

Effect of Genital Tuberculosis on Ovarian Reserve

Padma Rekha Jirge

Sushrut Assisted Conception Clinic and Shreyas Hospital, Kolhapur, Maharashtra, India

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Female genital tuberculosis (FGTB) is a known cause of infertility due to tubal damage and, less often, endometrial damage. However, its impact on ovarian damage is poorly understood and has only come to focus in recent years. Availability of robust ovarian reserve markers, such as anti-Mullerian hormone and antral follicle count, have contributed to an improved understanding of ovarian reserve in FGTB. Pre-treatment assessment of ovarian reserve and ovarian response during *in vitro* fertilization has shown that FGTB adversely affects the ovarian reserve. Interestingly, there is some evidence that treatment with antitubercular therapy may lead to both qualitative and quantitative improvement in ovarian reserve. As it appears to be a reversible cause of poor ovarian reserve, timely diagnosis and treatment may lead to an improvement in fertility outcome in women affected with FGTB.

Keywords

Female genital tuberculosis, latent genital tuberculosis, infertility, ovarian reserve, anti-Mullerian hormone

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Corresponding Author: Padma Rekha Jirge, Sushrut Assisted Conception Clinic & Shreyas Hospital, 2013 E, 6th Lane, Rajarampuri, Kolhapur – 416 008, Maharashtra, India. E: rekha.jirge@gmail.com

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Tuberculosis (TB), caused by *Mycobacterium tuberculosis*, continues to be a major cause of ill health and the most common cause of death attributed to a single microbial agent, across the world.¹ However, an important limitation to the efforts of World Health Organization (WHO) for ending TB is the presence of a large reservoir of latent TB infection.² In addition to the annual incidence of 8–10 million of pulmonary and extrapulmonary TB cases, nearly one-third of the world's population harbors latent TB infection.³ Though it is not communicable in itself, latent TB infection has a high conversion rate of 5–10% to active disease.^{2,3} This occurs usually within the first 5 years of initial infection, which is further accelerated in immunocompromised individuals.^{2,3} Importantly, it elicits an immune response from the host tissue to *Mycobacterium tuberculosis* antigens, with consequent damage to host tissue.^{3–6}

Genital TB (GTB) accounts for 9–15% of extrapulmonary TB.^{7–9} It is the underlying cause for infertility in 5–20% of women who are infertile.^{10–14} Further, infertility may be the sole symptom of female genital tuberculosis (FGTB) due to its paucibacillary nature.^{14–17} The implications to fertility as a result of tubal or endometrial damage are well-documented.^{18–22} Tuberculous involvement of the cervix, vagina, or vulva is rare and accounts for 5% of FGTB;^{23–27} the association of TB in these organs with infertility remains unexplored. Ovarian involvement is found in up to 30% of women with FGTB;^{11,13,28} however, its impact on female reproductive health is only beginning to be explored.^{29–31}

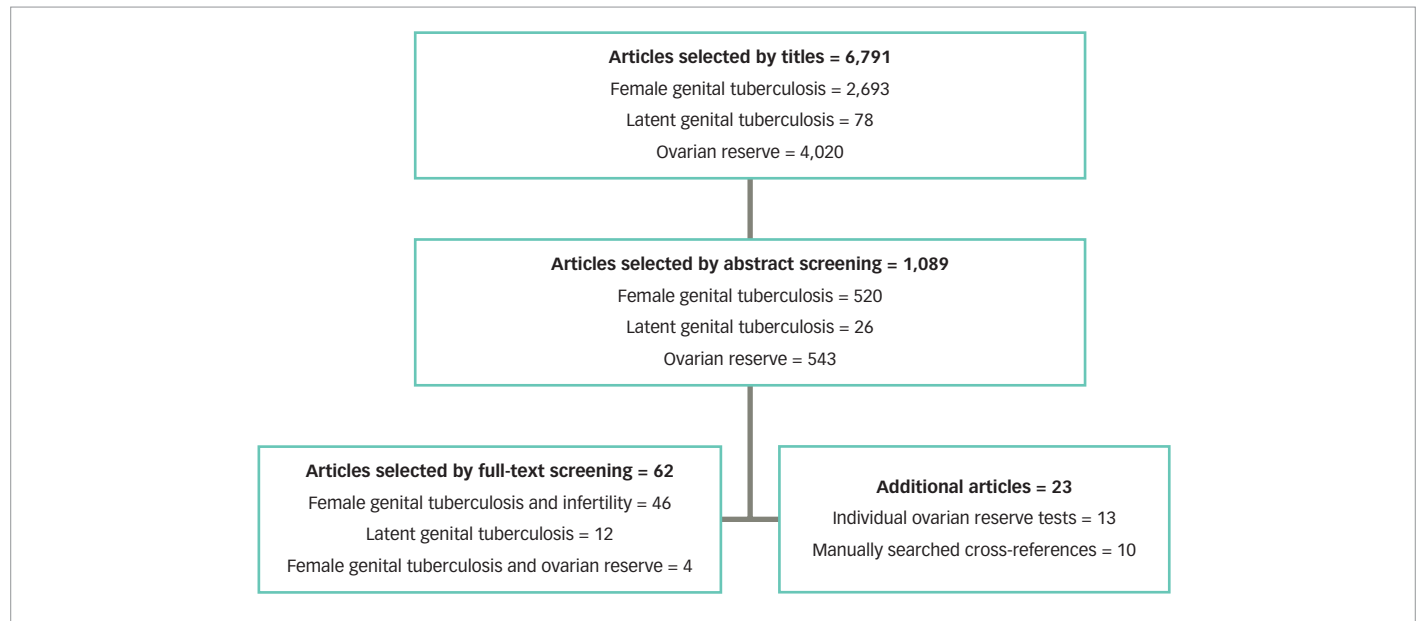
A comprehensive understanding of the impact of FGTB on reproductive health is necessary due to an increasing incidence of TB, even in low-burden countries, due to transnational and transcontinental migration of people from high-burden countries, and an accelerated conversion of latent TB infection to active TB in immunocompromised individuals.^{12,20,22,32} This narrative review critically looks at the role of FGTB on ovarian reserve and its implications to reproductive health of women.

An electronic literature search was performed in Medline (1966–2020) using search terms “female genital tuberculosis”, “latent genital tuberculosis”, and “ovarian reserve”. A total of 6,791 articles were retrieved. All studies that included 10 or more patients evaluating ovarian reserve in women who are infertile with FGTB, were included. Further searches were made for individual diagnostic modalities for FGTB and ovarian reserve tests using their titles as key words. Appropriate cross-references were manually searched. The search strategy is shown in *Figure 1*.

Genital tuberculosis and ovarian function

Ovarian damage consequent to a tuberculous ovarian abscess or tubo-ovarian mass is seen in up to 25–30% of women with suspected or diagnosed FGTB on ultrasound and/or laparoscopic assessment.^{19,23,33} Decline in ovarian reserve in such women, due to loss of part or all of the ovary, is evident. However, more subtle damage to ovarian function and ovarian reserve cannot be ruled

Figure 1: Flow chart of literature search strategy



out, even when the disease remains latent and entirely undetected.^{30,34} The paucibacillary nature of FGTB, its latency, the challenges involved in its diagnosis, and the diminished ovarian reserve are important limitations in understanding the association between FGTB and ovarian reserve.

Diagnosis of ovarian involvement in female genital tuberculosis

Radiological investigations such as transvaginal ultrasonography, hysterosalpingography, and magnetic resonance imaging (MRI); and endoscopic assessment by laparoscopy and hysteroscopy are useful modalities for pelvic evaluation and for clinical diagnosis of FGTB.^{19-21,33,35-40} Ultrasound findings of edematous ovaries, complex tubo-ovarian masses, calcification spots in ovaries, or hydrosalpinges should raise the possibility of FGTB.³³ MRI is helpful in the evaluation of a complex adnexal masses when the ultrasound findings remain inconclusive.³⁷ Further, both these modalities provide a comprehensive, non-invasive assessment of the pelvis and abdomen. However, the paucibacillary nature of FGTB makes bacteriological diagnosis through conventional methods challenging.^{14,41-43} Smear and microscopy, histopathology, and bacterial culture all require a high bacterial load for the diagnosis of TB. In addition, bacterial plasticity and mechanisms leading to latency result in loss of culturability.^{44,45}

Difficulties in obtaining an adequate tissue biopsy from various affected areas without causing further damage to the female genital tract makes endometrial tissue the most widely used source for bacteriological diagnosis of FGTB.^{38,41} Concerns regarding invasive nature of ovarian biopsy and risk of adhesion formation are important reasons against performing an ovarian biopsy.^{46,47} Possible damage to ovarian reserve and missing an area of localized infection are additional reasons for not performing an ovarian biopsy to establish a bacteriological or molecular diagnosis of ovarian TB. A single study evaluating the role of endo-ovarian biopsy in diagnosing FGTB found it to be an effective tool for diagnosis, identifying mycobacterial DNA in one-third of the biopsies; however, the study did not address the safety issues of the procedure.⁴⁸

Molecular diagnostic tests, in particular, DNA polymerase chain reaction (PCR), are increasingly used for the diagnosis of extrapulmonary TB, including FGTB.^{14,20,41,49-51} Molecular tests have high sensitivity and specificity in diagnosing paucibacillary conditions as they require very few copies of bacterial DNA. Multiplex DNA PCR, using gene probes specific to bacterial genotypes most prevalent in different geographic areas, are reported to be of high diagnostic value.^{14,51-54}

When FGTB is clinically suspected in an infertile woman with a tubo-ovarian mass in the absence of bacteriological or molecular confirmation, other causes of pelvic infection, endometriosis, and even ovarian malignancy should be considered and excluded.⁵⁵⁻⁶⁰ Conversely, women with protracted, unexplained infertility may benefit from an active evaluation for FGTB.

Ovarian reserve in female genital tuberculosis

The previous section highlights the difficulties in establishing a direct bacteriological diagnosis of ovarian TB. Hence, ovarian reserve assessment has been used as a surrogate marker to identify ovarian damage in those with FGTB.^{29,30,61} Ovarian reserve is the quantitative measure of primordial follicular pool. It shows a progressive decline with age and is accompanied by a qualitative decline in those older than 38 years of age.⁶²⁻⁶⁴ Ovarian reserve is assessed in two different ways. Historically, response to conventional protocols of ovarian stimulation in the first cycle of IVF has been considered as the "gold standard."⁶⁵⁻⁶⁷ Dose of gonadotropins required, duration of ovarian stimulation, and oocyte yield constitute the ovarian response and offer a post-treatment understanding of ovarian reserve.⁶⁴ However, pre-treatment assessment of ovarian reserve to predict ovarian response to *in vitro* fertilization (IVF) has become a routine practice in recent years. This includes endocrine markers of basal follicle-stimulating hormone (FSH), inhibin-B, anti-Mullerian hormone (AMH), and ultrasound markers of antral follicle count (AFC) and ovarian volume.⁶⁵⁻⁶⁸ AMH is the most widely used marker to predict ovarian response in IVF, due to its minimal intracycle and intercycle variations, and its high sensitivity and specificity, similar to that of AFC.⁶⁹⁻⁷³ In addition, AMH is the earliest marker to unmask declining

Table 1: Studies evaluating ovarian response *in vitro* fertilization and ovarian reserve in women who are infertile with genital tuberculosis

Study	Patient population	Parameters evaluated	Findings
Gurgan et al. 1996 ⁶¹	Comparative study: 24 women with tubercular tubal factor versus 366 with non-tubercular tubal factor	– Pre-IVF basal FSH – Ovarian response during IVF – Clinical pregnancy rate – Miscarriage rate	Women with GTB: – Higher basal FSH – In IVF: increased gonadotropin requirement reduced peak estradiol reduced oocytes, embryos low clinical pregnancy rate increased miscarriage rate
Dam et al. 2006 ³⁴	Latent GTB and RIF in IVF: 40 women with RIF before and after ATT	IVF parameters—pre- and post ATT: – Ovarian response – Clinical PR	Post treatment with ATT: reduced gonadotropin requirement increased oocyte yield higher grade I embryos increased clinical PR
Malhotra et al. 2012 ²⁹	Cross-sectional study: 104 infertile women with GTB versus 104 healthy fertile controls	– Basal FSH, LH, inhibin B – Ovarian volume, AFC – Ovarian stromal blood flow on doppler	In women with GTB: elevated basal FSH, LH low inhibin-B low ovarian volume and AFC reduced PSV and PI
Sharma et al. 2016 ³¹	Longitudinal Study: 50 women with GTB – Ovarian reserve markers pre- and post ATT	– FSH, AMH, AFC, ovarian volume – Ovarian Doppler—PSV, PI, and RI	Post ATT: improved AMH and AFC Improved Doppler parameters
Jirge et al. 2018 ³⁰	Comparative Study: 395 infertile women with latent GTB versus 383 infertile women with unexplained infertility	– FSH, AMH, AFC – Pregnancy outcome post ATT	In women with latent GTB: low AMH and AFC Post ATT: In ovulation induction—higher PR In IVF—better embryo grades despite less oocytes and higher PR

AFC = antral follicle count; AMH = anti-Müllerian hormone; ATT = antitubercular treatment; GTB = genital tuberculosis; FSH = follicle stimulating hormone; IVF = in vitro fertilization; LH = leutinizing hormone; PI = pulsatility index; PR = pregnancy rate; PSV = peak systolic velocity; RI = resistance index; RIF = recurrent implantation failure; TB = tuberculosis.

ovarian reserve even in young women, compared with any other marker of ovarian reserve.^{74,75} As AMH and AFC show an age-related decline, the diagnosis of poor ovarian reserve would be based on age-specific abnormal values, where population-based nomograms exist.^{76,77} However, an AMH of <1.2 ng/mL or AFC <5 in anyone below 40 years of age would be considered as indicators of poor ovarian reserve.⁷⁸

Suboptimal outcomes in women with FG TB undergoing IVF have been reported since the early years of IVF. Women with FG TB-associated tubal factor infertility have been seen to have lower pregnancy rates compared to those with non-tuberculous tubal infertility.^{61,79} Evidence from different patient populations has consistently revealed suboptimal ovarian response in women with FG TB. They exhibit an increased requirement of gonadotropin and duration of ovarian stimulation, and yield a lower number of oocytes and/or embryos during IVF.^{30,34,61} A study comparing ovarian response in women with latent GTB before and after antitubercular therapy has shown an improvement in ovarian response, including oocyte yield and embryo quality post-treatment.³¹

With the advent of endocrine markers for assessing ovarian reserve, attempts have been made to evaluate the effect of FG TB on ovarian reserve prior to IVF. Basal FSH, the oldest marker utilized to predict poor ovarian reserve, was found to be higher in women with FG TB compared to those with other causes of infertility during pre-IVF assessment.^{29,61}

Inhibin-B levels and AFC were lower in those with FG TB compared to healthy controls.²⁹ Importantly, evidence from a single large study shows that AMH and AFC are lower in women who are infertile with latent GTB without any laparoscopic evidence of TB compared to those with unexplained infertility.³⁰ The above evidence, albeit limited, does indicate an adverse impact of FG TB on ovarian reserve, and is summarized in *Table 1*.^{29-31,34,61}

Mechanism of ovarian injury in female genital tuberculosis

The mechanism/s of ovarian damage in FG TB remain poorly understood. A lipid, nitric oxide, and steroid-hormone-rich environment in the ovary may encourage both infection and its latency. Conditions such as endometriosis leading to altered local immunity may further enhance the occurrence of FG TB.⁵⁹ In those with ovarian abscess or clinically diagnosed oophoritis, inflammatory and vascular damage, followed by fibrosis similar to that seen in pulmonary TB, can be anticipated. Ovarian Doppler assessment has shown high resistance flow in the ovarian arteries in women with FG TB and poor ovarian reserve.^{29,31} However, when ovarian involvement is not diagnosed clinically, and in latent TB, there may be a combination of immunological and endocrine response resulting in chronic inflammatory damage.^{5,80-82} Alternatively, the damage may preferentially be to the growing pool of follicles, as observed during gonadotoxic chemotherapy.⁸³ This, in part, may explain the rise in AMH following antitubercular therapy

indicating restoration and recruitment from the unaffected primordial follicular pool.

Treatment of female genital tuberculosis

Treatment of FGTB involves standard antitubercular therapy for 6 months. This includes oral administration of four drugs—isoniazid, rifampicin, ethambutol, and pyrazinamide—for the initial 2 months of the intensive phase, followed by the first three drugs (isoniazid, rifampicin, ethambutol) for another 4 months of the continuation phase.¹⁴ Current evidence suggests improved pregnancy outcomes following treatment of FGTB, both with simple forms of treatment and IVF.^{30,34,84}

Fertility outcomes following antitubercular therapy

The evaluation of endocrine and Doppler parameters in women with FGTB, before and after antitubercular therapy, has shown an improvement in AMH, AFC, and other Doppler parameters.³¹ It is known that the pregnancy rate in IVF is influenced by the number of oocytes.⁸⁵ Observation from IVF in women previously treated for FGTB does not conform to this norm. On the contrary, they have higher number of good-quality embryos and a higher pregnancy rate compared to those with unexplained infertility, despite lower AMH and oocyte yield.³⁰ Similarly, in women with recurrent implantation failure diagnosed and treated for latent TB infection, improved ovarian response and embryo quality is noted in comparison to their failed IVF cycles.³⁴ This does suggest a qualitative improvement in the ovarian environment following antitubercular therapy. Also, these findings support the hypothesis that the adverse impact on ovarian reserve, due to FGTB, may be halted or even reversed with antitubercular therapy. This is very important in the context of poor ovarian reserve, encountered in about 20% of women who are infertile, and its negative correlation with fertility.^{64,86} Further, women with poor ovarian reserve are likely to experience early menopause.⁸⁷ These concerns underline the importance of active evaluation of women with infertility due to FGTB in high-burden countries, and selective screening and investigation in low-burden countries.²²

A high index of suspicion, molecular diagnostic tests on endometrial tissue, and assessment of ovarian reserve markers are necessary to diagnose both the infection and its adverse impact on ovarian function. There is a need for clarity on the diagnostic tests with high accuracy, that are effective in both latent and active conditions. Serological investigations do not have any place in the diagnosis of genital infection in high-burden countries.² Additionally, awareness among clinicians regarding the need for evaluation of ovarian reserve in women with suspected or confirmed FGTB is important. It would be interesting to evaluate any difference in the magnitude of reduction in ovarian reserve amongst those with clinically diagnosed and latent FGTB. A composite reference standard of infertility and the presence of one additional clinical, radiological, endoscopic, or endocrine criterion may be used to compare the diagnostic efficacy of bacteriological or molecular tests. Judicious application of tests is of paramount importance in view of the limited volume of samples available for any assessment. Very young women may pose a challenge as AMH reaches its physiological peak at 25 years of age.⁸⁸ Prevailing evidence also emphasizes the need for a strategy to evaluate all women with refractory infertility in high-burden countries and selectively in low-burden countries for FGTB.

Conclusions

Current evidence highlights an adverse impact of FGTB, including latent GTB, on ovarian reserve. Though the actual incidence of ovarian involvement in FGTB may not be known at present, its negative effect on ovarian reserve is seen in both pre-treatment assessment and following ovarian stimulation during IVF. With a lack of consensus regarding timing and type of investigations for FGTB, it is likely being underdiagnosed. Treatment with antitubercular therapy improves the fertility outcome in women with GTB and may also lead to an improvement in ovarian reserve. Development of a policy of selective or universal testing for FGTB in women who are infertile in low- and high-burden countries, respectively, is necessary to reduce the growing burden of poor ovarian reserve in women who are infertile. □

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