

Prevalence of female genital tuberculosis in infertile patient – a prospective study

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Abstract

Aim: Female genital tuberculosis (FGTB) is a major cause of infertility in low and middle-income countries despite the availability of highly effective treatment. Asymptomatic latent cases are more common in genital TB hence difficult to measure true incidence and prevalence. Data on the Indian population is scanty due to its subtle presentation. So, this research was planned to evaluate the epidemiology of genital tuberculosis in the Indian population.

Material & Method: A prospective cross-sectional study was organized in a medical college-associated hospital in Northern India. Female patients with infertility between 18 to 45 years of age were included in the study. A detailed clinical assessment and routine investigations were done in each case. In suspected cases, pelvic ultrasound, endometrial culture, polymerase chain reaction, and laparo-hysteroscopy were conducted.

Results: In this study, 100 infertile women were enrolled. Genital tuberculosis was diagnosed in 18 Women (18%). The most common abnormal laparoscopy findings were adhesions followed by hydrosalpinx, tubal mass, and tubo-ovarian mass.

Conclusion: Genital tuberculosis is an important etiology of infertility in India. Genital tuberculosis is diagnosed by a detailed history, clinical examination, and multiple investigations, including pelvic ultrasound, endometrial culture, polymerase chain reaction, and histopathology.

Clinical significance: Infertility due to genital tuberculosis is an important public health problem in India. Early diagnosis by multiple modalities and complete treatment is required. The conception rate after complete treatment is still low but newer assisted reproductive techniques like IVF-ET can be useful in-patient with fallopian tube blockage with healthy endometrium.

Keywords: Genital tuberculosis, Infertility, Laparohysteroscopy

Introduction

Infertility is a common problem in day-to-day practice and has significant negative social issues. Worldwide >180 million people have infertility. Infertility is more prevalent in low-resource countries due to multiple demographic factors. (1) Prevalence of infertility varies from 8 to 12 % in different countries. (2) Infertility due to tubo-peritoneal damage from infectious diseases is more common in developing countries. Anovulation is more common in developed countries. Secondary infertility is commonly due to infection of the reproductive tract (RTIs). (3)

Infertility due to Female Genital tuberculosis (FGTB) is a major public health problem in low and middle-income countries. At the national level, the tuberculosis control program is helping in the early diagnosis and treatment of tuberculosis; still, it is a leading cause of infertility in females. (4) The prevalence of FGTB in infertility centers across the country shows a marked difference, ranging between 15 and 25%. In most cases, FGTB affects the reproductive age group of women aged between 18 and 38 years. Genital tuberculosis most commonly involves fallopian tubes (90-100%), endometrium (40-50%), ovaries (10-30%), and cervix (5%). (5,6)

Asymptomatic latent cases are more common in genital TB hence difficult to measure true incidence and prevalence. Data regarding the prevalence of female genital tuberculosis in the Indian population is scanty due to its subtle presentation. So, we planned this research to study the epidemiology of genital tuberculosis in the Indian population.

Material & Methods

A prospective cross-sectional study was conducted from July 2014 to January 2018 in the Department of Obstetrics and Gynecology, a tertiary care center in Northern India. Infertile female patients between 18 to 45 years of age who visited infertility clinics were eligible for the study. Before enrollment, consent was taken from the patients. Women with male infertility were excluded.

After enrollment, baseline demographic characteristics and detailed history were recorded in the case reporting form. Menstrual history, prior obstetrics history, marital life, history of tuberculosis, and previous infertility treatments were recorded.

A detailed clinical examination was done in each case. Vitals Blood pressure, pulse rate, and temperature were noted. Routine investigations were sent, i.e., Hemogram, renal and liver function tests, erythrocyte sedimentation rate, and total and differential leucocyte count. An induration of 10mm or more was considered positive in the Mantoux test. Those with a positive Mantoux test or ESR (>20 mm/1st hr) underwent further evaluation. Two sputum samples were sent for the detection of mycobacterium tuberculosis by ZN staining. One specimen positive out of the two was considered smear-positive TB. In suspected cases, endometrial TB cultures were taken. Pelvic ultrasound, PCR, and laparohysteroscopy were also performed. was done to rule out uterine and adnexal pathology like fluid in the pouch of Douglas, tubo-ovarian mass, etc.

At laparohysteroscopy, the uterus, fallopian tubes, ovaries, uterosacral ligaments, and peritoneum findings were evaluated. Biopsy was taken in suspected areas for microbiological and histopathological diagnosis. The presence of miliary tubercles on the uterus and tubes, free fluid in the pouch of Douglas, hydrosalpinx, and presence of adhesions, were considered features suggestive of genital TB.

On histopathology examination, caseous necrosis, tubercle bacilli, epithelial cell clusters, and lymphocytic infiltration were considered for genital tuberculosis. Genital TB case was diagnosed cumulatively with the help of detailed clinical history, screening tests for tuberculosis, ultrasound,

AFP culture, and laparohysteroscopy. A patient diagnosed with genital TB was started on anti-TB treatment (ATT). Enrolled patients were followed up for 2 yr. After data collection, appropriate statistical analyses were done using SPSS Software.

Primary infertility was defined, as women who have never achieved pregnancy after 1 year of unprotected intercourse. (7) Secondary infertility was described as the inability to conceive after at least one prior conception. Genital TB was divided into two categories, confirmed and probable TB. Culture positive was considered as Confirmed TB and probable TB was defined based on other investigations findings.

Ethical considerations

The Ethics Committee (EC) of the Institute approved our study. Consent was taken from each patient before enrolment.

Result

In our study, 100 infertile women were enrolled. Genital tuberculosis was confirmed in 18 Women (18%). Most of the women (82%) were from low socio-economic status. Most of them were educated below middle school (80%) and were unemployed. In our study, infertile women were from 19-37 years. Most commonly (35%) were aged between 31 to 35 years (median age, 32 years). Of the 100 patients, 74 (74%) had primary infertility, while 26 (26%) had secondary infertility. In most cases, infertility duration was more than 3 years. Menstruation abnormality was present in only 20 % but it was more common (50 %) in a patient with genital tuberculosis. Hypomenorrhea was the commonest presentation (27.7 %). 26 women (26%) were underweight. Of the 18 women with genital TB, 9 (50 %) were underweight. (Table 1). Eight patients were previously treated with anti-tubercular drugs. Out of 8 patients with a previous history of TB, five (62%) were diagnosed with genital TB during our study.

Thirty-two women underwent diagnostic laparohysteroscopy to evaluate infertility as per clinical presentation and unit policy. Biopsies were taken from different areas for histological assessment. AFB was found in two cases. Positive PCR results were in 10 cases. Granuloma suggestive of tuberculosis was present in 3 patients. Tubercular endometritis was found in 11 patients. Multiple abnormal findings were found. Adhesions were the most common abnormal laparoscopy findings, followed by hydrosalpinx and tubal-ovarian mass. Adhesions were present in most cases of genital tuberculosis. Tubular, periovarian, and omental adhesion were common. Fallopian tubes were abnormal in 7 cases (39 %), and tortuous and blocked tubes were present in four patients. Hydrosalpinx was found in five patients. Fimbria and cornual block were present in two patients (Table 2). Of the 18 women with genital TB, 14 have a normal endometrium. Only four patients had abnormal (pale) endometrium (Table 2).

The commonest cause of infertility was ovulatory dysfunction, followed by tubal factor and pelvic factor endometriosis. In 12 patients, we were not able to find out the reason for infertility despite multiple investigations.

Anti-tubercular therapy was started for all 18 patients. All patients with genital TB were started on treatment under DOTS Category II. The intensive phase was started with four drugs (isoniazid, rifampicin, ethambutol, and pyrazinamide). The intensive phase continued for 2 months. The maintenance phase was given (isoniazid and rifampicin) for the next four months. Figure 1 depicts women with infertility and their outcomes. All 18 patients completed an entire course of Anti

tubercular therapy. Despite that, only four patients could conceive in the next year. One patient underwent IVF conception and successfully delivered a healthy neonate.

Discussion

Female genital tuberculosis is a type of extra-pulmonary tuberculosis. The primary focus of tuberculosis is usually in the lungs, intestines, and kidneys. Most commonly, fallopian tubes (90%) are involved (8). FGTB is a common reason for infertility in TB-endemic countries. The prevalence of genital tuberculosis varies globally from one percent in infertility clinics in the USA and Scandinavian countries (9) to 15-21.1 % percent in South Africa (10). The prevalence of genital tuberculosis is 1-19 percent in different areas of India (11). In our study, we tried to detect tuberculosis prevalence in Indian infertile women. In our study, 18 % of patients were diagnosed with genital tuberculosis based on histopathology, laparoscopy, PCR, and culture. This study indicates that FGTB is an important cause of infertility in the Indian population.

Female genital tuberculosis commonly affects reproductive age groups women. In Gupta et study mean age of genital TB was 26.8 years. In the present study, it was 26 years. Genital tuberculosis has a great variety of clinical presentations, and multiple investigations are required to make the diagnosis. In the present study, most cases of female genital TB (FGTB) presented with infertility; other systemic symptoms of tuberculosis were absent in those patients. Most women with FGTB have a normal Chest x-ray, and the respiratory system was normal on examination. The American Thoracic Society described that up to 75% of women with FGTB can have abnormal CXRs (12).

BMI of patients with genital TB was low as compared to others. But none of the patients was significantly malnourished. Most of the population in this study belongs to low socio-economic groups, and malnutrition is a common reason for low BMI in the developing world. This factor can contribute to low BMI in our population.

In this study, women with genital TB had more menstruation abnormality than women with other causes of infertility. This study highlight that physicians should consider a suspicion of genital tuberculosis in patients presenting with unexplained infertility and menstrual irregularities. M tuberculosis can stay in the basal endometrium and can cause endometrial blood flow impairment that can lead to menstrual abnormalities. (13)

Early diagnosis of Genital TB is very difficult in absence of other symptoms. Tuberculosis can be underdiagnosed in cases of infertility. Multiple diagnostic modalities and a high index of suspicion are required. Laparoscopic evidence of caseous nodules, tubercles, or beaded fallopian tubes (14) indicates the possibility of FGTB. Standard tests for genital TB, such as AFB smear, culture, and histopathologic examination, are less sensitive. Thangappah et al. (15) reported that endometrial PCR had a high specificity of 100% and sensitivity of 57.1%, Endometrial biopsy examination had a low sensitivity of 10.7% and AFB culture is very specific (100 %)specificity but it had a very low sensitivity of 7.1%. Other studies found that the PCR of the endometrial sample is the most sensitive test in detecting FGTB (16,17). PCR is a fast and sensitive technique, but it has many flaws. It can also detect dead organisms (18, 19). AFB culture can still detect FGTB cases with negative results by PCR (20). Granulomatous lesion on histopathology of endometrium sample has a high specificity (almost 100%) but very low sensitivity (21). To rule out FGTB in a case of infertility, multiple diagnostic tests, including endometrial sampling, should be used together in our population.

Genital tuberculosis most commonly involves the fallopian tubes that lead to tubal factor infertility. In our study, the conception rate was low (22.2 %) despite the completion of treatment. Other authors

have also found a low conception rate ranging between 16.6-19 percent. (11) we followed up on these patients for two years only. A low conception rate as compared to other studies can be due to the short follow-up of these patients. 1 patient went under IVF treatment and successfully delivered a healthy neonate. Assisted reproductive techniques like embryo transfer (IVF-ET) have been used successfully in treating genital tuberculosis and blocked tubes (22,23). IVF pregnancy outcomes primarily depend on the condition of the endometrium. After completion of ATT, different authors have found a success rate of 16-38 % in FG TB cases. Malik had shown a pregnancy rate of 38.2 percent with help of IVF-ET (23). If the endometrium is damaged despite of medical treatment, the chances of pregnancy are quite rare in these patients (24). Surrogacy or adoption can be advised in case of damaged endometrium and ovary. Surgical intervention has a limited role in the management of female genital TB. Drainage of abscesses can be done in selected patients (25).

Strengths and limitations

In this study, a relatively small number of patients were diagnosed with genital TB. This study was from a single center so limiting the generalizability of findings across the country. Rates of FG TB vary across India depending on the local prevalence of TB and regional factors. Follow-up of these patients was for two years only, so the efficacy of ATT on conception rate cannot be commented on such a short follow-up. There is a lack of a gold standard for FG TB diagnosis, which also contributes to an inherited limitation of this study.

Conclusion

Genital tuberculosis is an important etiology of infertility in India. Genital tuberculosis is diagnosed by a detailed history, clinical examination, and multiple investigations, including pelvic ultrasound, endometrial culture, polymerase chain reaction, and histopathology. Tuberculosis can be underdiagnosed in infertile women without the utilization of multiple diagnostic modalities. With a high index of suspicion in infertile women, multiple investigative modalities followed by anti-tubercular therapy are required for optimum outcomes. More studies with a large sample size are needed to evaluate the prevalence of FG TB in different geographic areas. Efforts are required to originate more sensitive screening tests and diagnostic modalities for FG TB.

Clinical significance:

Infertility due to genital tuberculosis is an important public health problem in India. Early diagnosis by multiple modalities and complete treatment is required. The conception rate after complete treatment is still low but newer assisted reproductive techniques like IVF-ET can be useful in-patient with fallopian tube blockage with healthy endometrium.

Declarations of interest: none

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Table 1 : Characteristics of women seeking care for infertility.

Variable	Total Case N= 100	Genital tuberculosis N= 18
Age Median (IQR)	32(28-36)	31(26-34)
<20	3 (3%)	0(0)
21-25	17(17%)	2 (11.1%)
26-30	25(25%)	8(44.4%)
31-35	45(45%)	5(27.7%)
>35	10(10%)	3(16.6%)
Type of infertility		
Primary infertility	74(74%)	13(73%)
Secondary infertility	26(26%)	5(27.8%)
Duration of marriage (IQR)	5(3-8)	7(4-10)
Menstrual Abnormality		
Normal menstruation	80 (80%)	9(50%)
Hypomenorrhea	10 (10%)	5(27.7%)
Menorrhagia	5(05%)	3(16.6%)
Amenorrhoea	5(05%)	1(5.5%)
BMI		

Underweight (<18.5)	26(26%)	8(44.4%)
Normal (18.5-24.9)	68(68%)	10(55.6%)
Overweight (>24.9)	6(6%)	0(0%)
Prior treatment of infertility		
Yes	22(22%)	6(33.3%)
No	78(78%)	12(66.6%)
Past H/o TB		
Yes	8(8%)	5(27.7%)
No	92(92%)	13(72.2%)
Diagnostic hysterolaproscopy	32(32%)	18(100%)
TB PCR positive	10(10%)	10(55.5%)
AFB positive	2(2%)	2(11.1%)
Education		
>Diploma	2(2%)	0(0%)
High school	18(18%)	2(11.1%)
< Middle school	80(80%)	16
Socioeconomic status		
Upper	0(0%)	0(0%)
Upper Middle	2(2%)	0(0%)
Lower Middle	16(16%)	4(22.3%)
Upper Lower	38(38%)	5(27.8%)
Lower	44(44%)	9(50%)
Employment		
> Semi skilled worker	32(32%)	2(11.1%)
Unskilled worker	22(22%)	6(33.3%)
Unemployed/ housewife	46(46%)	10(55.6%)

Table 2: Laparohysteroscopy findings among women with confirmed and probable genital tuberculosis with infertility

	Total Genital tuberculosis n=18
Laparoscopy findings	
Adhesions	17 (94.4)
Hydrosalpinx	5(27.7)
Tubal block	4 (22.2)
Tuboovarian mass	2 (11.1)
Other tubal abnormalities	3 (16.6)
Hysteroscopy findings	
Normal Endometrium	14 (77.7)
Abnormal (Pale endometrium)	4(22.2)

Table 3: Different etiology of Female Infertility

Etiology	No. of patients- n (%)
Ovulatory dysfunction (Anovulation)	30 (30%)
Tubal factor	22 (22%)
Uterine factors	18(18%)
Congenital	2(2%)
Acquired	16(16%)
Unexplained	12(12%)

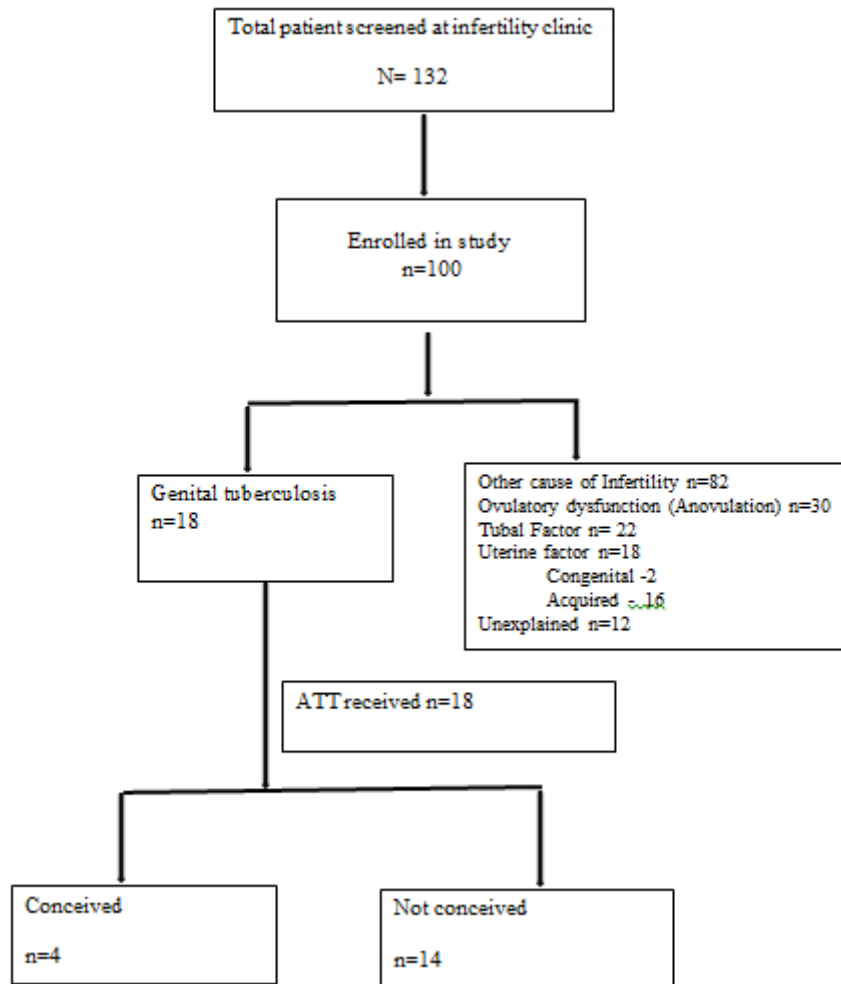


Figure 1: Flow diagram showing women with infertility and their outcomes