

Epidemiology of Genital Tuberculosis in Infertile Population

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Abstract

Objective: To assess the frequency of genital tuberculosis in infertile women, its clinical presentation and association with socio-economic status and geographical latitude and to compare various modes of diagnosis and efficacy of therapy.

Methods: This cross-sectional study was carried out in the Gynaecology and Obstetric Department (Unit III), Federal Government Services Hospital, Islamabad for a period of two years, from January 1, 2001 to December 31, 2003. A protocol for fertility work-up included complete history, examination, monitoring of ovulation and assessment of male factor. During laparoscopy peritoneal fluid was obtained for cytology and Ziehl-Neelsen(ZN) staining in suspicious cases of chronic inflammation was carried out. Endometrial curettings were obtained for histopathology and culture in Lowenstein-Jensen(LJ) medium. After confirmation of diagnosis, anti-tuberculosis therapy (ATT) was started. Surgical management was done in advanced stage disease with tubo-ovarian masses.

Results: Out of 7628 patients who attended the gynae out-patient department, 534 (7%) women were infertile, of which 2.43% had genital tuberculosis. Six patients had early stage disease (46.15%) and were completely cured, but three patients had successful pregnancy outcome (23%). Seven had advanced stage disease (53.85%) and required conservative surgery in addition to ATT. Among these patients, although tuberculosis was cured, yet fertility could not be achieved. All patients belonged to low socio-economic class, and 85% belonged to Northern areas of the country, who were poor and deprived of health facilities.

Conclusion: It is essential for a gynaecologist working in developing countries to anticipate possibility of genital tuberculosis in infertile patients (JPMA 56:306;2006).

Introduction

Tuberculosis (TB), once thought to be a disease of poor countries, and nearly completely eradicated in the Western world, has resurged worldwide and become a global issue. It is the second leading cause of death from infectious diseases¹ (4% of all deaths) and 88 million new cases of TB have occurred throughout the world during the last decade (1990-1999).² Latent TB infection is present in two billion people, and 7-8 million new cases are added each year.¹ The resurrection of TB in developed countries is mainly due to rising incidence of Human Immunodeficiency Virus (HIV) infection and devastating interaction between HIV infection and TB.^{3,4}

In the developing world, instead of HIV infection, more important promoting factors are poor case finding and poor compliance of the patients regarding dosage and duration of therapy resulting in emergence of 'multi-drug resistant TB'.⁵⁻⁷ In Pakistan 0.3 million new cases are added annually.²

Genital tuberculosis (GT) is a well recognized entity in the aetiology of infertility in developing countries like Pakistan, where tuberculosis is a prevalent disease. The

frequency of GT in a number of studies done in Pakistan has been 2-10%. Two studies are reported in the Rawalpindi region⁸; in Military Hospital, Rawalpindi and Rawalpindi General Hospital, the frequency was 10%. Another study carried out in Combined Military Hospital, Lahore, has revealed frequency of GT as 2%⁹, while another study done at Aga Khan University Hospital, Karachi has shown frequency of infertility 42.5% in patients presenting with genital tuberculosis.¹⁰ The situation is nearly same in the neighbouring country, India, where over all frequency of GT is reported as 3% in infertile women and 41% in tubal factor infertility.¹¹

Therefore, the present study was designed to assess the frequency of genital tuberculosis in infertile women, its clinical presentation and association with socio-economic status and geographical latitude, compare various modes of diagnosis and efficacy of therapy.

Patients and Methods

This cross-sectional study was carried out in Unit-III of Gynaecology and Obstetric department at the Federal Government Services Hospital, Islamabad, Pakistan for a two year period, spanning from January 1, 2001 to

December 31, 2003.

There are 3 units in the department. A separate fertility clinic in the gynaecology out patient department (GOPD) is run by a medical officer. Women with a history of fertility deprivation presenting in the GOPD are referred to fertility clinic where they are investigated and managed under supervision of concerned consultant incharge of each unit.

All patients attending the fertility clinic were included in the study irrespective of age, duration and type of fertility problem. The initial assessment for fertility deprivation was carried out according to the fertility clinic protocol. Each patient had a complete history including age, duration of fertility deprivation, years of living together, sexual history including male factor, history of contraception, any gynaecological history other than infertility, past medical/surgical history and previous treatment for fertility problem. General physical as well as systemic examination was performed alongwith pelvic examination. Assessment of ovulation was done by maintaining basal body temperature charting, cervical mucus studies, ultrasonic tracking of ovum and hormonal assay. Male factor was judged by semen analysis and postcoital test.

There was a set criteria for performing invasive investigations including diagnostic laparoscopy, hysteroscopy and hysterosalpingogaphy (HSG). Diagnostic laparoscopy was performed when there was inability to conceive for 2 years and certain factors contributing to infertility (male factor, sexual dysfunction and ovulation failure), were excluded. In a regular menstrual cycle, laparoscopy was performed in premenstrual phase. During laparoscopy, health of the pelvic organs was assessed and tubal patency was checked by methylene blue dye test. In suspicious cases of chronic inflammation, peritoneal fluid was obtained from the Pouch of Douglas (POD) for cytology, ZN staining to look for acid fast bacilli was also carried out. Endometrial curettings were taken, preserved in 10% buffered Formaline for histopathology and in Normal Saline for mycobacterium TB culture in LJ medium. Hysteroscopy was performed at the same session if there was suspicion of some local endometrial pathology such as polyp, submucous fibroid or a history of irregular bleeding. If the fallopian tubes were found blocked on laparoscopy, HSG was done to look for the site of tubal blockage and intra-uterine pathology.

Chest X-ray was done in suspicious cases to look for primary focus or a history suggestive of chest disease. After confirmation of diagnosis, the anti-tuberculosis therapy (ATT) was administered as follows:

For first three months Ethambutol 25mg/kg body

weight, Isoniazid 5mg/kg body weight, Rifampicin 10mg/kg body weight, Pyrazinamide 35mg/kg body weight. For next six months Ethambutol, Isoniazid and Rifampicin were given.

In advanced cases of genital tuberculosis, conservative surgery was done along with ATT. All the data collected were analysed as percentages and mean. The software package used for data computation and analysis was SPSS version 10.0.

Results

During the three year period, 7628 patients attended the GOPD for different gynaecological problems, 534 women (7%) presented for inability to conceive. Out of these 534 infertile women, a standard protocol of investigations revealed a number of causes for fertility deprivation. On the basis of differential diagnosis, 260 patients were subjected to diagnostic laparoscopy and HSG was performed in 84 women. Tubal blockage was confirmed in 77 patients.

There was histo-pathologically confirmed diagnosis of GT in 13 patients. The mean age of the patients was 28.153 years, standard deviation (SD) was 4.578 and Standard error (SE) was 1.319. There was no positive culture obtained in LJ medium. Peritoneal fluid cytology showed evidence of chronic inflammation (lymphocytosis), however, no ZN staining was positive for acid fast bacilli. Overall frequency of genital tuberculosis in infertile population in this study was 2.43%.

The ages of the patients were between 22 and 38 years, mean 28.15 ± 4.57 years. The maximum number of women (46.15%) fell in the age group of 26-30 years.

Geographical distribution of the GT patients was 5 from Skardu, 3 each from Gilgit and Azad Kashmir and 1 each from Islamabad and Murree. This revealed that the incidence of genital tuberculosis is high in far flung areas of the country where poverty, illiteracy, lack of health education and poor transport facilities are the main hurdles. As far as socio-economic background was concerned, all patients belonged to low socio-economic group.

Six patients had early stage disease, endometrial tuberculosis. They were given ATT as per regimen. Seven women had advanced stage disease with tubo-ovarian masses and presented with menstrual irregularities, pelvic pain and weight loss. These patients underwent laparotomy and conservative surgery. Histopathology confirmed tuberculosis lesion and they were put on ATT as per regimen. Only two patients gave a past history of pulmonary tuberculosis. Male partners of these patients gave no history of tuberculosis and showed poor compliance for further investiga-

Efficacy of treatment was good to cure the disease and no recurrence had been reported. However, infertility was resolved only in three cases (23%) with early stage disease.

Discussion

In communities where tuberculosis is still a major health problem, it is important to anticipate the possibility of genital tuberculosis in all patients presenting with infertility. In developed countries⁹, tuberculosis infection of the uterus and tubes is demonstrable in less than 1% of all cases of infertility. Different studies done in Pakistan have listed the frequency of GT between 2% to 10%.^{7,8} A study done in India¹¹ has revealed frequency of GT among infertile women as 3%, while in the same study, the frequency of GT in tubal factor infertility was 41%. Some studies have depicted the frequency of infertility in women with confirmed diagnosis of GT. A study done at Aga Khan University Hospital, Karachi has shown frequency of infertility in GT 42.5% and another study done in India has revealed the frequency of genital tuberculosis in infertility as 13%.^{9,11}

The possible explanation of comparatively lower frequency of GT in the present study is that the Federal Government Services Hospital covers capital city where literacy is nearly 100%, health education is satisfactory and nutritional status is better as compared to other regions of the country. However, this hospital is a tertiary level referral centre for Northern areas, from where mostly complicated cases come for management.

Genital tuberculosis is nearly always secondary and the patient may be unaware of primary focus that is mostly extragenital, and commonly, pulmonary lesion.¹² Moreover, it may recur despite early recognition and effective treatment of primary lesion. In fact, the spread of infection takes place at a very early stage of the disease, usually in adolescence or early maturity. By the time genital tract lesion is found, the primary lesion is often healed and becomes inconspicuous. Thus, it is imperative to trace past history of primary tuberculosis infection. It has been reported¹² that 50% of affected women may give a past history of extragenital tuberculosis and a further number may recall, if questioned closely, contact with the disease in childhood.

The involvement of the fallopian tubes, endometrium and ovaries due to genital tuberculosis is consistent with other studies.^{9,12}

As far as investigations for genital tuberculosis are concerned, histological diagnosis is confirmatory with a classical picture of granuloma, central caseation, Langhans' giant cells and lymphocytes.^{8,9,13} In this study, histological

confirmation was achieved in all affected cases.

ZN staining of acid fast bacilli requires a large number of bacteria, at least more than $10^5/\text{ml}$, to be present in the specimen.⁶ Thus in practical terms, it is a presumptive test with low sensitivity. In this study none of the patients had positive ZN staining.

Bacterial culture has 100% specificity but a major problem is that, in addition to high cost, weeks and months are required for precise identification of the species. Lowenstein-Jensen (LJ) medium is used for this purpose, however, mycobacterium tuberculosis is very difficult to grow. In this study no positive culture was obtained.

There have been major advances in the field of biotechnology and molecular biology with introduction of several new diagnostic techniques for TB and improvement in existing ones. The new automated culture techniques have appreciably reduced the time for detection and antimicrobial testing.⁶ The molecular amplification technique like PCR^{6,14} have made the same day diagnosis a reality. Introduction of novel new techniques like bacteriophage assays⁶ are showing a lot of promise. However, most of these techniques are too expensive and sophisticated to be of any practical benefit to the vast majority of TB patients living in developing countries like Pakistan for whom an early and inexpensive diagnosis remains as elusive as ever.

All patients in this study belonged to low socio-economic class. Geographical distribution also proves that tuberculosis is prevalent in those areas of the country where poverty and illiteracy dominate. Tuberculosis has always been associated with poverty, though devastating interaction between HIV and TB infection has made it a global issue.

In this study, six patients with early stage disease were asymptomatic while seven patients with advanced disease had menstrual irregularities, pelvic pain and weight loss. This proves that usually these patients are asymptomatic and a high index of suspicion is mandatory to diagnose the condition.

Tuberculosis had been described a disease of youth. However, in recent years because of interaction between HIV and TB^{3,4}, it can affect any age group.

It must be borne in mind that after treatment, if a patient conceives, there is increased chance of an ectopic pregnancy as a consequence of chronic salpingitis and tubal damage. Microsurgical reconstructive surgery of damaged and tortuous fallopian tubes in genital tuberculosis have been carried out but resulting in very poor prognosis. It has been recommended that in vitro fertilization (IVF) probably offers a better chance of pregnancy.¹⁵

In this study, six patients with early stage disease

were cured and three of them had successful pregnancies later on. There is a risk of for the newborn to contract TB if the mother has asymptomatic GT.^{16,17}

Timely therapy at an early stage of genital tuberculosis cures the disease completely resulting in successful pregnancy. Therefore, a high index of suspicion for genital tuberculosis is essential while investigating infertile patients in communities where tuberculosis is a prevalent disease.

Microsurgical reconstructive tubal surgery in genital tuberculosis does not give encouraging results. IVF and embryo transfer is a better option in such cases.

References

1. John Hopkins Centre for Tuberculosis Research; Global Tuberculosis Control , WHO Report 2002.
 2. Khan MH. Tuberculosis: need to revitalize its control programme in Pakistan (editorial). *J Coll Physicians Surg Pak* 1996;6:3.
 3. Narain JP, Raviglione MC, Kochi A. HIV associated tuberculosis in developing countries: epidemiology strategies for prevention. *Tubercle and Drug Dis* 1992;73:311-21.
 4. Corbett EL, Watt CJ, Walker N, Maher D, Williams BG, Raviglione MC, et al. The growing burden of tuberculosis: global trends and interactions with the HIV epidemic. *Arch Intern Med*. 2003;163:1009-21.
 5. Dolin PJ, Raviglione MC, Kochi A. Global Tuberculosis, incidence and mortality during 1990-2000. *Bull World Health Org*. 1994;72:213-20.
 6. Butt T, Ahmad RN, Kazmi SU, Raja KA, Mahmood A. An Update on the diagnosis of Tuberculosis. *J Coll Physicians Surg Pak* 2003;13:728-34.
 7. Butt T, Ahmad RN, Kazmi SY, Rafi N. Multi-Drug Resistant Tuberculosis in Northern Pakistan. *J Pak Med Assoc* 2004;54:469-72.
 8. Yousaf A, Zaman G, Sultana N. Frequency of Endometrial tuberculosis in Infertility. *J Coll Physicians Surg Pak* 2002;12:55-7.
 9. Luqman M, Mirza MD, Razzaq I. A histopathological study of Endometrial Curettage in cases of Infertility in Females. *Pak Armed Forces Med J* 1997;47:12-4.
 10. Qureshi RN, Samad S, Hamid R, Lakha SF. Female genital tuberculosis revisited. *J Pak Med Assoc* 2001;51:16-8.
 11. Tripathy SN, Tripathy SN. Infertility and pregnancy outcome in female genital tuberculosis. *Int J Gynecol Obstet* 2002;76:159-63.
 12. Maclean AB. Pelvic Infection. Dewhurst s' Textbook of Obstetrics and Gynaecology, Fifth edition, Great Britain, C.R. Whitfield 1995; 574.
 13. Khan N. Frequency of endometrial tuberculosis: a histopathological study of endometrial specimens. *J Postgrad Med Inst* 2005;19:97-100.
 14. Moatter T, Mirza S, Siddiqui M, Soomro I. Detection of Mycobacterium tuberculosis in paraffin embedded intestinal tissue specimens by polymerase chain reaction: characterization of IS6110 element negative strains. *J Pak Med Assoc* 1998;48:174-8.
 15. Soussis I, Trew G, Matalliotakis I, Margara R, Winston RM. In vitro fertilization treatment in genital tuberculosis. *J Assist Reprod Genet* 1998;15:378-80.
 16. Stahelin-Masssik J, Carrel T, Duppenhaler A, Zellinger G, Gnehm HE. Congenital tuberculosis in a premature infant. 'A case report'. *Swiss Medical Weekly* 2002;132:598-602.
 17. Kini PG. Congenital tuberculosis associated with maternal asymptomatic endometrial tuberculosis. *Ann Trop Paediatr* 2002;22:179-81.
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