

# Relevance of semen polymerase chain reaction positive for tuberculosis in asymptomatic men undergoing infertility evaluation

Subodh Kumar Regmi,  
Urvashi B. Singh<sup>1</sup>,  
Jai Bhagwan Sharma<sup>2</sup>,  
Rajeev Kumar

Departments of Urology,  
<sup>1</sup>Microbiology and <sup>2</sup>Obstetrics  
and Gynaecology, All India  
Institute of Medical Sciences,  
New Delhi, India

**Address for correspondence:**

Dr. Rajeev Kumar (Clinical)  
and Dr. Urvashi B. Singh,  
(Microbiology), Departments  
of Urology and Microbiology,  
All India Institute of Medical  
Sciences, New Delhi, India.  
E-mail: rajeev02@gmail.com;  
E-mail: drurvashi@gmail.com

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## ABSTRACT

**OBJECTIVE:** Male partners of infertile women with genital tuberculosis (TB) are often screened for genital TB. We aimed to evaluate the clinical significance of a positive screening semen polymerase chain reaction (PCR) for *Mycobacterium tuberculosis* test (TB-PCR) in asymptomatic men undergoing infertility evaluation and determine the need for a detailed investigation and treatment for TB. **MATERIALS AND METHODS:** Between March 2012 and January 2013, male partners of 15 infertile women with a diagnosis of genitourinary TB (GUTB) as the cause of infertility, tested positive either on semen PCR for TB (13 cases), or Mycobacterium Growth Indicator Tube-960 test (2 cases). These asymptomatic men underwent infertility evaluation along with evaluation for GUTB. Diagnosis of GUTB was based on standard clinical criteria, which included a high index of suspicion along with clinical, laboratory, and/or radiological evidence of GUTB. Men who had no clinical evidence of GUTB were followed up with clinical evaluation, semen analysis, and repeat semen PCR for TB after 6 months. **RESULTS:** Fourteen subjects consented for inclusion in the study. One had a history of pulmonary TB 20 years earlier. Another patient was found to have mediastinal lymphadenopathy (tubercular). All except one had a normal semen analysis. None of the patients met the standard clinical criteria for GUTB diagnosis. 8 patients followed up at 6 months with repeat semen analysis, which was similar to the baseline values and no clinical evidence of TB. **INTERPRETATION AND CONCLUSIONS:** Asymptomatic men with positive screening semen PCR for TB do not have clinical evidence of TB. Male partners of women with infertility and GUTB should not be screened if they have no symptoms.

**KEY WORDS:** Infertility, polymerase chain reaction, screening, semen, tuberculosis

## INTRODUCTION

Genital tuberculosis (TB) in the female population (FGTB) is a common problem in the developing countries.<sup>[1]</sup> Though patients usually remain asymptomatic, primary, as well as secondary, infertility continues to be an important issue in the premenopausal females with FGTB.<sup>[2]</sup> The incidence of infertility in these patients is between 58% and 87%.<sup>[3,4]</sup>

FGTB is usually secondary to hematogenous dissemination from a primary site, elsewhere in the body such as the lungs or the abdomen. Co-existent genital TB has been observed in up to 8–15% of patients with pulmonary TB.<sup>[5]</sup> Direct spread of the disease to the

genital system, from TB of the abdomen or the peritoneum, is also known to occur. The theoretical possibility of transmission from one mucosal surface to another during intercourse has been described in animal models,<sup>[6]</sup> however, sexual transmission of TB from the male partner to the female or vice

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versa is a rarity and has only been anecdotally reported.<sup>[7,8]</sup> Therefore, the need to evaluate the male partners of female patients with genital TB is not well established.

The use of highly sensitive diagnostic modalities, such as polymerase chain reaction (PCR) to detect mycobacterial DNA in patients with suspected TB, is increasing. During infertility evaluation, women diagnosed to have TB are often advised to get their male partners tested using semen PCR test. Most such men are asymptomatic with no clinical evidence of TB. However, a positive PCR test may indicate a subclinical infection that has the potential to manifest at a later stage. Our previous studies suggest that screening infertile men for TB should not be recommended.<sup>[9]</sup> However, since TB can result in male infertility, which is often difficult to treat unless detected early, it would be clinically relevant to treat these asymptomatic men with positive PCR if this could prevent future infertility.<sup>[10]</sup> Thus, the clinical dilemma is, which additional confirmatory tests should be done in these men and whether they should receive antitubercular therapy (ATT).

We conducted a prospective study to evaluate the clinical significance of semen PCR positive for TB in asymptomatic men and determine the need for a detailed workup and treatment for TB in these men. We also assessed the delayed development of genital TB or declining semen parameters in these patients who initially do not have clinical evidence of TB despite a positive PCR.

## MATERIALS AND METHODS

This study was approved by the Institutional Ethics Committee and all subjects provided informed consent for inclusion. At our institution, male partners of infertile women with a diagnosis of FGTB as the cause of infertility are screened for TB using a semen PCR test. Men whose test is positive are referred to us for further evaluation and management. Between March 2012 and January 2013, all such men who had positive semen PCR were screened for enrollment in this study. Patients who had a recent history of TB were excluded.

After enrollment, these asymptomatic men underwent a standard infertility evaluation, including history, physical examination, and a semen analysis. Semen analysis was performed on two separate occasions at induction into the study along with semen staining for acid fast *Bacilli* (AFB) and semen culture for TB. Urine for AFB as well as culture and PCR for TB were also obtained. The initial evaluation also included a complete hemogram with erythrocyte sedimentation rate (ESR). Radiological evaluation included a chest X-ray and ultrasonogram (USG) of the abdomen and pelvis, including the kidneys, ureter, and bladder region.

Patients who had abnormal findings on USG were advised to have further evaluation with intravenous urogram (IVU) or contrast enhanced tomographic urogram if clinically indicated.

A standard clinical criterion for the diagnosis of genitourinary TB (GUTB) was used, which includes a high index of suspicion along with clinical, laboratory, and radiological evidence of GUTB.<sup>[11]</sup> Men who met this criterion of GUTB were started on ATT. Men who had no clinical evidence of GUTB did not receive ATT and were followed up with clinical evaluation, semen analysis, and repeat semen PCR for TB at 6 months. If the semen PCR at 6 months continued to be positive, a repeat assessment for GUTB was planned.

The data were analyzed to assess the value of semen PCR for GUTB in these patients, using the standard clinical criteria for diagnosis of GUTB as the gold standard. A correlation was also attempted between various clinical, radiologic, laboratory, and the PCR test. The semen analysis parameters taken 6 months apart were compared with each patient to assess changes if any in the sperm count, motility, or the morphology.

## RESULTS

15 men were evaluated for inclusion in the study. This included 13 who tested positive on semen PCR for TB and another 2 patients who were negative on semen PCR for TB but had tested positive for culture using Mycobacterium Growth Indicator Tube-960 (MGIT-960) for TB. Of these 15 men, 14 agreed for enrollment and were inducted into the study.

The demographic and clinical data of these patients are given in Table 1. None of the patients had any urinary complaints (frequency, urgency, dysuria, or hematuria) that are typically associated with GUTB. One patient had a history of testicular swelling and another had a history of treated pulmonary TB, 20 years earlier. All patients had

**Table 1: Demographic and clinical parameters of the study population**

Patient parameters	Value (n=14)
Age in years (mean, range)	33.9, 25-40
Duration of marriage in years (mean, range)	7.8, 2-16
Infertility	
Primary	08
Secondary	06
History	
Urinary complaints	0
Testicular swelling	1
Past TB	1
Abnormal genital examination	3

TB= Tuberculosis

a normal systemic examination and three patients had an abnormal genital examination; one had bilateral epididymal cysts, which were confirmed by ultrasonography and fine-needle aspiration cytology (FNAC) from the cysts. The other two patients had small hydroceles, which were confirmed on ultrasonography.

The evaluation of female partners is given in Table 2. Three out of 14 women had an induration of more than 10 mm on tuberculin skin testing. All patients had some positive findings on diagnostic laparoscopy, which was then supported by additional laboratory evidence, most common of which was a positive finding on the TB-PCR of the endometrial aspirate. Tubercles were the most common finding on the diagnostic laparoscopy followed by tubal abnormalities.

The results of the initial evaluation for GUTB in the male partners are given in Table 3. None of the specimens (semen or urine) was positive for AFB on staining or culture for TB, and the USG was within normal limits. Hemogram and ESR were normal, the mean values for hemoglobin, total leukocyte count, and ESR were 15 g/dl, 7700/cubic mm, and 10 mm/h, respectively.

One patient had positive urine PCR for TB and further underwent an IVU to evaluate the urinary tract. This patient also underwent FNAC of fluid from cystic swellings in the bilateral testes. IVU was normal and the FNAC confirmed epididymal cysts with no evidence of TB. This patient had a history of pulmonary TB, 20 years earlier. Chest X-ray of another patient revealed an anterior mediastinal mass; his contrast enhanced computed tomography (CT) of the chest revealed mediastinal lymphadenopathy in the precarinal and paratracheal location, possibly tubercular.

Semen parameters on initial evaluation are given in Table 4. One patient had asthenospermia (40% forward motility) but all others were normal. Of the initial 14 patients, only 10 came for the follow-up visit. Two patients refused further evaluation, one had financial problems and one was started on a course of ATT by a private physician.

On the follow-up visit, history and clinical examination in all the 10 patients were unremarkable. Eight patients had a repeat semen analysis and semen PCR. There was no difference in the baseline and 6-month semen values [Table 4]. Only one patient had again positive semen PCR for TB. This patient was previously negative on semen PCR but positive by MGIT-960 culture for TB.

## DISCUSSION

GUTB, as a cause of male infertility, is well established.<sup>[10]</sup> Positive reports of highly sensitive diagnostic tests such as

**Table 2: Details of the female partners**

Patient parameters	Value (n=14)
Prior pregnancy loss	
Spontaneous abortion	4
Tubal pregnancy	1
Prior diagnosis or treatment of TB	
Tuberculoma of brain	1
Pulmonary TB	1
Spinal TB	1
Endometrial TB	1
TB lymphadenitis	1
Laboratory tests on the endometrium	
Positive TB PCR	9
Positive AFB stain	1
Positive histopathology	1
Positive findings on diagnostic laparoscopy	14

TB= Tuberculosis, AFB= Acid fast *Bacilli*, PCR= Polymerase chain reaction

**Table 3: Initial evaluation for TB in the male partners**

Parameter evaluated	Results (n=14)	
	Positive	Negative
Semen AFB staining ×3 times	0	14
Semen culture for TB	0	14
Urine AFB staining for TB	0	14
Urine culture for TB	0	14
Urine PCR for TB	1	13
USG abdomen and KUB	0	14
Chest X-ray	1	13

AFB= Acid fast *Bacilli*, PCR= Polymerase chain reaction, USG= Ultrasonogram, KUB= Kidneys, ureter, and bladder, TB= Tuberculosis

**Table 4: Semen parameters**

Semen parameters	Value	
	Baseline (n=14)	6-month follow-up (n=8)
Semen volume in milliliters	2.83 (2-3.5)	2.5 (2-4)
Total count in million/ml	110.8 (20-428)	101 (45-182)
Forward motility in percentage	74.1 (40-90)	65.8 (55-90)
Normal morphology in percentage	65.67 (20-86)	61 (50-70)
Forward motility in percentage	2.27 (0-8)	3.4 (1-8)

All values are mean (range)

semen PCR for TB in asymptomatic male patients, whose female partners have been diagnosed to have genital TB, creates a dilemma of the need to evaluate and treat them as they may be harboring subclinical tubercular infection. Early diagnosis and treatment with antitubercular drugs has been found to improve semen analysis or reverse azoospermia.<sup>[12]</sup> However, in cases with advanced disease or its complications, multiple obstructions develop in the vas deferens or the epididymis, which are difficult to treat surgically.<sup>[13]</sup> Early detection and treatment of TB is, thus, a clinically relevant issue in managing male infertility.

All patients in our study were asymptomatic on presentation. One of the patients had a prior history of treated pulmonary TB. He also tested positive for TB-PCR in urine, and another

patient was found to be suffering from mediastinal TB. After encountering similar findings in their study of infertile women with genital TB, Rana *et al.* have suggested that in certain cases, a positive TB-PCR may imply the ability of the test to detect circulating mycobacterial DNA elsewhere in the body when the primary site has already healed or is dormant.<sup>[14]</sup> This could possibly explain the positive screening tests in our patients.

Male patients with genital TB generally present with scrotal or testicular masses/abscesses, low volume ejaculate and rarely may present with ulcerated, disfigured penile shaft.<sup>[10]</sup> As reported by Lübke *et al.*, infertility as a first sign of male genital TB is uncommon; however, it warrants further evaluation to rule out the evidence of GUTB.<sup>[15]</sup>

None of our patients had the evidence of clinical TB, except for one patient who had mediastinal lymphadenopathy, which was picked up on chest X-ray and was subsequently confirmed by CT of the chest. The ability of the PCR test to detect TB DNA in a similar setting has also been described previously by Miller *et al.*, where a patient with a positive PCR and three negative sputum cultures went on to develop culture positive and clinical TB after 6 months.<sup>[16]</sup>

Patients with GUTB may have significant abnormalities in the semen analysis, including azoospermia, a low volume ejaculate, or even aspermia.<sup>[10]</sup> Rarely, the only abnormality seen may be the presence of leukocytospermia.<sup>[15]</sup> There were no abnormalities on reviewing the semen analysis of our patients as per the World Health Organization guidelines.<sup>[17]</sup>

PCR is a rapid, sensitive, and specific molecular biological method for detecting mycobacterial DNA in both pulmonary and extrapulmonary samples from suspected TB patients.<sup>[18]</sup> PCR assays that target various gene segments in the mycobacterial DNA have shortened the time required for the definitive mycobacterial detection in the laboratory to 1–2 days. They are also more sensitive than the conventional methods.<sup>[18]</sup> Various authors have reported the sensitivity of mycobacterial PCR assay to be between 70% and 100%.<sup>[19,20]</sup> The high sensitivity of PCR has been attributed to the ability of these assays to detect DNA even in the patients with a history of TB, but without active tubercular infection. These authors hypothesize that PCR assays not only may prove more sensitive than culture but may modify our present understanding of TB infection.<sup>[19]</sup> The high sensitivity also perhaps contributes to the increased false-positive rates of the TB-PCR test varying between 3% and 77%.<sup>[21]</sup> These false-positive rates have been attributed to various causes. Intra and prelaboratory contamination of buffers and materials used in the pretreatment of samples is one of the important causes. Patients may have a reactivation of the previously

silent tubercular infection due to immune-suppression in malignancy, which may show up as a positive TB-PCR test. PCR also detects DNA of nonviable or quantitatively irrelevant TB pathogens, which would not cause clinical disease or the need to be treated.<sup>[19]</sup> It is, thus, possible that these are not “false-positive” but “early-positive” reports and may indicate infection that is not diagnosable by the current clinical methods and are labeled as “false-positive” due to the absence of a more sensitive gold standard test for comparison.

The reason for TB-PCR positivity was unanswered for most of our study population. Though one patient had a history of pulmonary TB in the distant past and another was detected to have mediastinal lymph node TB, the rest did not have any identifiable/explainable reason for PCR positivity. Cross contamination from other samples is known, but with the current generation of PCR assays and multiple levels of quality control, this problem seems to be unlikely.

Of the 14 patients tested initially, semen PCR could be tested again on follow-up only on 8 patients. The other six had either refused further testing or were unavailable at follow-up. The evidence in our study would have been stronger if all these patients followed up or had their semen retested. However, in our society, the complex psychosocial factors associated with the problem of infertility have a strong role to play in the strict adherence of these patients to the study protocol, and thus influence the final outcomes.

The semen characteristics also remained unaltered at the end of 6 months in the 8 patients that followed up. This further highlighted the fact that the exhaustive evaluation of these patients and the extended follow-up was perhaps unnecessary. The reason for evaluating these male partners for TB of the genital tract was based on the positivity of a highly sensitive diagnostic test. Since clinicians are unlikely to start ATT in the absence of clinical, radiological, and supporting laboratory investigations, the need to screen asymptomatic male partners of female patients with genital TB undergoing infertility evaluation seems unjustified.

## CONCLUSIONS

Asymptomatic men with positive screening semen PCR for TB do not have clinical evidence of TB. Male partners of women with infertility and GUTB should not be screened for TB if they have no symptoms.

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### Conflicts of interest

There are no conflicts of interest.

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