THE JOURNAL OF OBSTETRICS AND GYNECOLOGY OF INDIA

The Journal of Obstetrics and Gynecology of India May / June 2011 pg 301-306

Original Article

Genital Tuberculosis in Infertile Women: Assessment of Endometrial TB PCR Results with Laparoscopic and Hysteroscopic Features

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Abstract

Objective: Mycobacterial infections of the genital tract have been implicated in the etiology of female infertility. The correlation of endometrial TB PCR with laparoscopic and hysteroscopic features in patients with infertility was evaluated. *Methods:* Women suffering from infertility and undergoing diagnostic laparoscopic and hysteroscopic examination were included. Endometrial specimens were assayed by Nested PCR for mycobacterium complex and the results were then retrospectively correlated with laparoscopic and hysteroscopic features. *Results:* Positive TB PCR was observed in 32.18% (n=56) women. Out of these 56 patients, 48 had endoscopic abnormalities suggestive of tuberculosis (TB) and rest 8did not reveal any endoscopic abnormalities. However, of 174 patients 139 had endoscopic abnormalities with positive TB PCR in only 48. Sensitivity and specificity of endoscopic evaluation was 85.71 and 22.8%, respectively. The presence of periovarian adhesions, cornual block, tubal beading, tubercles, intrauterine adhesions, and ostial fibrosis had very strong association with positive TB PCR. Total predictive value of endoscopic evaluation in diagnosis of genital TB was 42.52%. *Conclusion:* This study highlights that endoscopic evaluation is an important diagnostic tool, but can neither confirm nor exclude genital TB. Endometrial TB PCR may have to be routinely resorted to make a definite diagnosis of mycobacterial infection in endemic areas.

Keywords: genital tuberculosis, TB PCR, laparoscopy, hysteroscopy.

Introduction

The global prevalence of genital tuberculosis (TB) is estimated to be 8-10 million[1] cases with a rising incidence, partly as a result of HIV pandemic and emergence of resistant strains. A diagnosis of genital TB has profound implications for the asymptomatic women seeking fertility because the multidrug therapy required for ≥6 months is not very promising in terms of pregnancy outcome and TB is associated with social stigma as well in the country.

Moreover, this silent invader of genital tract tends to create diagnostic dilemmas because of varied clinical presentations, diverse results on imaging and laparoscopy, and limitations of histopathologic, serologic, bacteriologic, and culture methods. This is so because although the histopathologic evidence of mycobacterial infection is highly indicative of genital TB, its absence fails to exclude the infection and suggestive lesions may be seen in fungal

Paper received on 17/03/2009 ; accepted on 17/12/2010

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and sarcoid disease[2]. Similarly, culture methods, which have been considered gold standard in proving genital TB, fail to exclude mycobacterial infection. Furthermore, mycobacterium is a temperamental bacillus that needs 4-5 weeks to show growth on LJ media and 2 weeks time on Radiometric BACTEC media[3]. The minimum mycobacterial concentration at which histopathologic evidence appears is 10,000 bacilli/ml, and for positive culture the required concentrations are 1,000 and 10-100 bacilli /ml for LJ and BACTEC media, respectively[4].

During the last decade, major advances in understanding of the genetic structure of mycobacterium have led to the development of specific gene sequences and several gene amplification systems for diagnosis of TB. In multiplex PCR, gene sequences are simultaneously amplified in one tube. The advantage of this test is that it reveals the false negative, because each amplification provides an internal control for the other and false positives are also reduced due to amplification of targeted genes. For the same reason, PCR has been able to detect TB bacilli in the concentration as low as 10 bacilli/ml[4]. Hence in combination with accurate clinical assessment PCR test seems to be a very promising diagnostic tool.

Considering the high endemicity of genital TB, its strong association with infertility and limitations of available diagnostic tests, constant attempts have been made to develop definitive diagnostic criteria to be applied to make a conclusive diagnosis of genital TB. The present study was conducted with an objective to correlate the endometrial Nested TB PCR with endoscopic features in patients with infertility.

Materials and Methods

In total, 174 patients who presented at Disha fertility Center with infertility from April 2006 to October 2007 and underwent diagnostic laparoscopy and hysteroscopy were enrolled in the study. During the endoscopic evaluation, the presence of all those features that are considered suggestive of genital TB was assessed and noted by the same surgeon. The endometrial sample obtained by curettage was sent for analysis of Nested PCR for mycobacterium complex. The PCR results obtained were retrospectively correlated with the endoscopic features of the individual patient.

Assessment Criteria

The endoscopic features that are considered suggestive of TB for the given study were decided on the basis of microscopic and macroscopic pathogenesis of mycobacterium infection and computerized search in Medline[5,6] for endoscopic features suggestive of TB.

All patients were analyzed for presence of cornual or fimbrial block, tubal beading, presence of tubercles, tuboovarian masses peritubal, periovarian, and perihepatic adhesions, rigid tubes, fimbrial phimosis, hydrosalphinx, bowel and omental adhesions, intrauterine adhesions, small uterine cavity, and fibrosed ostia. The association of these features with polycystic ovary (PCO) and endometriosis was also noted.

All those patients who had any of the features suggestive of TB were considered to have abnormal endoscopy, whereas patients without any suggestive feature of TB were considered endoscopically normal for the present study.

Results

This study correlates the endometrial TB PCR results with laparoscopic as well as hysteroscopic features in a large group comprising of 174 patients with infertility. The suggestive structural lesions of genital TB-cornual and fimbrial block, tubal beading, periovarian and peritubal adhesions, tuboovarian masses, delayed spill and hydrosalphinx, intrauterine adhesions, and ostial fibrosis-have been retrospectively reviewed and analyzed with Nested TBPCR results (Table 1) to detect sensitivity and specificity of endoscopic evaluation.

We observed in our study that out of total 174 patients 139 had endoscopic abnormalities, with positive PCR in only 48. However, PCR was also positive in eight patients with normal endoscopic features. This means that out of total 56 PCR-positive patients (Table 2), 48 showed endoscopic abnormalities, whereas 8 who were endoscopically normal had TB PCR positive. Another important observation is that out of 139 patients with laparoscopic and hysteroscopic abnormalities, PCR was positive in only 48 and rest 91 with endoscopic abnormalities had negative PCR. Similarly out of total 35 patients with normal endoscopy, 8 were PCR positive.

Based on these observations, sensitivity and specificity of endoscopic evaluation was 85.71 and 22.8%, respectively. False-positive rate of endoscopic evaluation was found to be very high at 65.4% and false-negative rate at 14.28% (Table 3).

We found that in diagnosis of genital TB endoscopic evaluation has total predictive value of 42.52%, meaning

Table 1
Laparoscopic and hysteroscopic findings and results of TB PCR on endometrial samples (*n*=174)

Signs	No. of patients (%)	PCR positive (%)
Laparoscopic findings		
Normal findings	35 (20.11)	8 (22.86)
Periovarian adhesions	40 (22.98)	15 (37)
Cornual block	24 (12.64)	12 (50)
Tubal beading	22 (12.06)	10 (45.4)
Peritubal adhesions	21 (12.06)	5 (23.8)
Delayed spill	16 (9.19)	6 (37.5)
Perihepatic adhesions	13 (7.4)	4 (30.7)
Bilateral TO mass	12 (6.89)	2 (16.6)
Tubercles	10 (5.7)	5 (50)
Unilateral TO mass	8 (4.59)	1 (12.5)
Isolated beading	6 (3.4)	None
Fimbrial block	4 (2.29)	2 (50)
Isolated tubercles	4 (2.29)	None
Rigid tubes	3 (1.72)	None
Hydrosalphynx	3 (1.72)	1 (33)
Bowel and omental Adhesions	3 (1.72)	1 (33)
Fimbrial phimosis	2 (1.14)	None
Associated endometriosis	21 (12.06)	6 (28.57)
Associated PCO	18 (10.34)	8 (44.4)
Hysteroscopic findings		
Fibrosed ostia	9 (5.1)	4 (44.4)
Intrauterine adhesions	8 (4.59)	2 (25)
Small uterine cavity	4 (2.29)	2 (50)

TO: Tuboovarian; PCO: Polycystic ovary

that based on endoscopic evaluation the diagnosis of genital TB will match with PCR results in 42.52% of patients. We observed that of 139 endoscopically abnormal patients, only 48 (34.53%) had positive PCR and rest 91 did not have positive PCR. This means that the positive predictive value of abnormal endoscopic features in diagnosis of genital TB was 34.53%.

Discussion

Previous studies in the field of genital TB have found a very strong association of genital TB with tubal infertility. Yang Y et al.[6] conducted a large study comprising 1,120 patients with infertility to conclude that laparoscopic examination is a very valuable tool for etiological diagnosis of tubal factor infertility. The investigators observed that genital TB accounted for 63.6% of tubal infertility, and tubercular lesions observed laparoscopically were of four types: miliary ascites 9.4%, adherent mass 35.8%, adhesion and calcification 43.1%, and nodular sclerosis 11.7%. Shaheen et al.[7] studied 7,628 gynecological outpatients to assess frequency of genital TB as diagnosed by histopathologic and culture tests. They found 7% of OPD patients to be suffering

Table 2
Laparoscopic and hysteroscopic findings in patients with positive TB PCR (*n*=56)

Signs	No. of patients (%)
Normal laparoscopic findings	8 (14.29)
Periovarian adhesions	15 (26.78)
Cornual block	12 (21.43)
Tubal beading	10 (17.86)
Associated PCO	8 (14.29)
Associated endometriosis	6 (10.71)
Delayed spill	6 (10.71)
Perirubal aadhesions	5 (8.92)
Tubercles	5 (8.92)
Perihepatic adhesions	4 (7.14)
Bilateral TO mass	2 (3.57)
Fimbrial block	2 (3.57)
Unilateral TO mass	1 (1.78)
Hydrosalphynx	1 (1.78)
Bowel and omental	1 (1.78)
Isolated beading	None
Isolated tubercles	None
Rigid tubes	None
Fimbrial phimosis	None
Hysteroscopic findings	
Fibrosed ostia	4 (7.14)
Intrauterine adhesions	2 (3.57)
Small uterine cavity	2 (3.57)

Table 3
Analysis of laproscopic and hysteroscopic evaluation for diagnosis of TB in patients with infertility

Measures	Value (%)
Sensitivity	85.71
Specificity	22.8
Predictive value of the positive test	34.53
Predictive value of the negative test	77
Percentage of false positive	65.46
Percentage of false negative	14.28

from infertility and 2.3% of patients to have genital TB, and concluded that it is very essential for a gynecologist, especially in TB endemic countries, to anticipate the possibility of genital TB in infertile patients.

On the contrary, several studies have evaluated clinical utility of PCR in diagnosis of mycobacterial infections. Schluger et al.[8] correlated PCR results with AFB bacilli smears, cultures, and clinical histories in 65 patients and found PCR to be highly sensitive and specific in diagnosis of TB infection. The PCR test has been extensively studied and data show 87-100% sensitivity and 92-99.8% specificity.

Based on current knowledge that laparoscopy is a valuable tool for diagnosing tubal infertility as well as genital TB and the fact that PCR is very sensitive and specific for detecting mycobacterial infection, we conducted the present study.

In this study, out of total 35 endoscopically normal patients, 8 patients were found to be PCR positive, meaning that endoscopic evaluation was false negative in 8 patients. On the basis of these observations, negative predictive value of endoscopic evaluation was found to be 77%. This is a very important observation that 23% patients with normal endoscopy had positive TB PCR. This observation further emphasizes the fact that genital TB would be more frequently diagnosed if a high index of suspicion was considered in the evaluation of every infertile patient, especially in areas where TB is endemic.

Another significant observation of the present study is that 91 patients with endoscopic features suggestive of genital TB did not have positive TB PCR. This can be attributed to three factors. Firstly, the genital TB mostly results from hematogenous spread and fallopian tubes are almost universally involved, whereas endometrium is affected in 27-79%[9] of cases. Since in all patients salphingitis may not be associated with endometritis, isolated salphingitis is likely to be missed by analysis of endometrial sample for TB PCR but can be suspected by careful and judicious endoscopic assessment for the presence of tubercles, peritubal and periovarian adhesions, and cornual and fimbrial block. The second reason which can in part explain the high false-positive rate of endoscopy is that these patients might have taken antitubercular treatment for extragenital/genital TB and they fail to give the history because either the treatment was administered in their childhood about which they are not aware or they wish to conceal the treatment due to social stigma associated with TB. This is the situation in developing countries like India, where patients with infertility usually suffer from immense social pressure to conceive and face lack of family understanding about the disease. Thirdly, the features of hydrosalpinx, tubal block, and tuboovarian masses and adhesions can be the result of gonococcal/pyogenic bacilli infection as well, and can explain for the negative PCR in patients with endoscopic abnormalities suggestive of TB[9].

On analysis of the association of individual endoscopic feature suggestive of TB with TB PCR, 50% of patients with cornual block had positive PCR. Periovarian adhesion was seen in 22.98% cases of infertility. The association of periovarian adhesion with positive PCR was noted in 37.5% patients, whereas positive PCR was noted in 50% patients with tubercles. Tubal beading was seen in 12.64% patients, and 45.4% with tubal beading had positive PCR. Less than half (37.5%) patients with delayed spillage of dye through fimbrial end and 30.7% patients with perihepatic adhesions showed positive PCR. In another important observation, none of the patients with rigid tubes, fimbrial phimosis, isolated beading, and isolated tubercles had positive PCR. On hysteroscopy, intrauterine adhesions had positive PCR in 50% of patients with the same feature and ostial fibrosis was associated with positive PCR in 44.4% cases. It suggests that endoscopic features that showed very high association with positive PCR are cornual block, periovarian adhesions, tubercles, and tubal beading on laparoscopy, and ostial fibrosis and intrauterine adhesions on hysteroscopy.

An interesting observation of this study is that 12.06% of patients with features suggestive of TB had associated endometriosis evidenced by endometriotic spots, and PCR was positive in 28.57% of such patients. There is no proven theory to justify the association of genital TB with endometriosis but perhaps the change in intrauterine milieu and vascularity might play some role in provoking retrograde spillage of endometrial cells resulting in endometriosis.

Vijaya Bhanu et al.[4] conducted a study on 25 patients with infertility with the same objective and found TB PCR to be highly sensitive in detecting genital TB. The investigators found that all patients with laparoscopy suggestive of TB, 60% of those with a probable diagnosis, and 33% of those with incidental findings were positive by PCR. Similarly, Sharma et al.[10] studied 28 infertile women to conclude that genital TB as

diagnosed either by positive TB PCR or positive histopathologic or culture tests had a strong association with intrauterine adhesions leading to Ashermans syndrome. In another study, Gupta et al.[5] analyzed clinical and laparoscopic features of 40 infertile women with genital TB as diagnosed with histopathologic, culture, and PCR results. Laparoscopic examination revealed abnormally dilated, tortuous, and blocked fallopian tubes (n=13), peritubal and periovarian adhesions (n=18), bowel adhesions in 15, and intrauterine adhesions in 7 patients.

It is essential to emphasize that available studies in the literature do show a strong association of endoscopic features of genital TB with endometrial PCR, but most of them comprise a base of 25-40 patients. Probably this has been one encouraging factor for us to undertake present study on a large group comprising of 174 patients. The principal weakness of this study is that TB PCR test, considered as a gold standard for assessment of endoscopic features, is not 100% sensitive and specific. Like any other bacteriological test available for diagnosing TB, it is known to give a small number of false-positive and -negative results. Secondly, for the endoscopic features which are considered suggestive of TB, there are no defined criteria in literature. On the basis of microscopic as well as macroscopic pathogenesis of mycobacterial infection and the endoscopic features known to be strongly associated with genital TB, assessment criteria were defined for the present study.

It seems that the group of patients in whom endoscopic evaluation shows false-positive and -negative results can be prospectively studied for pregnancy outcome after antitubercular treatment to further enlighten the diagnostic accuracy of endoscopy as well as PCR in cases of genital TB. Although the study outcome will be limited by the fact that fertility rates are not optimistic in genital TB patients even after treatment. Those patients who achieve pregnancy post antitubercular treatment in such a study will definitely help in adding to our present knowledge of diagnostic role of endoscopic tests and nested PCR for mycobacterium complex in diagnosis of genital TB. In conclusion, the results of present study validate that endoscopic evaluation is undoubtedly a very valuable tool in diagnosing genital TB, but by itself can neither confirm nor exclude genital TB. The routine application of endometrial bacteriological PCR assays in addition to clinical and endoscopic evaluation carries a great potential in improving diagnosis of genital TB, especially in countries where TB is endemic.

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