E-ISSN 2250-0944
ISSN 2250-1150
doi: 10.48047/ijprt/16.01.40

Research Article

A Cross-Sectional Study on the Prevalence of Endometrial Tuberculosis Among Women with Unexplained Infertility Using CBNAAT

Dr Swati Sharma[1], Dr Ankur Pathak[2], Dr Chetna Yadav[3], Dr Fayaz Khan H[4]

1. Dr Swati Sharma, Assistant Professor, Department of Obstetrics and Gynecology, FH Medical College , Agra, UP, drswatisharmapathak@yahoo.com
2. Dr Ankur Pathak, Associate Professor, Department of TB and Chest, FH Medical College , Agra, UP, drankurpathak@yahoo.com
3. Dr Chetna Yadav, Assistant Professor, Department of Obstetrics and Gynecology, SMMH (Govt.) Medical College Saharanpur, dr.chetnayadav04@gmail.com
4. Dr Fayaz Khan H, Professor, Department of Obstetrics and Gynecology, FH Medical College , Agra, UP, drfayazkhanh@gmail.com

Corresponding author:
Dr Ankur Pathak, Associate Professor, Department of TB and Chest, FH Medical College , Agra, UP, drankurpathak@yahoo.com

Abstract

Background:
Female genital tuberculosis (FGTB) is the second most common form of extrapulmonary tuberculosis and is a well-recognized cause of infertility in women. Diagnosis of FGTB remains challenging due to its varied clinical presentation and the lack of highly sensitive conventional diagnostic modalities. Cartridge-based nucleic acid amplification test (CBNAAT) offers rapid and specific detection of *Mycobacterium tuberculosis* and may aid in early diagnosis. **Aims and Objectives:** To evaluate the role of CBNAAT in the detection of genital tuberculosis from endometrial tissue in women with infertility, to determine the institutional prevalence of FGTB among infertile women, and to compare CBNAAT with histopathological examination (HPE), Ziehl–Neelsen (ZN) staining, and acid-fast bacilli (AFB) culture. **Materials and Methods:** This observational study included women presenting with infertility. Premenstrual endometrial biopsy samples were obtained and subjected to histopathological examination, ZN staining, AFB culture, and CBNAAT (GeneXpert) for detection of *Mycobacterium tuberculosis*. **Results:** Out of 120 women evaluated, 25 tested positive for *Mycobacterium tuberculosis* by CBNAAT, giving an institutional prevalence of FGTB of **20.8%** among infertile women. Histopathological examination revealed nonspecific inflammatory changes in **10.8%** of cases. AFB culture was positive in only **2.5%** of cases, while ZN staining was negative in all samples. **Conclusion:** CBNAAT is a highly specific and more sensitive diagnostic modality for the detection of female genital tuberculosis compared to conventional methods. Histopathological findings were largely nonspecific, and ZN staining failed to detect any positive cases. Among the diagnostic methods evaluated, CBNAAT demonstrated the highest diagnostic utility and superior sensitivity over culture in detecting FGTB.

Keywords:
Female Genital Tuberculosis; Endometrial Biopsy; Infertility; CBNAAT; Premenstrual Phase

INTRODUCTION

Infertility is clinically defined as the inability to achieve conception after one

year of regular, unprotected sexual intercourse. [1] The global prevalence of infertility varies widely, affecting approximately 5–20% of couples worldwide. [2] Female infertility may result from a wide spectrum of causes, including ovulatory dysfunction, genital tract infections, tubal obstruction, uterine abnormalities, endometriosis, hormonal disturbances, and pelvic inflammatory disease. [3] Despite comprehensive evaluation, a considerable proportion of cases remain without an identifiable etiology and are classified as unexplained infertility, highlighting the need to explore subtle and underdiagnosed factors contributing to impaired fertility. [4]

Although female-related factors play a predominant role, male factors contribute to nearly 40–50% of infertility cases, either independently or in combination with female causes. Male genital tuberculosis may involve the epididymis, prostate, seminal vesicles, or testes, leading to obstruction of the reproductive tract, impaired spermatogenesis, and azoospermia. Due to its insidious onset and frequently asymptomatic course, male genital tuberculosis often remains undetected, particularly in individuals presenting with normal semen parameters or unexplained infertility.

Genital tuberculosis (GTB), an extrapulmonary manifestation of *Mycobacterium tuberculosis* infection, is an important yet underdiagnosed cause of infertility, especially in low- and middle-income countries. [5] Globally, GTB affects approximately 5–10% of infertile women, with prevalence rates below 1% in developed nations and reaching up to 13% in developing regions. In India, GTB has been reported in about 3% of infertile women, with prevalence increasing to nearly 41% among women with tubal factor infertility. [6] The disease predominantly affects women of reproductive age (20–40 years), thereby exerting a substantial impact on reproductive health. [7]

According to the Indian Council of Medical Research (ICMR), the prevalence of female genital tuberculosis (FGTB) in India increased from 19% in 2011 to 30% in 2015. [8] The fallopian tubes are the most commonly involved site (>95%), followed by the endometrium (60%), ovaries (20–30%), and cervix (15%), while involvement of the myometrium (2.5%) and vagina or vulva (1%) is rare. [9] Infertility is the presenting complaint in approximately 40–80% of women with FGTB. However, diagnosis remains challenging due to the paucibacillary nature of the disease and limitations of conventional diagnostic modalities. Serological tests and microscopy have low diagnostic yield, while histopathological examination, although supportive, lacks specificity. [10] Mycobacterial culture, considered the gold standard, is time-consuming and often delays diagnosis and treatment initiation.

To address these diagnostic limitations, the World Health Organization introduced the cartridge-based nucleic acid amplification test (CBNAAT) in 2010. CBNAAT, also known as GeneXpert MTB/RIF, was adopted by the Revised National Tuberculosis Control Programme (RNTCP) in India in 2012. This molecular diagnostic tool offers rapid and accurate detection of *Mycobacterium tuberculosis* and rifampicin resistance, making it particularly valuable for extrapulmonary tuberculosis. However, literature evaluating the diagnostic accuracy and utility of CBNAAT in female genital tuberculosis remains limited.

Diagnosis of genital tuberculosis is further complicated by its largely asymptomatic or latent presentation, necessitating a high index of clinical suspicion and extensive diagnostic evaluation. [11] Traditional diagnostic approaches include chest radiography, tuberculin skin testing, hysterosalpingography for tubal abnormalities, histopathological examination with acid-fast staining, and mycobacterial culture of endometrial tissue. Nevertheless, these methods exhibit

variable sensitivity and specificity and are often inadequate for detecting endometrial tuberculosis (ETB). [12]

Endometrial involvement plays a pivotal role in infertility, menstrual disturbances, chronic pelvic inflammatory disease, and dyspareunia. Endometrial tuberculosis accounts for a significant proportion of extrapulmonary tuberculosis cases worldwide, with reported prevalence ranging from 14% to 41%. [13] Epidemiological data indicate a rising global burden of genital tuberculosis, with similar increasing trends observed in India. [14]

The GeneXpert MTB/RIF assay is a fully automated, real-time polymerase chain reaction–based test that utilizes a single-use cartridge containing all necessary reagents for sample processing, DNA extraction, amplification, and detection. The system purifies and concentrates *Mycobacterium tuberculosis* bacilli, isolates genomic DNA by sonication, and detects rifampicin resistance through amplification of the *rpoB* gene using molecular beacon technology. Results are available within 90 minutes, with minimal biosafety risk and limited technical expertise required. Owing to its rapid turnaround time and high diagnostic accuracy, CBNAAT represents a promising tool for early diagnosis of endometrial tuberculosis in women with infertility.

Materials and Methods

Study Design and Setting

This was an observational study conducted to evaluate the role of cartridge-based nucleic acid amplification test (CBNAAT) in the detection of genital tuberculosis from endometrial tissue among women presenting with infertility. The study was carried out in the Department of Obstetrics and Gynecology in collaboration with the Department of Chest and Tuberculosis at FH Medical College and Hospital, Satauli, Uttar Pradesh, over a period of 12 months.

Study Population and Sample Size

A total of **120 women** presenting with infertility and fulfilling the inclusion criteria were enrolled in the study.

Criteria for Selection of Cases

Inclusion Criteria

- Women with infertility (primary or secondary) attending the outpatient department.

Exclusion Criteria

- Known cases of pulmonary tuberculosis or extrapulmonary tuberculosis.
- Women who did not give consent to participate in the study.

Data Collection

After enrollment, the study procedure was explained in detail to all participants, and **written informed consent** was obtained. Socio-demographic data including age, educational status, socioeconomic status, and rural or urban residence were collected and recorded in a predesigned proforma.

A detailed clinical history was obtained, including presenting complaints, duration and type of infertility, duration of marriage, number of living children, menstrual history, obstetric and gynecological history, and family history of tuberculosis. Sexual history was elicited, including frequency of intercourse, dyspareunia, impotence, or vaginismus. Information regarding past history of tuberculosis, contact with a tuberculosis patient, history of sexually transmitted infections, and prior treatment for infertility was also documented.

Sample Collection and Laboratory Evaluation

Premenstrual phase endometrial biopsy was obtained from all participants under aseptic precautions. The collected endometrial tissue samples were subjected to the following investigations:

- Histopathological examination (HPE)
- Ziehl–Neelsen staining and culture for acid-fast bacilli (AFB)
- Cartridge-based nucleic acid amplification test (CBNAAT/GeneXpert MTB/RIF)

Statistical Analysis

The collected data were compiled using Microsoft Excel and analyzed using **IBM SPSS version 28**. The diagnostic

performance of CBNAAT in detecting female genital tuberculosis was assessed by calculating sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV, and results were expressed as percentages.

Observations and Result

A total of **120 women** with infertility were enrolled in the study. The mean age of the participants was **28.03 ± 5.7 years**. The majority of women (**51.7%**) belonged to the **25–29 years** age group, followed by **26.6%** in the **30–34 years** age group. Women aged **20–24 years** and **35–39 years** constituted **16.7%** and **5%** of the study population, respectively.

Primary infertility was observed in **93.3%** of cases, while **6.7%** of women had secondary infertility. With regard to socioeconomic status, **29.2%** of women belonged to the **lower-middle socioeconomic class**, followed by **25.8%** and **20.8%** from the **lower** and **upper-lower** socioeconomic classes, respectively. Only **18.3%** of women were from the **upper-middle** socioeconomic class, and **5.8%** belonged to the **upper** socioeconomic class.

CBNAAT was performed in all 120 cases, of which **20.8%** tested positive for *Mycobacterium tuberculosis*. Histopathological examination of endometrial biopsy samples revealed **inflammatory changes in 10.8%** of cases, while other abnormal findings were noted in **1.7%** of cases. The remaining **87.5%** of biopsies showed normal histological features.

Ziehl–Neelsen staining for acid-fast bacilli was **negative in all cases (100%)**. Culture for *Mycobacterium tuberculosis* was positive in **2.5%** of cases. Overall, CBNAAT demonstrated the highest positivity rate (**20.8%**) among all diagnostic modalities, compared with histopathological examination (**10.8%**) and culture (**2.5%**), while smear microscopy failed to detect any positive cases.

Table 1: Distribution according to Age

Age (years)	Frequency (n=120)	Percentage
20-25	20	16.7
26-30	62	51.7
31-35	32	26.6
36-40	6	5

Table 2: Distribution of patients according to the type of infertility

Type of Infertility	Frequency (n=120)	Percentage
Primary	112	93.3
Secoundary	8	6.7

Table 3: Distribution of patients according to socioeconomic status

socioeconomic status	Frequency (n=120)	Percentage
Upper	7	5.8
Upper Midile	22	18.3
Lower midle	35	29.2
Upper lower	25	20.8
Lower	31	25.8

Table 4: Distribution of patients according to CBNAAT

CBNAAT	Frequency (n=120)	Percentage
Positive	25	20.8
Negative	95	79.2

Table 5: Distribution according to findings of endometrial biopsy

endometrial biopsy	Frequency (n=120)	Percentage
Normal	105	87.5
Inflammatory Cells	13	10.8
Other	2	1.7

Table 6: Distribution according to smear for AFB

Smear for AFB	Frequency (n=120)	Percentage
Positive	0	0
Negative	120	100

Table 7: Distribution according to culture findings

Culture	Frequency (n=120)	Percentage
Positive	3	2.5
Negative	117	97.5

Table 8: Results of various tests on endometrial samples

Test	Frequency (n=120)	Positive results (%)
CBNAAT	120	25 (20.8)
Smear	120	0
Culture	120	3 (2.5)

DISCUSSION

Female genital tuberculosis (FGTB) remains a significant public health problem in developing countries and is often clinically silent. When symptomatic, it commonly presents as chronic pelvic inflammatory disease, menstrual irregularities, and infertility. Isolation of *Mycobacterium tuberculosis* from genital tract tissue by culture is considered the gold standard for diagnosis; however, genital tuberculosis is one of the most common forms of extrapulmonary tuberculosis, and its true prevalence remains uncertain due to its predominantly asymptomatic nature. [16–18]

Although any part of the female genital tract may be involved, the fallopian tubes are affected in more than 95% of cases, followed by the endometrium (60%) and ovaries (20–30%), while involvement of the myometrium and vagina or vulva is rare. [19] Infertility is the most frequent presentation and may be observed in up to 80% of women with FGTB. Other clinical manifestations include menstrual disturbances and recurrent pregnancy loss. [20]

Several pathophysiological mechanisms contribute to infertility in FGTB. Tubal factors include tubal obstruction, loss of ciliary function, adhesions, hydrosalpinx, and tubo-ovarian mass formation. Uterine involvement results in reduced endometrial receptivity, implantation failure, endometrial atrophy, synechiae, and altered vascularization. Ovarian dysfunction may manifest as chronic anovulation, luteal phase defects, antigonadotropic effects of tuberculosis, implantation failure, and intrinsic oocyte defects. The present study was undertaken to evaluate the role of CBNAAT in detecting genital tuberculosis from endometrial tissue in women with infertility.

In the present study, 120 women with primary or secondary infertility were evaluated. The mean age of the study population was 28.03 ± 5.7 years, with the majority of women (51.7%) belonging to the 25–29-year age group. Previous literature suggests that female genital

tuberculosis occurs at a younger age in developing countries such as India (20–30 years) compared to developed countries (around 40 years). This earlier presentation may be attributed to early marriage and early childbearing practices. Our findings are consistent with these observations.

Socioeconomic status has been identified as an important determinant of reproductive health. [21] Poor socioeconomic conditions and inadequate genital hygiene have long been associated with genital tuberculosis. [22] In the present study, the majority of women belonged to the lower-middle socioeconomic class (29.2%), followed by the lower socioeconomic class (25.8%). Similar findings were reported by Keshari V et al., who observed that nearly 50% of patients belonged to the lower-middle class. [23] These observations are also supported by Surekha T et al. [21] The higher representation of women from lower socioeconomic strata in our study may reflect the patient population attending our tertiary care center.

CBNAAT is a real-time polymerase chain reaction–based assay that enables rapid detection of *Mycobacterium tuberculosis* and rifampicin resistance through targeting the *rpoB* gene. [24] Previous studies have demonstrated high specificity (98–100%) and variable sensitivity for extrapulmonary tuberculosis. [25] In the present study, CBNAAT was positive in 20.8% of women with infertility. Comparable findings were reported by Kumar et al., who observed CBNAAT positivity in 17.1% of genital tuberculosis cases. [26] In contrast, Kousar S et al. reported a very low positivity rate and questioned the utility of CBNAAT in diagnosing genital tuberculosis. [27] However, Keshari V et al. reported CBNAAT positivity in 25% of cases, supporting its diagnostic value. These variations may be attributed to differences in sample size, disease prevalence, and the paucibacillary nature of genital tuberculosis.

Genital tuberculosis is associated with both primary and secondary infertility, although it is more commonly linked with primary infertility. [23,28] In the present study, 93.3% of women had primary infertility, and most CBNAAT-positive cases were observed in this group. This may be related to the social stigma associated with childlessness and the tendency of women with primary infertility to seek medical care earlier.

No significant association was observed between CBNAAT positivity and the type of infertility. Since there is no universally accepted gold standard for the diagnosis of extrapulmonary tuberculosis, multiple diagnostic modalities were employed. Ziehl–Neelsen staining was negative in all cases, and culture was positive in only 2.5% of cases. These findings are consistent with those of Farhana A et al., who reported 100% smear negativity and low culture positivity. [29] Similar observations were made by Zahoor D et al., who reported nonspecific histopathological findings and smear negativity in all cases. [30]

In the present study, CBNAAT demonstrated higher sensitivity than culture in detecting genital tuberculosis. Similar results were reported by Tiwari K et al., where CBNAAT detected more cases compared to histopathology and culture. [31] The low yield of microscopy and culture may be attributed to the paucibacillary nature of endometrial tuberculosis, making conventional diagnostic techniques less reliable.

CONCLUSION

Infertility is a common reason for women to seek gynecological care, and female genital tuberculosis (FGTB) remains an important yet underdiagnosed cause, particularly in developing countries. *Mycobacterium tuberculosis* can cause irreversible damage to the endometrium and other genital organs; therefore, early diagnosis and prompt treatment are essential to improve fertility outcomes. This study demonstrates that CBNAAT is a rapid, sensitive, and specific diagnostic modality for detecting FGTB, with a higher detection rate than conventional methods such as microscopy, histopathology, and culture. Histopathology was nonspecific,

Ziehl–Neelsen staining was negative in all cases, and culture positivity was low, likely due to the paucibacillary nature of endometrial tuberculosis. CBNAAT also offers the advantage of rapid turnaround time and detection of rifampicin resistance. A high index of suspicion and a multimodal diagnostic approach can improve diagnostic yield and enable early treatment.

Strengths and Limitations of the Study

The strength of this study lies in its evaluation of the diagnostic utility of CBNAAT in detecting female genital tuberculosis using endometrial biopsy samples in women with infertility, a population in whom the disease is often underdiagnosed. A multimodal diagnostic approach was adopted by comparing CBNAAT with histopathology, Ziehl–Neelsen staining, and mycobacterial culture, providing a comprehensive assessment. The use of premenstrual endometrial sampling and conduct of the study in a tuberculosis-endemic region further enhance its clinical relevance.

However, the study has certain limitations. It was conducted at a single tertiary care center with a relatively small sample size, which may limit generalizability. The absence of a definitive gold standard for diagnosing female genital tuberculosis restricts precise evaluation of diagnostic accuracy. Additionally, only endometrial tissue was assessed, and long-term fertility outcomes following treatment were not evaluated.

REFERENCE

1. Makar RS, Toth TL. The evaluation of infertility. Am J Clin Pathol. 2002;117:S95-103.
2. MR. Epidemiology of infertility: a population-based study in Babol, Iran. Women Health. 2012;52(8):744- 54.
3. Templeton A. Infertility and the establishment of pregnancy overview. Br Med Bull. 2000;56(3):577- 87.
4. Belaisch-Allart J. Treatment options for age-related infertility. Rev Prat. 2010;60(7):819-23.
5. Ali AA, Abdallah TM. Clinical presentation and epidemiology of female genital tuberculosis in eastern Sudan. Int J Gynaecol Obstet. 2012;118(3):236-8.
6. Singh N, Sumana G, Mittal S. Genital tuberculosis: a leading cause for infertility in women seeking assisted conception in North India. Arch Gynecol Obstet. 2008;278(4):325-7.
7. Tripathy SN, Tripathy SN. Infertility and pregnancy outcome in female genital tuberculosis. Int J Gynaecol Obstet. 2002;76(2):159-63.
8. India TB report 2021. Central TB Division. Available from https://tbcindia.gov.in/showfile.php?lid =3587 Last accessed on 12th Sept 2021.
9. WHO. WHO global tuberculosis report 2016. Available from: http://www.who.int/tb/publications/glo bal_report/en/ Last accessed on 12th Sept 2021.
10. Yadav S, Singh P, Hemal A, Kumar R. Genital tuberculosis: current status of diagnosis and management. Translational andrology and urology. 2017 Apr;6(2):222.
11. Marzieh N. Epidemiology of infertility in the west of Tehran in 2000. J Am Med Womens Assoc. 2002;57(4):219.
12. Baum SE, Dooley DP, Wright J, Kost ER, Storey DF. Diagnosis of culture-negative female genital tract tuberculosis with peritoneal involvement by polymerase chain reaction. J Reprod Med. 2001;46(9):929-32.
13. Sharma JB. Current diagnosis and management of female genital tuberculosis. J Obstet Gynaecol India. 2015;65(6):362-71.
14. Bhanothu V, Lakshmi V, Theophilus JP, Rozati R, Badhini P, Vijayalaxmi B. Investigation of toll-like receptor-2 (2258G/A) and interferon gamma (+874T/A) gene polymorphisms among infertile women with female genital tuberculosis. PLoS One. 2015;10(6):e0125298.
15. Grace GA, Devaleenal DB, Natrajan M. Genital tuberculosis in females. Indian J Med Res. 2017;145(4):425-36.

16. Golden MP, Vikram HR. Extrapulmonary tuberculosis: an overview. American family physician. 2015 Nov 1;72(9):1761-8.
17. Sharma JB. Tuberculosis and obstetric and gynecological practice. Progress in obstetrics and gynecology. 2018; 18:395-427.
18. Sharma JB. Current diagnosis and management of female genital tuberculosis. The Journal of Obstetrics and Gynecology of India. 2015 Dec;65(6):362-71.
19. Das P, Ahuja A, Gupta SD. Incidence, etiopathogenesis and pathological aspects of genitourinary tuberculosis in India: A journey revisited. Indian journal of urology: IJU: journal of the Urological Society of India. 2018 Jul;24(3):356.
20. Chakravarty BN. Genital tuberculosisovarian function and endometrial receptivity. Genital tuberculosis. 2020;1.
21. Surekha T, Himabindu Y, Sriharibabu M. Impact of socio-economic status on ovarian reserve markers. Journal of human reproductive sciences. 2023 Jul;6(3):201.
22. Chowdhury NN. Overview of tuberculosis of the female genital tract. Journal of the Indian Medical Association. 1996 Sep;94(9):345-61.
23. Keshari V, Srivastava R, Kesarwani P, Pandey S, Mishra D. A study on role of cartridge based nucleic acid amplification test (CBNAAT) in diagnosis of genital tuberculosis among patients of infertility and pelvic inflammatory disease. Ind J. Obs. Gyn. Res.2021. (8)1; 70-6.
24. Standard Operating Procedure (SOP) for processing extrapulmonary specimens (CSF, lymph nodes and other tissues) for Xpert MTB/RIF assay. https://www.ncbi.nlm.nih.gov/books/NBK254320/
25. Sharma SK, Kohli M, Chaubey J, Yadav RN, Sharma R, Singh BK, Sreenivas V, Sharma A, Bhatia R, Jain D, Seenu V. Evaluation of Xpert MTB/RIF assay performance in diagnosing extrapulmonary tuberculosis among adults in a tertiary care centre in India. European Respiratory Journal. 2014 Oct 1;44(4):1090-3.
26. Kumar A, Singh A, Chaudhri S, VermaSK, Pandey K, Singh M, Kant S. A study to know the prevalence of genital tuberculosis in female's pulmonary tuberculosis patients and role of cartridge based nucleic acid amplification test in genital tuberculosis from north India. Int J Res Med Sci 2021; 9:395-400
27. Kousar S., Khanna A. Role of CBNAAT in diagnosis of genital tuberculosis in women. Int. J. Sci. Res. 2021. May. 10 (5); 36-7.
28. Parikh FR, Nadkarni SG, Kamat SA, Naik N, Soonawala SB, Parikh RM. Genital tuberculosis—a major pelvic factor causing infertility in Indian women. Fertility and sterility. 1997 Mar 1;67(3):497-500.
29. Farhana A, Zahoor D, Manzoor M, Kanth F. Evaluation of Xpert MTB/RIF assay for the detection of female genital tuberculosis in a tertiary care center-a descriptive cross-sectional study. Microbiology Research Journal International. 2018 Mar 13:1-6.
30. Zahoor D, Bhat MM, Kanth F, Farhana A. Prevalence of genital tuberculosis in infertile women; a study from a Tertiary Care Center in North India. Int. J. Cont. & Med Res. 2019. June. 6 (6); F1-3.
31. Tiwari K, Prasad S, Tanwar R. Role of Gene Xpert in the Detection of Genital Tuberculosis in Endometrial Tissue among Women with Infertility. Journal of Human Reproductive Sciences. 2020 Oct;13(4):285.