



Research Article

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Genital Tuberculosis: Is A Key Player for Ectopic Pregnancy in India: A Cross-Sectional Observational Study.

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Abstract

Background: Tuberculosis remains a major health problem in developing countries and genital tuberculosis is responsible for affecting a considerable number of women who presented in different manners as chronic pelvic pain, pelvic inflammatory infection, infertility and ectopic pregnancy. The average world-wide incidence of female genital tuberculosis in infertile population has been reported as 5-10%, with the range varying between <1% in USA and about 10% in India.

Objective: Present study is an attempt to find out the prevalence and relationship of Genital tuberculosis (GTB) and ectopic pregnancy and compare the different new diagnostic modalities.

Design: It was a cross sectional case control study.

Setting and population: The study was conducted in department of Obstetrics and Gynecology in association with Department of Microbiology, VMMC & Safdarjung Hospital, and New Delhi including:

Case: Women (n=95) presenting with ectopic pregnancy.

Control group: Women (n=95) subjected to tubal ligation.

Methods: After thorough history and examination, tubal sample is collected from case and control group.

Main outcome measures: Prevalence of ectopic pregnancy with genital tuberculosis

Results: The prevalence of the genital tuberculosis in general population was 1.1% and with ectopic pregnancy was 16.8%, that was quite significant so genital tuberculosis should be kept in mind and punctiliously anticipated in cases of ectopic pregnancy to prevent the counterattacks of genital tuberculosis.

Conclusion: It is inferred that the prevalence of ectopic pregnancy is higher among the women who had genital tuberculosis and

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Key Words: Genital Tuberculosis, Ectopic Pregnancy, Infertility, Maternal Morbidity

Introduction

Tuberculosis remains a major health problem in developing countries which can present as genital tuberculosis and responsible for affecting a considerable number of women who presented in different manners as chronic pelvic pain, pelvic inflammatory disease, infertility and ectopic pregnancy. The average world-wide incidence of female genital tuberculosis [FGTB] in infertile population has been reported as 15-20%, [1] with the range varying between <1% in USA and about 10% in India. [2] Genital tuberculosis is an elusive diagnosis and a high index of suspicion is the first step in the diagnostic process. A careful history with specific mention of previous exposure to or active tuberculosis is of importance. The actual incidence of FGTB cannot be calculated accurately due to accidental determination of the disease and asymptomatic course. [3]

During the past two decades an increase in the incidence of the ectopic pregnancy[EP] has been noted in many regions. The changes observed in the ratio of ectopic to intrauterine gestations cannot be explained solely by population changes. Various risk factors lead to the ectopic pregnancy, among them tuberculosis is one of the important risk factor which remains a major global health problem. FGTB is one form of extra pulmonary TB and is not uncommon, particularly in communities where pulmonary TB is prevalent, but it is rare in Western societies. Genital TB affects about 12% of patients with pulmonary tuberculosis [4]and represents 15–20% of extra pulmonary tuberculosis. [1] Genital TB may be asymptomatic and diagnosis requires a high index of suspicion. Incidence of EP is 2% out of the total pregnancies worldwide and most of them are not receiving supervision in early gestation and leads to the major cause of maternal mortality. [5]

The exact incidence of ectopic pregnancy is difficult to determine. It varies significantly in different countries, depending on the divisor used in its calculations and the facilities available for diagnosis. There are several risk factors for ectopic pregnancies. Risk factors include, pelvic inflammatory disease, infertility, use of an intra uterine device (IUD), previous exposure to DES, tubal surgery, intrauterine surgery (e.g. Dilatation & Curettage), smoking, previous ectopic pregnancy, and tubal ligation. A major proportion of salpingitis is the result of pelvic inflammatory disease. Chlamydia trachomatis, mycobacterium tuberculosis, and in some regions, Neisseria gonorrhoea are the most frequently implicating causative agents. The most common anatomical sites of GTB infection is mainly fallopian tube about 63.84%[6]. If infection is not recognized early, permanent fulminating destruction could result making women unable to do their reproductive functions properly and leads to ectopic pregnancy, menstruation irregularities and infertility. Combined with the fact that GTB is always hard to diagnose as it is a silent invader of the genital tract, we assume that a large proportion of women with ectopic pregnancy not attributed to specific disorder, GTB could be the underlying cause. The aim of this study was to identify the rate of GTB among women with ectopic pregnancy using different modalities and early for diagnosis.

Materials and Method

This study was a cross sectional observational study conducted in the department of Obstetrics and gynecology in conjunction with Department of Microbiology, VMMC & Safdarjung Hospital, New Delhi.

Sample Size: A total 190 women were recruited in the study and were allocated into two groups:

Study Group: 95 women presenting with ectopic pregnancy.

Control Group: 95 healthy women opted for tubal ligation.

Inclusion Criteria: Confirmed cases of ectopic pregnancy

Exclusion Criteria: Patients on conservative management of ectopic pregnancy

An informed written consent was obtained from all the participants. The complete work up was done in all cases which included a complete history, physical examination and investigations. A detailed obstetric and menstrual history along with the relevant past history, history of any co morbidity, history of any medical or surgical treatment and family history was taken.

Sample Collection

Sample of fallopian tube was taken under aseptic condition from both case and control and stored in sterile container and sent to the laboratory without exposure to the sunlight at room temperature. In emergency hours samples was stored in the refrigerator up to 24 hours for microbiological testing. Peritoneal fluid/blood was stored in normal saline while fallopian tube pieces were sent for microbiological examination (fixed in normal saline) and histopathological examination (fixed in 10% formalin).

Specific tests were done to detect Mycobacterium tuberculosis i.e.: Ziehl Nielsen Staining Amplified mycobacterium tuberculosis direct test Real Time Polymerase Chain Reaction (RT-PCR) TB culture by BACT ALERT 3D automated method Confirmation of the isolate with the ACCUPROBE

Data Analysis: Sample size is calculated by taking the prevalence (P)of ectopic pregnancy with tuberculosis in India is 1-2%, level of significance is 5%, power(1- β) =90%, and effect size is 0.5 allowing 10% loss to follow up using the software G power 3.1. Data will be analyzed by applying standard statistical test. p value of less than 0.05 will be taken as significant. Any other statistical test applicable will also used.

Statistical testing was conducted with the statistical package for the social science system version SPSS 17.0. Continuous variables are presented as mean \pm SD, and categorical variables are presented as absolute numbers and percentage.

The comparison of normally distributed continuous variables between the groups was performed using Student's t test. Nominal categorical data between the groups were compared using Chi-squared test or Fisher's exact test as appropriate. $P < 0.05$ was considered statistically significant.

Results

Epidemiological data: The mean age of the women in study group presenting with ectopic pregnancy was 30 ± 0.92 and in control group was 31 ± 0.3 and hence both groups were comparable in regards of age. According to Kuppuswamy scale for urban population, both groups were comparable in view of socioeconomic status. The most common complaint was bleeding per vaginum at the time of presentation i.e., 64.4% and most common sign was adnexal tenderness (90.5%).

Obstetrics history: Out of the total cases (15/95) 15.6% patient had history of previous ectopic pregnancy with $OR = 7.372$; $95\%CI = 1.616-33.640$ and p value was 0.005 that was significant represented that previous ectopic pregnancy further increased the risk of ectopic pregnancy. In our study, 13(13.5%) had previous one and two (2.1%) patients had previous two ectopic pregnancy. Among these patients who had recurrent ectopic after linear salpingostomy was 3.2%, after partial or total salpingectomy was 10.5% and after medical management was 2.1% while in control group only 2.1% had history of ectopic pregnancy. Patients with prior history of spontaneous abortion were 27, out of which with one, two, and more than three abortions were 14(14.7%), 3(3.2%) and 10(10.5%) respectively and $OR = 2.500$; $95\%CI = 0.956-6.540$ for one abortion, $OR = 1.250$; $95\%CI = 0.245-6.391$ for two abortion. Patients with prior history of induced abortion were sixteen out of which 13(13.7%) had only surgical abortion, 2 (2.1%) had only medical abortion and one (1.2%) had both medical and surgical abortion in the study group. Odd ratio for the previous one induced abortion was 2.414; $95\%CI = 0.876-6.653$ and for two induced abortion was 3.342 and $95\%CI = 0.341-32.786$. [Table 1]

Past history: History of tuberculosis was found in 21.1% and 28.4% had contact with tuberculosis. [Table 2]

Menstrual history: On taking the history of menstrual cycle we found that 20 cases had history of menstrual disturbances, out of them fourteen (14.7%) had history of decrease blood flow and rest six (6.3%) had heavy menstrual bleeding (p value=0.118) and fourteen (14.7%) had complaint of dysmenorrhea. (p value=0.014)

History of infertility: Out of the total ectopic pregnancies in our study, 17 women had a history of infertility and six patients conceived spontaneously, while five (29.4%) had history of ovulation induction with clomiphene citrate, four(23.5%) had history of intrauterine insemination and one (0.6%) had history of in vitro fertilization. Among these, four(23.52%) patients were diagnosed as GTB and started on ATT.

In the present study per operative finding were: [figure 1]

Tubo-ovarian mass was observed in four (4.2%) patients. Consistency of the tube: 10.5% tubes 9 were soft while in 6.3% patients' friable tube seen.

Status of the tube: 4.4% was fibrotic and 12.3% showed hydro salpinx.

In 14.7% patients, tubercles were observed.

Adhesions were observed in 16.8% patients in study group.

Beading was seen in 3.8% patients.

Table3: Histopathological Finding of tube:

Figure 3: High Power view showing granulomatous inflammation with or without epitheloid cells, langerhans type of giant cells, and caeseous necrosis

Table 4: Microbiological finding of tubal sample:

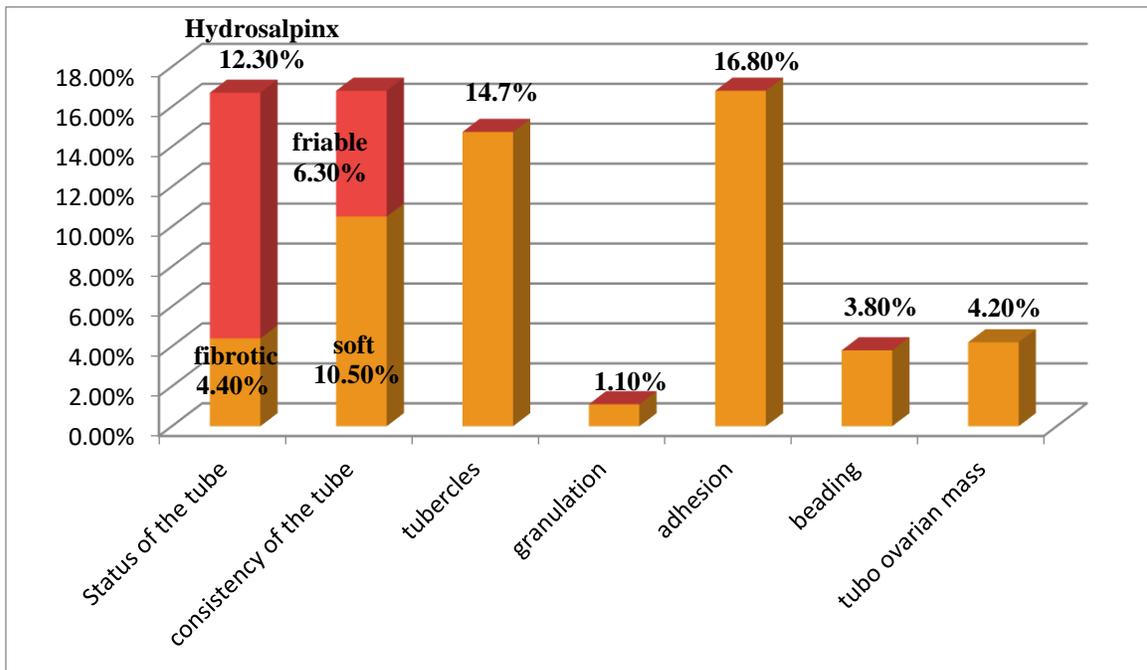


Figure 1: Per operative finding (study group n=95):

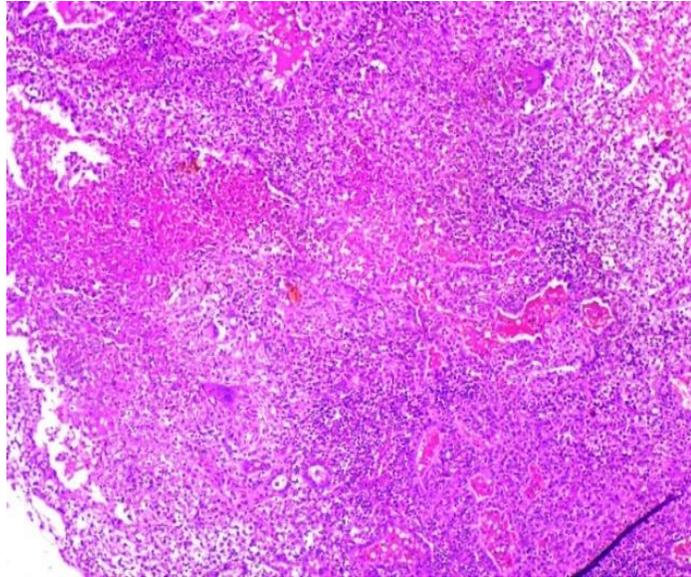


Figure 2: Low Power Showing Granulomatous Inflammation with Epithelioid Cells

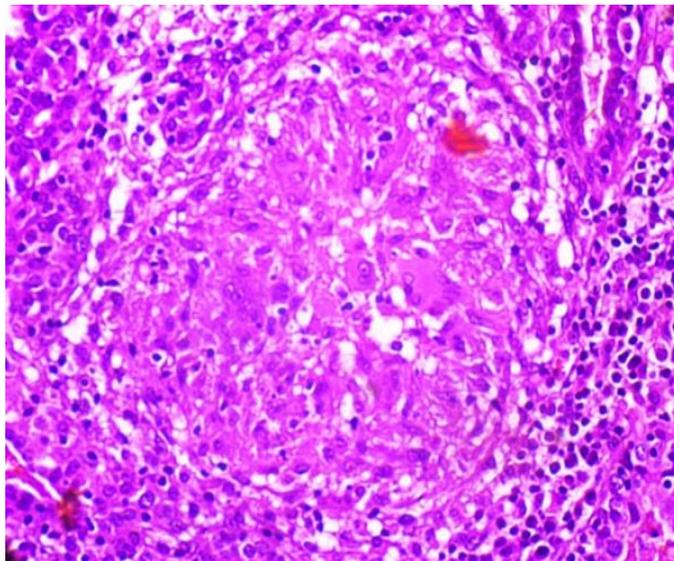


Figure 3: High Power View Showing Granulomatous Inflammation with Or Without Epithelioid Cells, Langerhans Type of Giant Cells, And Caseous Necrosis.

	Case(n=95)		Control(n=95)		OR	95% CI	P Value
	Frequency	%	Frequency	%			
Age of 1st intercourse							
<14	4	4.2%	1	1.1%	2.000	0.2009 - 19.916	0.021
15-17	22	23.2%	17	17.9%	0.647	0.253 - 1.654	
18-20	45	47.4%	64	67.4%	0.352	0.159 - 0.775	
>20	24	25.3%	12	12.6%	1.000		
Lifelong no. of sexual partner							
1	88	92.6%	93	97.9%	1.000		0.169
>1	7	7.4%	2	2.1%	3.699	0.748 - 18.289	
Prior history of PID							
None	83	87.4%	91	95.8%	1.000		0.085
yes, with probable PID	10	10.5%	4	4.2%	2.741	0.828 - 9.704	
yes, with confirmed PID	2	2.1%	0	0.0%	-	-	

Table 1: Ectopic pregnancy and sexual and infection history

Past history					
Tuberculosis/ATT	20	21.1%	2	2.1%	<0.001
Contact of tuberculosis	27	28.4%	14	14.7%	
No significant history	43	45.3%	78	82.1%	
Total	95	100%	95	100%	

Table 2: Past History

Histopathological finding:	Cases (n=95)		Control(n=95)		P Value
	Frequency	%	Frequency	%	
Inflammation & congestion	43	45.3%	8	8.4%	<0.001
Caseous granuloma	4	4.2%	0	0.0%	0.121

Table 3: Histopathological Finding

Microbiological Investigation (tubal sample)	Cases (n=95)		Control(n=95)		P Value
	Frequency	%	Frequency	%	
ZN staining	8	8.4%	2	2.1%	0.100
AMTDT	21	22.1%	3	3.2%	<0.001
RT-PCR	73	76.8%	8	8.4%	<0.001
TB CULTURE	16	16.8%	1	1.1%	<0.001
ACCUPROBE	16	16.8%	1	1.1	<0.001

Table 4: Microbiological finding of tubal sample

Discussion

Ectopic pregnancy continues to be the leading contributors to pregnancy related death in the first trimester in the developing countries so in our study we have determined the role of genital tuberculosis as cause of ectopic pregnancy due to damage to the tubes and again which causing psychological health problems to the patient. In fact the available medical literature reveals that there are few studies which studying association of ectopic pregnancy with genital tuberculosis so a proper study is thus required to further elaborate the existing knowledge and find out the association.

Genital tract TB is a chronic disease that often presents with low grade symptomatology and very few specific complaints. FG TB is an iceberg disease and need close monitoring especially in the developing countries.

It is reported that the incidence varies and can be as low as 0.69% in some developed countries and as high as 19% in India. It was reported that 50% of affected women may give a past history of tuberculosis.[3] In case of previous history of pregnancy losses, Li C et al[7] showed the comparative results that there is a significant association between prior abortion(spontaneous, medical, surgical) with adjusted odd ratio of 1.53 ,1.53 , 1.23 for spontaneous, medical and surgical abortion respectively similar to our finding. While other study conducted by Bouyer J[8] showed conflicting results to the present study that the risk of ectopic pregnancy was higher in women with previous induced abortions and the odds ratio differed according to the method used for abortion . The results were similar after adjustment: With prior surgical abortion only, the odds ratio = 1.1 (95 percent confidence interval (CI): 0.8, 1.6), whereas the odds ratio in women with prior medical abortion only (mifepristone and misoprostol) was 2.8 (95 percent CI: 1.1, 7.2).

On comparing the per operative and pathological finding, comparable results were found with Sharma et al[9] i.e.5.1% cases have caseous granuloma. We observed that the prevalence of the GTB in ectopic pregnancy was 16.8% and in control group was 1.1% considering culture as gold standard, akin to Sharma JB et al [9] and other study conducted by Banarjee A [5] showed the prevalence equals to 35.29%, high prevalence might be due to limited number of cases and BACTEC radiometric assay has high sensitivity.

In order to improve the diagnosis of GTB in ectopic pregnancy PCR a based method have proven to be the very useful for rapid diagnosis of infection in pulmonary and extra pulmonary sample and helps to decrease the maternal morbidity and mortality by early diagnosis. It is likely that the increased sensitivity of PCR in our results reflects the small number of culture positive samples, lysis of the mycobacterial cell wall and dissociation of DNA from particulate matter in the crude homogenate, allowing the recovery of supernatant after centrifugation and sufficient sample for extraction. A study conducted by Baxi A[10] analyzed with Nested TBPCR results to detect sensitivity and specificity of endoscopic evaluation was 85.71 and 22.8% and other study showed the sensitivity of PCR 75% in culture positive sample(2.6%)[11] while in our study 88.2% and 66.8% sensitivity and specificity respectively. The crux is to provide effective management and early diagnosis before damage to the reproductive organs has occurred.

Although the diagnosis of mycobacterium and susceptibility testing are still primarily based on conventional methods (staining, culture, biochemical analysis, proportional method), a series of molecular assays are increasingly introduced and incorporated in the workflow of clinical mycobacteriology laboratories worldwide.The amplified Mycobacterium tuberculosis direct (AMTD) test

(Gen-Probe, San Diego, CA, USA) can detect *M. tuberculosis* complex rRNA in approximately 3 h, detect drug resistance and identification of mycobacterial species but the method remains the costly and just begun to be used and validated for use.

The study conducted by Aggarwal VK [12] the comparison of results obtained by AMTDT and mycobacterial culture with culture as gold standard, the sensitivity of AMTDT was 62.5% (CI 25.9-89.8) and specificity was 100% (CI 82.8-100).

Verma JS et al[13] demonstrated that the sensitivity, specificity, positive predictive value(PPV) and negative predictive value (NPV) shown by accuprobe were 96.9%, 100%, 96.9%, and 88.9% while our results showed 100% sensitivity and specificity. Thus, accuprobe has showed impressive sensitivity and specificity giving results in < 3 hrs from culture-positive isolates and have sure edge over conventional biochemical methods which are, nonetheless, labour intensive and cumbersome to perform thus delaying prompt mycobacterium identification.

Conclusion

The prevalence of the genital tuberculosis in general population was 1.1% and with ectopic pregnancy was 16.8%, that was quite high so genital tuberculosis should be kept in mind and punctiliously anticipated in cases of ectopic pregnancy to prevent the counterattacks of genital tuberculosis. There is several other risk factor of ectopic pregnancy i.e. spontaneous abortion (17.9%), multiparty (49.5%), high risk behavior for PID, previous ectopic (15.9%). Ectopic pregnancy and spontaneous abortion or infertility had been found to be tightly linked, further research may concern both ectopic pregnancy epidemiology and the wider field of infertility required. Attention should be paid to women with planned pregnancies that have a history of infertility and/or abortion, to intercept convolution for EP. Secondary prevention of ectopic pregnancy is problematic because of the paucity of risk factors that can be modified to diminish the odds of recurrence. Clinicians' ability to both diagnose and counsel patients at risk for recurrent ectopic pregnancy can be optimized by awareness of the clinical features of this condition. The widespread introduction of new modalities of tests will allow TB to be diagnosed early and treatment delays will be reduced, case-fatality rates and adverse sequelae will be prevented; and patient outcomes will improve.

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