



Genital tuberculosis is common among females with tubal factor infertility: Observational study



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Abstract *Background:* Genital tuberculosis is mostly asymptomatic and infertility is a common presentation. The study objective was to identify the rate of genital tuberculosis among women with tubal factor infertility in non endemic area and to assess the outcome after administration of anti-tubercular therapy.

Methods: We conducted a prospective observational study in Al Thawra General Hospital (from March 2012 to February 2014). Of a total 151 women who had tubal factor infertility, 61 cases were investigated for genital tuberculosis. Women who were found to have the disease were treated by antitubercular therapy and the outcomes were analyzed.

Results: We found that 31.1% (47/151) of cases had genital tuberculosis contributing to infertility. Of these, 55.7% (34/61) were positive by histopathology, and 44.1% (15/34) were positive by polymerase chain reaction. Fallopian tubes were affected in almost all cases and the endometrium was involved in 82.9%. All patients were treated for tuberculosis and the conception rate after ATT was 12.8%.

Conclusion: Genital tuberculosis is still a common health problem contributing to infertility in area considered non endemic indicating underestimation of the condition and so neglected. Antitubercular therapy is not effective in restoration of women's fertility function as they often present with advanced pathology beyond recovery.

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1. Introduction

Female genital tuberculosis (GTB) is a common health problem in developing countries. ¹ It frequently causes chronic pelvic inflammatory disease, menstrual abnormalities, and infertility. ² The actual incidence of GTB cannot be assessed accurately because it is often silent and only 50% of cases

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are diagnosed without surgery.³ 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.⁴ It represents 15–20% of extra pulmonary tuberculosis.⁵ GTB is mostly secondary infection acquired by hematogenous spread from an extragenital source such as pulmonary or abdominal tuberculosis.¹ The fallopian tubes are affected in almost all cases followed by the endometrium and cervix.⁶ GTB occurs in the most economically productive age (15–54 years)⁷ causing infertility in 44–74% of the women affected.⁸

The anatomical predilection sites of GTB mainly fallopian tubes and the endometrium are the actual challenging problem. If infection is not recognized early, permanent fulminating destruction of these organs could result making women unable to do their reproductive functions namely menstruation and fertility. Given this, 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 infertility 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 tubal factor infertility in non-endemic area like ours, and to assess the outcome of women with confirmed GTB who received antitubercular therapy.

2. Methods and materials

This study was carried out at Al-Thawra hospitals during 2 years (from March 1st 2012 to Feb. 28th 2014). We included in this study all women attending the outpatient clinics within the hospitals who were diagnosed as tubal factor infertility based on hysterosalpingography and/or ultrasound findings. All patients included in this study were characterized by the absence of pregnancy in spite of regular sexual intercourse for at least one year without using any contraceptive method, had normal hormonal profile, and normal male parameters assessed by semen analysis.

Ethical approval was obtained from the ethics committee of the hospital and patient's consent was obtained from each participant. A detailed history about age, parity-if any, duration of infertility, years of living with the husband, sexual history, contraception use, menstrual cycle regularity, interval, duration of flow, associated symptoms, other medical disorders, past medical/ surgical history, and previous medication was obtained. General and gynecologic examination including pelvic examination was performed.

All patients were subjected to extensive work-up including complete blood count (CBC), white blood cells (WBC) with differential, erythrocyte sedimentation rate (ESR), HIV, tuberculin test, chest X-ray, and pelvic ultrasound. A positive Tuberculin test is defined as an induration size of more than 10 mm 48–72 h after intracutaneous injection of 0.1 ml of purified protein derivative.

Endometrial curettage (12 h prior to the expected menses) was carried out for laboratory studies. Histopathologic study was processed for all cases; acid fast bacilli (AFB) culture materials were sent for 19 cases and polymerase chain reaction (PCR) was evaluated in 33 cases. Laparoscopy was performed for 34 cases as indicated. The pelvic organs were visualized looking for tubercles of granulomatous inflammation, giant cells, epithelioid cells and central caseation with chronic inflammation. Also peritubal adhesions, cysts, hydrosalpinx

and other pathology were inspected. During procedure biopsy specimen was taken, processed and stained as usual using hematoxylin and eosin.

The diagnosis of GTB in this study was based on the presence of at least two positive tests of the following: histopathology, PCR, AFB culture, HSG, and laparoscopy.

All women diagnosed with GTB were managed by anti-tubercular therapy (ATT) for at least 6 months. Antitubercular therapy consisted of isoniazid, rifampicin, ethambutol, and pyrazinamide given for 2 months followed by isoniazid and rifampicin for the next 4 months. Patients were carefully followed up for compliance, toxicity and response to medication.

2.1. Statistical analysis

The data were collected and computed using IBM SPSS version 21. The continuous variables were presented as means \pm SD and the categorical variables presented as percentages. The Student *t* test and χ^2 were used to compare means and proportions, respectively. A *p* value of <0.05 was considered statistically significant.

3. Results

During the study period, 682 women attended the infertility clinic and 151 women of these (22.1%) had tubal factor infertility. The definitive cause of tubal factor infertility was not established in 61 women (40.3%) and genital TB was suspected based on clinical ground. The mean age of these women was 28.06 ± 2.33 years, the primary infertility was found in 55.7% while the remaining 44.3% had secondary infertility. Most of the women (62.3%) were from rural areas and approximately half of the women belonged to low socioeconomic status. Fifty-four women (88.5%) were asymptomatic and only 7 cases (11.5%) had mild chronic pelvic pain.

Past history of pulmonary TB was present in 9 cases (14.8%). All of the 61 women were investigated with hysterosalpingography during the initial part of the study. Among these, only 8 cases (13.1%) had the characteristic evidence of GTB: beading appearance 37.5% (3/8), bilateral/unilateral tubal block in 4 cases (50%), and extravasations in one case (12.5%). The uterine cavity appeared normal in these cases. Endometrial histopathologic study showed positive results in 55.7% (34/61), and 26.3% (5/19) were positive by AFB culture. PCR was performed for 34 cases, of these, 15 cases

Table 1 The results of investigations.

Test	No. of cases	+ve results	–ve results	<i>P</i> value
HPE	61	34 (55.7)	27 (44.3)	.104
PCR	34	15 (44.1)	19 (55.9)	.136
Laparoscopy	33	19 (57.6)	14 (42.4)	.1084
HSG	61	8 (5.4)	140 (94.6)	.0001
Tuberculin test	61	26 (42.6)	35 (57.3)	.052
ESR	61	21 (34.4)	40 (65.6)	.000
Culture	19	5 (26.3)	14 (73.7)	.0017
GTB	61	47 (77.0)	14 (22.9)	.0001

HPE: histopathological examination; PCR: polymerase chain reaction; HSG: hysterosalpingography; ESR: erythrocyte sedimentation rate; GTB: genital tuberculosis.

Table 2 The two tests that showed positive results among 61 patients.

Type of test	TP	TN	FN	Sensitivity (%)
HPE (no.)	34	14	13	72.3
PCR (no.)	15	14	5	75

TP: true positive; TN: true negative; FP: false negative; HPE: histopathological examination, PCR: polymerase chain reaction.

Table 3 Outcome of ATT for the 47 women with GTB.

Outcome	No (%)
Advised to do ART	13 (27.7)
Regular cycles	13 (27.7)
Menorrhagia	7 (14.9)
Conceived	6 (12.8)
Scanty period	8 (17)

ART: assisted reproductive technologies.

(44.1%) were positive and 55.9% were true negative as confirmed by both histopathology and laparoscopy. Only 5 cases were false negative confirmed by positive AFB culture making the sensitivity of PCR as 75%. Laparoscopy and biopsy were performed in 33 cases and 57.5% (19/33) had positive findings. Tables 1 and 2 show the results of all investigations. Of the total 61 cases, 47 women were diagnosed with GTB, and scheduled for ATT. The outcome of ATT is shown in Table 3.

4. Discussion

This study shows that the prevalence of GTB in women attended infertility clinics was 6.9%, similar to that reported in India (5–13%)⁹ and 4.2% in Saudi Arabia.¹⁰ The rate of GTB among women with tubal factor infertility was 31.10%. This rate is similar to the quoted average prevalence (39–41%).¹¹ However, in our settings where the prevalence of TB is low, this rate seems high and could be explained by the fact that infertile women due to TB are mostly misdiagnosed and refractory to the usual treatment for other pelvic infections. Thus, most of these women sought referral centers with high facilities for extensive investigation.

Based on histopathologic criteria of tissue specimens, we found that 31.1% of cases were negative but showed positive tubal involvement with HSG which suggests that the endometrium was not involved in these 8 cases.

In this study we found that the positive PCR results were 44.1% of cases and false negative cases were 15.1%, thus the PCR sensitivity was 75% based on histopathologic endometrial sampling and AFB culture results. These findings are in agreement with the study of Bhanu (2005) who found sensitivity of 76.9% based on both endometrial aspirate and biopsies.¹²

Although it is reported that PCR testing is associated with high rates of both false positive and false negative results it could be attributed to the fact that PCR detects even a single bacilli during subclinical disease and also to sample specimen contaminations.¹² We found in this study, PCR was the most rapid, sensitive and non invasive test.

In the present study, AFB culture on Lowenstein Jensen (LJ) medium was positive in 26.3% cases. This finding is similar to the previous study that reported a positive endometrial culture in 25% of cases¹³ but higher than recently reported by Jindal (2006) as 15.6%¹⁴ and Bose (2012) as 3.3–10.6%¹⁵.

This could be partly explained by obtaining the samples on the correct day of menstrual cycles when adequate tubercle bacilli were present in the endometrial cavity, proper processing, and rapid transportation. Although bacteriological isolation of Mycobacteria is being considered the gold standard test,¹¹ we found AFB culture the most unreliable test because it was slow and required up to 8 weeks to grow. Also, it is reported to show low sensitivity of only 30–35%.^{16,17} We think such disadvantages of AFB culture limit its practical utility and more rapidly applied technique is required.

Of 19 cases (57.6%) positive by laparoscopy only 16 cases (84.2%) had macroscopic pathology detected whereas 3 cases were positive by laparoscopic biopsies. This finding emphasizes the importance of obtaining biopsy specimens at time of laparoscopic procedure for detection of GTB from various suspicious sites because laparoscopy generally detects macroscopic changes that are not commonly present in early stage of disease.¹²

Also these findings indicate that many tests are often required to obtain a collective evidence for the diagnosis of GTB. However, laparoscopy is an invasive and expensive procedure and absolute diagnosis of GTB cannot be made.¹⁸

We found that ESR was raised in 34.4% of patients. Although it is non specific marker for TB as it may be raised in many other conditions,⁷ the value of this test remains important as it directs the suspicion toward specific disorders including TB.

Tuberculin test can be reactive either with active disease or if patient has had past infection.⁷ In the present study tuberculin test was positive in 42.6%, similar to other study.³ Although, it is likely that the test may be negative in certain circumstances such as severe infection and/or advanced immunosuppression, and has sensitivity of only 55%,³ we stress that the test should be requested in clinically suspected cases of GTB because positive result provides valuable clues to the diagnosis and further specific investigations such as PCR and/or laparoscopy are needed early.

This study shows that the conception rate after ATT course was 12.76%. It is reported that the pregnancy rate after ATT is 19.3%.⁴

The prognosis of infertility however, depends on early diagnosis and treatment. With advanced GTB with extensive tubal damage and extensive adhesion of the pelvis and uterus, the prognosis is obviously poor.⁴ The low rate of conception in the present study along with the finding that 88.5% of cases were asymptomatic reflects the likely advanced stage of the disease with possible tubal and/or endometrial damage to these women.

In the current study the tubal factor infertility rate was 22.1% and GTB was the cause in approximately a third of cases (31.1%). This figure indicates that GTB is more pronounced among infertile women even in settings where the prevalence is uncommon. Unfortunately, being secondary and non-infectious, the prevalence of this condition is underestimated and almost neglected.

Having children has significant personal, familial and social influences. In the developed countries, infertility caused by

GTB is resolved by easy access to assisted reproductive technologies (ART) without cost restraint.¹⁹ The situation is totally different in the low-income countries where ART is not always accessible owing to both much higher cost and also high failure rate.¹⁹ For these reasons, infertility diagnostic and therapeutic procedures should be simplified in the low resource settings so that the vast majority of infertile women can access such methods without an extra cost.

The limitations of this study are mentioned. We could not perform all various investigation modalities particularly PCR, laparoscopy and AFB culture for every woman due to high cost. For this reason, comparing between these tests should be interpreted with caution. Also we could not note the outcome results of those women advised for doing ART because this method is often offered at a much higher cost and longer time of follow-up was required.

5. Conclusion

GTB is a chronic disease presenting with infertility in the majority of women. There is underestimation of the GTB largely because it can exist without any clinical manifestation, has diagnostic difficulties and unfortunately the screening of GTB is not yet considered part of the infertility and menstrual dysfunction work-up in many centers. Because of the silent nature of GTB, which allows development of fulminating disease, the conception rate is very poor and therefore, early diagnosis and treatment is vital to improve outcome.

Conflict of interest

We have no conflict of interest, and the work was not supported or funded by any company or organization.

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