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Six months versus nine months anti-tuberculous therapy for female genital tuberculosis: a randomized controlled trial

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ABSTRACT

Objective: To compare six months versus nine months anti-tuberculous therapy in patients of female genital tuberculosis.
Study design: It was a randomized controlled trial in a tertiary referral center teaching institute on 175 women presenting with infertility and found to have female genital tuberculosis on clinical examination and investigations. Group I women (86 women) were given 9 months of intermitted anti-tuberculous therapy under directly observed treatment short course (DOTS) strategy while Group II (89 women) were given 6 months of anti-tuberculous therapy under DOTS. Patients were evaluated for primary end points (complete cure, partial response, no response) and secondary end points (recurrence rate, pregnancy rate) during treatment. All patients were followed up further for one year after completion of therapy to assess recurrence of disease and further pregnancies.
Results: Baseline characteristics were similar between two randomized groups. There was no difference in the complete clinical response rate (95.3% vs 97.7%, $p = 0.441$) between 9-months and 6-months groups. Four patients in 9-months group and two patients in 6-months group had recurrence of disease and required category II anti tuberculous therapy ($p = 0.441$). Pregnancy rate during treatment and up to one year follow up was also similar in the two groups (23.2% vs 21.3%, $p = 0.762$). Side effects occurred in 27(31.4%) and 29(32.6%) in 9-months and 6-months of therapy and were similar ($p = 0.866$).
Conclusions: There was no difference in complete cure rate, recurrent rate and pregnancy rate for either 6-months or 9-months of intermittent directly observed treatment short course anti-tuberculous therapy in female genital tuberculosis.
Clinical trial registration: The trial was registered in clinicaltrials.gov with registration no: **CTRI/2009/091/001088**.

Introduction

World Health Organization declared tuberculosis a global emergency in 1993 and promoted a strategy of providing anti-tuberculous therapy under direct observation 'Directly Observed Treatment Short Course' (DOTS) [1]. As per global tuberculosis report 2015, 3.2 million TB cases occur in women in a year with 480,000 deaths amongst them [2]. DOTS has also been adopted by the Government of India under the Revised National Tuberculosis Control Programme and is now routinely available for both pulmonary and extra-pulmonary tuberculosis throughout India with almost 86% cure rate [3].

Female genital tuberculosis is an important variety of extra-pulmonary TB causing significant morbidity and short and long term sequelae especially infertility in infected women [4,5]. Female genital TB is an important cause of infertility and recurrent implantation failure in developing countries [6,7]. It causes infertility due to blockage of fallopian tubes or through involvement of endometrium with Asherman's syndrome or through effect on ovarian function [8,9]. It also causes pelvic and

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perihepatic adhesions [10]. It may mimic ovarian cancer necessitating unnecessary surgery [11]. It is also an important cause of ectopic pregnancy in India [12].

Although gold standard in diagnosis is detection of acid fast bacilli on microscopy or culture on endometrial sampling (biopsy) or on demonstration of epithelioid granuloma on histopathology on endometrial or peritoneal biopsy, they are positive in few cases only due to paucibacillary nature of disease [13]. Polymerase chain reaction has high sensitivity but high false positivity and alone is not sufficient to make the diagnosis [14,15]. Imaging methods like ultrasound, computerized axial tomography, magnetic resonance imaging, positron emission tomography are more useful in tuberculous tubo-ovarian masses but cannot make definite diagnosis of female genital tuberculosis. Laparoscopy is the most reliable tool to diagnose genital tuberculosis especially tubal, ovarian and peritoneal disease and to see tubal patency [16,18]. However, dye test should be avoided in case of frank female genital tuberculosis for the fear of risk of further dissemination of disease. Hysteroscopy can also diagnose female genital tuberculosis by detecting pale cavity, tubercles and intrauterine adhesions. Treatment is medical with combination chemotherapy with surgical treatment being rarely required only as drainage of abscess [4,23]. American Thoracic Society [23] and National Institute of Clinical Excellence Guidelines recommended standard daily regimen of anti-tuberculous medicines. However, World Health Organization has recommended directly observed treatment short course (DOTS) treatment in which drugs are given intermittently thrice a week under direct supervision [1]. A 6-month anti-tuberculous drugs regimen using a combination of rifampicin, isoniazid, pyrazinamide and ethambutol for 2 months, followed by rifampicin and isoniazid for 4 months cures about 90% human immunodeficiency virus negative patients is universally accepted treatment for drug-susceptible, active tuberculosis especially pulmonary TB [1,2]. Poor compliance and irrational prescription of anti-tuberculous drugs enhances the emergence of drug resistant and multi drug resistant tuberculosis which is more difficult to treat necessitating toxic and expensive medicines for longer duration [25].

The duration of treatment and compliance are important issues in managing female genital tuberculosis. The duration of treatment of female genital tuberculosis, whether six months or longer continues to be controversial and debatable as there are no proper randomized controlled trials on treatment of female genital tuberculosis for 6 months or longer treatment [4,10]. The old studies performed in 1990 and 1992 recommended short course chemotherapy for 9 months to 1 year for female genital tuberculosis [26,27] but there is no direct comparison of 6 months versus 9 months therapy in literature. Although most guidelines recommend six-months treatment for pulmonary and extra pulmonary tuberculosis, evidences to support such recommendations are weak [1,2]. Furthermore, in spite of recommended 6-months treatment duration, many gynecologists continue to treat such patients for longer duration of 9 months or even up to 1 year [28].

Although the efficacy of therapy for pulmonary tuberculosis using DOTS strategy is well established there is lack of data on its efficacy in treatment of extra-pulmonary tuberculosis especially female genital tuberculosis [29].

We, therefore, conducted a randomized controlled trial to determine the efficacy of intermittent short-course anti-tuberculous drugs regimen for 9-months and 6-months under DOTS strategy for treatment of female genital tuberculosis with infertility. A secondary objective was to determine the pregnancy rate and differences in the recurrence rate at one year follow up after completion of primary treatment in the two groups.

Materials and methods

Study design and over sight

It was a prospective randomized controlled trial (between May 2010 and April 2014) conducted in a tertiary referral center. The study was approved by the Ethics Committee of the Institute and was conducted in accordance with the International Conference on Harmonization Good Clinical Practice Guidelines. The study was designed by the principal investigator (first author) with the involvement of academic investigators and a biostatistician in consultation with the funding agency. The first author authenticates the data accuracy and analysis and the fidelity of the study in accordance to the protocol. The randomized control trial was registered in clinical trials.gov with registered number **CTRI/2009/091/001088**.

The enrollment was done as per consort flow diagram.

Study population

Consecutive newly diagnosed patients (age between 20 years and 40 years) with female genital tuberculosis with infertility were recruited after obtaining their informed written consent. Women who took anti-tuberculous therapy during last 5-years; those with human immunodeficiency virus infection, malignancies or significant co-morbidities; those allergic to drugs and those not willing to participate and those who were pregnant or lactating at the time of enrollment were excluded. Patients who had received any investigational agents during past 6 months, were also excluded.

Clinical data collection

All patients underwent a detailed clinical and laboratory evaluation including hematological, biochemical tests, Mantoux test, chest radiograph and ultrasound of pelvis. Hysterosalpingography was not routinely performed but its findings were collected whenever it was already done from outside. Diagnostic video laparoscopy and video hysteroscopy (using glycine as distended medium) were performed whenever possible.

During laparoscopy, a careful inspection was performed of whole pelvic and abdominal cavity especially uterus, fallopian tubes, ovaries, uterovesical pouch, pouch of Douglas, intestines, peritoneum, liver and gall bladder for any tuberculous lesions like tubercles, shaggy areas, hydrosalpinx, pyosalpinx, beading of tubes, pelvic, abdominal or perihepatic adhesions, patency of tubes, tuberculosis of ovaries and all the findings were carefully recorded.

During hysteroscopy uterine cavity and both ostia were carefully inspected for color of endometrium, endometrial glands opening and for any tuberculous findings like tubercles, shaggy areas and intra-uterine adhesions. Endometrial biopsy was performed in all women in premenstrual phase and the specimens were sent both for histological and microbiological tests. For histology, biopsies were fixed in 10% buffered formaldehyde (Formaline) and for microbiological tests [culture, staining for acid fast bacilli and polymerase chain reaction were collected in sterile normal saline].

Diagnostic criteria for female genital tuberculosis

A '*definite*' diagnosis of female genital tuberculosis was made in presence of the followings: (i) acid fast bacilli on smear or culture of endometrial biopsies; (ii) presence of epithelioid granuloma on histopathological examination of endometrial biopsy; (iii) definite findings of tuberculosis on laparoscopy and hysteroscopy.

Presumptive (probable) diagnosis of female genital tuberculosis – positive polymerase chain reaction alone was not taken for diagnosis of female genital tuberculosis but these women if had positive findings on ultrasound (tubo-ovarain mass), hysterosalpingography (tuberculosis findings), laparoscopy (presumptive findings of tuberculosis) were taken as presumptive female genital tuberculosis and were treated.

Randomization

The randomization was done using computer-generated table in 1:1 ratio by a person not involved in the study.

Concealment of randomization

The randomized treatment allocation (i.e. 9- or 6-months) were printed and concealed in sealed envelopes bearing the serial number of the patients.

Intervention

Patients fulfilling inclusion and exclusion criteria were randomized into two groups: Group I and Group II received Revised National Tuberculosis Control Program of India category I treatment for 9-months and 6-months, respectively. In this regimen, the intensive phase included four drugs (rifampicin 450 mg [600 mg with weight >60 kg] isoniazid 300 mg, pyrazinamide 1500 mg and ethambutol 800 mg) three times a week for 2-months. The continuation phase included rifampicin and isoniazid for further 4-months in those randomized to 6-months and for 7-months to those randomized to receive 9-months of therapy.

Patients were registered with the DOTS center at near their residence areas and drugs were administered to them under supervision of health care provider at DOTS center. All the patients were followed up at clinics of respective centers and at the institute at regular intervals.

Follow-up and management of side effects

All the side effects were recorded. liver function tests were done at 2 months intervals. Drug-induced hepatitis was managed by substituting hepatotoxic drugs (isoniazid, rifampicin, pyrazinamide) by quinolones and streptomycin. While monitoring liver function tests closely first-line drugs were gradually reintroduced after resolution of hepatitis. The total duration of interruption due to hepatitis was compensated by prolongation of the treatment duration.

Adherence to treatment

All the women received treatment under direct supervision through the network of DOTS centers. They were asked to report to the enrolling center at 2-monthly intervals. Nodal officer and medical social workers kept track of all the patients for compliance. The drug intake was recorded in a diary and a drug intake for more than 80% of days was considered compliant. Poorly compliant patients were counseled again. Non-compliant patients were excluded from study.

Assessment at end of treatment

Randomized patients were clinically evaluated for symptoms resolution. All the women were subjected to the same investigations by which their initial diagnosis was made. Then all the women (except those who fell pregnant or lost to follow up or declined the second investigation) were subjected to ultrasound scan, relook laparoscopy, hysteroscopy and repeat endometrial biopsy (for acid fast bacilli microscopy, acid fast bacilli culture, polymerase chain reaction and histopathological examination. During repeat laparoscopy, adhesiolysis was performed for peritubal, pelvic adhesions to free tubes in selected cases (not for deep and dense adhesions with blocked tubes). Similarly hysteroscopic adhesiolysis was performed in grades I–III adhesions at repeat hysteroscopy.

Follow-up for one year for recurrence of tuberculosis

Patients were followed up three-monthly for one year after completion of the primary treatment. Those who failed to visit the clinics were contacted telephonically and interviewed for recurrence of disease and pregnancy outcome.

Outcome measures

Complete response was defined as resolution of symptoms, disappearance of acid fast bacilli on microscopy or culture, disappearance of tuberculous granuloma on histopathology and disappearance or healing of active tuberculous lesions on relook laparoscopy and hysteroscopy. A *partial response* was defined as resolution of clinical manifestations and partial disappearance of tuberculous lesions at end of therapy. *Non-response* was defined persistent clinical symptoms, persistence of acid fast bacilli on microscopy or culture, persistence of tuberculosis granuloma on histopathology or persistence of active tuberculosis lesion on relook laparoscopy or hysteroscopy at end of therapy. In patients not agreeing for end of treatment laparoscopy and hysteroscopy, endometrial biopsy or where repeat tests could not be performed due to pregnancy, the response in them was defined as 'Complete clinical response' if there was complete symptomatic response with normalization of biochemical and hematological tests.

Statistical analysis

The study was designed to test the hypothesis that 9-months of anti-tuberculosis drugs is more efficacious than 6-month regimen using DOTS strategy. To demonstrate a difference in the complete clinical response rate of 15% between 9-months and 6-months treatment and considering a power of 80% and 5% significance, 152 patients (76 patients in each group) were required. With an expected loss of 10% of patients on follow-up and some women conceive during treatment, 175 women were recorded. Statistical analysis was conducted using STATA software, version 12.0. Continuous variables were tested for normality assumption using Kolmogrov–Smirnov tests. Mean values of variables found to be approximate normal were compared using Student's '*t*' independent tests. Non parametric category of variables was compared using Chi Square/Fischer's Exact test. For all statistical tests, 2 tabled probability of $p < 0.05$ was considered for statistical significance.

Results

Study cohort

Of 285 patients who were screened, 110 were excluded and 175 were included in this study (Fig. 1). Of 175 eligible patients, 86 and 89 patients were randomized to 9-months (Group I) and to 6-months regimen (Group II), respectively.

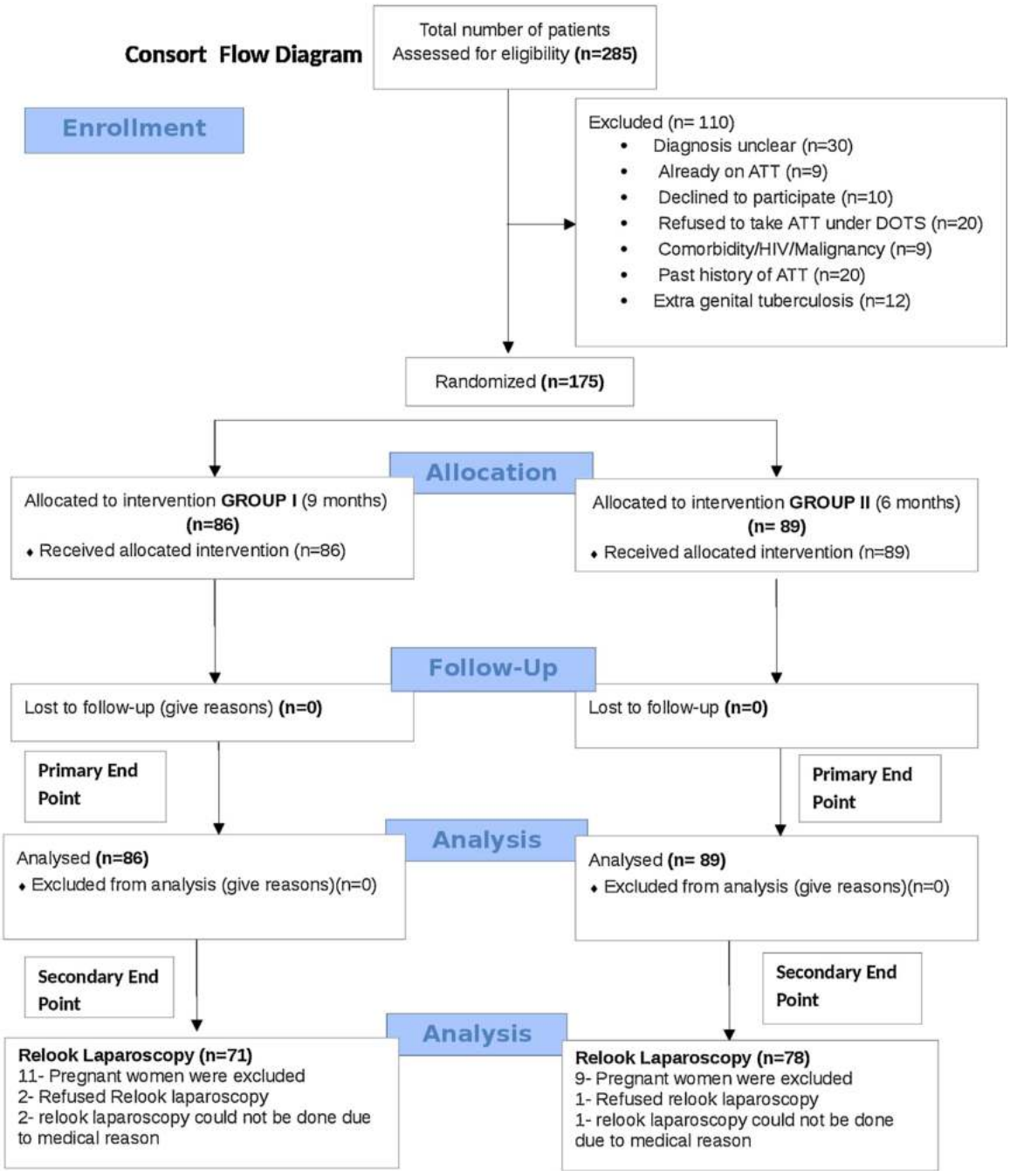

Fig. 1. Consort chart.

Characteristics of the patients and the disease at baseline

There was no difference in the demographic, clinical, hematological and biochemical parameters at baseline between the two groups (Table 1).

Endometrial biopsy findings

Endometrial biopsy findings in the two groups are shown in Table 1. The definitive findings of female genital tuberculosis were presence of acid fast bacilli on microscopy, positive acid fast bacilli culture and tuberculous granuloma on histopathology, positive polymerase chain reaction alone was not taken sufficient for diagnosis of female genital tuberculosis. An equal number of cases had definitive diagnosis of female genital tuberculosis in the two groups.

Radiological (ultrasound and hysterosalpingography findings)

Transvaginal ultrasound was performed in all the cases. The various abnormal ultrasound findings were hydrosalpinx, pelvic inflammatory disease, enlarged uterus, tubo-ovarian mass, enlarged cystic ovary which were equal in two groups. Only in some cases findings included beaded tubes, tubal block, hydrosalpinx, bicornuate uterus. The findings are given in Table 2. Thus, an equal number of findings of FGTB were present in the two groups.

Endoscopic (laparoscopic and hysteroscopic findings)

Various laparoscopic and hysteroscopic findings in the two groups are shown in Table 3. The various findings of FGTB like presence of tubercles, shaggy areas, caseous nodules, hydrosalpinx,

Table 1
Baseline demographic, clinical and laboratory characteristics of patients randomized in Group I and Group Ii.

Characteristics		Patients Randomized Group I (9 Months ATT) ($n=86$)	Patients Randomized Group II (6 Months ATT) ($n=89$)	p value
Mean age(±SD)		28.8 ± 4.4	29.1 ± 4.7	0.612
Body mass index (±SD)		22.4 ± 3.8	23.2 ± 3.6	0.527
Clinical features, n (%)	Weight loss	66 (76.7)	68 (76.4)	0.958
	Anorexia	58 (67.4)	61 (68.5)	0.875
	Fever	52 (60.5)	56 (62.9)	0.738
	Chronic cough	12 (13.9)	13 (14.6)	0.902
	Abdominal or pelvic pain	34 (39.5)	37 (41.6)	0.784
	Abdominal or pelvic lump	4 (4.6)	5 (5.6)	0.990
	Menstrual dysfunction	68 (79.1)	70 (78.6)	0.946
	Oligomenorrhea	34 (39.5)	37 (41.6)	0.784
	Hypo menorrhea	26 (30.2)	25 (28.1)	0.755
	Amenorrhea	5 (5.8)	6 (6.7)	0.999
	Menorrhagia	3 (3.5)	2 (2.2)	0.679
	Infertility	76 (88.4)	80 (89.9)	0.747
	Primary	64 (74.4)	66 (74.2)	0.968
	Secondary	22 (26.6)	23 (24.7)	0.902
Investigations	Anemia (Hb≤11) (n%)	11 (12.8)	12 (13.5)	0.892
	Mean (±SD) leukocyte count	5615 ± 2932.0	5522.2 ± 3041.2	0.854
	ESR infectious (>20) (n%)	45 (52.3)	41 (46.1)	0.438
	Infectious (≥10 mm) by Mantoux test (n %)	43 (50.0)	56 (62.9)	0.085
Endometrial biopsy	AFB on microscopy	10 (11.6)	11 (12.4)	0.882
	Positive BACTEC culture	9 (10.5)	10 (11.2)	0.870
	Positive gene Xpert	1 (1.2)	1 (1.1)	0.995
	Positive PCR	82 (95.3)	84 (94.4)	0.995
	Negative PCR	4 (4.7)	5 (5.6)	
Histopathology evidence, n (%)	Granulomatous endometritis	9 (10.5)	6 (6.7)	0.379
	Multiple epitheloid granuloma/Ill-defined granuloma	5 (5.8)	11 (12.4)	0.1333
	Isthmic endometrium	3 (3.5)	2 (2.2)	0.679
	Secretory endometrium	56 (65.1)	59 (66.3)	0.870
	Proliferative endometrium	12 (13.9)	9 (10.1)	0.434
	Inadequate specimen	1 (1.2)	2 (2.2)	0.990

Some patients had more than one findings.

Table 2
Details of radiological (ultrasound and hysterosalphinography) investigations among the patients in Group I And Group Ii.

Clinical investigations		Patients randomized Group I (9 months ATT) ($n=86$)	Patients randomized Group II (6 months ATT) ($n=89$)	p value
Ultrasonography,[a] n (%)	Normal USG	42 (48.8)	40 (44.9)	0.606
	Enlarged Uterus	6 (7.0)	8 (9.0)	0.624
	Hydrosalphinx	10 (11.6)	12 (13.5)	0.711
	PID	3 (3.5)	3 (3.4)	0.999
	Tubo-ovarian mass	12 (13.9)	9 (10.1)	0.434
	Enlarged ovary	11 (12.8)	10 (11.2)	0.752
		Patients randomized Group I (9 months ATT) ($n=60$)	Patients randomized Group II (6 months ATT) ($n=47$)	p value
Hysterosalpingography (HSG),[a] n (%)	Beaded tubes	4 (6.7)	4 (8.5)	0.728
	B/L tubal block	29 (48.3)	19 (40.4)	0.414
	B/L hydrosalpinx	6 (10.0)	3 (6.4)	0.728
	Right hydrosalpinx	2 (3.3)	1 (2.1)	0.999
	Left hydrosalpinx	1 (1.7)	0 (0.0)	0.999
	Right cornual block	7 (11.7)	5 (10.6)	0.995
	Left cornual block	4 (6.7)	4 (8.5)	0.728
	Normal	13 (21.7)	15 (31.9)	0.231
	Bicornuate uterus	0 (0.0)	1 (2.1)	0.439

[a] Some patients had more than one findings.
HSG was not done in all cases.

pyosalpinx, beaded tubes, pelvic or perihepatic adhesions were equal in two groups (Figs. 2–4). The various hysteroscopic findings of FGTB like tubercles, shaggy areas, pale endometrium and intrauterine adhesions were also equal in the two groups as shown in Table 3 and Figs. 5 and 6.

Post anti tuberculous therapy outcome measures and laboratory and endoscopic findings

At the end of treatment all women were evaluated for outcome by repeating endometrial biopsy, laparoscopy, hysteroscopy

Table 3
Details of endoscopic (laparoscopic and hysteroscopic findings) among the patients in Group I and Group Ii.

Clinical investigations		Patients randomized Group I (9 months ATT) (*N* = 86)	Patients randomized Group II (6 months ATT) (*N* = 89)	*p* value
Laparoscopic Findings,[a] *n* (%)	Fitz hugh curtis syndrome/perihepatic adhesions	18 (20.9)	20 (22.5)	0.805
	Abdominal adhesions	30 (34.9)	25 (28.1)	0.333
	Hydrosalpinx	11 (12.7)	13 (14.6)	0.727
	Pyosalpinx	4 (4.6)	2 (2.2)	0.438
	Convulated tubes/tortuous tubes	8 (9.3)	5 (5.6)	0.353
	Beaded tubes	6 (7.0)	7 (7.8)	0.823
	Congested tubes	8 (9.3)	8 (9.0)	0.943
	Tubo-ovarian mass	14 (16.3)	9 (10.1)	0.227
	B/L free spill absent	8 (9.3)	8 (9.0)	0.943
	B/L free spill present	15 (17.4)	21 (23.6)	0.314
	B/L cornual block	11 (12.8)	3 (3.4)	0.022
	Shaggy areas	16 (18.6)	14 (15.7)	0.614
	Tubercles	36 (41.9)	28 (31.5)	0.153
	Pelvic adhesions	17 (19.8)	23 (25.8)	0.339
	B/L tubes, ovaries, uterus normal	4 (4.6)	2 (2.2)	0.438
	Blebs	5 (5.8)	1 (1.1)	0.113
	Absence of one tube due to past Salpingectomy	2 (2.3)	0 (0.0)	0.240
	Fibroids	1 (1.1)	2 (2.2)	0.995
	Spill at one end of tube	8 (9.3)	3 (3.4)	0.128
	Cyst/bulky ovary	13 (15.1)	13 (14.6)	0.925
	Bicornuate uterus	0 (0.0)	1 (1.1)	0.999
	Bulky uterus	0 (0.0)	1 (1.1)	0.999
		Patients randomized Group I (9 months ATT) (*N* = 86)	Patients randomized Group II (6 months ATT) (*N* = 89)	*p* value
	Normal	32 (37.2)	33 (37.1)	0.986
	Adhesions	29 (33.7)	30 (33.7)	0.999
Hysteroscopy,[a] *n* (%)	Grade I adhesions	15 (17.4)	14 (15.7)	0.761
	Grade II adhesions	7 (8.1)	8 (9.0)	0.841
	Grade III adhesions	3 (3.5)	5 (5.6)	0.720
	Grade IV adhesions	4 (4.6)	3 (3.3)	0.717
	Both ostia not seen	14 (16.3)	16 (18.0)	0.766
	One ostium seen	18 (20.9)	20 (22.5)	0.805
	Tubercles	12 (14)	13 (14.6)	0.902
	Pale endometrium	28 (32.6)	26 (29.2)	0.632
	Shaggy areas	14 (16.3)	13 (14.6)	0.759

[a] More than one findings was recorded in majority of cases.

wherever possible. Repeated laparoscopy, hysteroscopy and endometrial biopsy could only be done on 71 women in Group I and 78 women in Group II (could not be done in women who become pregnant, refused repeat testing or due to medical reasons). The repeat findings are shown in Table 4 and were equal in two groups. Repeat laparoscopic findings are shown in Fig. 7.

The cure rate was 95.5% in Group I and 97.7% in Group II and was similar in the two groups (Table 5). The failure rate was equal in the two groups (4.7% vs 2.3%) and these women were given category II anti tuberculous therapy. They were diagnosed by persistent tubo-ovarian mass with positive polymerase chain reaction and presence of tubercles or other active lesion on repeat

Fig. 2. Laparoscopic picture showing tubercles (black arrow) and shaggy areas (white arrow) in a proven case of female genital tuberculosis.

Fig. 3. Laparoscopic picture showing caseous nodules (white arrows) and hydrosalpinx (black arrows) in a case female genital tuberculosis.

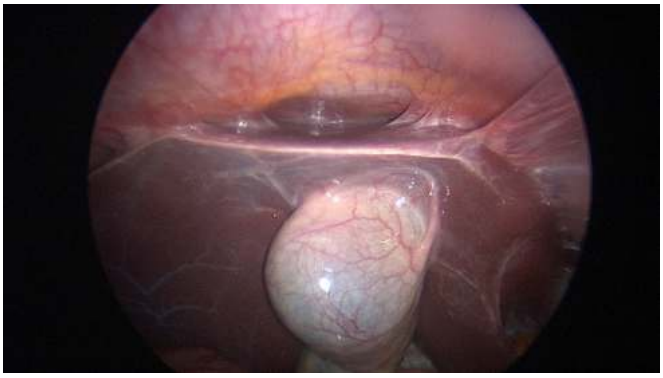

Fig. 4. Laparoscopic picture showing perihepatic adhesions with hanging gall bladder in a proven case of female genital tuberculosis.

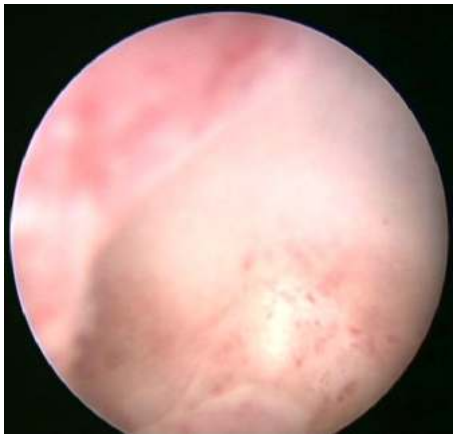

Fig. 5. Hysteroscopic picture showing pale endometrium in a case of female genital tuberculosis.

Fig. 6. Hysteroscopic picture showing grade III adhesions in a case of female Genital tuberculosis.

laparoscopy or hysteroscopy tuberculosis activity. They underwent another relook laparoscopy, hysteroscopy and endometrial biopsy after completion of category II treatment with disappearance of TB activity and tubo-ovarian masses. The pregnancy rate at completion of therapy (12.8% vs 10%) and up to 1 year after completion of therapy (10.5% vs 11.2%) which are equal in the two groups.

Mortality, morbidity and side effects

There was no death in any women in either groups. The various side effects in two groups are shown in Table 6. The side effects were nausea, vomiting, anorexia, epigastric pain, hepatitis. Overall

Fig. 7. Laparoscopic picture showing disappearance of tubercles and caseous nodules after completion of antituberculous therapy.

side effects were seen in 31.4% and 32.8% in Group I and Group II respectively and was equal ($p = 0.866$). Hepatitis was seen in 1(1.2%) and 2(2.2%) cases in Group I and Group II and they were managed as described above. All of them were followed closely and after resolution of hepatitis, the first line of drugs was reintroduced to them. All of them recovered and completed the treatment.

Discussion

Female genital tuberculosis is a common disease in developing countries causing significant morbidity especially infertility [4–7]. It affects fallopian tubes in 90–100% cases, uterus in 50–80% cases (causing intrauterine adhesions), ovaries in 20–30% cases, cervix in 5–15%, vagina and vulva in 1% of cases [4,13–25]. It also causes pelvic and perihepatic adhesions (Fitz Hugh Curtis Syndrome) [10]. It may mimic ovarian cancer necessitating unnecessary surgery [11].

Being paucibacillary disease, diagnosis of female genital tuberculosis is difficult. Endometrial biopsy in premenstrual phase for acid fast bacilli on microscopy, acid fast bacilli on culture, polymerase chain reaction, Gene Xpert and for epithelioid granuloma on histopathology is performed [4,13,14]. Ultrasound scan, computerised topographic scan, magnetic resonance imaging and positron emission tomography scan are only useful in tuberculous tubo-ovarian masses but are not specific for tuberculosis [4].

Polymerase chain reaction alone is not diagnostic of female genital tuberculosis due to false positivity and negativity [4,14,15]. Laparoscopy can be used to diagnose female genital tuberculosis by findings like tubercles, pelvic and perihepatic adhesions, caseous nodules, hydrosalpinx and pyosalpinx, beaded and convulated tubes [16–18]. Dye test should not be performed in suspected case of female genital tuberculosis due to risk of further dissemination of disease. In the present study, dye test was not performed in frank case of tuberculosis but in only those cases who were negative for acid fast bacilli on microscopy, culture and histopathology where chances of dissemination is much less.

However, one has to be very careful while performing laparoscopy in a case of abdomino-pelvic and female genital tuberculosis due to increased risk of complications like difficulty in creating pneumoperitoneum and insertion of trocal and cannula, excessive bleeding, risk of injury to intestines and post- operative complications as observed by us and other authors [25,27].

Hysteroscopy can also diagnose female genital tuberculosis by intrauterine adhesions, pale endometrium and tubercles [8,19]. Thus diagnosis of female genital tuberculosis is made by combination of tests [17].

This randomized controlled trial which was adequately powered demonstrates equal cure rates in 9 months (95.3%) and

Table 4
Comparative findings of post att outcome measures (laparoscopic, hysteroscopic, PCR and endometrial biopsies findings) between both groups.

Characteristics		Patients in Group I (9 months ATT) ($n=71$)[a]	Patients in Group I (6 months ATT) ($n=78$)[b]	p value
Laparoscopic findings, n (%)	Normal findings	29 (40.8)	37 (47.4)	0.419
	Tubercles	4 (5.6)	2 (2.6)	0.425
	Pelvic adhesions	25 (35.2)	22 (28.2)	0.358
	Hydrosalpinx	0 (0.0)	1 (1.3)	0.999
	Perihepatic adhesions	12 (16.6)	16 (20.5)	0.302
	Non-visualization of tubes	7 (9.9)	2 (2.6)	0.087
	Persistence to mass with TB activity	4 (5.4)	2 (2.6)	0.425
	Pelvic adhesiolysis	10 (14.1)	11 (14.1)	0.997
	Normal findings	60 (84.5)	68 (87.2)	0.640
Hysteroscopic findings, n (%)	Adhesions	11 (15.5)	10 (12.8)	0.640
	Grade I adhesions	2 (2.8)	2 (2.6)	0.999
	Grade II adhesions	2 (2.8)	1 (1.3)	0.605
	Grade III adhesions	3 (4.2)	4 (5.1)	0.999
	Grade IV adhesions	4 (5.6)	3 (3.8)	0.709
	Hysteroscopic adhesiolysis	7 (9.9)	5 (6.4)	0.551
Endometrial biopsy, n (%)	AFB microscopy	0 (0.0)	0 (0.0)	0.999
	AFB BACTEC culture	0 (0.0)	0 (0.0)	0.999
	PCR	63 (88.8)	51 (65.4)	0.001
	Positive			
	Negative	8 (11.2)	27 (34.6)	
	Histopathology evidence	61 (85.9)	71 (91.0)	0.327
	Secretory endometrium			
	Proliferative endometrium	10 (14.1)	7 (9.0)	0.327
	Tuberculous granuloma	0 (0.0)	0 (0.0)	0.999

[a] In Group I, 11 Patients got Pregnant and 2 refused for relook Laparoscopy, in another 2 women laparoscopy could not be done due to medical reasons.
[b] In Group II, 9 Patients got pregnant, 1 patient had lost to follow up and 1 patient relook laparoscopy could not be done due to medical reasons.
Few patients showed more than one findings.

Table 5
Details of treatment outcome measures between Group I and Group II.

Treatment outcome, n (%)	Patients randomized Group I (9 months ATT), ($n=86$)	Patients randomized Group II (6 months ATT), ($n=89$)	p value
1. Cured	82 (95.3)	86 (97.7)	0.441
2. Not cured	4 (4.7)	2 (2.3)	
3. Cat II ATT[a]	4 (4.6)	2 (2.3)	0.441
4. Refused laparoscopy	2 (2.3)	2 (2.3)	1.000
5. Pregnant at completion of therapy	11 (12.8)	9 (10.1)	0.578
6. Treatment for infertility advised			
i. OVI/IUI[b]	28 (32.6)	41 (46.1)	0.068
Pregnancies	4 (4.7)	6 (6.7)	0.747
ii. IVF (In Vitro Fertilization)	30 (34.9)	22 (24.7)	0.141
Pregnancies	5 (5.8)	4 (4.5)	0.744
iii. Adoption/Surrogacy	9 (10.5)	13 (14.6)	0.409
Pregnancies	0	0	NA
Total further pregnancies during 1 year follow up	9 (10.5)	10 (11.2)	0.870
Total pregnancies during treatment and up to 1 year follow up	20 (23.2)	19 (21.3)	0.762
Outcome			
• Spontaneous abortion	3 (3.4)	2 (2.2)	0.679
• Pre term intrauterine death	2 (2.3)	3 (3.4)	0.995
• Preterm delivery with live infant	4 (4.6)	4 (4.5)	0.995
• Full term pregnancy with live infant	11 (12.8)	10 (11.2)	0.752
• Take home baby rate	15 (17.4)	14 (15.7)	0.761
Recurrence at 1 year follow up	0 (0.0)	0 (0.0)	0.999

[a] Positive findings of active TB.
[b] Ovulation induction; intra-uterine insemination.

6 months (97.7%) of anti-tuberculous therapy in female genital tuberculosis. It also confirms the efficacy of intermittently given drugs under DOTS strategy. It also demonstrates no difference in the recurrence rate at 1 year follow up after completion of antituberculous therapy with no recurrence in either group. There was equal number of pregnancies during treatment (12.8% vs 10%) and up to one year of follow up after anti-tuberculous therapy (10.5% vs 11.2%) in the two groups. The study also confirms the safety of the new regimens while no significant difference in the side effects profile in the two groups (31.4% vs 32.6%) (Table 6).

Another finding was that pregnancy rate during antituberculous therapy and up to 1 year of follow up was similar in the two groups (23.2% vs 21.3%). A recent study by Makharia et al., [28] for abdominal tuberculosis found 6 months intermitted DOTS therapy to be as effective as 9 months intermittent DOTS therapy with equal success and recurrence rate. Jindal et al., [29] observed favorable fertility outcome following antituberculous treatment solely on assess of positive polymerase chain reaction.

Most women in both the groups tolerated drugs very well with overall side effects rates being equal in the two groups (31.4% vs

Table 6
Side effects of antituberculous therapy in the two groups.

Side effects	Patients randomized Group I (9 months ATT) (n = 86)	Patients randomized Group II (6 months ATT) (n = 89)	p value
Nausea	12 (13.9%)	11 (12.4%)	0.755
Anorexia	3 (3.5%)	4 (4.5%)	0.995
Epigastric discomfort or pain	7 (8.1%)	8 (9.0%)	0.841
Hepatitis	1 (1.2%)	2 (2.2%)	0.995
Vomiting	5 (5.8%)	6 (6.7%)	0.995
Overall Single Side Effects	27 (31.4%)	29 (32.6%)	0.866

32.6%) (Table 6). Most adverse events were mild. One and two patients in 9-months and 6-months therapy developed drug induced hepatitis, which resolved with modification of drugs and prolongation of the treatment duration.

The strengths of the study include it being adequately powered randomized controlled trail with significant observations including cure rates, recurrence rates and pregnancy outcome. The sample size was calculated by the statistician and was well powered to note the differences. We feel that the study has significant observations that six months therapy is equally effective as nine months therapy. To the best of our knowledge, this is the first randomized controlled trial comparing six months versus nine months antituberculous therapy for female genital tuberculosis from India. The trial has proven efficacy of six months antituberculous therapy to be equal to nine months therapy which appears to be useful addition to the knowledge. However, there are some limitations of this study. One limitation was that definite diagnosis of female genital tuberculosis could only be made in some cases, while in others diagnosis was presumptive (laparoscopic and hysteroscopic findings) which is an inherent problem in all the types of extra pulmonary tuberculosis including female genital tuberculosis due to its paucibacillary nature.

It was intended to perform repeat laparoscopy, hysteroscopy, endometrial sampling in all the patients at the end of antituberculous therapy, However, repeat testing could only be done in 71 out of 86 (82.5%) in Group I and in 78 out of 89 (87.6%) in Group II. It could not be done in others due to pregnancy, refusal for relook laparoscopy and testing or medical reasons. Another limitation was that late recurrence of the disease after one year was not evaluated due to financial and logistics constraints. There may have been some recurrence after one year in the study patients.

Conclusions

The current randomized control trial confirms that antituberculous therapy using DOTS for 6 months duration was as effective as 9 months duration. The cure rate, treatment, failure rates and recurrence rates were similar in the two groups. There was no significant difference in adverse effects in the two groups. The pregnancy rate was similar in two groups. The results of this study therefore demonstrate the efficacy and safety of 6 months duration of directly observed treatment short course (DOTS) for female genital tuberculosis to be equal to 9 months. The results provide evidence to policy makers for recommendation of intermitted DOTS therapy for 6 months for patients with female genital tuberculosis especially in developing nations where disease is more prevalent and where compliance to treatment is a barrier for effective treatment of tuberculosis.

Conflict of interest

We declare no conflict of interest.

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Laparoscopic evaluation of female genital tuberculosis in infertility: An observational study

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***Background & objectives*: Female genital tuberculosis (FGTB) is an important variety of extrapulmonary TB causing significant morbidity, especially infertility, in developing countries like India. The aim of this study was to evaluate the laparoscopic findings of the FGTB.**

***Methods*: This was a cross-sectional study on 374 cases of diagnostic laparoscopy performed on FGTB cases with infertility. All patients underwent history taking and clinical examination and endometrial sampling/biopsy for acid-fast bacilli, microscopy, culture, PCR, GeneXpert (only last 167 cases) and histopathological evidence of epithelioid granuloma. Diagnostic laparoscopy was performed in all the cases to evaluate the findings of FGTB.**

***Results*: Mean age, parity, body mass index and duration of infertility were 27.5 yr, 0.29, 22.6 kg/m^2 and 3.78 years, respectively. Primary infertility was found in 81 per cent and secondary infertility in 18.18 per cent of cases. Endometrial biopsy was positive for AFB microscopy in 4.8 per cent, culture in 6.4 per cent and epithelioid granuloma in 15.5 per cent. Positive peritoneal biopsy granuloma was seen in 5.88 per cent, PCR in 314 (83.95%) and GeneXpert in 31 (18.56%, out of last 167 cases) cases. Definite findings of FGTB were seen in 164 (43.86%) cases with beaded tubes (12.29%), tubercles (32.88%) and caseous nodules (14.96%). Probable findings of FGTB were seen in 210 (56.14%) cases with pelvic adhesions (23.52%), perihepatic adhesions (47.86%), shaggy areas (11.7%), pelvic adhesions (11.71%), encysted ascites (10.42%) and frozen pelvis in 3.7 per cent of cases.**

***Interpretation & conclusions*: The finding of this study suggests that laparoscopy is a useful modality to diagnose FGTB with a higher pickup rate of cases. Hence it should be included as a part of composite reference standard.**

Key words Adhesions - beaded tubes - caseous nodules - complications - diagnostic laparoscopy - endometrial sampling - tubercles

Tuberculosis (TB) continues to be a global problem but more so in developing nations, with drug-resistant TB compounding the problem[1,2]. Although pulmonary TB remains the most common type of TB globally,

the incidence of extrapulmonary TB (EPTB) is on the rise, especially due to co-infection with HIV, and this accounts for about 20 per cent of cases[3]. Female genital tuberculosis (FGTB) is observed in about 5-30 per cent of infertility cases[3]. The prevalence of FGTB varies in different countries and in different parts of India being 45.1 per cent of the patients per 1,00,000 population in the Andaman Islands to about 1-19 per cent in infertile patients being higher (about 16%) in tertiary referral centres and are still higher (up to 41%) in patients coming for *in vitro* fertilization with tubal factor infertility (up to 48.5%)[4-7].

FGTB may be asymptomatic or manifest with menstrual abnormalities especially oligomenorrhoea, hypomenorrhoea, abdominopelvic pain and pelvic mass[5-8].

Conventionally, diagnosis of genital TB is made by *Mycobacterium tuberculosis* (MTB) on microscopic examination or BACTEC culture or mycobacteria growth indicator tube (MGIT) culture or presence of epithelioid granuloma of endometrial or peritoneal biopsy. These are infrequently present and may lead to missing the diagnosis in majority of patients[5,7].

Polymerase chain reaction (PCR) is a sensitive test but has high rate of false positivity and hence, should not be used to start treatment[5,8,9]. Gene Xpert is specific and has been endorsed by the World Health Organization but has low sensitivity to detect FGTB[10,11]. Unlike pulmonary TB, diagnosis of EPTB, including FGTB, is difficult due to its paucibacillary nature. Dosanjh *et al*[12] tried to combine various methods of diagnosis of detection of tuberculosis which is a type of composite reference standard (CRS). Later, other authors formed CRS for FGTB also along with the other types of FGTB[13].

Composite Reference Standard (CRS) has become popular in the detection of genital TB and takes into consideration demonstration of Mycobacterium on microscopic examination or culture of endometrial/peritoneal biopsy or epithelioid granuloma on histopathology or positive GeneXpert and definite findings (beaded tubes/caseous nodules/tubercles) or probable findings (ascites, white areas, pelvic/abdominal/perihepatic adhesions, distended tubes, pyosalpinx and tubo-ovarian masses) on laparoscopy[13].

Laparoscopy by direct visualization of the abdomen and pelvis can detect most cases of FGTB missed by traditional tests and can be a part of CRS thus, can show a definite or probable finding of FGTB and also help in prognostication of infertility in addition to plan further treatment[5,9,12-14]. Although previous smaller studies of short duration have observed laparoscopy to be useful in the detection of FGTB, a bigger study with large sample size is needed for confirmation of findings of the prior studies.

Hence, the present study was done to report the laparoscopic observations in FGTB over a nine-year period, to help the clinicians in their day-to-day practice.

Material & Methods

This study was carried out at the department of Obstetrics and Gynaecology All India Institute of Medical Sciences, New Delhi, after seeking approval by the Institute Ethical Committee. An informed written consent was also taken from all the participants prior to the start of the study.

Study design: This was a cross-sectional study on 374 consecutive cases of diagnostic laparoscopy (pelviscopy) performed on FGTB with infertility as shown in Figure for nine years (July 2010 to July 2019) in an apex tertiary referral institute between 20 and 40 years. Inclusion criteria included infertile patients who were willing to participate in the study and had FGTB on CRS as in Figure which was formed for FGTB taking into consideration the study of Dosanjh *et al*[12] in 2008. Exclusion criteria included women with malignancy or any other gynaecological disease and who were not willing to participate.

Complete medical/obstetric history and history of TB was taken from all participants. General physical and gynaecological examinations including bimanual examination for uterine size and adnexal mass and tenderness were performed on all the participants.

Laboratory investigations and microbiological tests: Baseline investigations such as complete haemogram, Mantoux test, blood sugar, X-ray chest and ultrasound or computed tomography (CT) scan where abdominal or pelvic lump was palpable were performed on all participants. Endometrial biopsy/aspirate was taken from all the participants between day 21 and 24 of the menstrual cycle with no. 4 Karman's cannula in gynaecological outpatient minor operation theatre under all aseptic conditions; one part of the sample was sent in saline for detection of *M. tuberculosis* on microscopy and for culture, PCR and GeneXpert test.

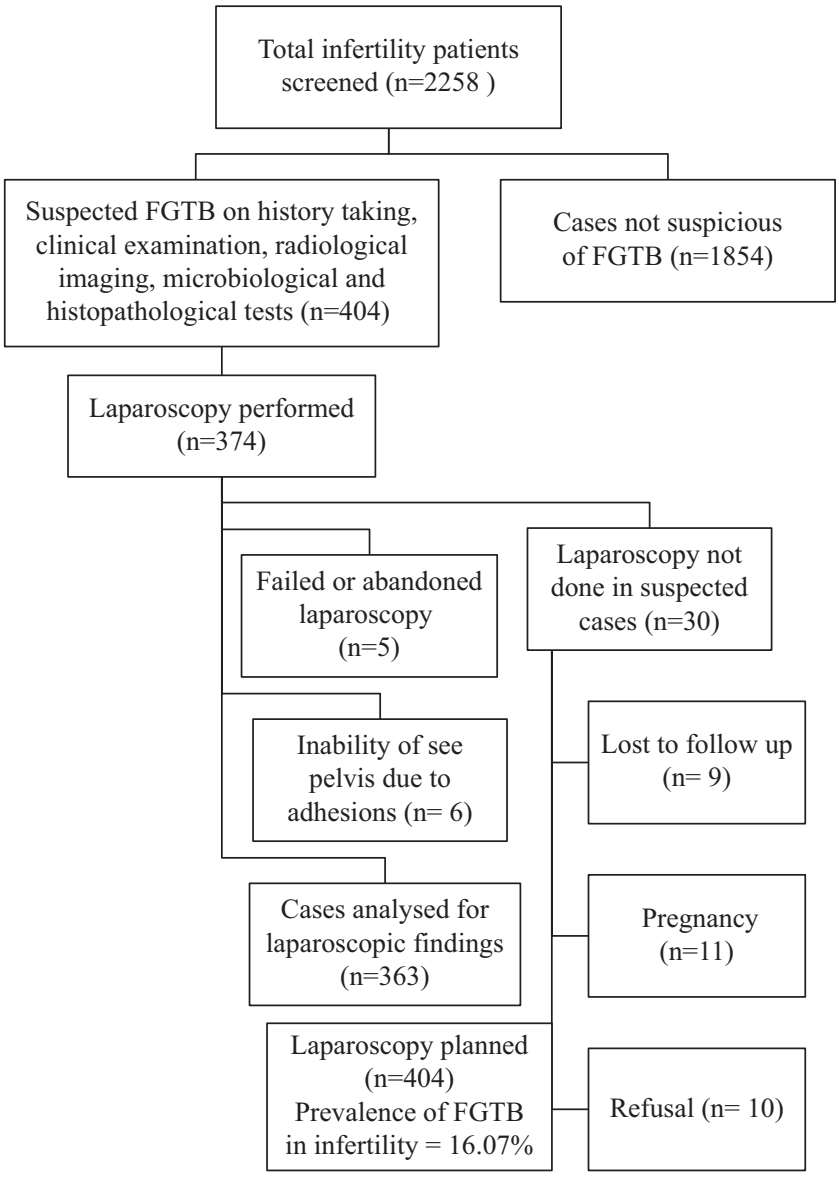

Figure. Diagnostic algorithm. FGTB, female genital tuberculosis

The second part of the sample was kept in formaldehyde solution for detection of tuberculous granuloma on histopathology.

Laparoscopy: Diagnostic laparoscopy was performed in all the cases under short general anaesthesia using no. 10 mm laparoscope (Karl Storz, Germany) as part of the infertility workup, and for findings of TB and for prognostication and treatment planning for infertility. During laparoscopy, the whole of the pelvis and abdomen along with their contents was meticulously examined for any definite or probable findings of FGTB. The laparoscopic findings were analyzed in two time periods (July 2010 to December 2014 and January 2015 to July 2019) to see changing patterns in laparoscopic findings and complications over time.

All patients with FGTB diagnosed by microscopy, culture, GeneXpert, histopathology or laparoscopy were treated with anti-tubercular therapy as per the protocol of the hospital where laparoscopic evidence of FGTB is taken as evidence of FGTB and treatment is started even in the absence of microbiological and histopathological evidence. Participants were given full oral anti-tubercular therapy for six months (rifampicin, isoniazid, pyrazinamide and ethambutol daily for two months in intensive phase, followed by rifampicin, isoniazid and ethambutol daily for

the next four months in continuation phase) through Directly Observed Treatment Short course (DOTS) strategy. The patients were kept on a regular follow up for compliance and any side effects of drugs. In the present study, diagnostic laparoscopy was performed for all suspected and confirmed cases of FGTB as part of research project and infertility protocol for tubal patency, confirmation of diagnosis and prognostication of the disease.

Criteria for the diagnosis of FGTB as per Composite Reference Standard (CRS): As per the study by Dosanjh *et al*[12] in 2008, FGTB was diagnosed in the presence of positive AFB on microscopy or culture or positive GeneXpert or positive epithelioid granuloma on histopathology of endometrial or peritoneal biopsy or definite or probable findings of FGTB on laparoscopy. PCR being non-specific was not taken as part of CRS. By combining various tests in CRS, most cases which otherwise would have been missed by traditional methods could be diagnosed and treated on time.

Statistical analysis: Data analysis was performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA) for continuous data using Kolmogorov–Smirnov test. Descriptive statistics (mean, standard deviation and range) were carried out for normally distributed data. Comparison of means across two groups was done using Student's t independent test and comparison of categorical values was done by Chi-square/Fisher's exact test.

Results

A total of 2258 patients screened for FGTB over a period of nine years, a total of 404 were suspected to have FGTB on histopathology taking, clinical examination, radiological imaging, microbiological and histopathological findings with the prevalence of FGTB. Out of the 404 cases, laparoscopy could not be done in 30 patients (9 patients were lost to follow up, 11 got pregnant while waiting for laparoscopy, and 10 refused laparoscopy; Figure).

Out of 374 women in whom laparoscopy was tried, findings were seen in 363 cases as laparoscopy was abandoned in five patients and pelvis could not be seen due to adhesions in six patients. Hence, only 363 cases with proven FGTB on laparoscopy were taken, making the prevalence of FGTB in infertility to be 16 per cent. Another 110 patients not found to have FGTB also underwent laparoscopy for other reasons and were not included in the study.

Table I. Characteristics of patients (n=374)

Characteristic	n (%)
Age (yr)	
Range	18-45
Mean±SD	27.5±4.8
Parity	
Range	0-4
Mean±SD	0.29±0.12
Body mass index (kg/m^2)	
Range	15.8-35.5
Mean±SD	22.06±2.58
Part history of tuberculosis	145 (38.77)
Pulmonary tuberculosis	92 (24.59)
Extrapulmonary tuberculosis	53 (14.17)
Duration of infertility (yr)	
Range	1-14
Mean±SD	3.78±1.58
Type of infertility	
Primary infertility	306 (81.81)
Secondary infertility	68 (18.18)
Socioeconomic status	
Lower	246 (65.77)
Middle	119 (31.81)
Upper	9 (2.40)
History of BCG vaccination	316 (84.49)

SD, standard deviation; BCG, bacillus Calmette–Guérin

The general characteristics of the participating women are shown in Table I, with mean age being 27.5±4.8 yr while mean parity was 0.29±0.12 and mean body mass index was 22.6±2.58 kg/m^2. History of tuberculosis was seen in 145 (38.77%), with pulmonary TB in 24.59 per cent and EPTB in 14.17 per cent of cases. Infertility was seen in all women, with a mean duration of infertility being 3.78±1.58 yr. Primary infertility was seen in 81.81 per cent of cases and secondary infertility in 18.18 per cent of cases. A total of 246 (65.77%) patients were from a lower socioeconomic status. History of Bacillus Calmette–Guérin (BCG) vaccine was observed in 84.49 per cent of cases.

The clinical features, examination findings and baseline investigations are depicted in Table II. Menstrual symptoms were most common, especially hypomenorrhoea in 27.80 per cent and oligomenorrhoea in 29.67 per cent of cases. Adnexal mass was palpable in 68 (18.18%) being unilateral in 46 (12.29%) and bilateral in 22 (5.8%) cases. Infectious Mantoux test

Table II. Clinical features and baseline investigations in patients of female genital tuberculosis (n=374)

Symptoms/signs	n (%)
Fever	67 (17.91)
Anorexia	127 (33.95)
Weight loss	119 (31.81)
Malaise	115 (30.74)
Night sweats	82 (21.92)
Menstrual symptoms	
Normal menstrual cycle	194 (51.87)
Abnormal uterine bleeding	8 (2.13)
Hypomenorrhoea	104 (27.80)
Oligomenorrhoea	111 (29.67)
Secondary amenorrhea	28 (7.48)
Dysmenorrhea	29 (7.75)
Abdominal pain	38 (10.16)
Chronic pelvic pain	48 (12.83)
Vaginal discharge	38 (10.16)
Signs	
Lymphadenopathy	12 (3.20)
Abdominal mass	34 (9.09)
Speculum examination	
Normal speculum examination	226 (60.42)
Abnormal vaginal discharge on examination	142 (37.96)
Cervical growth (later confirmed cervical tuberculosis)	4 (1.06)
Adnexal mass	68 (18.18)
Unilateral	46 (12.29)
Bilateral	22 (5.88)
Baseline investigations	
Haemoglobin (g/dl)	
Range	8.4-14.2
Mean±SD	11.8±0.98
Anaemia (Hb <11 g/dl)	67 (17.11)
Total leucocyte count (per cubic mm)	
Range	3887-12187
Mean±SD	5585±2274
Random blood sugar (mg/dl)	
Range	76-206
Mean±SD	112.68±16.88
Abnormal infectious Mantoux test (>10 mm)	142 (37.96)
Erythrocyte sedimentation rate (mm/first hour)	
Range	12.69
Mean±SD	32.74±12.84
X-ray chest	
Normal X ray chest	330 (88.23)
Old healed lesion of TB	26 (6.95)
Mediastinal lymphadenopathy	18 (4.81)

*Some patients had more than one finding, CBNAAT could only be done for the last 167 cases. AFB, acid-fast bacilli; CBNAAT, cartridge-based nucleic acid amplification test

(>10 mm) was observed in 142 (37.96%) cases, while erythrocyte sedimentation rate (ESR) ranged between 12 and 69, with a mean of 32.74±12.84 mm in the first hour. On X-ray chest, old healed lesions of tuberculosis were seen in 26 (6.95%) and enlarged thoracic lymph nodes were seen in 18 (4.81%) cases.

The numbers of patients based on methods of diagnosis of FGTB are shown in Table III. Positive MTB on microscopy of endometrial aspirate or biopsy was observed in 18 (4.81%) cases, 24 (6.41%) on culture, tuberculous granuloma on histopathology in 58 (15.50%) cases while on peritoneal biopsy, AFB microscopy or culture were seen in 14 (3.94%) cases, epithelioid granuloma was seen in 22 (5.88%) cases. Positive PCR on endometrial or peritoneal biopsy was seen in 314 (83.95%) cases. GeneXpert was positive in 31 (18.56%) cases out of 167 cases. If non-specific PCR was excluded, only 90 patients had definite evidence of FGTB on microscopy, culture, Gene Xpert or positive histopathology, with many patients having more than one positive finding. Hence, out of 363 cases, 273 were missed by traditional tests but diagnosed by laparoscopy. Definite findings of tuberculosis (tubercles, caseous nodules and beaded tubes) were seen in 164 (43.85%) cases, while probable findings of FGTB (straw-coloured fluid, pelvic adhesions, perihepatic adhesions, hyperaemic tubes, convoluted tubes, hydrosalpinx, pyosalpinx and shaggy areas) were seen in 210 (56.14%) cases.

Various abdominopelvic findings of TB on laparoscopy are shown in Table IV. The laparoscopy was abandoned or failed due to umbilical adhesions

Table III. Methods of diagnosis of female genital tuberculosis (n=374)*

Diagnostic modality	Number of women, n (%)
Positive AFB on microscopy of endometrial aspirate or biopsy	18 (4.81)
Positive AFB on culture of endometrial aspirate or biopsy	24 (6.41)
Positive AFB on microscopy or culture on peritoneal biopsy	14 (3.94)
Epithelioid granuloma or chronic granulomatous endometrium on histopathology of endometrial biopsy	58 (15.50)
Epithelioid granuloma on histopathology of biopsy from peritoneal lesions or caseous nodule	22 (5.88)
Positive CBNAAT or GeneXpert on endometrial or peritoneal biopsy	31 (out of 167 cases) (18.56)
Positive PCR on endometrial aspirate or peritoneal biopsy	314 (83.95)
Definite findings of female genital tuberculosis on laparoscopy	164 (43.85)
Probable findings of female genital tuberculosis on laparoscopy	210 (56.14)

*Some patients had more than one finding, CBNAAT could only be done for the last 167 cases. AFB, acid-fast bacilli; CBNAAT, cartridge-based nucleic acid amplification test

in five (1.377%) women and there was inability to see the pelvis due to adhesions in another six women. Of the definite findings, tubercles were seen mostly on uterus in 123 (33.68%) women (Supplementary Figure A), while caseous nodules in peritoneal cavity (Supplementary Figure B) were seen in 12 (3.30%) cases.

Of the probable findings, the most common adhesions were seen as pelvic adhesions in 198 (54.54%), abdominal adhesions in 88 (24.24%) while, perihepatic adhesions (Supplementary Figure C) in 179 (49.31%) cases. Shaggy areas (white deposits) on uterus (Supplementary Figure D) were seen in 22 (6.06%) cases.

Various probable fallopian tube findings of FGTB are shown in Table IV including unilateral hydrosalpinx (Supplementary Figure D and E) in 28 (7.71%) cases, bilateral hydrosalpinx in 48 (13.22%), unilateral tubo-ovarian masses (Supplementary Figure F) in 46 (6.71%), and hypermeic tubes (Supplementary Figure E) in 88 (24.21%) cases.

Further analysis of data between two the time periods (July 2010 to December 2014 and January 2015 and July 2019 was done (Table IV). It was found that bilateral beaded tubes which were more common in the second half (P=0.05) and abdominal adhesions which were more common (29.12%) in the first half, than in the second half (19.45%) (P=0.03) and bilateral tubal block was more common in the first half (49.45%) than in the second half of time (32.43%; P=0.001). There was no significant difference in various laparoscopic findings across the two time periods.

Discussion

Female genital tuberculosis (FGTB) is a type of extrapulmonary tuberculosis (EPTB) and is a significant cause of infertility, especially in developing countries[3-7]. Being a paucibacillary disease, its diagnosis remains a dilemma as the gold standard method of diagnosis like AFB positivity on microscopy or culture or positive Gene Xpert or epithelioid granuloma on endometrial and peritoneal biopsy are positive in selected cases and may miss the diagnosis in most cases[5,7,9]. The use of PCR picks up more cases but has a high false-positive rate and alone is not advisable to diagnose FGTB or to start anti-tuberculous therapy[5,7,9].

The role of radiological methods such as ultrasound, computed tomography (CT) scan, magnetic resonance imaging and positron emission tomography is more for tubercular tubo-ovarian masses and to differentiate between abdominopelvic TB and ovarian cancer, while hysterosalpingography can detect uterine and tubal pathophysiology[15-18]. Molecular tests like nucleic acids have been used for the diagnosis of pleural TB, a variant of EPTB and can be used for FGTB also[19].

In the present study also, CRS was used for diagnosis of FGTB as it can pick up more cases which can be missed by gold standard culture and histopathology but avoid diagnosing FGTB by non-specific and highly false-positive tests like PCR.

Laparoscopy can detect more cases of genital TB and abdominal TB by direct viewing of the abdomen and pelvis for various TB findings. Definite findings

Table IV. Laparoscopic findings in female genital tuberculosis (n=363)

Laparoscopic	n (%)	July 2010-December 2014 (n=178), n (%)	January 2015-July 2019 (n=185), n (%)
Definite findings			
Beaded tubes			
Overall	46 (12.29)	21 (11.79)	25 (13.54)
Bilateral	34 (36)	5 (2.81)	19 (10.25)
Unilateral	12 (30)	10 (5.62)	6 (3.241)
Tubercles			
On uterus	123 (33.88)	59 (33.15)	64 (36.59)
On fallopian tube	111 (30.57)	56 (31.46)	55 (29.73)
On ovaries	39 (14)	14 (7.87)	15 (8.11)
On pouch of Douglas	58 (97)	30 (16.85)	28 (15.14)
On pelvic peritoneum	74 (20.38)	35 (19.66)	39 (21.08)
On general peritoneal cavity	22 (6.06)	10 (5.62)	12 (6.49)
Caseous nodules overall	56 (15.42)	29 (16.29)	27 (14.59)
Pelvic region	44 (12.12)	23 (12.92)	21 (11.35)
General peritoneum	12 (3.30)	6 (3.37)	6 (3.24)
Probable findings			
Adhesions			
Pelvic adhesions	198 (54.54)	106 (59.55)	92 (49.73)
Perihepatic adhesions (Fitz-Hugh–Curtis syndrome)	179 (49.31)	94 (52.81)	85 (45.95)
Abdominal adhesions	88 (24.24)	52 (29.21)	36 (19.46)
Shaggy areas (white deposits)			
Overall	44 (12.12)	21 (11.80)	23 (12.43)
On uterus	22 (6.06)	10 (5.62)	12 (6.49)
Fallopian tube	14 (3.74)	7 (3.93)	7 (3.78)
Pouch of Douglas	6 (1.65)	2 (1.12)	4 (2.16)
Upper abdomen and liver	2 (0.55)	1 (0.56)	1 (0.54)
Fallopian tube findings			
Unilateral hydrosalpinx	28 (7.71)	18 (10.11)	10 (5.41)
Bilateral hydrosalpinx	48 (13.22)	28 (15.73)	20 (10.81)
Unilateral pyosalpinx	2 (0.55)	2 (1.12)	0 (0.0)
Bilateral pyosalpinx	1 (0.27)	1 (0.56)	0 (0.0)
Unilateral tubo-ovarian mass	46 (12.67)	26 (14.61)	20 (10.81)
Bilateral tubo-ovarian mass	22 (6.06)	13 (7.30)	9 (4.86)
Unilateral tubal block	58 (15.97)	30 (16.85)	28 (15.14)
Bilateral tubal block	148 (40.77)	88 (49.44)	60 (32.43)
Congested or hyperaemic tubes	88 (24.24)	43 (24.16)	45 (24.32)
Dried and rigid tubes	22 (6.06)	14 (7.87)	8 (4.32)
Encysted ascites	39 (10.74)	16 (8.99)	13 (7.03)
Fluid filled pockets in pelvis	42 (11.57)	22 (12.36)	20 (10.81)
Frozen pelvis	14 (3.85)	15 (8.43)	9 (4.86)
Inability to see pelvis due to adhesions	5 (1.65)	4 (2.25)	2 (1.08)

like beaded tubes, caseous nodules or tubercles or probable findings such as encysted ascites, pelvic, abdominal or perihepatic adhesions, hydrosalpinx, pyosalpinx or tubo-ovarian masses and tubal blockage are seen[5,6,9,13,14].

Laparoscopy in suspected cases of FGTB should be done by an experienced gynaecologist after proper counselling of the patients due to complications in surgery[20]. All patients are treated with six months of anti-tubercular drugs as has been recommended by the WHO[1], National TB Elimination Program of India[2] and a previous randomized controlled trial[21], which confirmed that six-months therapy was equally effective to nine month therapy. Rarely, multidrug-resistant FGTB can be there, necessitating longer treatment (18-24 months) therapy with reserved drugs in consultation with infectious disease experts[22]. Various other studies have also proven the utility of diagnostic laparoscopy alone or in combination with other molecular methods in better and early detection of FGTB[23-30].

Tuberculosis has a major impact on both female and male fertility, but there are many controversies and pitfalls in its diagnosis[29,30]. However, laparoscopy appears to be a useful diagnostic modality in the diagnosis of FGTB along with other tests.

The strength and novelty of the study is the large sample size of successful cases of laparoscopy in FGTB patients diagnosed on CRS with the observation of various laparoscopic findings in abdominopelvic TB.

Furthermore, laparoscopy could detect most cases of FGTB missed by traditional methods for timely treatment to prevent permanent damage and sterility. The limitations of the study are dependence on CRS for diagnosis as laparoscopy may overdiagnose some cases, inability to do testing for pelvic infections like chlamydia or gonorrhoea due to financial and logistics constraints and also lack of long-term follow up data of these patients regarding improvement in fertility outcome with anti-tuberculous therapy.

In the current study, diagnostic laparoscopy was performed for all suspected and confirmed cases of FGTB as part of a research project and infertility protocol which is also a limitation as anti-tubercular treatment can be started on the basis of these tests without subjecting the patients to laparoscopy.

Overall, although laparoscopy is a useful method in diagnosing FGTB and abdominopelvic TB and, for prognostication of infertility, it should not be done in isolation, it should be combined with conventional methods as part of CRS for increased detection of FGTB for timely treatment.

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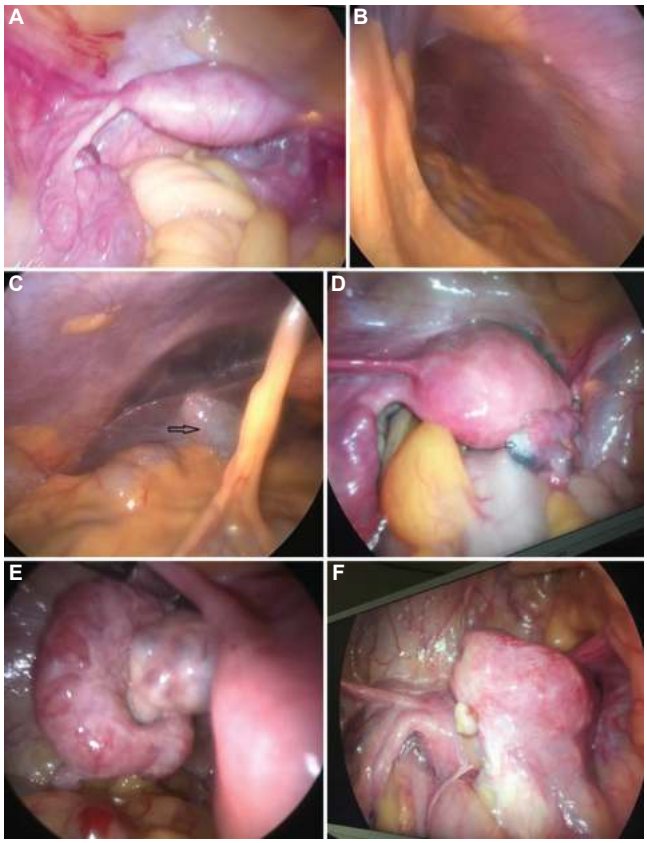

Supplementary Figure. Diagnostic laparoscopy showing (**A**) tubercles on uterus with peritubal and pelvic adhesions, (**B**) caseous nodules on peritoneum and abdominal adhesions, (**C**) perihepatic adhesions (Fitz-Hugh–Curtis syndrome) with Sharma's hanging gallbladder sign (arrow) and omental adhesions, (**D**) shaggy areas on the uterus and left-sided hydrosalpinx (arrow) with delayed spill on the right side, (**E**) hyperaemia and hydrosalpinx of the left fallopian tube, (**F**) large right-sided tubo-ovarian mass with caseous material coming out in a case of FGTB. FGTB, female genital tuberculosis.