

## SYSTEMIC REVIEW

# Genital Tuberculosis and Infertility: A Comparative Analysis of Imaging Modalities

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## ABSTRACT

**Background:** Female genital tuberculosis is caused by *Mycobacterium tuberculosis* and occurs usually secondary to pulmonary tuberculosis or other organs with infection reaching through hematogenous route, lymphatic route or direct spread from abdominal tuberculosis. Diagnosis of genital tuberculosis is often made from history taking, meticulous clinical examination and use of investigations such as endometrial aspirate/biopsy and endoscopy. Female genital tuberculosis damages the genital organs causing menstrual dysfunction and infertility. The aim of the study was to evaluate co relation of genital tuberculosis with infertility and role of imaging modalities in diagnosing genital TB. During December 2020 we searched Google scholar, pub med, Medscape research articles from 2010 -2020.

Genital TB is one most common cause of infertility in developing countries while diagnostic ultrasonography plays a limited role to diagnose. Laprothysteroscopy and histo-pathological analysis are confirmatory for genital tuberculosis.

**Keywords:** Genital tuberculosis, Infertility, Pyosalpinx, Tubo-ovarian mass, Ultrasonography and Hysterosalpingography.

## INTRODUCTION

Despite a declining trend in mortality, efficient diagnosis and treatment, tuberculosis is still a major health problem worldwide. In year 2015, almost 10.4 million individuals developed TB and 60% tuberculous cases were seen in Western Pacific and South-East Asian Regions.<sup>1</sup> Pulmonary tuberculosis is prevalent in more than two-thirds of patients. Extra-pulmonary tuberculosis develops in lymph nodes, genitourinary tract and genital ulcers which account for 10-15%.<sup>2</sup> Genital tuberculosis occurs usually secondary to pulmonary tuberculosis or other organs with the infection reaching genital region via lymphatic route, hematogenous route or direct spread in case of abdominal tuberculosis. *Mycobacterium tuberculosis* is the organism which is thought to be culprit in pathogenesis of tuberculosis.<sup>3</sup> In year 1744, Morgagni first reported female genital tuberculosis on young woman's autopsy who died of tuberculous peritonitis. The incidence of genital tuberculosis is increasing in young women all over the world.<sup>4</sup> Although genital tuberculosis can occur in any age group, 75% cases belongs to 20-45 years age group and 7-11% are females of post-menopausal age group.<sup>5</sup> High-risk factors for tuberculosis included overcrowding, poverty, poor ventilation, diabetes, lack of healthcare provision, kidney ailment, illegal drug use and human papilloma virus infection.<sup>4,6</sup> Genital tuberculosis is a chronic disease with non-specific clinical presentation of PID that is resistant to medical treatments.<sup>2</sup> The commonest presenting symptoms is infertility (42.5%), other clinical presentations are menstrual irregularities such as amenorrhea, oligo-menorrhea, menorrhagia, abnormal vaginal discharge and dysmenorrhea. In postmenopausal women, genital tuberculosis exhibits symptoms resembling endometrial malignancy, such as postmenopausal bleeding, leucorrhoea and pyometra.<sup>7</sup> In some cases, genital tuberculosis can coexist with other gynaecological pathologies such as PID, genital carcinomas or ectopic pregnancy<sup>8-9</sup>. The uterine tubes are involved in 90% women with genital tuberculosis, endometrium in 70% cases and ovaries in about 25% women. Diagnosis of genital tuberculosis is established after detailed history taking, diligent clinical examination and appropriate investigations such as ultrasound, HSG, MRI, endometrial aspirate/biopsy and endoscopy.<sup>3</sup> Early detection and commencement of treatment regimens in proposed dosage can decrease damage to genital organs and infertility.

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## MATERIAL AND METHODOLOGY

**Search strategy:** International databases {Google scholar, PubMed and Web of Science} and National databases {Magiran and Scientific Information Database} were searched for relevant studies which were published until 2020 December. All words like Genital tuberculosis, Infertility, Pyosalpinx, Tuboovarian mass, Ultrasonography and Hysterosalpingography. We studied 55 articles and applied additional methodological filter for paper selection and searched articles published between 2010 -2020. 40 articles were selected for systematic review. Articles containing data from Asia were preferred.

## DISCUSSION

Genital tuberculosis is a rare form affecting mainly the women of reproductive ages. Despite of significant decrease in prevalence of genital tuberculosis in developed countries, this specific type of tuberculosis is most challenging health problem in developing countries.

**Infertility:** Infertility is defined as failure to conceive after one year of regular unprotected sex.<sup>10</sup> The reported rate of infertility in Pakistan is 21.9%, out of which 3.5% have primary causes of infertility and 18.4% accounts for having secondary causes.<sup>11</sup> During 2010 to 2011, an epidemiologic survey at Fatemeh Hospital in Hamadan was carried out to rule out the causes of infertility. This epidemiological survey revealed that the prevalence of primary infertility was 69.5% whereas the secondary infertility accounts for 30.5% cases respectively. Among the causes of female infertility high prevalence was noted in cases with menstrual disorders, diabetes, thyroid diseases, obesity, uterine factor, fallopian tubes, ovulation dysfunction and cervical factor.<sup>12</sup>

**Genital TB and infertility:** It is asymptomatic in most cases, therefore commonly diagnosed accidentally on infertility referrals. Infertility is the most common marker of pelvic tuberculosis and accounts for about 40 to 70% of the complaints with which the patients visits the infertility clinics.<sup>13</sup> Studies have demonstrated that there is close relationship between infertility and genital tuberculosis. Researchers have concluded that infertility is the most common complication in patients with genital tuberculosis<sup>14</sup>. The exact incidence of infertility and genital tuberculosis is not yet defined, but in areas where incidence of tuberculosis is high, genital tuberculosis is the main cause. From 1st Jan 2013 to 31st Dec 2013, a prospective study assessed the causes of infertility by laparoscopy at Imdad hospital & Mahnaz Laparoscopy Center, Quetta which revealed that 54.3% patients comprised of primary

infertility and 45.7% patients had secondary infertility secondary to tuberculosis, pelvic inflammatory disease, polycystic ovaries, endometriosis and previous surgery. The study further demonstrated that out of the total infertile females, 22.9% of the cases had pelvic tuberculosis, concluding that pelvic tuberculosis was most common pathology causing infertility.<sup>15</sup> According to a study carried out to determine the prevalence of genital tuberculosis among infertile patients at the Obstetrics and Gynecology Unit-I, Allied Hospital, Faisalabad a very high frequency of female genital tract tuberculosis was found among infertile patients. The histopathological and bacteriological examination of endometrial biopsy and laparotomy of these females revealed tuberculous endometritis in 80% of cases.<sup>16</sup> A study at university of the Philippines manila general hospital was carried out to determine the clinical presentation, prevalence and treatment outcomes in patients diagnosed with disseminated tuberculosis from January 2011 to December 2015 which revealed that the prevalence was 1.7%, most common presenting symptoms was abdominal pain and the most commonly involved site was lungs in about 86% cases. Other sites involved were the gastrointestinal tract (22%), the vertebra (27%) and genitals (13%)<sup>17</sup>.

**Sites of genital TB:** Most patients had multifocal female genital tuberculosis with involves extra-genital involvement especially the peritoneum or lymph node. The most commonly involved organs are uterine tubes in 63.84% cases, ovaries in 46.15%, endometrium in 38.46% and the cervix in about 23.07% cases.<sup>18</sup> According to a study performed to identify the rate, clinical presentation and diagnostic technique for genital tuberculosis, genital tuberculosis accounts for 1.32% of all tuberculous cases. Tuberculous endometritis was detected in 72.03% cases, whereas 34.03% had tubal involvement, 12.9% had ovarian tuberculosis and 2.4% patients suffered cervical tuberculosis<sup>19</sup>.

**Involvement of Fallopian tubes:** In 90% cases, fallopian tubes are involved and it may be tuberculous exosalpingitis, endosalpingitis, interstitial tuberculous salpingitis or salpingitis isthmica nodosa. Hematogenous route of spread is seen in tuberculous endosalpingitis. The infection starts from endosalpinx causing swollen and irregular uterine tubes leading to complications such as formation of pyosalpinx, hydrosalpinx, tubo-ovarian mass and dense adhesions<sup>6 20</sup>.

**Involvement of endometrium:** The endometrium is affected through lymphatic, hematogenous or contagious route. No obvious lesions are seen in the endometrium initially but gradually ulcers formation is noted. In advanced stage, synechiae causes distortion of the anatomy of uterus. Asherman's syndrome causes destruction of the endometrium which manifests as amenorrhea and infertility<sup>21</sup>.

**Involvement of ovaries:** Ovaries are affected with caseation, adhesions, adnexal mass or cyst formation with defect in ovarian reserve and function followed by complete destruction of ovary in some cases. Patient with tubo-ovarian cyst presents as acute abdomen mimicking acute appendicitis. It is accurately diagnosed on laparoscopy or during laparotomy.<sup>22</sup>

**Imaging Modalities:** Diagnosis of female genital tuberculosis is often made from detailed history taking, clinical examination and specific investigations. The two imaging techniques useful in the diagnosis of female genital TB are ultrasonography (USG) and hysterosalpingography (HSG). Other modalities are MRI, endometrial biopsy and endoscopic evaluation.

**Ultrasonography:** Ultrasound is first line radiological investigation carried out for the diagnosis of genital tuberculosis. The specific diagnostic criteria for genital tuberculosis on transvaginal ultrasound is free fluid, dilated fallopian tubes and a cystic mass.<sup>23</sup> The uterine tubes may appear thickened, dilated and sometimes may be filled with clear fluid called hydro-salpinx or a thick caseous material termed as pyo-salpinx.<sup>24</sup> Most common appearances in female diagnosed with genital tuberculosis is tuberculous endometritis with salpingitis. Fig 1. shows transvaginal pelvic ultrasound appearance as thickened hypoechoic endometrium and

fallopian tube. Fig 2 shows transvaginal pelvic ultrasound appearance of chronic tuberculous endometritis which appears as a heterogeneous endometrium with a tiny focus of calcification. The endometrium appears heterogeneous with hyper-echoic areas of foci of calcification, adhesions or fibrosis and a distorted uterine cavity<sup>24</sup>. Sometimes free and loculated peritoneal fluid may be seen. The heterogeneous enlargement of ovaries containing follicles with echogenic rims are also revealed on ultrasonography. In 2019 a study was carried out at Women's Hospital, Zhejiang University to evaluate the sonographic findings and clinical features of infertile women who were diagnosed with female genital tuberculosis. It revealed that endometrial tuberculosis presents with intrauterine adhesions and a heterogeneous endometrium whereas in cases with tubal tuberculosis hydrosalpinx and thickened fallopian tube are seen, peritoneal tuberculosis represents as free or loculated peritoneal fluid or may exhibit a pelvic mass<sup>25</sup>.

**Hysterosalpingography:** Hysterosalpingography plays important role in evaluation of the internal structures of the female genital tract and tubal patency. In patients with genital tuberculosis, hysterosalpingography is an excellent imaging modality for evaluation the abnormalities of the fallopian tubes. The presentation of tubal tuberculosis varies from non-specific pattern which may be tubal dilatation, hydrosalpinx, irregular contour, tubal occlusion or diverticular outpouching to specific changes such as pipestem tube, cotton wool plug, golf club tube, beaded or cobblestone tube, leopard skin tube, tubal occlusion and adhesions in the peri-tubal region which shows as straight spill, peri-tubal halo and corkscrew appearance.<sup>26</sup> Fig 3. Shows hysterosalpingographic appearance of genital tuberculosis showing bilateral tubal blockage<sup>24</sup>.

**Computerized axial tomography:** In patients with genital tuberculosis, abdomino-pelvic mass with ascites in appreciated on CT-scan report. The peritoneum may be thickened and appear as enhanced. Sometimes lesions within abdominal organs and lymph node are also identified on CT-scan<sup>27</sup>.

**Magnetic Resonance Imaging:** MRI plays important role in diagnosing genital tuberculosis. It has high-resolution and may reveal tubo-ovarian masses in patients with genital TB. Other features may include a heterogeneous masses involving both ovaries, nodular peritoneal implants with diffusion restriction, free fluid in the pouch of douglas and pathological post-contrast enhancement (Fig.5 and Fig.6). Hydrosalpinx, adnexal cysts, tubo-ovarian masses or tuberculous deposits on liver and peritoneum are reported on MRI.<sup>28</sup>

**Positron-emission tomography scan:** PET scan shows tubo-ovarian masses, which may be unilateral or bilateral with increased FDG uptake by the tuberculous lesion. Fig.4 shows PET and CT scan showing unilateral increased fluoro-deoxy-glucose uptake in tubo-ovarian masses<sup>29</sup>.

**Hysteroscopy:** Hysteroscopy is endoscopic visualization of endometrial cavity. In early disease and in cases when endometrial is not affected, hysteroscopy may be normal<sup>2</sup>. Hysteroscopy may reveal a pale looking endometrial cavity, small caseous nodules, tubercles, synechiae and Asherman's syndrome<sup>30</sup>. According to a study, the most common presentations on hysteroscopy are irregular thin endometrial thickness which may be dirty in appearance or pale with white deposits on the surface of endometrium. Presence of adhesions and a small distendable uterine cavity may be seen<sup>31</sup>.

**Laparoscopy:** A laparoscopy is the most reliable imaging modality for detection of genital tuberculosis and abdominopelvic tuberculosis, particularly affecting the fallopian tubes, ovaries and peritoneum. It is generally performed under general anaesthesia and it is performed with hysteroscopy. Careful visualization of the peritoneal cavity along with pelvis is achieved by rotating the laparoscope systematically by 360 degrees to observe lesions of tuberculosis and any other coincidental findings.<sup>7</sup> In 2020 an article was published to study the efficiency of laparoscopy in detecting genital TB in infertile females. The study assessed diagnostic

accuracy of PCR as compare to conventional investigations for the diagnosis of genital TB in endometrial aspirates in women with unexplained infertility. This concluded that PCR is a diagnostic test for endometrial tuberculosis, but is not justifiable to confirm diagnosis solely on PCR and initiate anti-tuberculous therapy.<sup>32</sup> A descriptive study was carried at Military Hospital Rawalpindi, Pakistan to study the causes of female infertility, diagnosed at laparoscopy. It was concluded that the commonest etiological factor was tubal blockade and laparoscopy is minimally invasive technique for visualization of internal structure of the female pelvis.<sup>33</sup> Various laparoscopic findings of genital tuberculosis are illustrated in Fig.7-8 as congested inflamed hydrosalpinx, tobacco pouch, beaded tube, tubo-ovarian masses, tubercles on uterus, fallopian tubes and ovaries, adhesions, frozen pelvis, caseous nodules in utero-vesicle pouch<sup>34</sup> and omental adhesions.<sup>8</sup>

**Endometrial biopsy, curettage or aspirate:** Endometrial curettage and biopsy is performed in the luteal phase (day 21) of menstrual cycle. Efforts are made to achieve microbiological confirmation. Multiple biopsies may increase pick up rate of pathology. The diagnosis of tuberculosis is confirmed on presence of epithelioid cell granuloma with multinucleate giant cell and caseous necrosis, but a definite evidence is established on histopathology by demonstrating mycobacteria on culture or smear.<sup>20</sup> A clinico-pathological report of genital tuberculosis was carried out at Hassan University hospital, Morocco from 2006 to 2016. The diagnosis of female genital TB has been made by histological analysis which concluded that the fallopian tubes are most affected (63.84%) genital organs. The histopathological report reveals granulomatous lesions with caseous necrosis.<sup>18</sup> Fig.9 shows histopathological appearance of genital tuberculosis as multiple granulomas with multinucleated giant cells in the endometrial stroma.<sup>30</sup> According to a study carried out in year 2019 at Gynecological Tumor Centre and European Competence Centre for Ovarian Cancer, Institute of Pathology, Berlin, Germany, even after significant ultrasound and laparoscopic findings the histological investigation should be carried out for confirmation of genital tuberculosis.<sup>35</sup> A study carried out to evaluate the clinical utility of polymerase chain reaction as compared to other diagnostic modalities in diagnosing of genital tuberculosis causing infertility in year 2011 stated that since hysteroscopy, laparoscopy and other endoscopic procedures are associated with operative risks and other laboratory tests such as histopathology have poor sensitivity, as compared to other conventional methods of diagnosis, PCR-based detection of 65 kDa gene of *Mycobacterium tuberculosis* in endometrial biopsy specimens could be a promising molecular diagnostic technique<sup>36</sup>.

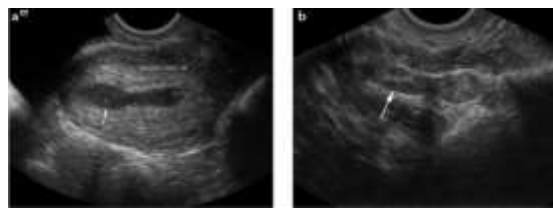


Fig 1. a, b. Tuberculous endometritis with salpingitis in a 26-year-old woman with primary infertility and oligomenorrhea. Transvaginal pelvis US shows a thickened hypoechoic endometrium (a, arrow) and a thickened undilated right fallopian tube (b, arrow). Endometrial curettage performed later, yielded positive tuberculous culture.<sup>28</sup>



Fig 2. Chronic tuberculous endometritis in a 28-year-old woman with primary infertility. TVS image of the uterus shows a heterogeneous endometrium with a tiny focus of calcification (arrow).<sup>28</sup>

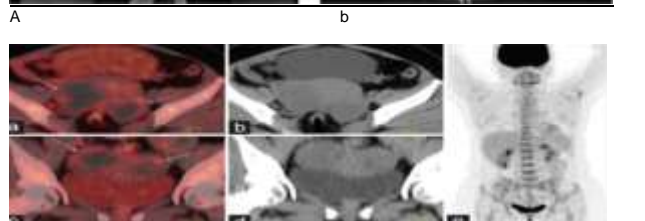
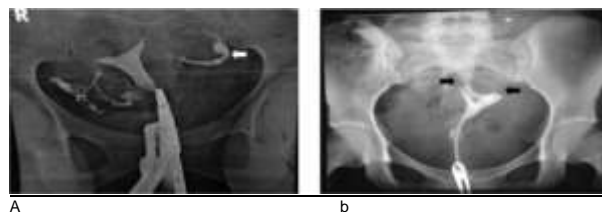


Fig.4 A 36-year-old female presented with genital tuberculosis. She received antitubercular therapy. She was referred for 18F-fluorodeoxyglucose-positron emission tomography/computed tomography scan. (a and b) Axial fluorodeoxyglucose-positron emission tomography/computed tomography and computed tomography, (c and d) Coronal fluorodeoxyglucose-positron emission tomography/computed tomography and computed tomography images show lobulated cystic masses in bilateral adnexae with increased tracer uptake in peripheral rim. (e) Maximum intensity projection 18F-fluorodeoxyglucose-positron emission tomography image shows metabolically active residual disease involving both tubo-ovarian masses<sup>34</sup>



Fig 5. Magnetic resonance imaging scans of a patient presenting with primary infertility and chronic pelvic pain. A. Transverse T1-weighted image showing masses of heterogeneous signal intensity in the bilateral adnexae. B. Transverse gadolinium-enhanced T1-weighted fat-suppressed image showing a well-formed enhancing capsule, a thick-walled convoluted tube adjacent to enlarged ovaries, and inflammation of the surrounding fat; suggestive of bilateral tubo-ovarian masses.<sup>33</sup>



Fig 6. MRI scans of a left tubo-ovarian mass confirmed on laparotomy. A. Transverse T1-weighted image showing an enlarged left ovary with a hyperintense rim and a tortuous tubular structure that is isointense to the myometrium, suggestive of a dilated fallopian tube. B. Transverse T2-weighted fat-suppressed image showing a thick-walled enlarged left ovary and a dilated fallopian tube; suggestive of a tubo-ovarian mass lesion. C. Operative specimen of the tubo-ovarian mass excised on laparotomy.<sup>33</sup>



Fig 7. Laparoscopy showing A. Beaded tube, tobacco pouch B. Congested inflamed hydrosalpinx<sup>37</sup>



Fig 8. Laparoscopy showing A. tubercles on uterus, fallopian tubes and ovaries (arrows), B. bilateral hydrosalpinx, tubo-ovarian masses, adhesions and frozen pelvis (arrows), C. caseous nodules in uterovesical pouch (single arrow) and on anterior abdominal wall (double arrow).<sup>40</sup> D. omental adhesions.<sup>8</sup>

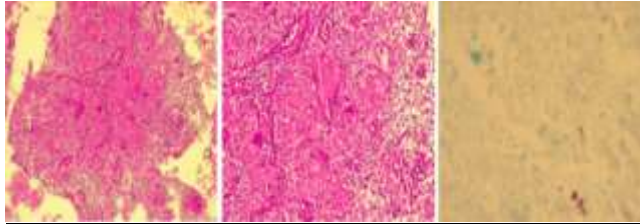


Fig 9. Endometrium. On the left, multiple granulomas in the endometrial stroma (hematoxylin and eosin stain, 20x). In the middle, granulomas with multinucleated giant cells (hematoxylin and eosin stain, 40x). On the right, some acid-fast bacilli in areas of caseous necrosis (Ziehl-Neelsen, 100x).<sup>35</sup>

## CONCLUSION

In developing countries, genital tuberculosis is one of the leading cause of infertility while diagnostic ultrasonography plays a limited role to in its diagnosis. Laparo-hysteroscopy and histopathological analysis also evaluates various presentations of genital tuberculosis. PCR-based detection in endometrial aspirates is confirmatory molecular diagnostic technique in diagnosis of genital tuberculosis. Early detection and specific treatment regimens can reduce damage to genital tract and future infertility.

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