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Correlation between Clinical Presentation and Confirmation of Female Genital TB among Infertility Patients

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Abstract:

Background : *Female genital tuberculosis (FGTB) is a Mycobacterium infection in the female reproductive organ which may be a cause of female infertility. The prevalence of pulmonary TB in Bangladesh is high whereas prevalence of extra-pulmonary tuberculosis such as Female Genital Tuberculosis (FGTB) affecting infertility is unknown. Diagnosis of FGTB is difficult. Early detection of the disease can prevent irreversible damage to the reproductive system and can prevent fertility complication.*

Methods: *This cross-sectional observational study was done with an aim to find out the correlation of presenting symptoms with the confirmatory findings of FGTB among 60 infertility patients from July 2020 to June 2021 in Reproductive Endocrinology & Infertility Unit, Dhaka Medical College Hospital, Dhaka, Bangladesh.*

Results: *Our study cases were 60. Among them 11.67% patients was found TB-PCR positive and 1.67% was found histopathologically positive. Among the confirmed cases 62.5% had chronic pelvic pain,50% had menstrual disorder, 12.5% had pelvic mass and 12.5% was asymptomatic except infertility. In histopathology/TB-PCR positive group 4(50%) patients had cornual block in their HSG but in histopathology/TB-PCR negative group 13(25%) patient had cornual block. The difference was statistically significant (p< 0.05) between two groups.*

Conclusion: *Infertile patients who live in countries where Tuberculosis is an endemic disease like Bangladesh, a comprehensive history taking along with USG,HSG and laparoscopy findings can be used to diagnose FGTB. Confirmation can be achieved through AFB smear, TB-PCR and histopathological results.*

Key words: *Infertility, FGTB, Chronic pelvic pain, Tubal block, TB-PCR, Histopathology of endometrial curettings.*

Introduction:

World Health Organization has defined infertility as failure to conceive despite more than 12 months of regular and unprotected intercourse. Among the various causes of female infertility tubal factor infertility constituting about 30-40% cases. Tuberculosis, a chronic infectious disease caused by Mycobacterium Tuberculosis, is one of the major etiological factors of female infertility due to tubal factors. According to WHO Global TB Report 2019, Bangladesh is one of the world's 30 high TB burden countries and near about 73,000 people die annually due to tuberculosis.[1] Female genital TB is most likely secondary infection acquired by hematogenous or by lymphatic spread from an extragenital source such as pulmonary or abdominal tuberculosis. Primary genital tuberculosis

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is rare but also has been reported in women whose male partner have acute genitourinary tuberculosis by transmission through infected semen. The prevalence of female genital TB in infertile women is reported to vary from 7-15% in developing countries and 1-2% in developed countries.[2,3] Female genital TB occurs most commonly in the reproductive age group (15-45 yrs) causing infertility in 44 to 74% of the affected women.[4] The fallopian tubes are affected almost all cases (90-100%) followed by the endometrium (50-60%), ovaries (20-30%), cervix (5-15%) and vulva and vagina (1%).[5] Female genital TB causes irreversible severe damage of fallopian tubes & endometrium. It is therefore suggested that every patient consulting for infertility in developing countries should have high clinical suspicion for female genital TB. FGTB tends to create diagnostic dilemma because of its varied clinical presentation, the diverse results on the imaging, laparoscopy, histopathology and each of which has its limitation in diagnostic sensitivity & specificity. Hence diagnosis of FGTB for early institution of treatment remains a clinical challenge[6] as 10-15% of women suffering from genital tuberculosis is asymptomatic.[2] Symptomatic patients presents with menstrual disorders such as heavy menstrual bleeding, intermenstrual bleeding, amenorrhea and oligomenorrhoea, or chronic pelvic pain and/or pelvic mass. Various diagnostic aids including past or family history of tuberculosis, the laboratory tests of blood hemoglobin, raised ESR, Mantoux test, chest x-ray for the presence or absence of tuberculosis helps a lot in diagnosing genital TB among infertility patients. Ultrasound is not the gold standard for diagnosis but it may help to confirm the disease suggesting hydrosalpinx, pelvic mass, thin endometrium. Hysterosalpingography (HSG) can diagnose genital TB by finding a hydrosalpinx image resembling a tobacco pipe and a uterus resembling a honeycomb appearance. PCR of menstrual blood is another option of diagnosing genital TB where invasive procedure is contraindicated.[7]

Both diagnostic and operative laparoscopy along with endometrial curettage is done to diagnose genital TB. Laparoscopy allows better visualization of fallopian tubes, ovaries and peritoneal cavity and biopsies taken from appropriate sites can confirm the diagnosis.

Endometrial curettage is performed in premenstrual phase and sent for AFB smear, histopathological exam and PCR assay. In the recent years the molecular diagnostic methods such as PCR and Cartridge based nucleic acid amplification test CB-NAAT or GeneXpert have shown very promising results for early & rapid diagnosis of genital tuberculosis.[8]

As known, there are very limited number of studies in Bangladesh regarding the presentation and confirmation of genital TB among infertile patients. The aim of the present study is to find out the presenting symptoms and correlation with the confirmatory diagnosis of female genital TB among infertile patients attending fertility clinic in a tertiary level hospital in Bangladesh.

Materials & Methods

This cross sectional observational study was conducted in Reproductive Endocrinology & Infertility Unit of Dhaka Medical College Hospital, Dhaka from July 2020 to June 2021, on 60 women between the age of 20 to 40 years who presented with infertility along with clinical features of genital TB like amenorrhea, scanty menstruation, heavy menstrual bleeding, pelvic pain refractory to treatment, past or family history of TB, tubal factor infertility proved by HSG, presence of adnexal mass diagnosed by USG were included in the study. Patients having medical disorders like DM, thyroid disorder, hyperprolactinemia & male factor infertility were excluded from the study. This is a questionnaire based cross sectional study. Ethical clearance for the study was obtained from the Ethical Review Committee of Dhaka Medical College Hospital (DMCH). Diagnostic laparoscopy was done in 15 patients as number of surgeries were limited due to COVID-19 pandemic. Endometrial curettage was performed in every cases and sample were subjected to do 3 investigations, one in 10% formalin for histopathological examination & the two other in normal saline for AFB smear and TB-PCR. Confirmation was done by AFB smear, histopathological findings and PCR assay. Patients data, clinical & laboratory findings were noted and correlated.

Statistical analyses were carried out by using the Statistical Package for Social Sciences version 23.0 for Windows (SPSS Inc., Chicago, Illinois, USA). The mean values were calculated for continuous variables. The quantitative observations were indicated by frequencies and percentages. Chi-Square test with Yates correction was used to analyze the categorical variables, shown with cross tabulation. P values <0.05 was considered as statistically significant.

Results:

Among 60 patients majority (56.67%) belonged to age 21-30 years. The mean age was found 26.84±5.67 years with range from 18 to 39 years, 41(68.33%) patients presented with primary infertility and 19(31.67%) with secondary infertility. Almost two thirds (65.00%) of the patients came from lower socio-economic status, 19(31.67%) from middle class family and 2(3.33%) from upper class family (Table I).

It was found that 25(41.66%) patients had chronic pelvic pain, 21(35.01%) menstrual disorder, 3(5.00%) vaginal discharge, 2(3.33%) pelvic mass and 1(1.67%) had history of loss of weight (Table II). Regarding menstrual history 6(10.00%) patients was found hypomenorrhea, 5(8.33%) heavy menstrual bleeding, 5(8.33%) oligomenorrhoea, 3(5.00%) intermenstrual bleeding, 2(3.33%) amenorrhea and 39(65.01%) were having regular cycles. This study showed that 7(11.67%) patients were found TB-PCR positive and 1(1.67%) histopathologically positive but chronic pelvic pain, menstrual disorder, pelvic mass were not statistically significant (p> 0.05) between two groups (Table III & IV).

In this study 4(6.67%) patients disclosed history of pulmonary TB, 2(3.33%) abdominal/intestinal TB and 1(1.67%) bone/joint TB. Among them only one patient (14.28%) confirmed genital TB histopathologically.

Among the study population HSG report showed that 19(31.67%) patients had patent both tube, 17(28.33%) cornual block, 9(15.00%) hydrosalpinx, 8(13.33%) fimbrial block, 6(10.00%) infiltration into blood vessels and 1(1.67%) cervical stenosis. Total 8(13.33%) patients were found confirmed genital TB by TB- PCR and histopthologically. In this study showed that that 4(50.0%) patients was found cornual block in histopathology/ TB-PCR positive and 13(25.0%) in histopathology/ TB-PCR negative group. The difference was statistically significant (p<0.05) between two groups (Table V).

In this study among the 15 laparoscopic cases 2(13.33%) patients had pelvic congestion, 2(13.33%) had cornual block, 2(13.33%) showed delayed spillage, 1(6.67%) peritubal adhesions, 1(6.67%) bowel/omental adhesions, 1(6.67%) hydrosalpinx and 1(6.67%) had pelvic mass. Biopsy were taken when needed and endometrial curettage were taken from all patients and sent for set investigations but only 2(13.33%) patients were found positive for genital TB.

Table-I

Distribution of patients according to their socio economic status (n=60)

Socio economic status	No of patients	Percentage
Lower	39	65.00
Middle	19	31.67
Upper	2	3.33

Table I shows that almost two thirds (65.00%) of the patients came from lower socio economic group, 19(31.67%) from middle class family and 2(3.33%) from upper class family.

Table-II

Distribution of infertility patients according to the clinical presentation (n=60)

Clinical presentation	No of patients	Percentage
Chronic pelvic pain	25	41.66
Menstrual disorder	21	35.01
Loss of weight	1	1.67
Vaginal discharge	3	5.00
Pelvic mass	2	3.33
No symptoms	8	13.33

Table II shows that 25(41.66%) patients had chronic pelvic pain, 21(35.01%) menstrual disorder, 3(5.00%) vaginal discharge, 2(3.33%) pelvic mass and 1(1.67%) showed loss of weight .

Table-III

Distribution of clinically diagnosed Genital Tuberculosis patients presenting with infertility according to the test positivity of endometrial sample (n=60)

Endometrial biopsy	No of patients	Percentage
AFB stain		
Positive	0	0.0
Negative	60	100.0
TB- PCR		
Positive	7	11.67
Negative	53	88.33
Histopathology		
Positive	1	1.67
Negative	59	98.33

Table III shows that 7(11.67%) patients were found TB-PCR positive and 1(1.67%) were histopathologically positive. AFB stain was negative in all cases.

Table-IV

Correlation between clinical features with confirmed genital tuberculosis among infertility patients (n= 60)

Clinical features	Histopathology/ TB- PCR Positive (n=8)		Histopathology/ TB- PCR Negative(n=52)		P value
	n	%	n	%	
Chronic pelvic pain	5	62.5	20	38.46	0.271^{ns}
Menstrual disorder	4	50	17	32.69	0.065^{ns}
Loss of weight	0	0	1	1.92	0.867^{ns}
Vaginal discharge	0	0	3	5.77	0.646^{ns}
Pelvic mass	1	12.5	1	1.92	0.251^{ns}
No symptoms	1	12.5	18	34.62	0.204^{ns}

ns= not significant

P value reached from chi square test / Fisher's Excel with Yates correction

Table-V

Correlation between Hysterosalpingogram (HSG) findings with confirmed genital tuberculosis among infertility patients (n=60)

HSG findings	Histopathology/ TB- PCR Positive (n=8)		Histopathology/ TB- PCR Negative(n=52)		P value
	n	%	n	%	
Cervical stenosis	1	12.5	0	0.0	
Infiltration into blood vessels	0	0.0	6	11.5	
Fimbrial block	2	25.0	6	11.5	0.065^{ns}
Cornual block	4	50.0	13	25.0	0.030^{s}
Hydrosalpinx	0	0.0	9	17.3	
Patent both tube	1	12.5	18	34.6	

s= significant

P value reached from chi square test / Fisher's exact test with Yates correction

Table IV shows that chronic pelvic pain, menstrual disorder, loss of weight, vaginal discharge, pelvic mass and no clinical symptoms were not statistically significant relationship.

Table V shows that 4(50.0%) patients had cornual block in histopathology/ TB- PCR positive group and 13(25.0%) in histopathology/ TB- PCR negative group. The difference was statistically significant ($p<0.05$) between two groups, but those 2 patients having fimbrial block with TB positive and 6 patients having fimbrial block with TB negative, the difference was not statistically significant between two groups.

Discussion:

This study observed that majority (56.67%) patients belonged to age 21-30 years. The mean age was found 26.84±5.67 years with range from 18 to 39 years. Similar observation was found by Arpitha et al.[2], they reported the mean age was 29.89±4.23 years. In present study showed that 41(68.33%) patients presented with primary infertility and 19(31.67%) with secondary infertility. Al eryani et al [9]. observed primary infertility in 55.7% while the remaining 44.3% had secondary infertility. This study observed that almost two thirds (65.00%) of the patients came from lower socio economic status, 19(31.67%) from middle class family and 2(3.33%) from upper class family. Shahzad[10] observed almost all the patients (96.66%, n=29) belonged to lower socio-economic group but only one (3.33%) of the cases was seen in the higher socio-economic group. In this study we observed that 25(41.66%) patients had chronic pelvic pain followed by 21(35.01%) menstrual disorder, 3(5.00%) vaginal discharge, 2(3.33%) pelvic mass and 1(1.67%) loss of weight. Patel and Dhand[11] study also

observed that the most common presentation reported earlier in the study by Carter (1990) were infertility (44%), pelvic pain (25%), vaginal bleeding (18%), amenorrhoea (5%), vaginal discharge (4%) and post menopausal bleeding (2%). Less common were ascites, tubo-ovarian mass, abdominal mass, abdominal distension.

This study observed that 6(10.00%) patients had hypomenorrhea, 5(8.33%) heavy menstrual bleeding (HMB), 5(8.33%) oligomenorrhoea, 3(5.00%) was found with intermenstrual bleeding (IMB), 2(3.33%) amenorrhea and 39(65.01%) was on regular cycles. Similar findings were reported in an Indian study where normal menstrual pattern was seen in 57.6% of patients and most common menstrual abnormality was hypomenorrhea (30.1%) followed by oligomenorrhoea (3.5%).[12] Madjid et al.[13] observed infertile TB patients had significantly more intermenstrual bleeding and endometrial synechiae than fertile TB patients ($p<0.05$ and $p<0.001$, respectively).

In this study, we found that 4(6.67%) patients had history of pulmonary TB, 2(3.33%) abdominal/intestinal TB and 1(1.67%) was bone/joint TB. Shukla et al.[14] reported that 20 % of the patients with genital TB had history of TB in their family.

In this study HSG report showed that 19(31.67%) patients had patent both tubes, 17(28.33%) cornual block, 9(15.00%) hydrosalpinx, 8(13.33%) fimbrial block, 6(10.00%) infiltration into blood vessels and 1(1.67%) cervical stenosis. Arpitha et al.[2] reported 33.3% patients was found atypical spill, 28.9% cornual block, 14.5% hydrosalpinx, 13.1% fimbrial block, 10.1% infiltration into blood vessels, 5.8% filling defect, 2.9% rigid tubes and 1.4% cervical stenosis. In this study 15 patient underwent laparoscopy, among them 2(13.33%) patients was found pelvic congestion, 2(13.33%) cornual block, 2(13.33%) delayed spillage, 1(6.67%) peritubal adhesions, 1(6.67%) bowel/ omental adhesions, 1(6.67%) hydrosalpinx and 1(6.67%) pelvic mass, but only 2(13.33%) patient among the 15 patient who underwent laparoscopy had positive histopathology findings. Al-eryani et al.[9] reported laparoscopy and biopsy were performed in 33 cases and 57.5% (19/33) had positive findings. Of 19 cases positive by laparoscopy only 16 cases (84.2%) had macroscopic pathology detected whereas 3 cases were positive by laparoscopic biopsies.

In this study premenstrual endometrial curettage was done in 60 patients among them 7(11.67%) patients was found TB-PCR positive and 1(1.67%) was histopathologically positive. Naaz et al.[5] reported amongst 50 cases, GeneXpert was positive in two, AFB were detected on smear in three while one showed both AFB smear and positive GeneXpert.

This study showed that among the total 60 patients only 8 patients were found Genital TB confirmed either by histopathology or by PCR from endometrial curettage. None of them had positive AFB smear. Among the confirmed 8 cases 4(50.0%) patients had cornual block on HSG though the other 13(25.0%) cases who had cornual block on HSG, they were not found positive in histopathology or TB-PCR . The difference was statistically significant ($p<0.05$) between two groups. Farrokh et al.[15] observed hydrosalpinx was associated with complete tubal blockage in 4 cases and in 2 (10%) patients there was incomplete blockage with a mild peritoneal spillage of contrast medium.

Conclusion:

Infertile patients who live in countries where Tuberculosis is an endemic disease, like Bangladesh, a comprehensive history taking along with USG, HSG and laparoscopy findings can be used to diagnose female genital TB. Confirmation of this diagnosis can be achieved through PCR and histopathological result. There were total 60 patients in our study who had clinical features of genital TB but only 8(11.67%) patients showed confirmed genital TB on histopathology or by PCR study of endometrial curettage. Many patients had symptoms but they were not found positive on investigations. Culture of Mycobacterium was not possible due to lengthy process, if it would be done it might diagnose the case with more accurately. If FGTB can be possible to diagnose earlier by using clinical features with relevant investigations then it can prevent many subsequent infertility due to tubal & endometrial factors. In future it will help to plan a larger study to get epidemiological pattern of disease and also possible ways to prevent genital TB which will help to reduce the prevalence of infertility due to TB.

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