

## Endometrial Tuberculosis and Chances of IVF Success Rates after Enhanced ART Techniques, Combining Intracytoplasmic Sperm Injection, the Role of Various Laboratory Diagnoses and its Implication of Frozen Human Embryo Transfer and its Outcomes

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### Abstract

*Mycobacterium tuberculosis* is among the many different types of *Mycobacterium* species present that causes tuberculosis (TB). A vast majority of female genital tuberculosis (FGTB) is observed in the endometrium which causes infertility in women. FGTB mainly causes failed implantation, affects endometrial receptivity and causes a defect in endometrial vascularisation. Different tests are available to determine TB in an individual such as culture of *Mycobacterium tuberculosis* on LJ media, erythrocyte sedimentation rate (ESR), acid fast bacilli, tuberculosis-PCR and Mantoux test. Even after the treatment of tuberculosis, women still find it difficult to conceive naturally and may need to undergo treatments like IVF/ICSI followed by embryo transfer. Not only is the conception rate lowered, but the live birth rates are also poor. There is a lot of conflict on whether ART helps women with FGTB, as some researchers have mentioned that after infection with TB, the blood flow to the endometrium is lowered which would lead to implantation failure. On the other hand, ART treatments is successful in women with good endometrial thickness. This review aims to determine whether women with FGTB require ART treatment after taking anti-TB drugs.

**Aim:** To determine whether conventional IVF/ICSI is successful as a treatment alternative in endometrial tuberculosis and role of various laboratory diagnosis.

**Keywords:** Endometrial Tuberculosis; IVF Success Rates; ART Techniques; Intracytoplasmic Sperm Injection; Frozen Human Embryo Transfer

### Introduction

*Mycobacterium tuberculosis* exponentially adds to mortality rates globally even though there are many different kinds of *Mycobacterium* species [1]. *M. tuberculosis* can affect other parts of the body like the female genital tract, mainly the endometrium and can cause infertility in the infected patients [2]. This study aims to determine whether conventional *in vitro* fertilization (IVF) or Intracytoplasmic sperm injection (ICSI) can be used as successful methods in patients presenting with endometrial tuberculosis.

### Epidemiology

Tuberculosis (TB) caused by *Mycobacterium tuberculosis* is a contagious disorder that is established primarily involving the respiratory system (lungs) but can have an impact on other parts of the body, like the female genital network [3]. The endometrium is extremely

involved in around 50 - 80% of female infertile cases, whereas the oviducts, ovaries, cervix, vagina, and vulva are respectively involved in 90 - 100%, 20 - 30%, 5 - 15% and 1 - 2% of infertile cases [4]. According to the World Health Organization (WHO), approximately 10.4 million TB cases were seen worldwide in 2016, out of which 34% (3.5 million) of cases affected females [3]. It has been identified that China and India together account for almost 40% of TB cases [5]. In developing countries, more than 95% of TB outbreaks affect people in the economically productive age group (15 - 54 years). This causes a decline in the economy and financial hardships on the family [3]. Due to globalization, there is an increase in the incidence of TB cases around the world [4]. Due to the co-infection with human immunodeficiency virus (HIV) in sub-Saharan Africa, there has been a 3-fold increase in TB cases [3]. Further, it has been noticed that poor case management that leads to resistance to TB, as well as multi-drug resistance (MDR), are causes of concern [3].

### **Female genital tuberculosis (FGTB)**

One of the most generally established extra-pulmonary TB diseases is female genital tuberculosis (FGTB) [6,7] that directs to female infertility [8-10]. The incidence of FGTB cases varies depending on geographical locations with cases being minimal in the United States (1%) [11] and a spike in cases in developing countries like Pakistan (3.5 to 23%) [12,13] and in various parts of India (1 to 19%) [7,14,15]. FGTB is also seen in countries like Sweden (1.4%) [16], Italy (0.8%) [17], Nigeria (16.7%) [18] and Saudi Arabia (4.2%) [19]. FGTB is quickly increasing over the years and 7 - 15% of times is seen as the cause of infertility in women [20]. In developing countries, FGTB is reported in women belonging to the fertile age group (20 - 40 years), whereas in developed nations, it is diagnosed in pre-menopausal women [21]. FGTB causes short and long-term consequences on women and in some cases can be fatal. Women with FGTB are involved with infertility due to fibrosis and scarring is observed as a part of the healing process [15]. Diagnosis of FGTB is relatively low because the course of the disease is slow and the examination is not very sensitive or specific [21]. A diagnosis can be made by detecting fast acid bacilli on microscopy or by culturing endometrial biopsy. Polymerase chain reaction (PCR) alone cannot be used as a diagnostic method as it can produce false positives. The best method for detection of FGTB is by laparoscopy and hysteroscopy [20]. Symptoms of FGTB include chronic pelvic pain, menstrual irregularities, and infertility. It has also been noted to coexist with endometriosis [22]. In 2016, Guo and colleagues showed that 5.8% off *in vitro* fertilization and embryo transfer were observed in FGTB patients [23]. The endometrium plays an important role in implantation and embryo development. When infected with TB, and even after treatment with anti-TB drugs, the damage to the endometrial blood flow and morphology is irreversible. This leads to female infertility as implantation is affected [21]. Hence, these women have to opt for assisted reproductive therapy (ART) like IVF as a treatment option to conceive. This paper aims to determine whether conventional IVF is successful as a treatment option in endometrial tuberculosis (ETB).

### **Endometrial tuberculosis**

The endometrium contributes to approximately 70% cases of FGTB. In the initial stages of endometrial tuberculosis (ETB), there is no macroscopic disease, symptoms such as caseation and ulceration occur in advanced stages of ETB. In Asherman's syndrome, the endometrium gets completely destroyed. This leads to secondary amenorrhea and infertility [15]. During the pre-menstrual phase near the endometrial surface, epithelioid cells, Langhans cells and TB granulomas can be seen when viewed microscopically. ETB can also be observed if there is complete destruction of the epithelium and if there is a group of lymphocytes that may or may not be accompanied by dilated glands, even if granulomas are absent [15].

### **What endometrial factors cause infertility in ETB?**

#### **Failed implantation is often observed with ETB**

First, there is a release of harmful cytokines and growth factors (GF) such as TNF $\alpha$ , IL8, and IL2 in the endometrium. This is followed by the production and release of symmetric antibodies (Ab), natural killer cells (NKC) and lymphocyte activates killer cells (LAKC). Instead of T-helper-2 cell (Th-2) the response that is required for successful implantation of the embryo, a shift is observed in the endometrium and

instead T-helper-1 cell (Th-1) initiates a response that leads to implantation failure. Repeated IVF failure was observed in Kolkata, India by Dam and colleagues due to latent FGTB [23].

**FGTB affects endometrial receptivity**

FGTB alters the endometrial markers necessary to make the endometrium receptive for implantation of the embryo. These markers include cellular adhesion molecules (CAM) families (i.e. cadherins, immunoglobulins, integrins, and selectins), mucins, cytokines, interleukins (IL-1 and IL-6), and prostaglandins [24].

**FGTB causes a defect in endometrial vascularization**

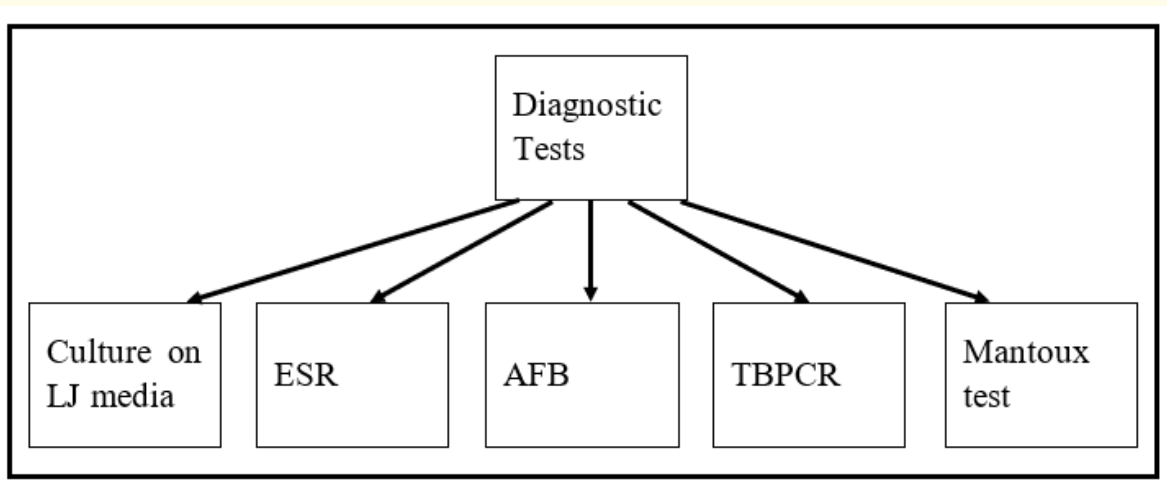
In FGTB patients, there is activation of antiphospholipid antibodies (Ab) with a prominent reduction in sub-endometrial blood flow that causes endometrial vascularisation. And alternate pathway is through the production of procoagulase enzyme with immunomodulation that results in vascular thrombus formation [25].

**Asherman’s syndrome is commonly observed with ETB**

In Asherman’s syndrome there is complete endometrial atrophy and synechiae formation which is accompanied by infertility due to failed implantation and amenorrhea [25].

**Lab diagnostic approach before frozen embryo transfer**

FGTB is observed worldwide, however, its diagnosis is still questionable. Diagnosis of FGTB at the earliest is important for treatment and to prevent any further complications of infertility. A basic family history of past TB cases is done, followed by an HIV test. After which a detailed examination of the external genitalia or transvaginal ultrasound is performed to determine FGTB [25]. A few common tests performed to confirm FGTB are highlighted in figure 1.



**Figure 1:** Flowchart of diagnostic tests for the detection of *Mycobacterium tuberculosis*.

**Culture of *Mycobacterium tuberculosis***

Culturing of *Mycobacterium* is a gold standard for detecting TB. Lowenstein-Jensen (LJ) growth medium is mostly used for the isolation and cultivation of *Mycobacterium* species, such as *Mycobacterium tuberculosis*. It was developed by Lowenstein and modified by Jensen. Initially, the media consisted of congo red and malachite green to inhibit the growth of unwanted bacteria. The glycerinated egg-based media present in the market today eliminates the use of congo red and uses an increased concentration of malachite green. This formulation encourages the growth of *Mycobacterium* for detection and differentiation of mycobacterial infections and different species respectively. *Mycobacterium tuberculosis* that is cultured on LJ medium appears in brown and granular colonies. Due to the slow doubling time of *Mycobacterium tuberculosis* (15 - 20 hours), the medium is incubated for longer periods of time (4 weeks) [27]. The media consists of potato starch and L-Asparagine that act as good sources of nitrogen and vitamins. Monopotassium phosphate and magnesium sulfate together act as buffers and amplifies mycobacterial growth. The egg suspension supplies proteins and fatty acids that are needed for the metabolism of Mycobacteria. The albumin in the egg coagulates when heated. This provides a solid surface for inoculation of Mycobacteria. Glycerol serves as a carbon source. Another modification of the media is by adding small amounts of penicillin, nalidixic acid, and RNA. This is known as the Gruft method. Penicillin and nalidixic acid prevent the growth of unwanted bacterium and stimulate the growth of *Mycobacterium* whereas RNA stimulates and enhances the isolation rate of *Mycobacterium*. A major drawback of this technique is the contamination with other strains of bacteria, fungi, and viruses. Therefore, aseptic techniques and care must be implemented when culturing *Mycobacterium* species [28].

Components	Concentration
Potato Starch	30.0g
L-Asparagine	3.6g
Monopotassium Phosphate	2.4g
Magnesium Citrate	0.6g
Malachite Green	0.4g
Magnesium Sulfate	0.24g
Glycerol	12 mL
Egg Suspension	1000 mL
Distilled Water	600 mL

**Table 1:** The ingredients and concentration of LJ media for the culture of *Mycobacterium tuberculosis*.

**Erythrocyte sedimentation rate (ESR)**

ESR is an easy, quick, and inexpensive diagnostic test used to determine whether there is any inflammation in the body. The principle behind this test is that normal erythrocytes will sediment slowly to the bottom of the test tube. Whereas, if any inflammation is present, sedimentation rates increase. A study conducted in Makassar, Indonesia showed that inflammation due to an elevation in plasma globulin and fibrinogen are the reason why ECR rates increase. And this is closely observed in the cases of TB. However, ESR rates increase in various cases of inflammation like in arthritis, and hence this test is not so specific with regards to TB. ESR plays a vital role in determining whether anti-TB drugs are working or not [29]. An ESR test was conducted on 100 HIV-negative subjects that were diagnosed with cases of pulmonary and extra-pulmonary TB. Out of these 100, 45 patients were diagnosed with extra-pulmonary TB and the remainder showed cases for pulmonary TB. ESR rates were higher in TB-infected patients, without co-infection with any other disease like HIV. This shows that this is a reliable test to determine TB, especially in underprivileged countries due to its low cost [30].

### **Acid fast bacilli**

AFB is a quick and simple test that gives a conjectural diagnosis of TB. This test requires a microscopic examination of the sputum from possibly infected personnel. Sputum smears in patients with TB that has a negative result for AFB is less prone to spread the disease than those with a positive smear. This tells us that in theory, they can transmit TB to other people. A clinic in San Francisco elucidated that AFB smears point out the severely infected patients. It was also observed that 17% of patients were recognized with TB (when the culture was done) transmission even though their test results were negative. This interpretation shows us that AFB is not the most optimal technique to determine TB [31]. Another study that contained a cohort of 100 infertile patients demonstrated that only 3 out of the 100 showed positive results with the AFB test, out of which one patient who was AFB test positive, was negative for the polymerase chain reaction (PCR) test [32]. These findings suggest that though the AFB culture test is considered a gold standard in detecting TB, other diagnostic approaches should be considered. In the case of FGTB patients, biopsies of the endometrium and endometrial aspirates are taken as samples for detection [32].

### **Tuberculosis polymerase chain reaction**

Tuberculosis Polymerase Chain Reaction (TBPCR) is a tool that is routinely adopted for the screening and diagnosis of TB. Studies have shown that it is a better method for the detection of TB. A study conducted in India compared results between TBPCR and AFB. It revealed that 56% of patients were positive for TBPCR but only 3.2% of patients were positive for AFB. Moreover, findings by Rozati., *et al.* (2006) demonstrated that if TBPCR of the endometrial biopsy was not conducted on these patients, 88.46% of patients would have been missed. Another study showed that TBPCR had a sensitivity of 96.4% [33]. BACTEC radiometric culture system has become available for usage instead of LJ media. The advantages of this media are that the mean detection rate is drastically decreased from 24.03 days by LJ media to 12.89 days by BACTEC, to 1 day using PCR [32]. This shows that PCR provides quick, robust results. However, many researchers have also seen false positives with PCR.

### **Mantoux test**

The Mantoux test or the tuberculin skin test was devised by Robert Koch and named after Charles Mantoux. This test is relatively common in investigating tuberculosis-positive patients as it is low in cost and can easily be performed in the clinic. This test involves injecting 5 tuberculin units sub-dermally into suspected patients. A positive response (a person who is infected with a disease) is observed in the skin of these patients as a delayed hypersensitivity reaction that takes 48 - 72 hours for inflammation to be visible. This hypersensitivity response is mediated by T-cells, macrophages, and monocytes. T-cells release lymphokines at the test site if they have previously been sensitized to tuberculosis [34]. Lymphokines will further cause inflammatory processing deposits macrophages, edema, erythema, and fibrin to the test site. Skin induration marks the end of the reaction [34]. A patient who is infected with the disease or has come into contact with other patients who were positive for tuberculosis show a response even to low doses of tuberculin [35]. A study by Raut., *et al.* (2001) showed that the Mantoux test has limited use in detecting genital tuberculosis in women [36]. A major disadvantage of this test is that it has very low sensitivity and specificity [37]. However, an advantage of using this technique is that detection of tuberculosis can be done in both symptomatic and asymptomatic individuals [37].

### **Assisted reproductive technologies (ART) in FGTB**

Women with FGTB have a poor prognosis for fertility and generally find it hard to conceive even after ART and anti-tubercular treatment [20]. FGTB decreases the conception rate in women as well as the live birth rates (LBR) [35]. The only option for these women affected with FGTB is either IVF/ICSI followed by embryo transfer (ET). But this is restrained to women with a good endometrium that is not damaged [20]. A positive PCR test that confirmed endometrial TB in women showed that fertility treatments help these women

conceive after their treatment with anti-TB drugs [36]. A different study showed that in patients with FGFB there is poor endometrial blood flow to the endometrium [37] and ovaries [38] which could lead to implantation or fertilization failure.

A study conducted at the Peking university third hospital by Lin and colleagues demonstrated that there was a total of 184 ETB cases that were detected by polymerase chain reaction (PCR) for the detection of *Mycobacterium* and by using AFB microscopy. These women were treated with anti-TB drugs for a period of 3 to 24 months between December 2010 and 2015. Out of 184 patients that were treated with anti-TB drugs, 71 did not return for ART treatment. The remainder of 113 cured patients opted for IVF using either fresh or frozen-thawed cycles. The control group (non-TB patients) included a total of 452 patients. In the TB group, it was observed that there was no statistical difference between fresh and frozen cycles in terms of clinical pregnancy rates (CPR), live birth rates (LBR), and spontaneous abortion rates. Cumulative clinical pregnancy rates were similar between the two groups however, cumulative live birth rates were lower, and spontaneous abortion rates were significantly higher in the TB group [21].

Unexplained repeated IVF failure in young Indian women is associated with latent FGFB. These women have IVF failure even with the normal-looking ultrasound of the pelvis and tubes [39]. Their pregnancy rates and LBR can be increased when detection is made earlier as there would be minimal damage to the female genital tract [38]. Treatment, however, remains controversial due to high false positivity in TB-PCR results. Many Indian fertility centers treat latent TB with the theory that treatment at an early stage will dismiss permanent damage to the endometrium and other genital organs with better IVF/ICSI results [15]. 31% CPR after anti-TB treatment was achieved by Kulshrestha, *et al.* (2011) in patients that were TBPCR positive [39]. Promising results were additionally noted by Jindal, *et al.* (2012), with a CPR of 30.8% after anti-TB treatment [36].

A cohort of 120 FGFB cases was taken and a pregnancy rate of 38.2% was observed by Malik, (2010), [42] after IVF followed by ET. Her patients were diagnosed through PCR and aggressive treatment was given to these patients till their endometrial biopsies came back with a negative result. Further, it was observed that there was no difference in pregnancy rates in patients that stopped or continued anti-TB drugs. Therefore, in FGFB patients after anti-TB drugs are administered, if their endometrium is receptive with no adhesions, IVF-ET is a good treatment option [42].

Another prospective study which contains 97 cases that determined the prevalence of TB in infertility and tubal factor infertility was conducted by the S.B.C medical college, India between the years 1988 and 2001. These patients were given prednisolone and short-term chemotherapy. The results from this study demonstrated that 58% of the time, infertility was observed in FGFB. After chemotherapy, patients were symptom-free and TB was not detected, however conception and live birth rates were relatively low. In these patients, IVF and ET can be performed [35]. However contradicting views were observed by Sharma, *et al.* (2016), who said that, if the endometrium is damaged, the only treatment option is either surrogacy or adoption. In women whose fallopian tubes are damaged, but endometrium was healthy, IVF and embryo transfer (ET) can be done [40].

Malik, *et al.* also suggests that if the endometrium is compromised and there is a small shrunken uterine cavity, surrogacy or adoption is a suitable option for them [42]. Similar suggestions are advised by Sharma, who says that if the ovaries are non-functional, the tubal blockage is seen or the endometrial receptivity is impaired, adoption is their best option [15]. It has furthermore been noticed that even Indian women who have migrated to Western countries have a poorer prognosis with IVF despite having similar embryo quality to Caucasian women. This may be due to the fact that these women have latent FGFB [43]. Additional studies by Sharma, *et al.* (2014) show that ectopic pregnancy is high in patients with FGFB in India [44].

## **Conclusion**

A common consequence of FGFB is infertility and a decline in pregnancy rates. In some FGFB patients ET would not be beneficial. From all these studies it can be noted that IVF/ICSI proves to be a good fertility treatment option in patients with a good endometrium.

The moment the endometrium gets impaired, it leads to implantation failure and subsequent pregnancy loss. The only option then for these women with FGTV is to opt for either surrogacy or adoption. Further studies are required for developing better detection methods of FGTV in the upcoming years.

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