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Original Research Article

Comparison of the Diagnostic Performance of CBNAAT/Xpert Assay and Histopathology of Genital Tissue in Female Genital Tuberculosis

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Abstract:

Background: Female genital tuberculosis (FGTB) is an important cause of infertility and menstrual disorders, but its diagnosis remains challenging because of its paucibacillary nature and nonspecific clinical presentation. Histopathology is commonly used for diagnosis but has limited sensitivity, while CBNAAT/Xpert MTB/RIF offers rapid molecular detection of Mycobacterium tuberculosis. This study compared the diagnostic performance of CBNAAT with histopathological examination of genital tissue in clinically suspected FGTB.

Methods: A prospective observational study was conducted on 188 women with clinically suspected FGTB over a two-year period at a tertiary care hospital. Endometrial and other genital tissue specimens were subjected to both histopathological examination and CBNAAT testing, with histopathology considered the reference standard. Diagnostic indices including sensitivity, specificity, positive predictive value, and negative predictive value were calculated.

Results: The mean age of participants was 29.8 years, with primary infertility being the most common presentation (42.0%). Histopathology confirmed female genital tuberculosis in 4 (2.1%) patients. CBNAAT correctly identified 3 of the 4 histopathology-positive cases and yielded 2 false-positive results. Compared with histopathology, CBNAAT demonstrated a sensitivity of 75.0%, specificity of 98.9%, positive predictive value of 60.0%, and negative predictive value of 99.5%.

Conclusion: CBNAAT demonstrated high specificity and excellent negative predictive value, supporting its role as a rapid adjunctive diagnostic tool for female genital tuberculosis. However, its moderate sensitivity indicates that it should be interpreted in conjunction with histopathological and clinical findings, and larger multicentric studies are needed to further validate its diagnostic performance.

Keywords: Fallopian Tube, Infertility, Gene Expert, Mycobacterium Tuberculosis.

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Introduction

Tuberculosis remains a formidable public health challenge in India, which recorded 2.8 million new cases in 2022—over a quarter of the global burden—with an estimated 342,000 TB-related deaths that year. Extrapulmonary TB accounts for roughly 15% of all new diagnoses, and female genital tuberculosis (FGTB) is a particularly under-recognized but clinically significant form within this group [1,2]. FGTB typically presents with vague complaints such as infertility, menstrual disturbances, and chronic pelvic pain, delaying diagnosis and driving substantial reproductive morbidity. Prevalence estimates vary widely: genital TB accounts for about 5% of infertility cases globally, ranging from under 1% in high-income countries to 3–26% in low- and middle-income settings, while an ICMR nationwide survey documented rising prevalence from 19% to 30% between 2011 and 2015 [3,4]. A recent meta-analysis of 42 studies and over 30,000 infertile women placed pooled FGTB prevalence at approximately 20%, contributing to 88% of overall infertility, 66% of primary infertility, and 34% of secondary infertility in affected women—underscoring the need for a high index of clinical suspicion, supported by thorough history, examination, and targeted testing [5,6].

Diagnosing FGTB remains difficult due to its paucibacillary nature: serology and microscopy add little value, culture is slow and often yields few positives despite strong clinical suspicion, and histopathology—while able to show granulomatous inflammation—lacks specificity since similar findings occur in other infectious or inflammatory

conditions [7]. The cartridge-based nucleic acid amplification test (CBNAAT/Xpert MTB/RIF) has emerged as a rapid, WHO-endorsed molecular alternative delivering results within about two hours while also screening for rifampicin resistance, but its performance in FGTB is inconsistent across studies—some report near-100% concordance with histopathology, while others report sensitivity as low as 11–67% despite consistently high specificity, making CBNAAT more reliable as a rule-in than a rule-out test [8-11]. Newer versions like Xpert Ultra appear to improve detection of low bacillary loads, often flagged as "trace" positives [12]. The reported diagnostic performance of CBNAAT in female genital tuberculosis remains inconsistent, and studies directly comparing it with histopathological examination of genital tissue are limited. Therefore, the present study aimed to compare the diagnostic performance of CBNAAT with histopathological examination in clinically suspected cases of female genital tuberculosis.

Materials & Methods

Study Design and Setting: This prospective study was conducted over a period of 2 years in the Department of Obstetrics and Gynecology at a tertiary care Hospital, in collaboration with the Departments of Pathology and Microbiology. The study was initiated after obtaining approval from the institutional ethics committee.

Patient Selection: A total of 188 clinically suspected cases of female genital tuberculosis (FGTB) were enrolled by consecutive sampling from women attending the gynecology outpatient department and infertility clinic. Written informed consent was obtained from all participants. Enrollment was based on detailed history, systemic examination, and baseline investigations, including complete blood count, chest radiography, HIV I and II serology, and abdominal-pelvic ultrasonography. Demographic details, presenting symptoms, and clinical signs — along with imaging and intraoperative findings on laparoscopy or laparotomy, where performed — were recorded to assess the clinical spectrum of FGTB.

Inclusion and Exclusion Criteria: Women with primary or secondary infertility, tubal blockage on hysterosalpingography, or menstrual abnormalities of idiopathic origin (secondary amenorrhea, oligomenorrhea, or menorrhagia) were included. Patients with a prior completed course of anti-tubercular treatment, or with intrauterine fibroids, endometrial polyps, or endometriosis on ultrasonography, were excluded.

Sample Collection: Premenstrual endometrial biopsy was the primary sampling method, performed in women presenting with infertility or menstrual disorders. In patients undergoing surgical intervention (hysterectomy, laparotomy, or laparoscopy) for other indications, tubal tissue, peritoneal tissue, or suspicious nodules were additionally sampled when intraoperative findings suggested tuberculosis. Each specimen was divided into two parts: one fixed in 10% formalin for histopathological examination (HPE) and the other placed in a sterile container with normal saline for CBNAAT testing.

Statistical Analysis: Histopathological examination was taken as the gold standard for diagnosing FGTB. The diagnostic performance of CBNAAT — including sensitivity, specificity, positive predictive value, and negative predictive value — was calculated against HPE findings using appropriate statistical methods.

Results

The study population of 188 patients was predominantly young, with 37.2% falling in the 21–25 year age group and 31.9% in the 26–30 year group, giving a mean age of 29.8 ± SD years and confirming that FGTB chiefly affects women in their reproductive prime. Nulliparous women made up the largest proportion (45.2%), while primiparous and multiparous women were almost equally represented (27.7% and 27.1%, respectively), reflecting the strong link between FGTB and impaired fertility outcomes. A past personal history of TB was noted in only 6.4% of patients, and a family history in 5.3%, while the vast majority (88.3%) had no prior TB history, underscoring the largely occult nature of genital involvement. Primary infertility emerged as the most common presenting complaint (42.0%), followed by menorrhagia (25.5%) and secondary infertility (22.9%), with amenorrhea and oligomenorrhea being comparatively less frequent (3.2% and 6.4%, respectively) (Table 1).

Table 1: Demographic and Clinical Profile of Patients

Characteristic	Category	Number (n=188)	Percentage	Mean ± SD
Age group (years)	21–25	70	37.2%	
	26–30	60	31.9%	
	31–35	23	12.2%	29.8 years
	36–40	10	5.3%	
	41–50	25	13.3%	
Parity	Nullipara	85	45.2%	

	Primipara	52	27.7%	1.07
	Multipara	51	27.1%	
History of TB	Past history	12	6.4%	
	Family history	10	5.3%	
	No history	166	88.3%	
Presenting symptoms	Amenorrhea	6	3.2%	
	Menorrhagia	48	25.5%	
	Oligomenorrhea	12	6.4%	
	Primary infertility	79	42.0%	
	Secondary infertility	43	22.9%	

Chest radiographs were normal in all 188 patients (100%), confirming the absence of concurrent active pulmonary disease and pointing to isolated genital involvement in this cohort. Ultrasonography findings were largely unremarkable, with only 2.1% of patients showing a tubo-ovarian mass, while hysterosalpingography, performed in a subset of 70 patients, revealed tubal blockage in 22.9% of cases, consistent with tubal damage as a hallmark of genital tuberculosis. Histopathological examination of endometrial tissue (n=178) showed proliferative (52.8%) or secretory (39.3%) epithelium in the majority of samples, reflecting normal cyclical endometrial changes, while a smaller subset showed endometrial hyperplasia (3.4%) or nonspecific endometritis (2.2%). Frank tubercular endometritis was identified in only 2.2% of endometrial samples, reaffirming the paucibacillary and often histologically silent nature of the disease (Table 2).

Table 2: Investigation and Histopathology Findings

Investigation	Finding	Number	Percentage
Chest radiograph (PA view)	Normal	188	100%
Ultrasonography (n=188)	Tubo-ovarian mass	4	2.1%
	Normal	184	97.9%
Hysterosalpingography (n=70)	Normal	54	77.1%
	Tubal block	16	22.9%
Histopathology of endometrium (n=178)	Endometrial hyperplasia	6	3.4%
	Nonspecific endometritis	4	2.2%
	Proliferative epithelium	94	52.8%
	Secretory epithelium	70	39.3%
	Tubercular endometritis	4	2.2%

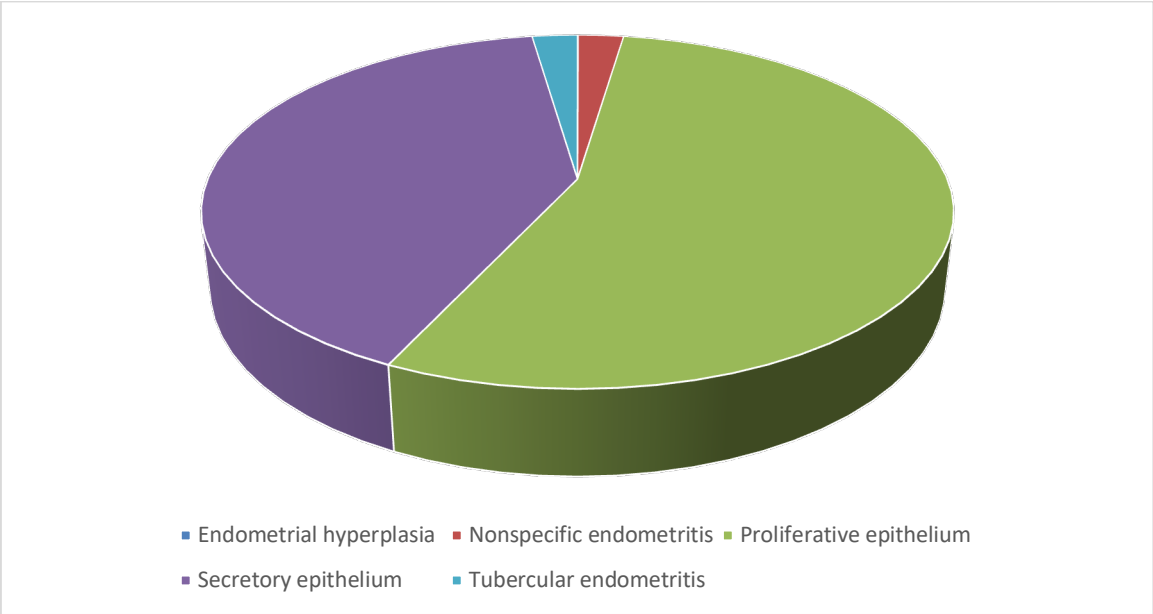

Figure 1: Distribution of Histopathological Findings of the Endometrium (n=178).

Among the 188 patients evaluated, histopathology identified tuberculosis in 4 (2.1%) cases. CBNAAT correctly detected 3 of these cases but failed to identify 1 histopathology-confirmed case.

Additionally, CBNAAT yielded positive results in 2 histopathology-negative patients. Compared with histopathology as the reference standard, CBNAAT demonstrated a sensitivity of 75.0%, specificity of 98.9%, positive predictive value of 60.0%, and negative predictive value of 99.5%. These findings indicate that CBNAAT has excellent specificity and negative predictive value, making it a useful adjunctive diagnostic tool, although negative results should be interpreted cautiously in clinically suspected FGTB (Table 3).

Table 3: Association of Histopathological Findings with CBNAAT for Tuberculosis

Histopathology (for TB)	CBNAAT Negative	CBNAAT Positive	Total
Negative	182	2	184
Positive	1	3	4
Total	**183**	**5**	**188**

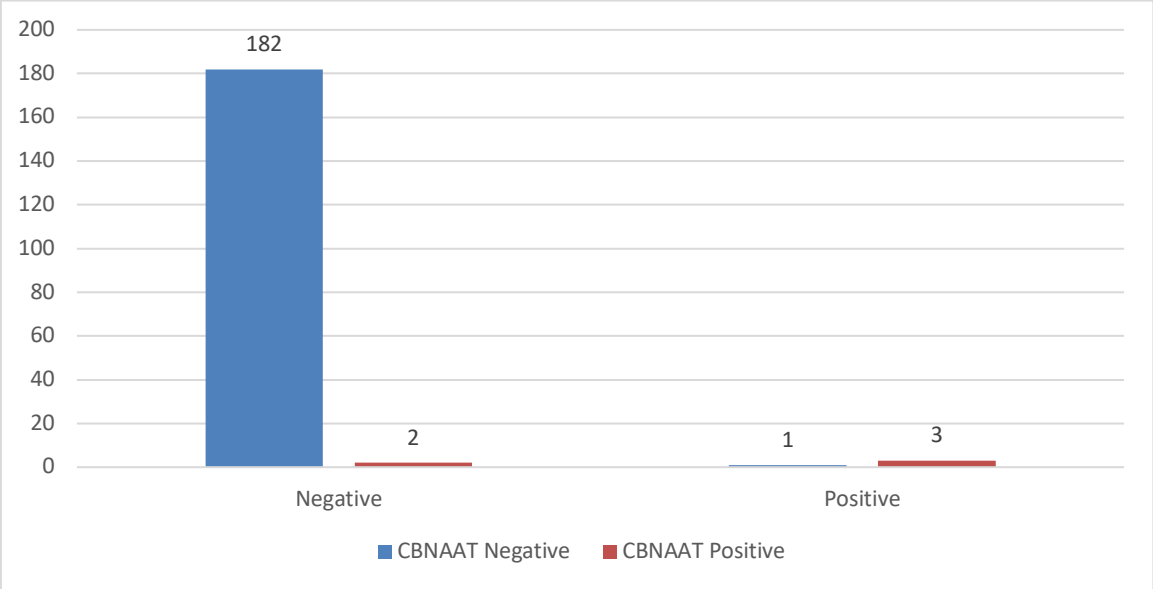

Figure 2: Comparative Distribution of Histopathology and CBNAAT Findings for Tuberculosis.

Discussion

Diagnosing female genital tuberculosis (FGTB) remains inherently challenging because of its paucibacillary nature and the difficulty of obtaining tissue from deep pelvic structures such as the fallopian tubes without resorting to invasive procedures like laparoscopy or laparotomy [13]. In the present study of 188 clinically suspected cases, endometrial tissue was the primary specimen type collected (178 cases), consistent with its established role as the most accessible and least invasive sampling site for FGTB evaluation, while tubal and peritoneal tissue were reserved for patients already undergoing surgical intervention. This approach mirrors the strategy adopted by Thangappah et al., who similarly prioritized endometrial biopsy and tubal/peritoneal sampling based on operative findings, reporting histopathological positivity in 6.9% of endometrial samples and PCR positivity in 36.7% of laparoscopically diagnosed cases [13]. The comparatively lower positivity observed in the present cohort likely reflects differences in the diagnostic gold standard used (histopathology alone versus combined laparoscopic and molecular criteria) as well as variation in referral patterns and disease prevalence across study populations.

The proportion of endometrial tuberculosis identified by histopathology in this study was lower than several previously reported figures. Goel et al. found histopathological evidence suggestive of TB in 2.6% of infertility cases [14], while an Ethiopian cohort evaluating endometrial biopsies reported histopathology-confirmed TB in only 1.3% of cases, notably lower than the PCR-based detection rate of 4.6% in the same population, highlighting the relatively low sensitivity of histopathology compared with molecular methods [15]. In contrast, CBNAAT/Xpert-based studies have shown considerable variability in detection rates: Farhana et al. reported improved detection using Xpert MTB/RIF, identifying TB in a meaningfully higher proportion of suspected FGTB cases compared with conventional methods [16], whereas Garg et al., evaluating 81 infertile women, found histopathology positive in only a single case and CBNAAT negative in all specimens tested, illustrating the inconsistency in CBNAAT yield reported across different settings [17]. The present study's findings, where all histopathology-positive cases were concordantly

CBNAAT-positive, align more closely with reports describing strong agreement between the two modalities when disease is histologically confirmed.

Molecular testing methods beyond CBNAAT have also been evaluated extensively in this context, generally showing higher sensitivity than histopathology but with trade-offs in specificity. Jindal et al. combined laparoscopy with endometrial PCR and found this combination improved early diagnostic yield compared with histopathology alone [18], while Dua et al. reported endometrial PCR sensitivity of 73.8% against a composite diagnostic reference standard, considerably higher than the 10.7% sensitivity observed for histopathology in the same cohort, though endometrial PCR carried a higher false-negative burden as its principal limitation [19]. Similarly, a study using nested PCR on menstrual blood as a non-invasive alternative to endometrial biopsy reported promising screening utility for early GTB detection, suggesting a potential adjunct for settings where biopsy is not feasible [20]. Sharma et al., in their broader review of FGTB diagnostics, emphasized that no single test can be considered a true gold standard, and that combining histopathology, culture, and molecular assays offers the most reliable diagnostic approach, a principle that the present study's design — evaluating CBNAAT against histopathology as the reference standard — sought to directly address [21].

In the present study, CBNAAT demonstrated good agreement with histopathology, with a sensitivity of 75.0%, specificity of 98.9%, positive predictive value of 60.0%, and negative predictive value of 99.5%. One histopathologically confirmed case was missed by CBNAAT, while two CBNAAT-positive cases were histopathology negative. The high specificity and negative predictive value observed are consistent with previous studies reporting that CBNAAT is highly reliable for confirming FGTB when positive, although its sensitivity may be reduced because of the paucibacillary nature of the disease and variability in specimen quality [16,17]. These findings support the use of CBNAAT as a valuable adjunct to histopathological examination rather than a standalone diagnostic test. Combining molecular assays with histopathology and other clinical findings is likely to improve diagnostic accuracy. Further multicentric studies with larger numbers of confirmed FGTB cases are required to validate these findings.

Conclusion

CBNAAT demonstrated high specificity and excellent negative predictive value in the diagnosis of female genital tuberculosis, supporting its utility as a rapid adjunctive diagnostic tool. Although its sensitivity was moderate, the assay showed good overall agreement with histopathology and may facilitate earlier diagnosis when interpreted alongside histopathological and clinical findings. Given the paucibacillary nature of FGTB, a multimodal diagnostic approach remains essential, and larger multicentric studies are warranted to further validate the diagnostic performance of CBNAAT in diverse clinical settings.

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