrics and Gynecology (JPOG) and American Editor of International Journal of Gynecology and Obstetrics, India. He edited three textbooks and has been awarded merits by Royal College of Obstetricians and Gynaecologists (RCOG), London. His special areas of interest include genital tuberculosis, urogynecology and anemia in pregnancy. There is no conflict of interest. 1.Dye C, Watt CJ, Bleed DM, et al. Evolution of tuberculosis control and prospects for reducing tuberculosis incidence, prevalence and deaths globally. 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It can affect both men and women and may cause pain, swelling, and ulcers in the genital area. It is also possible to develop a discharge from the vagina or penis. Genital TB can spread through skin-to-skin contact with an infected person or sexual intercourse. It usually occurs in people who have weakened immunity (Y. P. Coe with genital TB). Tuberculosis of the female genital tract in patients with tubal factor infertility. J Reprod Med. 1990;77:562–564. [DOI] [PubMed] [Google Scholar] 34.Sharma JB, Pushparaj M, et al. Increased complications rates associated with laparoscopic surgery among patients with genital tuberculosis. Int J Gynecol Obstet. 2010;109:242–244. doi: 10.1016/S0020-7292(02)00228-X. [DOI] [PubMed] [Google Scholar] 35.Mittal S, Sharma JB. Dilemmas in diagnosis of female genital tuberculosis. In: Mukherjee GG, Tripathy SN, Tripathy SN, editors. Genital tuberculosis. 1. Delhi: Jaypee Brothers Medical Publishers (P) Ltd.; 2010. pp. 83–91. 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