



GENITAL TUBERCULOSIS AS A CAUSE OF FEMALE INFERTILITY: A DIAGNOSTIC CHALLENGE

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ABSTRACT

Background: Infertility is an important health issue which has definite physiological, psychological and social implications. 40 to 50% cases of infertility are attributed to the female factors. Although genital tuberculosis is among the main causes of female infertility, it poses a great diagnostic challenge in women of reproductive age. A high degree of suspicion aided by intensive investigations is important in the diagnosis of the disease, especially in its early stage, so that treatment may improve the prospects of cure before the tubes are damaged beyond recovery.

Objective: To find out the prevalence of genital tuberculosis in females presenting with infertility in a tertiary care hospital over a given period of time, and diagnostic comparison of endometrial tuberculosis by Histopathological examination (HPE) and GeneXpert.

Methods: The prospective observational study was conducted over one year duration. A total of 176 endometrial samples were collected from the women, satisfying the inclusion and exclusion criteria.

Results: GeneXpert test was positive in 1 patient (0.56%) in our study. On histopathological examination of endometrium, 10 cases (5.7%) were found positive for tubercular endometritis. Hysteroscopy of patients with past history of tuberculosis revealed chronic inflammatory changes (intrauterine synechia, periostial fibrosis, and calcification) in 39.5 % cases.

Conclusions: Endometrial histopathological examination shows not only the tuberculous endometritis, but also gives additional information about local factors of endometrium concerning non-specific and specific infections and anovulatory cycles. GeneXpert if positive on endometrial biopsy is a reliable test for FGTB and treatment can be started on its basis.

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INTRODUCTION

According to WHO, infertility is defined as “failure to conceive despite over 12 months of regular and unprotected intercourse”. Tuberculosis, a chronic infectious disease, is one of the major etiological factors of female infertility. Global TB Report 2016 estimated 10.4 million new tuberculosis (TB) cases worldwide (3.5 million in women), with 2 million deaths.¹ Although infertility is a global issue, the magnitude of infertility is reported differently worldwide. The infertility rate ranges from 5–30% as reported for different countries.² India has one of the highest incidences of TB in the world. It is therefore, suggested that every patient consulting for infertility in developing countries should be investigated for female genital tract tuberculosis (FGTB).

Unlike pulmonary tuberculosis, the clinical diagnosis of genital tuberculosis is difficult because in majority of cases, the disease is either asymptomatic or has varied clinical presentation. Routine laboratory investigations like microscopy and culture are of little value in the diagnosis. PCR (Polymerase chain reaction) has highest sensitivity as compared to other methods for diagnosis of tuberculosis but due to false positive results, specificity is low.³ Only histo-

pathological evidence in premenstrual endometrial tissue biopsy can provide diagnosis with certainty. GeneXpert MTB/RIF (Mycobacterium Tuberculosis/Resistance to Rifampicine) has potentially led to revolution in diagnosis of active tuberculosis disease and MDR-TB (multidrug resistance tuberculosis). WHO recommended use of GeneXpert assay by ‘December 2010’.⁴ It is an important breakthrough in fight against tuberculosis.

The present study evaluates the prevalence of FGTB among infertile patients. It aims at evaluating the histological patterns of endometrium in infertile women in an attempt to establish the cause of infertility. It has also been designed to evaluate the efficacy of GeneXpert test for diagnosing endometrial tuberculosis.

MATERIAL AND METHODS

The study was a prospective observational study, conducted over a period of one year from January 2019 to December 2019. All infertile women attending the out-patient Department of Obstetrics & Gynaecology at Santosh Medical College Hospital were included. Since it was a time bound study, all the samples received during the study period and

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satisfying the inclusion and exclusion criteria were considered. On the basis of the clinical presentation, 184 women of infertility were included.

Inclusion Criteria

1. Primary infertility
2. Secondary infertility

Exclusion Criteria

1. Endometriosis
2. Fibroid
3. Cervical polyp
4. Sexually transmitted diseases

METHODOLOGY

After getting approval from the ethical committee and after taking informed consent from the patients, all females were subjected to a detailed history and thorough clinical examination, including gynecological examination. Their husbands were also evaluated to rule out male factor of infertility. The couples were then subjected to baseline investigations pertaining to infertility, to rule out any organic cause in uterus.

All females were then called for endometrial aspiration or biopsy one week before start of menstrual cycle or within 12 hours of onset of menses. Patients were advised abstinence in menstrual cycle before the month of procedure. Two samples were taken by Karmann’s cannula number 4 or endometrial biopsy curette.

In patients with past history of tuberculosis, hysteroscopy was done to evaluate the sequel of tuberculosis on endometrium, if any, and endometrial samples were taken in same sitting.

One sample was sent for Histopathological Examination in formalin and second sample in normal saline for GeneXpert test. The results of the two were analysed and compared.

Outcome measures

Primary outcome measure

1. To find out the prevalence of genital tuberculosis in all females presenting with infertility in a tertiary care hospital over a given period of time.
2. Diagnostic comparison of endometrial tuberculosis by Histopathological examination (HPE) and GeneXpert test.

Secondary outcome measure

To find out the sequel of tuberculosis on endometrium in patients with past history of tuberculosis.

Statistical Analysis

In the statistical analysis, percentages (frequencies) of various parameters were calculated and subjected to statistical test using chi-square test. The computation was done using Microsoft Excel 2007.

RESULTS

One hundred and eighty four (184) patients with primary or secondary infertility were recruited for the study, out of which 8 patients were lost to follow up. Hence total sample size was 176 patients.

Table 1 describes the baseline characteristic of the study participants.

Table 1 Socio-demographic Factors Of the Patients

Characteristic	n=176	%	
Age (years)	21-25	57	32.4
	26-30	91	51.7
	≥30	28	15.9
Religion	Hindu	136	77.3
	Muslim	35	19.9
	Others	5	2.8
Family history of tuberculosis	Yes	26	14.8
	No	150	85.2
Past history of tuberculosis	Yes	38	21.6
	No	138	78.4

Mean age of the patients was 26.4 +/- 1.2 years, with range from 20 to 40 years. Maximum patients were from age group 26-30 years (51.7%). (Table1)

Table 2 Distribution According To Type of Infertility

Type of infertility	n=176	%
Primary	80	45.5
Secondary	96	54.5

Out of 176 women, 45.5% were primary infertility patients and 54.5% were secondary infertility patients. (Table 2)

Table 3 Results of GeneXpert and Histopathology

Investigation	n=176	%	
Genexpert Test	Positive	1	0.56
	Negative	175	99.4
Histopathology of Endometrium	Secretory phase	98	55.6
	Proliferative phase	70	40
Chronic inflammatory changes in endometrium on Histopathology	Atrophic endometrium	8	4.4
	Non-specific Endometritis	166	94.3
	Tubercular Endometritis	10	5.7

GeneXpert test was positive in 1 patient (0.56%) in our study. On histopathological examination of endometrium, proliferative endometrium (anovulatory) was found in 70 cases (40%). 10 cases (5.7%) were found positive for tubercular endometritis, and 166 cases (94.3%) for non-specific endometritis. (Table 3) (Chart 1)

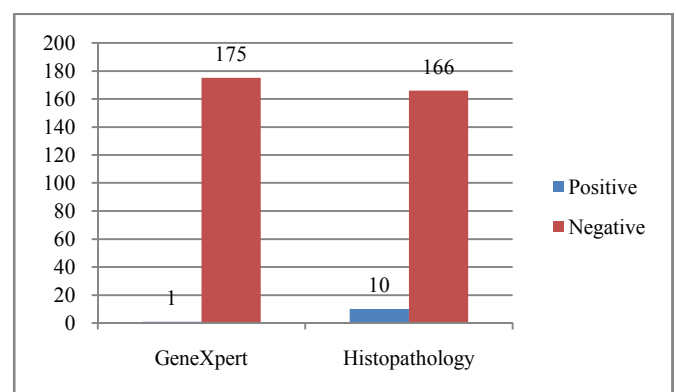


Chart 1 Comparison of endometrial tuberculosis by Histopathology and GeneXpert test

Table 4 Hysteroscopic findings in patients with Past H/o Tuberculosis (n=38)

Hysteroscopic Findings	Past History of Tuberculosis		Genexpert Positive		TB Positive On Hpe	
	n	%	N	%	n	%
Intrauterine Synechiea	3	7.9	1	2.6	3	7.9
Periosteal Fibrosis	4	10.5	0	0	4	10.5
Normal Looking Cavity	23	60.5	0	0	1	2.6
Calcification	8	21.1	0	0	2	5.2

In patients with past history of tuberculosis (n=38), hysteroscopy was done to evaluate the sequel of tuberculosis on endometrium, if any, and endometrial samples were taken in the same sitting. (Table 4). 60.5% patients (n=23) had normal looking endometrial cavity, although 1 patient from this was found positive for tuberculosis on histopathology.

A significant finding was the presence of Intrauterine Synechia in 3 patients (7.9%), and all 3 of them were later found to be positive for tuberculosis on histopathology, and one out of these was also positive on GeneXpert test. Periosteal Fibrosis and Calcification were found in 10.5% (n=4) and 21.1% (n=8) patients respectively on hysteroscopy. (Chart 2)

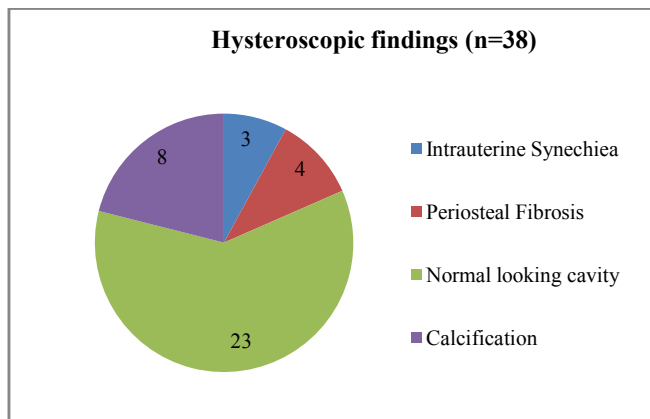


Chart 2 Hysteroscopic Findings (patients with past history of tuberculosis)

DISCUSSION

Due to the lack of specific test and diagnostic modalities, it is difficult to diagnose and conclude the presence of genital tuberculosis. On the basis of clinical presentation alone, a woman cannot be diagnosed with FG TB. Multiple imaging techniques are not specific for tuberculosis confirmation. Endometrial biopsy should be taken in premenstrual phase for good results on AFB smear, culture, GeneXpert, PCR and other tests.⁵ Early diagnosis and treatment will improve fertility outcome.

Very few studies have been done on GeneXpert as a diagnostic modality for endometrial tuberculosis and hence not much data could be made available to compare our results. GeneXpert scored positive in 0.56% cases and negative in 99.4% cases in present study, whereas one study showed 1.6% positive results.⁵ The sensitivity of Xpert MTB/RIF in detecting TB is quite high (88%).⁴ GeneXpert if positive on endometrial biopsy is a reliable test for FG TB and treatment can be started on its basis.⁶ The negative predictive value (NPV) is greater than 98% both in settings with a low prevalence of TB and in those with a high prevalence of TB; that is, a negative result accurately excludes TB in most situations. When XPERT MTB/RIF does not detect *M.tuberculosis*, the disease can be ruled out in most cases unless there is still a strong suspicion of TB.⁴

Histo-pathological evidence of tuberculous granulomas in tissue samples leads to definitive diagnosis of genital tuberculosis. The technique is easy, quick and cheap and provides characteristic features of MTB. The reported incidence from various studies ranges from 0% to 4.92%. Prasad *et al*⁷ and Kafeel S⁸ showed 0.6% and 0.8% positive cases respectively. In the study by Srinivas Rao,⁹ 1.5% cases were positive for FG TB, and 2.6% in study by Goel G.¹⁰

Murmu *et al*¹¹ reported 2.5% positive cases on HPE. In the present study, we diagnosed 5.68% of GTB cases on endometrial HPE. Our results were comparable with other studies. A study by Shende P¹² documented 10% women of GTB having positive histopathological reports. The detection rate by HPE was also low in study by Thangappah,¹³ as only 4% samples were positive for tuberculosis. The low prevalence of *M. tuberculosis* in endometrial biopsy may be due to various reasons. Due to secondary nature of the genital tuberculosis, the infecting organisms are sparse in number, and the sampled site may not represent the infected area; or in 50% of cases, the infection may be limited to the fallopian tube.¹⁴ Moreover, due to the cyclical shedding of the endometrium, granulomas do not have enough time to form; so, the endometrium may not show evidence of tuberculosis in all the cycles.¹⁵ The incidence may also be lower because of improved health care facilities over the years.

In our study, we tried to correlate the hysteroscopic changes to the presence of Mycobacterium in the endometrial tissue in cases of infertility where there was a past history of tuberculosis. The major physical changes to the endometrium takes a long time to appear because of the repeated shedding, and hence subtle as well as gross hysteroscopic changes may suggest any low-grade inflammation.¹⁶ Therefore, changes like periosteal fibrosis and fundal fibrosis, intrauterine synechia, and calcification were all taken into consideration for assessing the possible involvement of the endometrium in present study. 39.5 % patients had one or other of these changes in our study, indicating that past exposure to primary tuberculosis causes chronic inflammatory changes in endometrium, contributing to major cause of infertility.

The limitation of our study was that hysteroscopy was done in a small group of patients only due to financial reasons, because of which not every patient was ready for the test.

CONCLUSION

Tuberculous endometritis as a cause of infertility is still a major problem in the developing countries; any woman having infertility with no definite cause found should be investigated for tuberculosis. Therefore, in countries where tuberculosis is endemic, early and aggressive strategies should be pursued to diagnose and treat it. A multi-pronged approach to diagnosis increases the chances of successfully diagnosing this destructive disease.

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