

Female Genital Tuberculosis and Subfertility: Nobel Approaches for Successful Reproductive Outcome with Anti Tubercular Drug Therapy in Bangladesh Perspective

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Abstract

Original Research Article

Background: Female Genital Tuberculosis is one of the important causes of infertility in Bangladesh. An early diagnosis and treatment with ATT (Anti Tubercular Therapy) is important to prevent adverse sequelae and can improve reproductive outcome. **Aims and Objectives:** The aim of the study is to evaluate the reproductive outcome of infertile patients with GTB. **Methods:** The present prospective observational study was conducted in Reproductive Endocrinology and Infertility Department of BSMMU from January 2018 to December 2021. Thirty (30) infertile women suspected of Genital Tuberculosis (GTB) who undergone hystero-laparoscopy as a part of infertility work up were included in our study. **Results:** GTB is the disease of young women with the mean age 27.5 ± 5.49 years in our study and most commonly present with primary infertility (63.33%). After completing antitubercular treatment, 90% of the study group had resumed normal menstrual cycles. A comparable proportion (16.67%) of GTB patients receiving ATT conceived, all without the aid of IVF. Among those who were conceived, 60% pregnancy remained uneventful, 20% had abortion, and 20% had ectopic pregnancy. The median length of time to conception after initiation of ATT was 4 months, stressing the role of ATT in conception in women with GTB. **Conclusions:** In low-income countries like Bangladesh where IVF is costly, Anti Tubercular Therapy may be started even on the basis of positive DNA PCR result or on the basis of laparoscopic and hysteroscopic findings. Effective anti-tubercular therapy can provide successful reproductive outcome in infertile patients with Genital TB.

Keywords: Genital tuberculosis, Infertility, Quantiferon TB Gold Plus.

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INTRODUCTION

Even more than a century after its isolation and description by Robert Koch, Tuberculosis (TB) still remains a global health problem [1]. Of its world health burden, more than 90% of the infected individuals belong to the developing countries [2]. Female genital tuberculosis (GTB) is an uncommon type of EPTB (Extra Pulmonary Tuberculosis) and almost always occurs secondary to pulmonary tuberculosis (commonest) or from other extra genital sources such as

gastrointestinal tract, kidneys, skeletal system, meninges and military tuberculosis [3].

The incidence of GTB varies and can be as low as 0.69% in Australia or as high as 19% in India [4]. The disease can spread more commonly through hematogenous route or via lymphatics or less commonly from surrounding infected organ to the affected part [5]. In GTB nearly 95-100% of the patients, the fallopian tube forms the primary focus, followed by endometrium, ovaries, cervix and vagina in 50-60%, 20-30%, 5% and 1% respectively [6]. Once the immune defence system is

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activated, *Mycobacterium tuberculosis* would enter a dormant state and be retained for a long time and can reactivate in later life [7, 8]. Genital TB produces extensive damage in the reproductive organs, disrupting the fine cillial lining of the Fallopian tube and decimating the ever-renewing endometrium through the formation of granulomas and caseous necrosis which prevents normal conception and implantation [9]. Yet another reason for poor fertility is a diminished ovarian reserve because of GTB [10].

Due to extensive damage to the female reproductive organs patients with GTB often presents with infertility (58%) [11, 12]. Other symptom includes menstrual dysfunction (especially hypomenorrhoea, oligomenorrhoea and amenorrhoea), lower abdominal pain, chronic pelvic pain, and/or a pelvic mass. However, It remains asymptomatic in 10-15% women [5]. Due to diverse clinical manifestations and the lack of specific symptoms and signs, Female GTB can be easily misdiagnosed [7, 8]. In women with advanced disease, who have extensive tubal damage and extensive adhesions in the pelvis and uterus, the reason for the poor fertility prognosis is obvious. The rate of conception is very poor, and when conception does occur, the pregnancy is more likely to be ectopic or result in a spontaneous abortion [13]. There is even a role for latent GTB in infertility because dormant mycobacteria present in the basal endometrium may impair the endometrial and subendometrial blood flow [10].

Because there is no gold standard, the diagnosis of GTB presents a dilemma to clinicians and there remains a high index of suspicion. However, an early diagnosis and treatment with ATT (Anti Tubercular Therapy) is important to prevent adverse sequelae and can improve reproductive outcome. The purpose of this original study is to inform all clinicians, particularly those in reproductive medicine, that genital tuberculosis is a diagnosis that requires a high index of suspicion, especially when the patient's history and clinical examination are not suggestive of the disease. The present clinical study was undertaken to evaluate the outcome of infertile patients with GTB.

MATERIALS AND METHODS

The present prospective observational study was conducted in Reproductive Endocrinology and Infertility Department of BSMMU from January 2018 to December 2021. Thirty infertile women suspected of Genital Tuberculosis attending Reproductive Endocrinology and Infertility Department of BSMMU. Explanation of procedure to all women participating in the study. Consent from every woman was taken. All women had detailed history, general examination, abdominal examination, local examination, Mantoux test, CBC with ESR, Chest X-ray, TVS, Quantiferon TB

Gold Plus and other routine investigations for G/A fitness were done. The diagnosis of GTB was made if the laparoscopy result was classified as definitive or probable or if any of the laboratory test (AFB smear, Culture, Histopathology, PCR or Quantiferon TB Gold Plus) was positive for GTB. Patients with GTB received ATT for 6 months. Antitubercular therapy consisted of isoniazid, rifampicin, ethambutol, and pyrazinamide given for 2 months, followed by isoniazid and rifampicin for the subsequent 4 months. They were followed up for at least 6 months after ATT.

Inclusion Criteria:

- Infertile women suspected of Genital Tuberculosis (GTB) who undergone hystero-laparoscopy as a part of infertility work up were included in our study. The diagnosis of GTB was made if the laparoscopy result was classified as definitive or probable or if any of the laboratory test (AFB smear, Culture, Histopathology, PCR or Quantiferon TB Gold Plus) was positive for GTB.

Exclusion Criteria:

- Morbid obese patients
- Patients with cardio respiratory disease and
- Patients who are not fit for laparoscopy and hysteroscopy.

RESULTS

Table-1 describes the demographic characteristics of the patient. All cases presented with GTB were from lower socioeconomic condition 19(63.33%). The mean age was 27.5 ± 5.49 years. Maximum patients were from rural area 18(60%). In our study 19(63.33%) patient presented with primary infertility and 11(36.67%) with secondary infertility. Regarding menstrual cycle, 15(50 %) had regular menstruation with average flow. Among the menstrual abnormality hypomenorrhoea 8(26.67%) was the commonest, followed by oligomenorrhoea 5(16.67%) and amenorrhoea 2(6.67%). Among 30 patients in the study, previous H/O pulmonary TB was seen in 9(30%) and 13(43.33%) had contact with TB patients. Regarding initial evaluation, ESR ranged from 30-55 mm in 1st hour in 14(46.67%), Montoux test was positive in 6(20%) cases. Chest X-ray was normal in 25(83.33%) cases, Quantiferon TB Gold Plus positive 04(13.33%) in case. All of the patients 30(100%) patients were diagnosed by laparoscopy and hysteroscopy. Regarding laboratory tests, positive PCR for MTB was found in (6)20%, positive Histopathology was found in 1(3.33%) and MTB was found in AFB stain and Culture in 1(3.33%) patients. Figure 1 demonstrates that improvement of menstrual symptom was noted in 27(90%) patients. Figure 2 shows that after initiation of Anti-TB therapy, 5(16.67%) patients conceived

spontaneously without any aid. Among 5 patients, 1(20%) patient suffered from spontaneous abortion, 1(20%) with ectopic pregnancy and rest of the pregnancies 3(60%) remained uneventful. Two (40%)

patient conceived within 2 months of starting of ATT, 2(40%) within 2 to 6 months and 1(20%) after completion of 6 months ATT.

Table 1: Demographic Profile

Parameters	No of patients (n=30)	Percentage
Age in years		
20-29	19	63.33%
30-40	11	36.67%
Residence		
Urban	12	40%
Rural	18	60%
Socio-economic Status		
Lower	19	63.33%
Middle	08	26.67%
High	03	10%

Table 2: Presenting Symptoms

Parameters	No of patients (n=30)	Percentage
Nature of infertility		
Primary infertility	19	63.33%
Secondary infertility	11	36.67%
Menstrual pattern		
Regular cycle with average flow	15	50%
Regular cycle with scanty flow	08	26.67%
Oligomenorrhoea	05	16.67%
Secondary amenorrhoea	02	06.67%
Heavy bleeding	00	0.0%
Other Symptoms		
Undue fatigue	12	40%
Vaginal discharge	09	30%
Lower abdominal pain	08	26.67%
Weight loss	01	03%

Table 3: Initial evaluation

Name of the investigations	No of patients (n=30)	Percentage
ESR (30-55 mm in 1 st hour)	14	46.67%
Mantoux Test (positive)	06	20%
Chest X-Ray (Abnormal)	05	16.67%
Quantiferon TB Gold Plus	04	13.33%

Table 4: Rate of Diagnosis by Diagnostic Modality

Diagnostic Modality	No of patients (n=30)	Percentage
By Laboratory test		
Endometrial Aspirate		
PCR for MTB	06	20%
Histopathologic examination	01	3.33%
AFB stain and Culture	01	3.33%
By Laparoscopy & Hysteroscopy		
Definitive GTB	13	43.33%
Probable GTB	17	56.67%

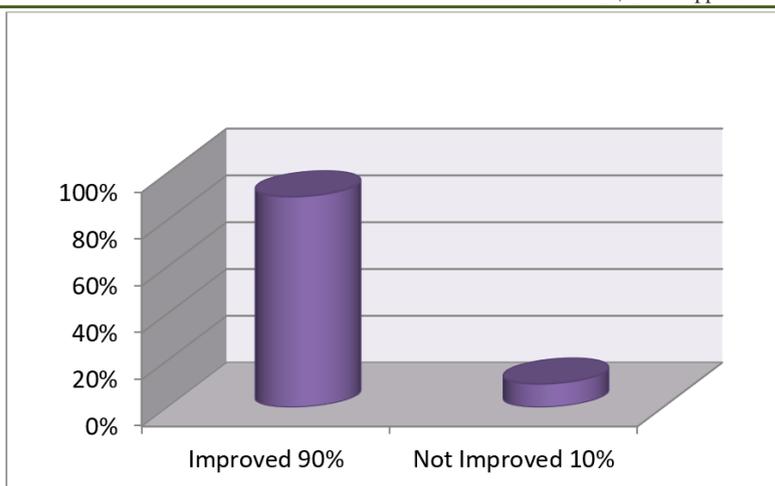


Fig. 1: Improvement of menstrual symptom

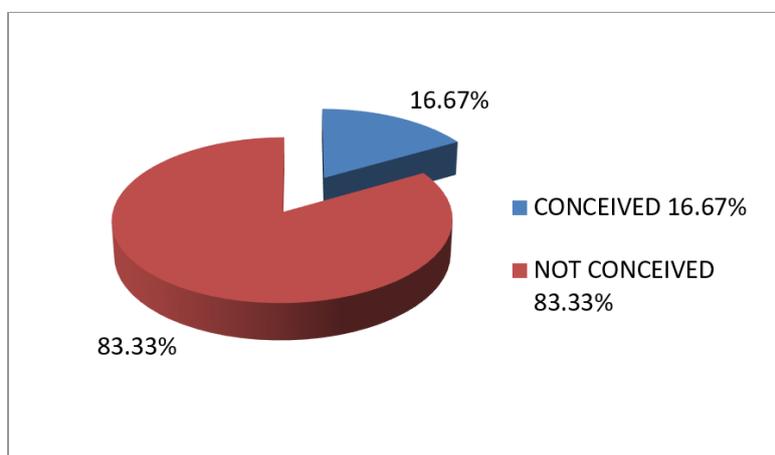


Fig. 2: Fertility outcome

Table 5: Duration between conception and Anti-Tubercular Therapy (ATT)

Duration between conception and ATT	No of patients (n=05)	Percentage
< 2 months of starting ATT	02	40%
Within 2-6 months of ATT	02	40%
>6 months of starting ATT	01	20%

DISCUSSION

Female Genital Tuberculosis is difficult to diagnose in infertile women because of absence of symptoms other than infertility, or varied clinical presentation, the limited sensitivity and specificity of findings of the imaging, laparoscopy, and histopathology, bacteriological and serological tests [5]. Hence early diagnosis of genital tuberculosis remains a clinical challenge.

Female genital tuberculosis is a disease of young age, with 80-90% of patients diagnosed between 20-40 years of age and most of the women present with infertility [5]. In our study the mean age of women with genital tuberculosis was 27.5 ± 5.49 years and 63.33% women presented with primary infertility. Early

marriage is prevalent in Bangladesh and adolescents are most vulnerable to genital tuberculosis, a factor that explains the findings.

Primary genital tuberculosis is extremely rare. A history of previous diagnosis or treatment of extra genital tuberculosis is present in 25-50% of patients [4]. In our study 30% patients had a previous history of extra genital TB and 43.3% patients had history of exposure to TB patient, thus 70% had no relevant history. The relative absence of history of extra genital tuberculosis may be due to its subclinical nature in infertile women.

The menstrual cycle may be regular and undisturbed in many cases of genital TB. Abnormal uterine bleeding in genital TB has been reported in 10%-40% of patients [14, 15]. In our study majority of the

patients had a normal menstrual cycle 50% and 50% patients presented with menstrual abnormality. Hypomenorrhoea was the most common menstrual abnormality present in 26.67% patients followed by oligomenorrhoea in 16.67% of patients and secondary amenorrhoea in 6.67%. 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 hypomenorrhoea (30.1%) followed by oligomenorrhoea (3.5%) [16].

In our study, 6(20%) cases of positive TB-PCR, 1(3.33%) case of positive Histopathology was found and MTB was found in AFB stain and Culture in 1(3.33%) patient. In few other studies, in which mycobacterial cultures were performed, positivity rates were between 10% and 15% [17-21]. PCR positive but culture and smear negative cases could be explained by the fact that even though smear and culture has remained a gold standard in diagnosis of pulmonary TB, the very low sensitivity for diagnosis of paucibacillary disease limits its practical utility in extra-pulmonary TB [22-25].

Laparoscopy and hysteroscopy is now increasingly being used for the early detection of GTB in infertile women because it offers the dual advantage of pelvic organ visualization and sample collection from inaccessible sites. In our study laparoscopy and hysteroscopy findings suggestive of definitive GTB was found in 13(43.33%) cases and probable GTB was about 17(56.67%) demonstrated. Several reports have described findings suggestive of GTB [17, 26, 27].

With the advent of effective chemotherapy and the wider use of IVF, the outcome of infertile women suffering from GTB has improved significantly [28-32]. After completing antitubercular treatment, 90% patients of this study had resumed normal menstrual cycle.

The rate of conception in women with GTB is very poor, and when conception does occur, the pregnancy is more likely to be ectopic or result in a spontaneous abortion. Overall, the conception rate among women with GTB varies from 10% to 20% throughout the world [32-34]. In non-IVF settings, Tripathy reported a pregnancy rate of 19.6% (with 7.2% live births, 5.1% ectopic pregnancies, and 7.2% abortions) in a prospective study of 97 women with GTB on receiving Anti Tubercular Therapy (ATT) [23]. In the present study, a comparable proportion (16.67%) of GTB patients receiving ATT conceived (with 60% pregnancy remained uneventful, 20% abortion and 20% ectopic pregnancy) all without the aid of IVF. The median length of time to conception after initiation of ATT was 4 months, stressing the role of ATT in conception in women with GTB. In a study done in India 22.9% patient conceived after 6 months of Anti Tubercular Therapy [35]. This is because India is a highly TB prevalent

country (19%) than Bangladesh and this higher pregnancy rate could be explained by the detection of early disease.

CONCLUSION

Genital tuberculosis poses as a diagnostic dilemma. In low-income countries like Bangladesh where IVF is costly, Anti Tubercular Therapy may be started even on the basis of positive DNA PCR result or on the basis of laparoscopic and hysteroscopic findings. As early diagnosis and timely intervention can prevent the permanent and irreversible sequelae of genital tuberculosis and effective anti-tubercular therapy can provide successful reproductive outcome in infertile patients with Genital TB.

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CONFLICT OF INTEREST

The authors have no conflicts of interest.

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