

Original Research Article

FEMALE GENITAL TUBERCULOSIS AND INFERTILITY; A CROSS-SECTIONAL TERTIARY CARE-CENTRE BASED STUDY

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ABSTRACT

Background: Female genital tuberculosis is an important cause of infertility in developing nations. However, the disease burden remains largely undetected due to its variable clinical presentation and lack of sensitive diagnostic tests. **Objective:** To determine the prevalence of genital tuberculosis in women with infertility. **Design:** Prospective cross sectional cohort study. **Study population:** Two hundred four women with primary and secondary infertility.

Materials and Methods: This study was conducted in Department of obstetrics and gynaecology at Government medical college Srinagar, India. A total of 204 patients were included in the study. All the 204 study participants underwent diagnostic/therapeutic hysteroscopy-laparoscopy for evaluation of infertility. Endometrial curettings of patients suspected of having genital tuberculosis were sent for TB evaluation via AFB staining, Culture, Gene-xpert and HPE. Cultures were incubated for 8 weeks before declaring a sample negative.

Results: Of all 204 study participants, 70 endometrial curettings were sent for TB evaluation, 6 samples (8.57%) were positive on ZN staining, 4(5.7%) positive by gene-xpert, 3(4.28%) positive on culture, with an overall prevalence of 8.5%.

Conclusion: Female genital tuberculosis is an important cause of infertility in developing nations. Screening for genital TB needs to be a part of evaluation of infertility and menstrual abnormalities. Most of the patients present in advanced stage and treatment outcomes, particularly with regard to infertility, are poor. Early diagnosis and correct treatment is vital to avoid complications and to restore fertility.

Keywords: Infertility, tuberculosis, female genital tuberculosis.

INTRODUCTION

Infertility is defined as the inability to conceive after one year of regular unprotected intercourse¹. Infertility is said to be primary when a couple has not previously had a pregnancy and secondary when at least one successful pregnancy has been achieved previously irrespective of the outcome.^[1]Female infertility is rising globally, with variation in etiology between high-income (HIC) and low-and middle-income countries (LMIC).^[2]While anovulation is common in HICs, infectious etiology remains prevalent in LMICs where tubo-peritoneal damage affects fertility.^[3]Genitourinary tuberculosis (TB) is

a common form of extra pulmonary TB (EPTB) worldwide, accounting for 9% of EPTB.^[4]Genital TB is a known cause of infertility in women where endometrial damage, tubal obstruction, ovarian and cervical affection can lead to infertility.^[5,6] In the infertility clinics globally, an estimated 5% of the women presenting with infertility have genital TB, with prevalence rates ranging from less than 1% in HICs to as high as 3–26% in LMICs.^[7,8,9,10]India's TB incidence for the year 2021 is 210 per 100,000 population,^[11] of which the proportion of pulmonary TB is 75.2% and that of extrapulmonary TB is 24.8%.^[11]Females with genitourinary TB comprise

approximately 0.5% of all TB cases, and among genitourinary cases less than 50% are genital TB cases.^[12] The exact incidence of female genital tuberculosis (FGTB) is not known due to underreporting of cases, asymptomatic cases, vague symptomatology and the lack of reliable diagnostic tests with high sensitivity.^[13,14,15,16] The reported incidence is different in different nations being one per cent in infertility clinics of the USA,^[17] one per cent in the Scandinavian countries^[18], 4-8 per cent in Pakistan.^[19,20,15-21] 1 per cent in South Africa,^[21] 1-19 per cent in different areas of India.^[22,23] High incidence (26%) has been reported from tertiary care hospitals due to referred cases,^[24] as also (up to 48%) in women registering for assisted reproduction.^[25]

Pathogenesis

Human tubercle bacillus is the most common causative organism for TB and it is spread predominantly via the air. People with active pulmonary TB can release infectious aerosol droplets, with a diameter ranging from 0.5 to 5 mm, via coughing, sneezing, spitting, or even speaking. A single sneeze releases up to 40,000 droplets. Statistical data have shown that one third of the world's population has been infected with *Mycobacterium tuberculosis*, and of concern, new infections occur at a rate of one per second.^[26] FGTB can be transmitted from the lungs via hematogenous route or by the lymphatic circulation or adjacent organs, such as the bowels or lymph nodes. FGTB can also spread sexually through male semen with active TB.^[27] Studies have shown that people with low immunity, malnutrition, diabetes, excessive smoking, alcohol/drug abuse, renal hemodialysis, or HIV infection are susceptible populations for TB.^[28] FGTB usually occurs secondary to pulmonary TB or extra-pulmonary TB, which includes the gastrointestinal tract, kidney, skeletal system, and meningeal TB. Primary FGTB occurs in women whose male partners have active genitourinary TB, such as tubercular epididymitis and transmits through infected semen.^[27] FGTB can also directly spread from nearby abdominal organs, such as the intestines or abdominal lymph nodes.^[29,30] Patients with fallopian tube TB account for 90% of the total FGTB cases and the affected tubes show congestion, tubercles, hydrosalpinx, pyosalpinx and tubo-ovarian masses.^[31] Patients with endometrial TB account for 50% of the total FGTB cases, and show intrauterine adhesions, caseation, and ulceration.^[31] Patients with ovarian TB account for 10% of the total FGTB cases and show tubo-ovarian masses.^[32] Patients with cervical TB account for 5% to 15% of the total FGTB cases and show granulomatous lesions.^[33] Vaginal and vulval TB cases are rare and only account for 1% to 2% of the total FGTB cases and often have hypertrophic lesions or a non-healing ulcer.^[34,35]

MATERIAL AND METHODS

This prospective cross-sectional study was carried out in the department of gynecology and obstetrics, Government Medical College Srinagar from April 2021 till October 2022 after obtaining ethical clearance from the Institutional Ethical Clearance Committee. During this time period, around 204 consenting women from age group 25 to 40 years were admitted for diagnostic hysteroscopy/laparoscopy for the evaluation of infertility. History of smoking, alcohol, diabetes was recorded. Other clinical history including menstrual history such as irregular menstrual cycles, flow, and duration of infertility, prior pregnancy outcomes and prior infertility treatments was recorded as per routine practices. Clinical examination including per abdominal, per speculum and per vaginal examinations and ultrasonography were done. History regarding high-risks which is: close exposure to patients with pulmonary TB, medical history of TB infection, travel to an epidemic high-risk area, and HIV infection was recorded. Baseline investigations including complete blood count, chest x-ray P/A view, trans-vaginal sonography, husband's semen analysis were done after excluding other causes of infertility. Endometrial curettings of patients suspected of having genital tuberculosis were taken and sent for: Acid-fast staining, histopathological examination, culture on Lowenstein-Jensen (LJ) media and GeneXpert testing.

For histopathological studies, samples were sent in 10% formalin solution while for microbiological studies, samples were sent in normal saline. The samples were grinded in 1ml of normal saline in mortar and pestle and decontaminated with H₂SO₄ method. Homogenized decontaminated sediment was used for AFB microscopy, culture, and GeneXpert testing. Acid Fast Bacillus (AFB) staining was done by Ziehl-Neelsen staining method and observed under oil immersion microscope. Culture was put on LJ medium. Samples were observed on 3rd day to check the growth of contaminants and weekly thereafter for the growth of colonies typical of mycobacteria. *Mycobacterium tuberculosis* was identified by colony morphology and biochemical characteristics. Cultures were incubated for eight weeks before being declared as negative. For Xpert testing, a sample diluent was added to the samples in the ratio of 2:1 to kill mycobacteria and liquefy the samples. After intermittent shaking and incubation for 20 minutes, 2ml of the mixture was added to the cartridge and loaded in to the instrument. Tests were rerun if the results were invalid or error was reported.

Statistical Analysis

Data was entered in a Microsoft excel sheet. Categorical variables were summarized as frequency and percentage. Continuous variables were

summarized as mean and standard deviation. Data analysis was done using EpiInfo 7.0.

RESULTS

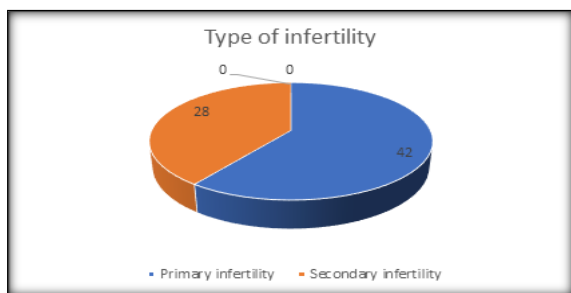


Figure 1: Type of infertility in study population.

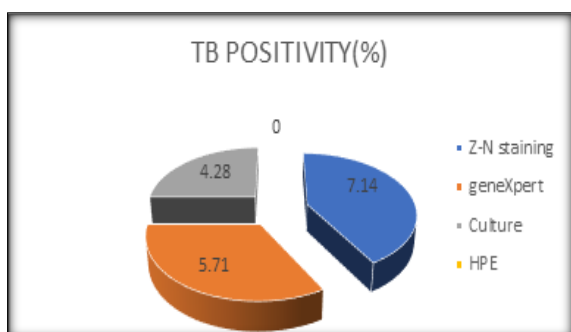


Figure 2: TB Positivity (%) of endometrial curettings by various methods.

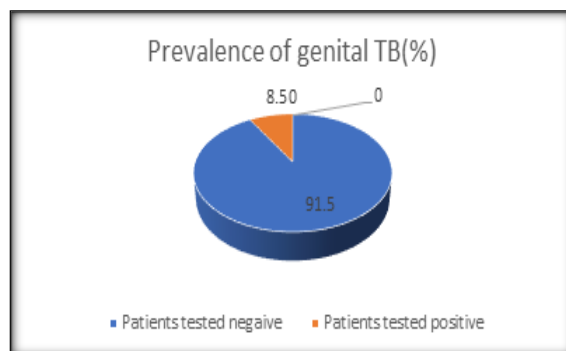


Figure 3: Prevalence of FG TB in patients of infertility.

A total of 204 patients were admitted in the hospital for diagnostic as well as therapeutic hysteroscopy/laparoscopy for infertility during April 2021 to October 2022, out of which endometrial curettings of 70 patients were sent for genital TB evaluation which were enrolled in the study. 42 (60%) out of the 70 patients had primary infertility while 28(40%) had secondary infertility. Out of the 70 patients, total 6 patients tested positive for genital tuberculosis by different diagnostic modalities; 6 tested positive with Z-N staining; 4 tested positive with GeneXpert test; only three had positive culture reports on L-J media and no patient had any positive findings in HPE (Table-I). Two patients had Z-N staining positive but GeneXpert and culture reports negative suggesting atypical mycobacteria. [Table 2, Figure 1, Figure 2, Figure3]

Table 1: Microbiological and histopathological results of endometrial samples in patients of infertility with suspected FG TB.

Type of infertility	Number of patients; n=70 (%) ^a	Z-N staining with microscopy; n=70(%) ^a	GeneXpert; n=70(%) ^a	Culture on L-J media; n=70(%) ^a	HPE; n=70(%) ^a
Primary	42(60)	3(4.28)	2(2.85)	1(1.42)	0(0)
Secondary	28(40)	3(4.28)	2(2.85)	2(2.85)	0(0)
Total	70(100)	6(8.57)	4(5.71)	3(4.28)	0(0)

a- Data expressed as percentage(%).

Table 2: Comparative results on different testing methods

Z-N Staining; n=6	GeneXpert; n=6	L-J media; n=6	HPE; n=6
+	+	+	-
+	+	-	-
+	-	-	-
+	-	-	-
+	+	+	-
+	+	+	-

(+) – positive result; (-)– negative result.

DISCUSSION

Female genital tuberculosis (FGTB) is a type of extra pulmonary TB with rising incidence globally. The exact incidence of FGTB is however not known due to under-reporting of cases, asymptomatic nature, vague symptoms and lack of sensitive and reliable diagnostic tests. Conventional methods of FGTB diagnosis include various imaging, bacteriological, molecular, and pathological

techniques are positive in a small percentage of patients only, leaving many cases with undiagnosed condition. Diagnostic delay of genital TB can lead to severe irreversible tubal damage with poor fertility outcomes.

The present study was carried out in the department of obstetrics and gynecology (Government Lalla Ded hospital), Government medical college, Srinagar from April 2021 to October 2022 with the aim of detecting the prevalence of genital TB in

patients with infertility. 204 Patients with primary or secondary infertility were admitted for diagnostic as well as therapeutic hysteroscopy/laparoscopy during this period. Amongst these, endometrial curetting of 70 patients suspected of genital TB were taken and sent for microbiological, molecular and histopathological evaluation which were subsequently included in the study.

The study participants were from the age group 25 to 40 years. Out of the 70 patients, 42(60%) patients had primary infertility while 28(40%) patients had secondary infertility. The overall prevalence of genital tuberculosis in our study was found to be 8.5%(figure-3) which is higher than that reported by Danish et al.,^[36] in their study in 2019 in the same region (6.73%) and still much higher than that of the developed countries (<1%). Prajakta Shende et al.^[37] found that the prevalence of FGTB to be 27% in West India. The prevalence of non-tubercular mycobacteria was found to be 2.85% in our study. The study by T Radha Bai Prabhu et al.,^[38] found 23.7% prevalence of NTM in patients with unexplained infertility and also concluded that it may be associated with significant tubal damage and infertility.

Conflict of interest: None

CONCLUSION

Genital TB is a major cause of infertility in women, and prevalence is generally underestimated because of the asymptomatic nature of the infection and diagnostic challenges. Large multicenter studies are needed to estimate the magnitude of FGTB and to identify the most sensitive test for diagnosis. Screening for genital TB needs to be a part of evaluation of infertility and menstrual abnormalities. Most of the patients present in advanced stage with scarring, severe fibrosis and adhesions and treatment outcomes, particularly with regard to infertility, are poor. Hence, early diagnosis and correct treatment is vital to avoid complications and to restore fertility.

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