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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.