

Should men with idiopathic obstructive azoospermia be screened for genitourinary tuberculosis?

Rajan Gupta,
Prabhjot Singh,
Rajeev Kumar

Department of Urology, All
India Institute of Medical
Sciences, New Delhi, India

Address for correspondence:

Dr. Rajeev Kumar,
Department of Urology,
All India Institute of
Medical Sciences,
New Delhi - 110 029, India.
E-mail: rajeev02@gmail.com

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ABSTRACT

OBJECTIVE: Infertility may be the sole manifestation of genitourinary tuberculosis (TB) and men with idiopathic obstructive azoospermia are often screened for TB using semen polymerase chain reaction (PCR) test. We assessed the benefits of such screening. **DESIGN:** Totally, 100 infertile men with idiopathic obstructive azoospermia were screened with a kit-based PCR for semen TB. Confirmatory tests for TB were performed in PCR positive men before administering anti-tubercular therapy (ATT) for 6 months. Semen analysis was repeated to assess benefits of treatment. **RESULTS:** Seven subjects (7%) had positive semen PCR for TB. Four of them had other clinical evidence of TB (history and physical signs) and were administered ATT. None had any improvement in semen parameters. No subject had any other laboratory evidence of TB and no other subject (96%) was administered ATT. **CONCLUSIONS:** Screening for TB using semen PCR did not identify any men who would have been missed on clinical evaluation and is thus not indicated in men with idiopathic obstructive azoospermia.

KEY WORDS: Azoospermia, infertility, male genital, polymerase chain reaction, screening, tuberculosis

INTRODUCTION

Azoospermia, the absence of sperm in the ejaculate is seen in 10–15% of infertile men.^[1] Examination of the testis and vas-deferens along with semen volume and serum follicle stimulating hormone (FSH) levels help in identifying the cause of azoospermia.^[2] Obstruction of the ductal system is responsible for approximately 40% cases of azoospermia^[1] and in the absence of injury to vas or elective vasectomy, the obstruction is commonly at the level of the epididymis.^[2,3] Intratesticular obstruction is less common and is attributed to obstruction of the rete testis, either inflammatory or idiopathic.^[3,4] Microsurgical reconstruction is possible for obstruction at the level of the epididymis or vas-deferens, and thus its identification is important for managing these men. In a significant number of men, the cause of obstruction cannot be identified. Infections are a potential cause of male infertility but have been poorly documented.^[5] The common organisms implicated are *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Escherichia coli* and *Mycobacterium tuberculosis*.

Tuberculosis (TB) is a well-documented cause of male infertility in Asia.^[6,7] Tubercular infection is insidious in onset and often without overt physical symptoms and signs, making a specific diagnosis difficult. Infertility may be the first sign of male genitourinary TB that is the most common extra-pulmonary form of TB.^[8-10] Genital TB most commonly involves the epididymis followed by the prostate. While the exact pathogenesis is not known, factors like reflux of infected urine, hematogenous spread or lymphatic spread may play a role. The globus minor is affected alone in around 40% cases, owing to greater blood supply. The vas-deferens and epididymis may become nodular and rarely may form a discharging sinus. Ejaculatory duct involvement generally manifests as low volume ejaculate with azoospermia.^[9,11,12] Infertility usually results from structural obstruction or anatomic distortion of the epididymis, vas-deferens or ejaculatory ducts. Early detection of TB and its treatment with anti-tubercular therapy (ATT) may help restore sperms in the ejaculate.^[13] Considering the high prevalence of TB in the

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developing world, the frequent absence of a contributory history and its known association with obstructive azoospermia, men with idiopathic obstructive azoospermia are often screened for TB.

Polymerase chain reaction (PCR) is a rapid, sensitive and specific molecular biological method for detecting mycobacterial DNA in both pulmonary and extra-pulmonary samples.^[14] Using *in vitro* diagnostics with primers targeting IS6110 and MPB64, it can detect as small as 10 *Bacilli*.^[15] It is rapid and more sensitive than conventional methods^[14] and the sensitivity varies between 92% and 95% and specificity between 95% and 98% for different samples.^[15] These rapid tests have further added to the interest in such screening. Among women, a positive PCR test may be the sole criterion for initiating ATT.^[16,17]

There are no studies evaluating the validity of such screening in men. We, therefore, planned a prospective cohort study to assess the need for screening for genitourinary TB among infertile men with idiopathic azoospermia and to evaluate the impact of early treatment with ATT on semen parameters.

MATERIALS AND METHODS

Infertile men (inability to conceive after at least a year of unprotected intercourse) presenting to the out-patient clinic of our tertiary care hospital were screened for inclusion. The study population included azoospermic men (azoospermia confirmed on at least two semen analysis) diagnosed to have idiopathic vaso-epididymal junction obstruction or ejaculatory duct obstruction. Idiopathic vaso-epididymal junction obstruction was diagnosed if the subjects had normal testis size, bilateral palpable vas-deferens, normal secondary sexual characters, normal FSH levels and normal spermatogenesis on fine needle aspiration cytology of the testis in the absence of any known cause for azoospermia such as previous vasectomy, inguinal or scrotal trauma or surgery, orchitis, radiation or chemotherapy. Men who fulfilled the above criteria, but also had a low volume ejaculate (below 1.5 mL) in the presence of normal libido and orgasm were considered to have ejaculatory duct obstruction. This group of men also underwent trans-rectal ultrasound (TRUS) to identify dilated ejaculatory ducts that would suggest ejaculatory duct obstruction. If ejaculatory ducts were not dilated and semen volume was persistently low, a provisional suspicion of fibrotic ejaculatory duct obstruction was made.

Between January 2013 and May 2014, 100 consecutive patients who fulfilled these criteria and consented for participation were screened for genitourinary TB with a kit-based semen PCR test for *M. tuberculosis*. If the test

was positive, confirmatory tests which included semen acid fast *Bacilli* (AFB) smear, urine AFB smear and culture, chest X-ray, Mantoux test and ultrasound of the kidney-ureter and bladder were performed. Additional contrast imaging was obtained where indicated. Men with a clinical and laboratory evidence of TB based on the above investigations were provided standard ATT for 6 months, and semen analysis was repeated at 6 months. If they were still azoospermic, they were offered assisted reproduction. Men without any clinical evidence of TB and those with negative screening PCR were offered surgical reconstruction or assisted reproduction. Outcome analysis included the incidence of a positive screening test, incidence of isolated PCR positivity in the absence of others symptoms, signs or laboratory evidence of TB, and the impact of ATT on semen analysis.

This prospective, cohort study was approved by our institutional ethics committee, and all subjects provided a written informed consent for inclusion.

RESULTS

The mean age of the 100 subjects was 30.6 years (range: 24–38 years) and their mean duration of infertility was 38.2 months. Totally, 7 of these 100 subjects (7%) had positive semen PCR for TB. None of these 7 had any additional laboratory test positive for TB [Table 1].

Four of the 7 PCR positive subjects had a history or physical findings consistent with a diagnosis of genitourinary TB. All four had low volume ejaculate, a known symptom of genitourinary TB. Three of them had physical signs of TB that included nodular vas-deferens or epididymis in two

Table 1: Patient profile and results

Number of patients	100
Mean age in years (range)	30.6 (24-38)
Mean duration of infertility in months	38.2
Semen PCR positive patients	7/100
Normal semen volume	3
Low semen volume	4
Low volume ejaculate (<1.5 ml)	18/100
PCR positive	4
History of TB	7/100
Pulmonary TB	5 (all completed ATT)
Cervical TB	2 (1 had completed ATT)
Patients who were given ATT	4
Abnormal physical findings	3
Semen PCR positive	4
Low volume ejaculate	4
Semen analysis before ATT	Low volume azoospermia
Semen analysis after ATT	Low volume azoospermia
Improvement in semen parameters with ATT	Nil

PCR: Polymerase chain reaction, ATT= Anti-tubercular therapy, TB= Tuberculosis

patients and a chronic scrotal sinus in one. The patient with scrotal sinus had a history of recurrent epididymitis 6 years earlier. He also had bilaterally thickened spermatic cords. The fourth patient reported progressively decreasing semen volume with painful ejaculation over the last 3 years. He had a history of cervical lymphadenopathy 5 years earlier and had received 8 weeks ATT at that time. His physical examination was normal. While none of these four patients had any laboratory confirmation of TB, they were advised ATT in view of their history and physical examination that was consistent with a diagnosis of TB. All four patients underwent repeat semen analysis, twice, after 6 months of ATT. None of them had improvement in any of the semen parameters. None of the patients developed drug-induced adverse events or discontinued treatment.

The remaining three patients with positive semen PCR for TB had no physical findings or laboratory evidence of active TB. One of them had completed 6 months of ATT in the past for pulmonary TB. None of them was started on ATT [Figure 1].

Previous history of TB was present in 7 of 100 subjects (5 pulmonary, 2 cervical lymph nodes). Totally, 2 of these 7 subjects had positive semen PCR for TB including one patient with cervical TB who had received incomplete (8 weeks) ATT and continued to have a low volume ejaculate and one who had previously been fully treated for pulmonary TB. The other 5 who had negative PCR had completed ATT in the past. A total of 18 subjects had a low volume ejaculate (<1.5 mL). None of them had any abnormality on TRUS. A total of 4 of them who were PCR positive have been previously described. All other 14 had negative PCR for TB.

DISCUSSION

Our findings suggest that infertile men with obstructive azoospermia should not be screened with a semen PCR

test for TB. Azoospermia is a vexing clinical problem. Among azoospermic men, obstruction as a cause often portends a better prognosis than testicular impairment since surgical correction of the obstruction is potentially curative. Obstruction may account for 40% cases of azoospermia.^[3] In countries where vasectomy is a popular modality of sterilization, this is the commonest indication for surgical reconstruction.^[2] However, nonvasectomy related obstruction may often remain idiopathic.^[6]

Infertility resulting from TB may be due to direct involvement of epididymis, occlusion of the tubules or due to scarring and distortion of normal anatomy including that of the ejaculatory ducts when the involvement extends into the prostate.^[8,10,18,19] In the absence of symptoms and signs, the diagnosis of TB is based on a suggestive history and bacteriologic examination with nucleic acid amplification assays.^[14,15,20] Infertility may be the first presentation of genitourinary TB and patients may have no recollection of any other symptoms.^[21] The wide-spread prevalence of TB, its known association with infertility, and the lack of a suggestive history and signs make it appear logical that men with idiopathic infertility should be screened for TB. This would not only allow an etiological diagnosis but also a potential therapeutic target. This is further encouraged by the availability of a plethora of investigations for TB including PCR and previous reports that treatment of TB may enable return of sperms to the ejaculate of some selected azoospermic men.^[13]

Our study suggests that such screening may not be useful. Only 7% of our patients had a positive PCR. None of these had any other laboratory corroborative evidence of TB. On the other hand, four among these seven patients had physical findings of TB, low ejaculate volume, or a definitive history of untreated TB. The physical examination and untreated TB history would have been indications for

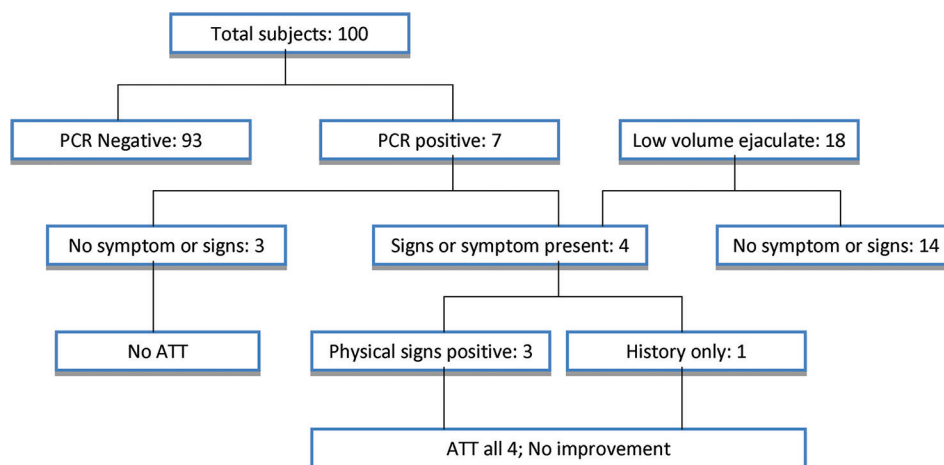


Figure 1: Summary of results PCR: Polymerase chain reaction for TB in semen; ATT: Antitubercular therapy

treatment with ATT in these men, even without a screening PCR. However, none of them benefitted from the ATT in terms of infertility.

We also found that TRUS was unable to identify obstruction in any of the 18 men with low volume ejaculate. This is in contrast to the study by Raviv *et al.*^[22] who found obstructive lesions in 13 of 42 men with a low volume ejaculate. Fibrotic, atrophic seminal vesicles with ejaculatory duct obstruction have been considered a feature of TB and progressively decreasing semen volume with azoospermia may be an indirect indicator of tubercular infection of the genital system.^[9,23,24] Since we were unable to document TB in any of the 14 men with low volume ejaculate who did not have a simultaneous physical abnormality, the value of this investigation too remains in doubt. However, the incidence of TB requiring treatment was 22% (4/18) in men with a low volume ejaculate, and this may form a subgroup that should be evaluated for TB.

A study of infertile couples in Mongolia found postinfectious obstructive azoospermia and accessory gland infection in 8.4% and 6.7% of men respectively.^[25] Bapna *et al.*^[26] opined that genital TB is almost always secondary to TB elsewhere, and the mode of dissemination is usually hematogenous, lymphatic or via direct contiguity. Primary genital TB is rare. However, in our study, in three of the four patients who were diagnosed to have genital TB and started on ATT we were unable to obtain a history of or document extragenital TB.

Ajantha *et al.*,^[27] reported that PCR, which is simple and rapid, is superior to conventional methods and should be performed in all patients with extra-pulmonary TB and when combined with staining and culture, the sensitivity can be increased. PCR is performed on tissue, pus, CSF, urine or other fluids. Its sensitivity varies from 88% to 95%, and the specificity is 95–98%.^[4,14,20,27] Three of our subjects had positive semen PCR but no other evidence of TB; one of them had a history of treated pulmonary TB. These may be false positive results for PCR.

None of our patients benefitted from ATT for their infertility. This is in contrast to the report by Shah,^[13] who presented a series of 34 cases in which epididymal inflammation due to TB could be completely resolved by ATT and steroids in 6 of 10 men with enlarged epididymis, but no sinus and normal ejaculate volume, resulting in reversal of azoospermia. It is possible that this could be due to the early stage of diagnosis in their series, but this would need further data to support ATT in such men.

Our study is limited by the fact that this was performed at a tertiary care center with a significant delay in presentation. It is possible that early diagnosis and treatment may have helped reverse azoospermia in some men. We also did not

follow-up men with positive PCR who did not receive ATT. It is possible that their PCR was not false positive but a sign of infection that had not yet manifest clinically in the form of physical signs. These men may have actually benefitted from ATT. However, it is difficult to justify ATT without corroborative evidence or in a clinical trial of treatment.

CONCLUSIONS

Screening for TB is not indicated in men with idiopathic obstructive azoospermia. It has a low yield and does not change clinical management. A meticulous history and physical examination, particularly in men with low volume ejaculate may identify the subset that needs to be investigated. ATT does not resolve azoospermia in such men.

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