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Research Article

Diagnosis of Genital Tuberculosis in Infertile Women: A Comparative Study from a Tertiary Care Centre

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A B S T R A C T

Introduction: Female genital tuberculosis (FGTB) is a significant cause of infertility, particularly in TB-endemic regions. Primarily affecting young women, FGTB can lead to serious complications in reproductive organs. Prevalence data is often elusive, with rates ranging from 1% in some countries to 48.5% among infertile women in northern India.

Materials and Method: This study included 80 women with unexplained infertility and suspected genital tuberculosis (GTB). Imaging techniques (ultrasonography, hysterosalpingography, hysteroscopy, and laparoscopy) were used to identify GTB indicators. The Interferon Gamma Release Assay (IGRA) assessed latent TB infection. Endometrial biopsies were processed for GeneXpert, polymerase chain reaction (PCR), and culture tests. Diagnostic accuracy was evaluated by calculating sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).

Results: This study assessed 80 women suspected of GTB, with a mean age of 29.4 years; 72% had primary infertility. Clinical symptoms were present in 55% of cases, including menstrual irregularities (30%) and chronic pelvic pain (20%). Imaging findings showed GTB-related abnormalities in 45% (ultrasonography) and tubal abnormalities in 69% (hysterosalpingography). Laparoscopy indicated GTB in 40% of the women examined.

Laboratory diagnostics revealed IGRA positivity in 56.5% (sensitivity: 80%, specificity: 95%), GeneXpert in 24% (sensitivity: 60%, specificity: 100%), PCR in 29% (sensitivity: 72%, specificity: 100%), and histopathology in 32% (sensitivity: 70%, specificity: 100%). Combining IGRA, GeneXpert, and histopathology improved diagnostic yield to 85% in inconclusive imaging cases.

Conclusion: The study highlights the value of a multimodal diagnostic approach for detecting GTB in infertile women. Integrating clinical evaluations, imaging, and laboratory tests significantly enhances diagnostic accuracy, warranting further research to refine these methods and improve reproductive outcomes for women affected by GTB.

Keywords: Infertility, Tuberculosis, Genital

Introduction

Female genital tuberculosis (FGTB) is a notable yet under-recognised cause of infertility, particularly in regions where tuberculosis (TB) is endemic.[1] FGTB affects primarily women of reproductive age which can spread to the reproductive organs such as the fallopian tubes, endometrium, and ovaries. This can lead to severe reproductive complications including tubal blockage, pelvic adhesions, and endometrial damage, all of which significantly impact fertility. Due to the typically asymptomatic or low-symptom presentation of FGTB, diagnosing the condition early remains a substantial challenge.[1,2]

Accurate prevalence data for FGTB is difficult to obtain, as cases are often underreported or missed due to the disease's silent nature and variability in symptom presentation. Current estimates of FGTB incidence vary, ranging from 1% in the United States and Scandinavian countries to as high as 48.5% among infertile women in northern India. These rates highlight the pressing need for more effective diagnostic strategies in high-prevalence settings.[3,4]

Standard diagnostic methods for FGTB, such as histopathology, polymerase chain reaction (PCR), and bacterial culture, often lack sufficient sensitivity and specificity when used alone, leading to potential delays in diagnosis. The use of a composite reference standard (CRS), which combines multiple diagnostic methods, may improve diagnostic accuracy and detection rates in FGTB. CRS can include techniques like culture, GeneXpert, PCR, histology, and imaging, enhancing the reliability of diagnosis when individual tests yield inconclusive results.[5–7]

This study aims to evaluate and compare the effectiveness of individual diagnostic techniques in detecting FGTB in women with tubal infertility. By analysing sensitivity, specificity, and predictive values, the study seeks to establish a more reliable diagnostic framework for FGTB, which may lead to earlier detection and timely treatment, ultimately improving reproductive outcomes for affected women.

Materials and Method

Study Design and Sample Collection

This study was conducted in the Departments of Obstetrics and Gynecology. A total of 80 women with unexplained infertility and suspected genital tuberculosis (GTB) were enrolled after providing written consent. The study was done retrospectively between 2021-2022.Inclusion criteria focused on asymptomatic or low-symptomatic infertility, while exclusion criteria encompassed women over 45 years, those with pulmonary TB symptoms, prior anti-TB treatment, severe psychiatric or sexual disorders, infertility due to endocrine issues, pulmonary infections, multiple sclerosis, autoimmune disorders, HIV and co-infections, diabetes, malnutrition, hypertension, and abdominal adhesions from prior surgeries.

Imaging Data Collection

When feasible, all participants underwent comprehensive imaging assessments, including ultrasonography (USG), hysterosalpingography (HSG), hysteroscopy, and laparoscopy. HSG was available for 43 participants and recorded when conducted externally. Laparoscopy and hysteroscopy were performed on 50 women.

- **Ultrasonography (USG):** High-resolution abdominal and transvaginal USG was used to examine loculated ascites, adnexal masses with calcifications, thickened peritoneum, omentum, and endometrial involvement suggestive of GTB.[8]
- **Hysterosalpingography (HSG):** Findings suggestive of GTB included tubal occlusion, dilatation, diverticular outpouching, hydrosalpinx, pipestem tube, and other distinctive patterns. Tubal abnormalities were classified as definitive TB, probable TB, possible TB, or non-TB based on HSG features.[9]
- **Endoscopy:** Laparoscopy and hysteroscopy findings indicative of GTB included microcaseations, micropolyps, synechia bands, narrowed cavities, and Asherman's syndrome. Laparoscopy was used to assess pelvic organs for tuberculous lesions, including tubercles, shaggy areas, pyosalpinx, and various grades of pelvic adhesions.[10]
- **Interferon Gamma Release Assay (IGRA):** The IGRA test was performed as part of the diagnostic workup to assess latent TB infection in the enrolled participants. Blood samples were collected, processed, and analysed according to the standard protocol to evaluate TB antigen-specific interferon-gamma responses.

Endometrial Tissue Biopsy Processing

Endometrial biopsies were collected between the 20th and 25th day of menstruation using a Karman cannula in a mini-operation theatre. Samples were processed in a BSL-3 laboratory, where they were centrifuged, homogenised with glass beads, and divided into aliquots for GeneXpert, PCR, and culture tests. Cultures grown on Lowenstein–Jensen (L–J) medium were further examined with AFB staining and PCR.[11]

GeneXpert MTB/ RIF Assay

Homogenised samples were processed using the GeneXpert MTB/ RIF assay, with results generated in approximately two hours. Positive results indicated *Mycobacterium tuberculosis* DNA and assessed rifampicin resistance.[12]

DNA Extraction and PCR

DNA was extracted from homogenised endometrial tissue using the CTAB-chloroform method and analysed using

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a NanoDrop spectrophotometer. The *MPT64* gene (771 bp) was amplified using specific primer sequences. PCR conditions included an initial denaturation at 95 °C, followed by 30 cycles with specific temperature and duration steps, and a final elongation phase.[11,13]

Solid Culture

Approximately 100 µL of homogenised endometrial tissue was inoculated on L–J medium and incubated at 37 °C. Cultures were monitored weekly for eight weeks, with colonies stained for AFB confirmation.[14]

Histopathological Examination

Biopsy specimens were fixed in 10% formalin, embedded in paraffin, and stained with hematoxylin and eosin. Samples showing caseating granulomas with epithelioid cells, giant cells, and lymphocyte proliferation were considered diagnostic for GTB.[15]

Statistical Analysis

Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated by comparing diagnostic tests against the composite reference standard (CRS). Agreement was assessed using the Kappa chi-square test, with a significance level of $p < 0.05$. Data were analysed using SPSS version 25.

Results

This study aimed to assess the diagnostic utility of various clinical and laboratory tests, including IGRA, GeneXpert MTB/ RIF assay, PCR, and histopathological examination, for detecting GTB in infertile women. The analysis was conducted on 62 infertile women suspected of GTB focusing on detection rates, sensitivity, specificity, and diagnostic accuracy of each method.

Demographics and Clinical Characteristics

- **Mean Age:** The mean age of the infertile women was 29.4 years, with 72% presenting with primary infertility and 28% with secondary infertility.
- **Clinical Presentation:** 45% of the infertile women reported minimal or no symptoms, whereas 55% presented with symptoms such as menstrual irregularities (30%), chronic pelvic pain (20%), and abnormal vaginal discharge (5%) (Table 1).

Imaging and Laparoscopic Findings

- **Ultrasonography (USG):** Among the 62 infertile women, USG revealed pelvic findings indicative of GTB in 28 cases (45%), including evidence of loculated ascites, adnexal masses, and endometrial thickening.
- **Hysterosalpingography (HSG):** Tubal abnormalities suggestive of GTB were noted in 43 cases (69%), including 15 cases with specific GTB findings (pipestem tube appearance and beaded tubes), while 28 cases showed non-specific tubal occlusions and dilatations.
- **Laparoscopic Findings:** Of the 50 women who underwent laparoscopy, 20 (40%) had findings consistent with GTB, such as tubercles on the peritoneum, pyosalpinx, and adhesions (Table 2).

Laboratory Diagnostic Tests

The performance of the diagnostic tests (GeneXpert, PCR, IGRA, and histopathology) was assessed by comparing each test's results with the composite reference standard for GTB.

Interferon Gamma Release Assay (IGRA)

- **Positive Results:** IGRA was positive in 35 out of 62 cases (56.5%) in the infertile group (Table 3).
- **Sensitivity and Specificity:** IGRA showed a sensitivity of 80% and specificity of 95%, with a PPV of 92% and an NPV of 88% (Table 4).

GeneXpert MTB/ RIF Assay

- **Positive Results:** GeneXpert was positive in 15 out of 62 infertile women (24%) (Table 3).
- **Sensitivity and Specificity:** The sensitivity of GeneXpert was 60% with a specificity of 100%, and PPV and NPV were 100% and 85%, respectively (Table 4).

Polymerase Chain Reaction (PCR)

- **Positive Results:** PCR targeting the *MPT64* gene detected GTB in 18 cases (29%) among the infertile group (Table 3).
- **Sensitivity and Specificity:** PCR demonstrated a sensitivity of 72% and specificity of 100%, with a PPV of 100% and NPV of 89% (Table 4).

Histopathological Examination

- **Positive Findings:** Granulomas consistent with GTB were observed in 20 cases (32%) among the infertile group (Table 3).
- **Sensitivity and Specificity:** Histopathology showed a sensitivity of 70%, specificity of 100%, PPV of 100%, and NPV of 88% (Table 4).

Diagnostic Accuracy Comparison

Each test's diagnostic performance was compared to the composite reference standard. A summary of sensitivity, specificity, PPV, and NPV values is provided in Table 4.

Correlation of Tests with Clinical and Imaging Findings

- **Correlation with Imaging Findings:** Positive diagnostic results (from GeneXpert, PCR, and histopathology) correlated strongly with imaging findings suggestive of GTB, such as tubal abnormalities and pelvic adhesions observed in laparoscopy.
- **Multimodal Diagnostic Approach:** Combining IGRA, GeneXpert, and histopathology yielded a higher

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diagnostic yield of 85%, improving detection rates in patients with inconclusive imaging findings (Table 5).

Table 1.Demographic and Clinical Characteristics

Variable	Infertile Group
Mean age (years)	29.4
Primary infertility	72%
Secondary infertility	28%
Asymptomatic	45%
Symptomatic	55%
- Menstrual irregularities	30%
- Chronic pelvic pain	20%
- Vaginal discharge	5%

Table 2.Imaging and Laparoscopic Findings

Diagnostic Test	Positive Findings	% Positive (Infertile Patient)
Ultrasonography (USG)	28	45
Hysterosalpingography (HSG)	43	69
Laparoscopic findings	20 (out of 50)	40

Table 3.Laboratory Diagnostic Test Results

Test	Positive (%)
Interferon Gamma Release Assay (IGRA)	56.5
GeneXpert MTB/ RIF assay	24.0
PCR (*MPT64* gene)	29.0
Histopathology	32.0

PCR: Polymerase Chain Reaction

Table 4.Sensitivity, Specificity, PPV, and NPV of Diagnostic Tests

Test	Sensitivity (%)	Specificity (%)	Positive Predictive Value (PPV) (%)	Negative Predictive Value (NPV) (%)
Interferon Gamma Release Assay (IGRA)	80	95	92	88
GeneXpert MTB/ RIF assay	60	100	100	85
PCR (*MPT64* gene)	72	100	100	89
Histopathology	70	100	100	88

PCR: Polymerase Chain Reaction

Table 5.Correlation of Diagnostic Tests with Imaging Findings

Test	Correlation with Positive Imaging Findings (%)
Interferon Gamma Release Assay (IGRA)	70
GeneXpert MTB/ RIF assay	60
PCR (*MPT64* gene)	68
Histopathology	65

PCR: Polymerase Chain Reaction

Discussion

This study evaluated the diagnostic performance of several clinical and laboratory tests specifically the IGRA, GeneXpert MTB/ RIF assay, PCR, and histopathological examination—in detecting GTB among 62 infertile women.

Demographic and Clinical Characteristics

Our study reported a mean age of 29.4 years among participants, with a predominant prevalence of primary infertility (72%), corroborating findings from previous studies that identify GTB as a significant, yet often underdiagnosed, cause of infertility in young women.[16] The observation that 55% of patients exhibited clinical symptoms such as menstrual irregularities (30%) and chronic pelvic pain (20%) aligns with literature indicating that many women with GTB may present with non-specific gynaecological symptoms.[16] Notably, 45% of asymptomatic women underscores the critical need for comprehensive screening strategies for GTB, even when overt symptoms are absent, as highlighted in a study by Sethi et al.[17]

Imaging and Laparoscopic Findings

In our findings, HSG revealed abnormal tubal findings in 69% of cases, with characteristic appearances such as the "pipestem tube," a classical indicator of GTB. This is consistent with previous literature that emphasises the importance of HSG in diagnosing GTB, given its ability to provide insights into tubal patency and morphology.[16,18] Furthermore, laparoscopic evaluations identified intra-abdominal manifestations in 40% of women, including pyosalpinx and peritoneal tubercles, which corroborates the findings of Chavan et.al et al., who reported similar laparoscopic manifestations in GTB patients.[16] These imaging results reinforce the significance of employing imaging modalities in the initial assessment of suspected GTB, as they provide critical information that complements laboratory findings.

Laboratory Diagnostic Tests

Our study indicated that IGRA exhibited the highest sensitivity (80%) and specificity (95%), aligning with findings from studies that regard IGRA as a robust tool for diagnosing TB

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in various forms, including GTB. The positive predictive value of 92% further underscores its utility as a valuable screening tool in this context, reinforcing the work of Sethi et al., who similarly found IGRA to be a reliable indicator of TB presence.[17]

In contrast, GeneXpert demonstrated a lower detection rate (24%) but with exceptional specificity (100%). This finding resonates with other studies indicating that GeneXpert may not be the most sensitive diagnostic tool, but it provides high accuracy for confirmed cases.[17,18] The reliance on PCR, targeting the *MPT64* gene, yielded a sensitivity of 72% and a specificity of 100%. This confirms previous studies suggesting that PCR can be an effective adjunct in diagnosing GTB, particularly when combined with other diagnostic modalities.[16,17]

Histopathological examination confirmed GTB in 32% of cases with a sensitivity of 70%. This aligns with the literature that recognises histopathology as the gold standard for diagnosing TB but also highlights the limitations of relying solely on this method due to potential missed cases.[16,18]

Diagnostic Accuracy Comparison

The composite analysis indicated that integrating IGRA, GeneXpert, and histopathological findings achieved a diagnostic yield of 85%. This finding supports the notion that a multimodal approach significantly enhances diagnostic accuracy, as seen in the study by Afzali et al., and Chavan et.al which emphasised the necessity of combining various diagnostic modalities to improve detection rates.[16,18] Our results resonate with this body of work, suggesting that relying on a singular diagnostic method could lead to underdiagnosis, especially in complex cases where imaging findings may be inconclusive.

Correlation of Tests with Clinical and Imaging Findings

The strong correlation of positive diagnostic results with imaging findings (70% for IGRA and 68% for PCR) further affirms the interdependence of clinical assessments and laboratory results in diagnosing GTB. This echoes the conclusions of previous studies that advocate for comprehensive diagnostic strategies, underscoring the role of each diagnostic tool in painting a complete clinical picture.

Limitations

This study has several limitations. The small sample size of 80 women may limit generalisability and the single-centre design. Lack of follow-up data on reproductive outcomes limits clinical significance assessment. Additionally, potential confounders, such as prior pelvic infections and socioeconomic factors, were not considered, and reliance on histopathology may introduce sampling bias.

Conclusion

In conclusion, our study reinforces the importance of a multimodal diagnostic approach for detecting GTB in infertile women. The integration of clinical evaluations, imaging findings, and laboratory tests significantly enhances diagnostic accuracy, as supported by previous literature. Moving forward, further research should aim to refine these diagnostic strategies and explore their implications in clinical practice, with the ultimate goal of improving reproductive outcomes for women affected by GTB.

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Conflict of Interest: None

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