Genital Tuberculosis Among Women: A Narrative Review

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Abstract

In poor nations, "female genital tuberculosis (FGTB)" is a widespread health issue. It frequently results in pelvic inflammatory disease, menstrual irregularities, and infertility. 15-20% of extrapulmonary TB is represented by it. Most often, it is a secondary infection brought on by hematogenous dissemination from an extra-genital cause, like abdominal or pulmonary tuberculosis. In virtually all cases, the fallopian tube is the first to be harmed, followed by the endometrium and cervix. 44–74% of those affected, who are between the ages of 15 and 45, are infertile as a result of it. Genital TB must be clinically diagnosed with a high degree of suspicion. The most typical presentations are menstrual abnormalities and infertility. A multi-modality approach to diagnosis is necessary, incorporating clinical, radiographic, bacteriological, molecular, and histological techniques. Pyrazinamide, Ethambutol, Isoniazid, and Rifampicin must be used in combination for at least six months during treatment. Reserve medications are administered for a prolonged period of time in cases with drug-resistant TB.

Keywords: Tuberculosis, Women, Genital, Infertility, Mycobacterium

INTRODCUTION

The second-leading cause of death from a single infectious agent (behind HIV/AIDS) and one of the top 10 global causes of death. In 2017, it was estimated that 1.3 million HIV-negative people died from tuberculosis, while 300,000 more HIV-positive persons died from the disease. While affecting people of all ages, adults under the age of 15 make up more than 90% of those affected by tuberculosis. HIV-positive individuals made up 9% of those with tuberculosis, with 72% of them living in Africa and 2/3 in each of the following eight nations: India (27%), China (9%), Indonesia (8%), the Philippines (6%), Pakistan (5%), Nigeria (4%), Bangladesh (4%) and South Africa (3%). Males (64%) account for the majority of cases and deaths from the condition, while females (36%) are also significantly affected. From 8% in the WHO Western Pacific Region to 24% in the WHO Eastern Mediterranean Region, 14% of the 6.4 million incident cases that were reported in 2017 were extrapulmonary. Extrapulmonary tuberculosis was reportedly still underreported.[1-5] 5% of all female pelvic infections are caused by "female genital tuberculosis (FGTB)," a kind of extrapulmonary tuberculosis. Developing nations are more seriously infected, which causes pelvic inflammatory disease, which is a substantial cause of morbidity and has consequences that lead to infertility. Infertility and other FGTB-related consequences can be avoided with early diagnosis and appropriate treatment.[4-6]

EPIDEMIOLOGY

Due to underreporting, it is difficult to determine the exact incidence of FGTB. The unavailability of extremely sensitive diagnostic tests, the disease's silent nature, ambiguous symptoms, and other comorbidities like HIV, diabetes, and other bacterial infections all contribute to the under-reporting of cases. 15–25% of extrapulmonary tuberculosis is caused by genital tuberculosis.[7] According to socioeconomic and public health factors, the reported incidence of FGTB varies significantly from region to region. It typically correlates with the prevalence of abdominal and pulmonary TB. The reported incidence of FGTB in the Swedish study was just 0.002%, but it was reported to be 1% in the USA. In contrast, throughout the course of 17 years in Malaysia, FGTB was only detected in 12 cases. Saudi Arabia stated that 4.2% of the 945 infertile women who were investigated had infertility that was caused by a tubal factor. 5.7% of female genitourinary system involvement was recorded in Turkey in 2009.

Several studies from India have estimated the prevalence of genital TB to be anywhere between 1 and percent. FGTB affects 20–30-year-old poor women. Western countries diagnose FGTB in premenopausal women over 40. Just 1% of postmenopausal bleeding is FGTB. [6-13]

TRANSMISSION

Human "*Mycobacterium Tuberculosis* (MTb)" transmission can happen in a number of ways. The most frequent method is inhaling droplets of aerosol from people who are coughing or sneezing who have active laryngeal or pulmonary tuberculosis. Consumption of dairy products from infected cattle that have Mycobacterium bovis in them can also cause tuberculosis. The infection of Mycobacterium bovis has decreased significantly due to the increased usage of pasteurized milk. Other unique Mtb transmission routes include congenital transmission, sexual transmission, inadvertent inoculation, immunization, and therapeutic instillation. The recognized mechanism of congenital and/or neonatal transmission combines transplacental transmission by blood or lymphatics from the mother's active tuberculosis with aspiration or ingestion of Mtb-infected amniotic fluid at birth.[1] HIV-positive and immunocompromised individuals who received the live BCG vaccine developed both local and widespread BCG M. bovis strain TB. BCG is routinely used intravenously as an adjuvant therapy for urinary bladder transitional cell carcinoma. This may also result in TB of the kidney, prostate, bladder, and epididymis. Even TB of the spine can develop after intravenous BCG administration. TB can also be spread through sexual contact. Spouse may be carrying the same strain of endometrial TB that was reported to cause tubercular penile ulcers. Similarly a male partner who has the disease may deposit infected semen, which can lead to cervical tuberculosis. [1,14]

RISK FACTORS

Immunosuppressive conditions including diabetes and HIV, chronic kidney and liver disorders, alcoholism, and malnutrition are all risk factors for the development of tuberculosis. Risk factors for the development of tuberculosis include inadequate housing, homelessness, pneumoconiosis, heredity, nutritional deficiencies, immunosuppressive drug use, and renal transplantation. A patient receiving renal dialysis to treat chronic renal failure also has a higher risk of contracting tuberculosis. Smoking is a separate risk factor that raises mortality and latent TB infection as well as active TB disease by around a factor of two.[15,16] Few socioeconomic risk factors, such as poor housing conditions with few windows per room, indoor air pollution, and household socioeconomic status, can be effective predictors of tuberculosis infection and sickness.[17,18]

PATHOGENESIS

The most common ways that M. tuberculosis infects FGTB are through hematogenous or lymphatic transmission from pulmonary TB, while direct transfer from infected pelvic organs is also a possibility. Every component of the female reproductive system is impacted by tuberculosis. The female genital organs most frequently affected by TB in India are the fallopian tubes, uterine endometrium, ovaries, cervix, uterine myometrium, and vagina and/or vulva. A case of FGTB diagnosed retrospectively from 2006 to 2016 at Morocco, revealed a similar outcome. It revealed that the fallopian tubes were the genital organs most commonly affected, followed by the ovaries, endometrium, and the cervix. The majority of women with FGTB (>90%) had both fallopian tubes affected; this involvement could have been caused by *"TB endosalpingitis, exosalpingitis, interstitial TB salpingitis, or salpingitis isthmic nodosa"*.[2,19]

CLINICAL APPEARANCE

The site of infection affects how FGTB presents clinically. Asymptomatic FGTB infertility affects about 40% of women. Infertility caused by obstructed or damaged fallopian tubes, very low endometrial receptivity, or ovarian injury with low ovarian reserve and volume are the most typical presentations of FGTB. The majority of patients report having persistent lower abdomen and pelvic pain along with a variety of symptoms, including menstrual dysfunction, dysmenorrhea, pelvic mass, cyst, abscess, dyspareunia, and postmenopausal hemorrhage. Discovering these signs in infertile female patients could result in the FGTB.[2,19]

DIAGNOSIS

Confirmation of the FGTB diagnosis is needed from a number of tests. Table 3 demonstrates the many approaches frequently used to diagnose FGTB. Gynecologists may begin by gathering data by conducting a patient history check, complete physical examination, abdominal exam, and gynecological exam. A chest X-ray may reveal ongoing lung disease or previously healed TB lesions, raising the possibility of genital involvement. Moreover, the

diagnostic usefulness of ultrasonography is enormous. On an ultrasound, endometrial tuberculosis may appear as bands and intrauterine synechiae, as well as heterogeneous and thin endometrium, endometrial fluid, calcification, or both. Inhomogeneous enlarged ovaries with free peritoneal fluid and fixed adnexal masses can also be shown by USG, along with hydrosalpinges with cogwheel signals.[20] Laparoscopy and hysteroscopy are carried out as directed. In the absence of endometrial TB, the endometrial cavity can be seen during hysteroscopy and may appear normal. Typically, the hollow appears pale, the intrauterine is of various grades, tubercles are present, and there are little white caseous nodules. 90% of FGTB cases involve the fallopian tubes, hence laparoscopic discoveries may aid in diagnosis. These observations include abdominal and pelvic adhesions, miliary tubercles, white, yellow, and opaque patches on the uterus, tubes, ovaries, and peritoneum, small swollen tubes with agglutinated fimbriae, tubal block, hydrosalpinx, tube dilatation, fimbria end fusion, and calcified tubes.

Some fallopian tubes may appear normal, show signs of tuberculosis, caseous granuloma, pyosalphinx, hydrosalpinx, or beaded tube, or they may be impossible to see.[21] In four cases, hysteroscopy revealed caseation, fibrotic synechia, and thin endometrium as a result of the endometrium's destruction by TB's chronic inflammation. Because the endometrium sheds each month during menstruation, it is difficult to identify the physical signs of inflammation in the endometrium. On the "*Ziehl-Neelsen*" examination, there may occasionally be signs of inadequate granuloma formation and acid-resistant bacteria. As a result, samples from various endometrial locations should be obtained.[22] To establish the presence of TB, clinical and imaging tests may be supplemented with biomolecular assays such the Mantoux/tuberculin, "*interferon-gamma release assay (IGRA)*", and microbiological test from the samples. [23] The microbiological test can be carried out using a bacterial culture, "*enzyme-linked immunosorbent assay (ELISA)", "conventional polymerase chain reaction (PCR)",* or GeneXpert to detect M. tuberculosis nucleic acid. The combination of tests will increase the accuracy of the diagnosis, but the samples' quality will ultimately determine this. Based on the findings of two or more tests, a final diagnosis could be made using a composite reference standard. A recommendation for the suspicion, diagnosis, and management of extrapulmonary TB has also been created by the Indian health department.[24]

TREATMENT

The basic treatment for FGTB involves multiple medication treatments administered in suitable quantities for a long enough period of time. The best medical treatment for FGTB is short-course combination therapy for 6–9 months. For new cases, whether microbiologically confirmed or clinically diagnosed and drug-sensitive, combination therapy is administered to previously treated patients, such as nonresponders, failures, recurrent TB, and loss to follow-up for one month after receiving one month of "Antitubercular Therapy (ATT)". For FGTB, medical treatment with antitubercular medications is beneficial. Further surgery can be required for IVF patients to increase the likelihood of conception. Salpingectomy is a reliable and efficient treatment choice. After receiving ATT for a year, the procedure increased patients' clinical pregnancy and take-home baby rates.[25,26] A direct impact of hydrosalpinges may include embryotoxicity, decreased endometrial receptivity, and the potential flushing of the embryo from the uterus as a result of tubal fluid. Salpingectomy significantly improves clinical pregnancy when compared to no treatment, according to a meta-analysis research. Prior to IVF, salpingectomy for hydrosalpinges enhanced the likelihood of a clinical pregnancy. [2,27,28]Another study found that enhancing IVF pregnancy rates in women with hydrosalpinges by using laparoscopic tubal occlusion rather than laparoscopic salpingectomy. To evaluate the structural and physiological harm brought on by TB infection in the endometrium, more research is necessary. It can also be necessary to have further therapies to increase endometrial receptivity. The best approach for treating female infertility brought on by tubal TB at this time is ICSI-ET.[29-32] To prevent TB transmission during pregnancy, it is crucial to screen out the presence of FGTB in infertile patients before doing IVF. FGTB may manifest during pregnancy and harm the success of IVF. If the moms are not appropriately assessed and treated prior to the implantation of the embryos, assisted reproductive technology opens the door to the risk of congenital TB. Infertile women in endemic regions should take genital TB into account, and comprehensive TB screening should be performed before the IVF treatment. Early ATT in FGTB enhanced the menstrual cycle, thickened the endometrium, and decreased the occurrence of grade I adhesions. To enhance pregnancy outcomes, a

salpingectomy or tubal ligation may also be explored.[2]

CONCLUSION

To diagnose FGTB, a high index of suspicion is mandatory. Menstrual abnormalities and infertility are two prevalent FGTB manifestations. FGTB occasionally shows no symptoms. The majority of female patients with TB arrive at an advanced stage when the fallopian tube and uterus have already been damaged by adhesions. Using multi-modality diagnostic procedures, an accurate diagnosis is necessary because the treatment is long-term in nature. The FGTB should not be diagnosed with the serodiagnostic test.

REFERENCES

1. Singh SK, Gupta M, Yadav P. Female genital tuberculosis. Indian J Obstet Gynecol Res 2022;9(4):442-451
2. Tjahyadi D, Ropii B, Tjandraprawira KD, Parwati I, Djuwantono T, Permadi W, Li T. Female Genital Tuberculosis: Clinical Presentation, Current Diagnosis, and Treatment. Infect Dis Obstet Gynecol. 2022 Nov 18;2022:3548190. doi: 10.1155/2022/3548190. PMID: 36438172; PMCID: PMC9699775.
3. WHO Global tuberculosis control: WHO report 2018. Geneva: World Health Organization. Available from: http://apps.who.int/iris/ bitstream/handle/10665/274453/9789241565646-engpdf?.
4. Duggal S, Duggal N, Hans C, Mahajan RK. Female genital TB and HIV co-infection. Indian J Med Microbiol. 2009;27(4):361–3.
5. Kumar S. Tuberculosis. In: Sharma SK, Mohan A, editors. Female genital tuberculosis. New Delhi, India: Jaypee Brothers Medical Publisher Ltd; 2015. p. 311–24.
6. Neonakis IK, Spandidos DA, Petinaki E. Female genital tuberculosis: a review. Scand J Infect Dis. 2011;43(8):564–72. 5. Sharma JB, Sharma E, Sharma S, Dharmendra S. Female genital tuberculosis: Revisited. Indian J Med Res. 2018;148(Suppl 1):71–83
7. Bhanothu V, Theophilus JP, Rozati R. Use of Endo-Ovarian Tissue Biopsy and Pelvic Aspirated Fluid for the Diagnosis of Female Genital Tuberculosis by Conventional versus Molecular Methods. PLoS One. 2014;9(5):e98005.
8. Falk V, Ludviksson K, Agren G. Analysis of 187 newly diagnosed cases from 47 Swedish hospitals during the ten-year period 1968 to 1977. Am J Obstet Gynecol. 1980;138(7 Pt 2):974–7.
9. Schaefer G. Female genital tuberculosis. Clin Obstet Gynecol. 1976;19(1):223–39. 10. Sivanesaratnam V, Lim BH, Sivanesan S, Menon A. Pelvic tuberculosis: an uncommon gynaecological problem in Malaysia. J Trop Med Hyg. 1986;89(4):167–9.
10. Chattopadhyay SK, Sengupta BS, Edrees YB, Al-Meshari AA. The pattern of female genital tuberculosis in Riyadh, Saudi Arabia. Br J Obstet Gynaecol. 1986;93(4):367–71.
11. Türkmen IC, Ba¸ssüllü N, Comunoglu C, Ba ˘ gcı P, Aydın O, ˘ Comunoglu N, et al. Female genital system tuberculosis: a ˘ retrospective clinicopathological study of 1,548 cases in Turkish women. Arch Gynecol Obstet. 2012;286(2):379–84.
12. Chow TWP, Lim BK, Vallipuram S. The masquerades of female pelvic tuberculosis: case reports and review of literature on clinical presentations and diagnosis. J Obstet Gynaecol Res. 2002;28(4):203– 10.
13. Maestre MAM, Manzano CD, López RM. Postmenopausal endometrial tuberculosis. Int J Gynaecol Obstet Off Organ Int Fed Gynaecol Obstet. 2004;86(3):405–6
14. Muneer A, Macrae B, Krishnamoorthy S, Zumla A. Urogenital tuberculosis - epidemiology, pathogenesis and clinical features. Nat Rev Urol. 2019;16(10):573–98
15. Loddenkemper R, Brönnecke M, Castell S, Diel R. Tuberculosis and Tobacco Smoking. Pneumol Stuttg Ger. 2016;70(1):17–22.
16. Saunders MJ, Wingfield T, Tovar MA, Baldwin MR, Datta S, Zevallos K. A score to predict and stratify risk of tuberculosis in adult contacts of tuberculosis index cases: a prospective derivation and external validation cohort study. Lancet Infect Dis. 2017;17(11):1190–9.
17. Albuquerque M, Coimbra I, d'Arc Batista J, Maruza M, Ximenes RAA, Lacerda HR, et al. Empirical treatment for TB in HIV: lessons from a cohort study of people living with HIV treated in Recife, Brazil. BMC Public Health. 2014;14:289.
18. . Simmons JD, Stein CM, Seshadri C, Campo M, Alter G, Fortune S. Immunological mechanisms of human resistance to persistent Mycobacterium tuberculosis infection. Nat Rev Immunol. 2018;18(9):575–89
19. Shahzad S. Investigation of the prevalence of female genital tract tuberculosis and its relation to female infertility:An observational analytical study. Iran J Reprod Med. 2012 Nov;10(6):581-8. PMID: 25246930; PMCID: PMC4169853.
20. Khurana A. and Sahi. OC14.04: Ultrasound in female genital tuberculosis: a retrospective series. Ultrasound Obstet Gynecol. 2013; 42: 28-28. https://doi.org/10.1002/uog.12660
21. Sharma JB, Sharma E, Sharma S, Dharmendra S. Female genital tuberculosis: Revisited. *Indian J Med Res*. 2018;148(Suppl):S71-S83. doi:10.4103/ijmr.IJMR_648_18
22. Harzif AK, Anggraeni TD, Syaharutsa DM, Hellyanti T. Hysteroscopy Role for Female Genital Tuberculosis. *Gynecol Minim Invasive Ther*. 2021;10(4):243-246. Published 2021 Nov 5. doi:10.4103/GMIT.GMIT_151_20.
23. Sharma JB, Singh UB, Kriplani A, Kumar S, Roy KK, Kumari A, Dharmendra S. Hysteroscopic observations in 348 consecutive cases of female genital tuberculosis: A prospective study. Indian J Tuberc. 2022 Jan;69(1):48-57. doi: 10.1016/j.ijtb.2021.02.010. Epub 2021 Mar 9. PMID: 35074151..
24. Sharma SK, Ryan H, Khaparde S, et al. Index-TB guidelines: Guidelines on extrapulmonary tuberculosis for India. *Indian J Med Res*. 2017;145(4):448-463. doi:10.4103/ijmr.IJMR_1950_16
25. Arora R, Rajaram P, Oumachigui A, Arora VK. Prospective analysis of short course chemotherapy in female genital tuberculosis. Int J Gynaecol Obstet. 1992 Aug;38(4):311-4. doi: 10.1016/0020-7292(92)91024-i. PMID: 1358690..
26. Sharma JB, Singh N, Dharmendra S, Singh UB, P V, Kumar S, Roy KK, Hari S, Iyer V, Sharma SK. Six months versus nine months anti-tuberculous therapy for female genital tuberculosis: a randomized controlled trial. Eur J Obstet Gynecol Reprod Biol. 2016 Aug;203:264-73. doi: 10.1016/j.ejogrb.2016.05.035. Epub 2016 Jun 28. PMID: 27391900.
27. Cheng M, Yuan T, Liu Y. A woman with disseminated tuberculosis experienced preterm delivery, fallopian tube pregnancy, and delivered successfully following in vitro fertilization: a case report. *BMC Pregnancy Childbirth*. 2021;21(1):27. Published 2021 Jan 7. doi:10.1186/s12884-020-03487-6.
28. Caliskan E, Cakiroglu Y, Sofuoglu K, Doger E, Akar ME, Ozkan SO. Effects of salpingectomy and antituberculosis

treatments on fertility results in patients with genital tuberculosis. J Obstet Gynaecol Res. 2014 Oct;40(10):2104-9. doi: 10.1111/jog.12450. Epub 2014 Aug 11. PMID: 25131900.

29. Tsiami A, Chaimani A, Mavridis D, Siskou M, Assimakopoulos E, Sotiriadis A. Surgical treatment for hydrosalpinx prior to in-vitro fertilization embryo transfer: a network meta-analysis. Ultrasound Obstet Gynecol. 2016 Oct;48(4):434-445. doi: 10.1002/uog.15900. Epub 2016 Sep 13. PMID: 26922863..
30. Practice Committee of American Society for Reproductive Medicine in collaboration with Society of Reproductive Surgeons. Salpingectomy for hydrosalpinx prior to in vitro fertilization. Fertil Steril. 2008 Nov;90(5 Suppl):S66-8. doi: 10.1016/j.fertnstert.2008.08.089. PMID: 19007649..
31. Johnson NP, Mak W, Sowter MC. Surgical treatment for tubal disease in women due to undergo in vitro fertilisation. Cochrane Database Syst Rev. 2004;(3):CD002125. doi: 10.1002/14651858.CD002125.pub2. Update in: Cochrane Database Syst Rev. 2010;(1):CD002125. PMID: 15266464.
32. MacNeil A, Glaziou P, Sismanidis C, Maloney S, Floyd K. Global Epidemiology of Tuberculosis and Progress Toward Achieving Global Targets - 2017. MMWR Morb Mortal Wkly Rep. 2019 Mar 22;68(11):263-266. doi: 10.15585/mmwr.mm6811a3. PMID: 30897077; PMCID: PMC6478060.