Markers of genital tuberculosis in infertility

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ABSTRACT

Introduction: Although genital tuberculosis is a condition that is prevalent worldwide, it is still a diagnostic dilemma. This study aimed to find an effective diagnostic modality for the condition.

Methods: A total of 100 infertile women were clinically evaluated with haemoglobin estimation, total and differential count, Mantoux test, tubercle bacilli enzyme-linked immunosorbent assay (TB ELISA), hysterosalpingography, pelvic ultrasonography, laparohysteroscopy, premenstrual endometrial biopsy for histopathology, culture and tubercle bacilli polymerase chain reaction (TBPCR). The womens' Day 2 hormonal profile (luteinising, follicle-stimulating, prolactin and thyroid-stimulating hormones) and their husbands' semen analysis were also conducted.

Results: A total of 58 women had primary infertility and 42 had secondary infertility. Female factor infertility was present in 63 percent of the cases (mostly tubal; 45.97 percent). 26 women tested positive for endometrial TBPCR. Erythrocyte sedimentation rate, Mantoux test, TB ELISA and hysterosalpingography were found to have high negative predictive value (greater than 80 percent), while the positive predictive value was 35–45 percent. Laparoscopy findings were suggestive of tuberculosis in 13 percent of the women, out of which 83.3 percent were positive for endometrial TBPCR. Hysteroscopy revealed intrauterine adhesions in 34.8 percent of the women, with 68.8 percent being positive for tubercular bacilli.

Conclusion: Our study established that in cases of genital tuberculosis, the use of expensive endometrial TBPCR tests may be avoided with a detailed workup, which would also help in the institution of anti-tubercular treatment in early disease, thus enhancing the chance of pregnancy.

Keywords: genital, infertility, markers, polymerase chain reaction, tuberculosis

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INTRODUCTION

The global prevalence of genital tuberculosis has increased from 22 million cases in 1995 to 1.86 billion cases in 2005, with a rate of 5%–10% in infertility clinics. This condition is endemic in India, with a prevalence of 3%–39%.[1,2] Genital tuberculosis is a diagnostic dilemma with varied clinical presentations, diverse imaging, laparoscopy results and a mixed bag of bacteriological and serological tests. Therefore, this study aimed to find a diagnostic modality for this disease that is simple, feasible, specific and sensitive, and facilitates early diagnosis.

METHODS

A total of 100 women with a history of infertility who attended the gynaecological outpatient department of Sir Sunderlal hospital, Varanasi, India from December 2006 to June 2008 were subjected to detailed history-taking and clinical examination. Thereafter, haemoglobin estimation, total and differential count, Mantoux test, tubercle bacilli enzyme-linked immunosorbent assay (TB ELISA), hysterosalpingography, pelvic ultrasonography, laparohysteroscopy, premenstrual endometrial biopsy for histopathology, acid-fast bacilli (AFB) culture (in Lowenstein-Jensen [LJ] medium) and tubercle bacilli polymerase chain reaction (TBPCR) (IS6110) was performed.[3] Day 2 hormonal profile (luteinising hormone, follicle-stimulating hormone, prolactin, thyroid-stimulating hormone) for the patients and their husbands' semen analysis were also performed.

RESULTS

Out of 100 patients, 58 had primary infertility while 42 had secondary infertility. Female factor infertility was present in 63 cases, male factor in 13, combined male and female factor in 13 and unexplained infertility in the rest. Tubal/peritoneal factor was found in 45.97% of the patients, while ovulatory dysfunction was found in

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24.13% of the patients. Premenstrual endometrial biopsy was taken for all the patients and sent for histopathology, AFB culture and TBPCR. 26 patients were found to be positive for TBPCR. The mean age of these patients was 27.23 ± 4.16 years, compared to 29.14 ± 4.80 years for those who were negative for TBPCR. The majority of the patients (15/26) who tested positive for TBPCR belonged to the lower socioeconomic group.

The symptoms of patients who tested positive for TBPCR are shown in Table I. A history of extragenital tuberculosis was present in 12.2% of the patients. 13.8% of those who were positive for TBPCR were on anti-tubercular therapy (< three months) at the time of examination. The findings on bimanual examination are shown in Table II. The mean haemoglobin of patients who were positive for TBPCR was 9.55 ± 1.56 g/dL while that of those negative for TBPCR was 10.66 ± 1.69 g/dL. The mean differential lymphocyte count of patients who tested positive for TBPCR was 33.46 ± 10.76 as compared to 28.24 ± 8.63 in patients who tested negative for TBPCR. 53.8% of the TBPCR positive patients had significant lymphocytosis.

The mean erythrocyte sedimentation rate (ESR) of patients who were positive for TBPCR was 24.15 ± 10.52 mm as compared to 16.48 ± 8.16 mm for patients who showed negative results. The sensitivity, specificity and predictive values of ESR, Mantoux test, TB ELISA and hysterosalpingography are shown in Table III. AFB culture in LJ medium showed positive results in only four cases, only three of which were positive for endometrial TBPCR. Histopathology of the endometrial biopsy showed endometritis in only two patients, both of whom were positive for TBPCR but showed no growth in LJ culture medium. Pelvic ultrasonography revealed irregular endometrial lining in 16 patients, out of which only six (37.5%) were positive for TBPCR. Eight out of the 21 patients (38.1%) with tubo-ovarian mass were positive for TBPCR.

Laparohysteroscopy was done in 46 patients. The laparoscopic and hysteroscopic findings are shown in Tables IV and V, respectively. Out of the six cases that were labelled as tubercular on laparoscopy, five were positive for endometrial TBPCR. Only 26.3% of patients who were positive for TBPCR had findings that were suggestive of tuberculosis on laparoscopy. Seven patients (26.9%) patients who were positive for TBPCR had associated hyperprolactinaemia. After anti-tubercular therapy for 6–9 months, 19.2% of our patients became pregnant during a minimum six-month follow-up period; however, one patient had an ectopic pregnancy.

Table I. Symptoms of patients who were positive for TBPCR

Symptom	No. (%)
Menstrual complaints	
Hypomenorrhoea	11 (42.3)
Dysmenorrhoea	8 (30.7)
Oligomenorrhoea	3 (11.5)
Metrorrhagia	2 (7.7)
Polymenorrhagia	2 (7.7)
Menorrhagia	0 (0.0)
None	9 (34.6)
Other symptom (%)	
Abnormal discharge per vaginum	5 (19.2)
Galactorrhoea	7 (26.9)

Table II. Adnexal findings.

Adnexal finding	No. of patients		
	Positive TBPCR	Negative TBPCR	Total
Normal	17	58	75
Palpable adnexa	4	2	6
Tenderness	2	5	7
Thickening	3	9	12

TBPCR: tubercle bacilli polymerase chain reaction

Table III. Markers of genital tuberculosis.

Test	Sensitivity	Specificity	PPV	NPV
ESR	57.69	63.51	35.71	81.03
Mantoux test	61.50	66.21	39.02	83.05
TB ELISA IgG	61.53	72.97	44.44	84.37
TB ELISA IgM	69.23	63.51	40.00	85.45
Hysterosalpingography	76.90	52.70	36.40	86.70

PPV: positive predictive value; NPV: negative predictive value; ESR: erythrocyte sedimentation rate; TB ELISA: tubercle bacilli enzyme-linked immunosorbent assay

DISCUSSION

A total of 26 out of the 100 infertility patients in our study were positive for TBPCR. Of these, only three patients had positive results on AFB culture, which is said to be the gold standard for tuberculosis. One patient was AFB-culture positive but negative for TBPCR. Parikh et al calculated the incidence of tuberculosis in patients with infertility as 39% based on clinical suspicion and conventional modalities.[2] Another study in New Delhi documented 56% of infertile patients as TBPCR-positive and only 3.2% as AFB culture-positive (taking endometrial aspirate, endometrial biopsies and fluid from the pouch of Douglas as samples).[3] Rozati et al's study found that TBPCR had a 96.4% sensitivity.[4] In our study, it had a 75% sensitivity, and 88.46% of our patients with genital tuberculosis would have been missed if TBPCR of the endometrial biopsy had not been conducted. Hence,

Table IV. Laparoscopic findings.

Finding	No. of patients		
	Positive TBPCR	Negative TBPCR	Total
Normal	1	7	8
Tubal block + fine adhesions	4	1	5
Tubal block − fine adhesions	4	5	9
Tubal block + cystic ovaries	1	1	2
Tubal patency + cystic ovaries	1	2	3
Tubal patency + fine adhesions	1	3	4
Caseation/tubercles/dense adhesions ± tubal block	5	1	6
Endometriosis (moderate–severe)	2	7	9
Test not done	7	47	54

TBPCR: tubercle bacilli polymerase chain reaction

Table IV. Hysteroscopic findings.

Finding	No. of patients		
	Positive TBPCR	Negative TBPCR	Total
Normal	7	13	20
Small uterine cavity	0	2	2
Intrauterine synechia	11	5	16
Other findings*	1	7	8

*Findings include fibroid, polyp and uterine malformations cervical stenosis
TBPCR: tubercle bacilli polymerase chain reaction

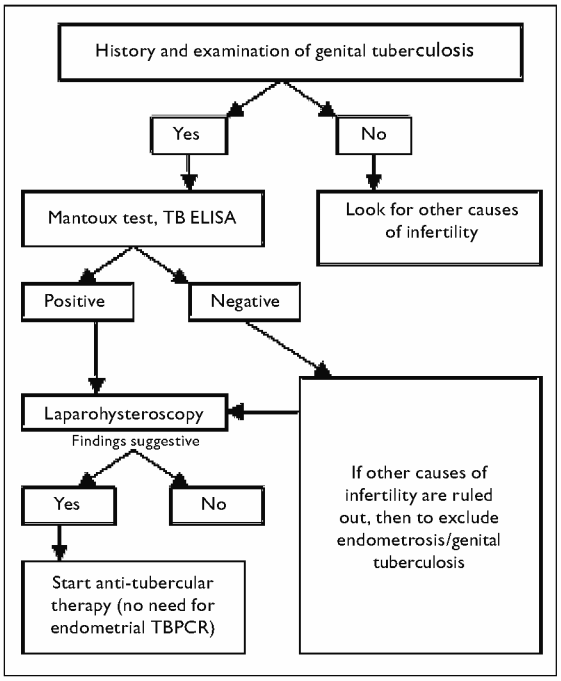

Fig. 1 Algorithm for management of infertility cases with genital tuberculosis.

tissue culture for tubercle bacilli is not necessary for the diagnosis of genital tuberculosis. Nowadays, the BACTEC radiometric culture system has become available. The mean detection time for Mycobacterium tuberculosis was 24.03 days by LJ medium culture, 12.89 days by BACTEC and less than one day by PCR test. Various studies have found the sensitivity of PCR test as well as BACTEC culture method to be comparable in both pulmonary and extrapulmonary tuberculosis.[5,6]

Investigating patients with menstrual abnormalities (such as oligomenorrhoea and amenorrhoea) and personal/family history of this infection increases the positive predictive value of the diagnostic tests for genital tuberculosis. In our study, significant lymphocytosis (> 30% of total leukocyte count) was seen in 53.8% of the patients who were positive for endometrial TBPCR. In Akintunde et al's study, lymphocytosis was seen in 6% of patients with pulmonary tuberculosis.[7] In other studies, leucocytosis was present in 12.8% of patients with extrapulmonary tuberculosis and 22.3% of patients with pulmonary tuberculosis.[8,9] ESR was raised in 57.69% of our patients who were TBPCR-positive, which was similar to a study conducted in patients with abdominal tuberculosis in China.[10] In our study, Mantoux test was 61.5% sensitive and 66.21% specific in diagnosing TBPCR-positive cases. Raut et al have found the Mantoux test to be 55% sensitive and 80% specific in diagnosing laparoscopy-proven genital tuberculosis.[11]

The role of TB ELISA for diagnosing genital tuberculosis is debatable. In our study, the sensitivity and specificity of TB ELISA IgG was 61.53% and 72.97%, respectively. The sensitivity and specificity of TB ELISA IgM was 69.23% and 63.51%, respectively in diagnosing TBPCR positive patients. In another study, ELISA was reported as 81.6% sensitive in active extra-pulmonary TB, which decreased to 30% in inactive forms,[12] suggesting that ELISA can be used as a supporting test. In our study, the incidence of positive endometrial TBPCR result was higher in cases with laparoscopic findings of complete tubal block, adhesions, calcifications, adherent mass and miliary tubercles. Chavhan et al found a significant correlation between positive TBPCR results and findings suggestive of tuberculosis by hysterosalpingography and laparohysteroscopy.[13] Our study showed high negative predictive value (> 80%) of ESR, Mantoux test, TB ELISA, hysterosalpingography and laparohysteroscopy in diagnosing genital tuberculosis. Therefore, if a patient is negative for these tests, she should not be continued on anti-tubercular therapy, thus avoiding the unnecessary adverse effects of anti-tubercular drugs, such as hepatotoxicity, ototoxicity and neuropathy. Other causes of infertility can then be thoroughly investigated.

In this study, hyperprolactinaemia was seen in 26.92% of the patients who were positive for endometrial TBPCR. The mean level of prolactin in TBPCR-positive patients was 19.28 ± 12.48 ng/ml, which was significantly greater than that (14.15 ± 10.25 ng/ml) in the remaining patients ($p < 0.05$). In Tripathy and Tripathy's study, hyperprolactinaemia was reported in 37.14% of patients with pulmonary tuberculosis, the mean level being 42.7 ± 12.2 ng/ml, which was also significantly higher than the mean level of 18.6 ± 4.7 ng/ml in their remaining patients. This might be due to weight loss and stress affecting pituitary function, as stated by Tripathy and Tripathy.[14]

In our study, 19.2% of patients who were positive for TBPCR conceived after anti-tubercular therapy during a minimum six-month follow-up period. Tripathy and Tripathy's study showed that if a patient is adequately treated before her tubes are irreversibly damaged, the chance of successful pregnancy is 19.6%.[1] Algorithm for management of infertility cases with genital tuberculosis is shown in Fig 1.

In conclusion, our study established that in cases of genital tuberculosis, the use of expensive endometrial TBPCR tests may be avoided with a detailed workup, which would also help in the institution of anti-tubercular treatment in early disease, thus enhancing the chance of pregnancy. Moreover, the adverse side effects caused by the unnecessary use of anti-tubercular drugs could also be avoided.

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