

ORIGINAL ARTICLE

A STUDY ON CO-RELATION OF INFERTILITY AND FEMALE GENITAL TUBERCULOSIS

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ABSTRACT

Introduction: Female Genital Tuberculosis (FGTB) is an important cause of sub fertility. It can cause tubal obstruction and dysfunction, impair implantation due to endometrial involvement and rarely lead to ovulatory failure.

Objective: To evaluate the rate of female genital tuberculosis and its presentational symptoms in patients of infertility, to study the genital tuberculosis by hystero-laparoscopy and different methods available for its diagnosis including PCR technique and histo-pathological examination and to study conception rate after ATT (Anti tubercular treatment) in positive cases of PCR.

Methodology: This was a prospective observational study conducted in the Department of Obstetrics and Gynecology, SMIMER, Surat, on 54 subjects from May 2007 to December 2009. Patients of reproductive age group from 18 years to 36 years with the duration of infertility of more than 2 years were included.

Results: Out of 54 subjects, cases of primary infertility were 44 (81.5%) and secondary infertility were 10 (18.5%). Chronic pelvic pain in 16 patients (29.6%) was the most common associated complaint apart from infertility. On investigation ,cases found positive were 19 by PCR from endometrial biopsy, 22 cases (40.7%) by laparoscopy, 2 cases (3.7%) by histology and 3 cases (5.6%) by hysteroscopy. 19 cases were given ATT, out of those 6 cases (31.6%) had conceived.

Conclusion: Infertility is one of the most common symptoms of FGTB and more cases of genital TB would be diagnosed in patient of infertility in endemic areas.

Keywords: Female genital tuberculosis (FGTB), Infertility, Anti tuberculosis treatment (ATT), Polymerase chain reaction (PCR)

Abbreviations: Female genital tuberculosis (FGTB), Anti tubercular treatment (ATT), Polymerase chain reaction (PCR), Erythrocyte sedimentation rate (ESR), Tuberculosis (TB), Histo pathological examination (HPE)

INTRODUCTION

Female genital tuberculosis affects about 12 % of patients having pulmonary tuberculosis.¹The prevalence of FGTB in infertility clinics shows marked variation ranging from 15% to 25%.² It is involved in about 5 -16 % cases of infertility among Indian women. ^{3, 4, 5.} In 80 -90 % of cases, FGTB affects young women of 18 -38 years of age and is an important cause of infertility.^{2, 6}The most common mode of transmission to the genital tract is through haematogenous spread from lungs ,other sites being kidney and intestine.⁷ The fallopian tubes (92-100%) are the most commonly affected genital organs, followed by endometrium(50%),² ovary(10-30%), cervix(5%) and vulva and vagina(<1%).According to

Novak's,⁸ the tubes are already affected when the diagnosis of tubercular endometritis is made. The characteristic feature is the presence of yellowish-grey tubercles on the peritoneal surface of the tubes and mesosalpinx with fimbrial end of tube remaining open in half the cases.⁹ Endometrial appearance may be unremarkable initially but may end up in Asherman's syndrome leading to secondary amenorrhoea.

Infertility is one of the commonest presentations of genital TB. Other clinical symptoms & signs can be fever, anorexia, menstrual disorders ranging from menorrhagia to amenorrhoea, chronic pelvic pain, abnormal vaginal discharge, urinary or defecation problems, lymphadenopathy, abdominal masses, ascites,

doughy feel of abdomen, fornix tenderness, TO masses etc.

Diagnosis of FG TB is often limited to clinical suspicion. A pelvic USG is of help in presence of TO masses. Definitive diagnosis of FG TB is possible only by the isolation of Mycobacterium tuberculosis bacteria from genital tract or histological demonstration of granuloma. The material taken for culture or biopsy is the endometrium and menstrual discharge.¹⁰ The best time for collecting endometrial sample is several days before expected menses when tubercles reach maximum growth. The polymerase chain reaction (PCR) is a rapid method for detection & quantification of few DNA copies with high sensitivity & specificity, the results being available in 1 day. PCR may be positive with only 1-10 organisms /ml.¹¹ On hysteroscopy, no classical features are described but intrauterine adhesions, scarring or narrowing of cavity may be found.

Short - course chemotherapy (DOTS) for 6-9 months has been found to be effective for medical treatment of FG TB.^{12, 13} The chances of pregnancy in females suffering from genital TB have so far been poor (5%) even after completion of treatment.¹⁴

METHODOLOGY

This prospective observational study was conducted in the Dept. of Obstetrics & Gynecology, SMIMER, Surat, from May 2007 to Nov 2009. All infertility patients fulfilling the inclusion criteria reported during the study period were included in the study. Inclusion criteria were: a) Reproductive age group female from 18 years to 36 years; b) Medically fit patients; c) Infertility duration should be more than 2 years; and d) at least 3 times ovulation induction with follicular monitoring done in past. Subjects were selected from patients visiting infertility clinic with the written consent.

On admission, subject's detailed history (menstrual, obstetrical, past, medical & familial) was taken and thorough general examination, systemic, gynecological examinations were carried out. Routine investigations were done including CBC, blood group, RFT, RBS, ESR, CXR, urine routine & microscopy, & HIV, HBsAg, VDRL. Informed consent was taken from all patients.

All enrolled patients underwent diagnostic hystero-laparoscopy to look for the status of fallopian tubes, presence of any granulations, caseation or adhesions over tubes or uterus. In all patients, endometrial biopsy was taken especially from both cornual ends & sent for histological examination in formalin & for PCR analysis in normal saline solution respectively to the lab immediately.

After confirmation of diagnosis of genital TB, ATT was started. DOTS (category-1) were given to all patients with positive PCR. Treatment was given in 2 phases- **initial phase(2 months)**- isoniazide, rifampicin, pyrazinamide & ethambutol along with vitamin B6 were given, **continuation phase-(4 months)** – isoniazide & rifampicin were used. Patients were followed for two years for conception. In order to improve pregnancy rates intrauterine insemination (IUI) was done in some patients. Statistical analysis was carried out using SPSS sum & Chi square test. The study was approved by institutional ethical committee.

RESULTS

Total 54 patients were included in the study. Out of 54 subjects, 46(86.2%) were in age group between 20 to 30 years, with mean age of 26.33 years. 44(81.5%) cases had primary infertility & 10(18.5%) had secondary infertility. In present study, there was positive history of extra genital TB in past in 11(20.3%) cases and family history was positive in 13(24%) cases. The patients were considered to be FG TB positive or negative on basis of diagnostic methods used in alone or in combination. In present study significant association has been found between positive past history and laparoscopic findings statistically. Out of 11 cases of positive past history, laparoscopy showed positive findings in 8 cases (72.7%).

Table 1: Co-relation between PCR and past history

Past history	PCR for Tuberculli		Total
	Negative	Positive	
Absent	31(72.1)	12(27.9)	43
Present	4(36.4)	7(63.6)	11

As shown in Table - 1, significant association has been found between negative past history & negative PCR. Out of 11 cases with positive past history, 7 cases (63.6%) were PCR positive for genital TB, while out of 43 cases with negative past history 31(72.1%) were PCR negative for genital TB.

Table 2: Distribution of associated signs and symptoms (n=54)

Symptoms	No. (%)
Chronic pelvic pain	16 (29.6)
Irregular period	15 (27.7)
Vaginal discharge	14 (25.9)
Scanty menses	12 (22.2)
Pelvic mass	6 (11.1)
Dysmenorrhea	2 (3.7)
Amenorrhea	00

Table - 2 shows that on history and examination chronic pelvic pain was found in 16 patients (29.6%), irregular menses in 15 patients (27.7%), vaginal discharge in 14 cases(25.9%), scanty menses in 12 patients(22.2%), pelvic mass in 6 patients(11.1%), and dysmenorrhoea in 2patients(3.7%).Not even a single case of amenorrhoea (primary or secondary) was found in our study.

Out of 16 cases of chronic pelvic pain, 10 cases (62.5%) had positive PCR, 6 cases (37.5%) had positive laparoscopy and only 1 case (6.2%) has positive hysteroscopy for FG TB. Thus PCR may be the most sensitive method to diagnose FG TB in clinically suspected women especially those who have h/o chronic pelvic pain. In 14 cases of vaginal discharge with infertility, 10 (71.5%) cases were negative for FG TB. In 6 cases of pelvic mass, 5(83.3%) cases were positive by both PCR as well as laparoscopy. In 12 cases of scanty menses, laparoscopy was positive in 9(75%), PCR was positive in 4(33.3%), hysteroscopy was positive in 1(8.3%) and HPE was positive in 1(8.3%) case. In 15 cases of irregular menses, 6 cases (40%) of positive PCR, 5 cases (33.3%) of positive laparoscopy and only 1 case of positive hysteroscopy & HPE were found. In 2 cases of dysmenorrhoea, PCR was positive in both cases and laparoscopy was positive in 1 case.

Table 3: Comparison of the diagnosis yield of genital tuberculosis by different methods (N=54)

Test	Female Genital Tuberculosis	
	Positive (%)	Negative (%)
PCR	19 (35.2)	35 (64.8)
HPE	2 (3.7)	52 (96.3)
Laparoscopy	22 (40.7)	32 (59.3)
Hysteroscopy	3 (5.6)	51 (94.4)
Dye test	20 (37.0)	34 (63.0)

Table - 3 shows that among the 54 patients suspected of suffering from FG TB, 21 were confirmed to have the evidence of M. tuberculosis infection by either HPE 2 (3.7%) or PCR 19 (35.2%). 22 cases (40.7%) were positive in laparoscopic findings which included tubercles on peritoneum, ovary, TO masses, caseous nodules, encysted ascites, pelvic adhesions, hydrosalpinx, pyosalpinx, beaded tubes etc. Only 2 cases (3.7%) showed typical classic features on HPE like caseous necrosis, Giant cells, epithelial cell clusters and lymphocyte infiltration. On hysteroscopy only 3 cases (5.6%) were positive for FG TB in which 1 case had pale endometrium, 1 case had intrauterine adhesion and 1 case had granular lesion at cornual region.

On laparoscopy during dye test done by methylene blue, 20 cases (37%) out of 54 were considered posi-

tive for FG TB who had either unilateral block, bilateral block or delayed spillage.

Table 4: Correlation of ATT and pregnancy rate on follow-up

ATT	Conceived	Not conceived	Total
Given	6(31.6)	13(68.4)	19
Not given	3(8.6)	32(91.4)	35

In this study out of 19 cases of positive PCR, 13 cases (68.4%) were found positive on laparoscopy, 6 cases (31.5%) found positive on dye test, and hysteroscopy & HPE were positive in only 1case(5.3%).Here statistically significant association was found between laparoscopy and PCR technique to detect FG TB. (p=.002) . There were also statistical association found between laparoscopy& dye test (p=0.001), it means if the tubes were not damaged grossly on laparoscopy, in majority of cases normal bilateral free spillage was present.

Out of 54 cases, 19 cases who were PCR positive were given ATT for 6months according to DOTS. Table - 4 shows that out of 19 treated cases, 6 cases (31.6%) conceived on follow up spontaneously or with other assisted techniques like ovulation induction or intrauterine insemination, while 13 didn't conceive even after 1 year of follow up. But out of 35 cases that were not given treatment, 3 cases (8.6%) conceived spontaneously. Of these 6 cases who conceived after ATT, 4 cases became pregnant within 6 months of starting treatment and 2 cases conceived after 6 months.

DISCUSSION

In present study maximum patients 46(85.2%) were in age group of 20 to 30 years. Statistically significant association had been found between age and infertility specially primary infertility .Mean age in our study was 26.3 years which was comparable to studies of Roya rozati et al¹⁵& N Gupta et al¹⁶.In our study ,11 cases(20.3%) had positive H/o extra genital TB and 13 cases(24%) had family H/o TB. In contrast to present study, U N Jindal et al¹² found positive past history in 73.5% cases & positive family history in 10.1% of infertile patients. Chronic pelvic pain in 16 patients (29.6%) and irregular menses in 15 patients (27.7%) were the most common symptoms in patients apart from infertility. In our study we found that most of these symptomatic patients were found positive on PCR & laparoscopy for FG TB.

As far as diagnostic test were concerned, out of 54 subjects suspected of suffering from FG TB, 19 cases(35.2%) were positive on PCR, 22 cases(40.7%) were positive on laparoscopy, 2 cases(3.7%) were positive on HPE and 3 cases(5.6%) were positive on

hysteroscopy. Our results depicted that PCR is the best method of diagnosing FGTB and a combination of PCR and laparoscopy is totally dependable for the diagnosis. In clinically suspected symptomatic cases, PCR could be the technique of choice for its higher sensitivity and specificity. Hysteroscopy and HPE were found non specific. There was also statistical association found between laparoscopy & dye test ($p=0.001$), it means that if the tubes were not damaged grossly on laparoscopy, in majority of cases normal bilateral free spillage was present.

In present study 19 cases were given ATT out of which 6 cases (31.6%) conceived, 4 of which got pregnant within 6 months of starting ATT. Most of these conceived patients had positive PCR test and maximum number of these cases were having negative (normal) dye test (i.e. 3 out of 4). So when tubes were found grossly damaged on laparoscopy &/or dye test, conception rate was very poor but the patient of FGTB found in early stages by PCR, and where the laparoscopy and dye test were normal, conception rate was very good. Sin SY et al studied that if patients are adequately treated before tubes are irreversibly damaged, chance of successful pregnancy is reasonably good with 20% pregnancy rate reported.¹⁷

CONCLUSION

Infertility is one of the commonest symptoms of FGTB and more cases of genital TB would be diagnosed if this disease is considered in evaluation of every patient of infertility in areas where TB is endemic. PCR represents a rapid and sensitive method for detection of mycobacterium DNA in early FGTB cases. The patients of FGTB found in early stages by PCR and where laparoscopy and dye tests are normal, ATT can improve the conception rates.

REFERENCES-

1. Aka N. Vural TZE. Evaluation of patients of active pulmonary tuberculosis for genital involvement. *J Obstet Gynecol Res* 1997; 23:337-40.

2. Varma TR. Genital tuberculosis and subsequent fertility. *Int. J. Gynecol Obstet* 1991; 35: 1-11.
3. Krishna, U. R., Sheth, S. S. & Motashaw, N. D. Place of laparoscopy in pelvic inflammatory disease. *J Obstet gynecol India* 1979; 29: 505-510.
4. Parikh, F. R., Naik, N., Nadkarni, S. G., Soonawala, S. B., Kamat, S. A. & Parikh, R. M. Genital tuberculosis- a major pelvic factor causing infertility in Indian women. *Fertil Steril* 1997; 67: 497-500.
5. Roy A., Mukherjee, S., Bhattacharya S., Adhya S. & Chakraborty P. Tuberculous endometritis in hills of Darjeeling: clinicopathological and bacteriological study. *Indian J Patho Microbiol* 1993; 36: 361-369.
6. Crofton J, Horne N, Miller F. *Clinical Tuberculosis*, 1st edition. London: Macmillan Education Ltd.; 1992; p 502-10.
7. Simon HB, Weinstein AJ, Pasternak MS et al. Genitourinary tuberculosis: Clinical features in a general hospital population. *Am J Med* 1997; 63: 410-20.
8. Novak and Woodruff. *Novak's gynecological and obstetrical pathology*, 6th edition. p 1988.
9. Arora R, Rathore A. Female genital tract tuberculosis. In: Arora VK, Arora R. (eds) *Practical Approach to Tuberculosis Management*, 1st edition. Delhi: Jaypee, 2006; p 113-119.
10. Bazaz Malik G, et al. Tuberculous endometritis: a clinicopathological study of 1000 cases. *Br J Obstet Gynecol* 1983; 90:84.
11. Bhanu NV, Singh UB, Chakraborty M et al. Improved diagnostic value of PCR in diagnosis of female genital tuberculosis leading to infertility. *J Med Microbiol* 2005; 54: 927-931.
12. Jindal UN. An algorithmic approach to female genital tuberculosis causing infertility. *Int J Tuber Lung dis* 2006; 10: 1045-1050.
13. Arora R, Rajaram P, Oumachigui A, Arora VK. Prospective analysis of short course chemotherapy in female genital tuberculosis. *Int J Obstet Gynecol* 1992; 38: 311-314.
14. Dawn C.S. Dwan C. S. *Textbook of Gynecology and Contraception*, 9th ed. Calcutta: Arati Dawn; 1998 p 320.
15. Roya Rozati, Sreenivasgari Roopa, Cheruvu Naga Rajeshwari; *J Obstet Gynecol India* 2006; 56:423-426.
16. Gupta N, Sharma JB, Mittal s, Singh S, Mishra R, Kukreja M. Genital tuberculosis in infertility patients. *Int J Gynecol Obstet* 2007; 97: 135-138.
17. Sin SY. Female Genital Tuberculosis; An Update. *Hong Kong Practitioner* 1995; 17(1): 18-25.