

Hysteroscopic and Laparoscopic finding in Infertile Women with proven Endometrial Tuberculosis

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Abstract

Background: Currently, none of the diagnostic procedures for detecting female genital tuberculosis (FGTB) are 100 percent reliable, and the same is true for endoscopic results. There are several studies accessible on hysteroscopic and laparoscopic findings that are suggestive of TB. However, no study to our knowledge summarises the findings of laparoscopic and hysteroscopic examination in subfertile female patients with biopsy, culture, or other laboratory test-proven endometrial tuberculosis. **Objective:** Evaluation of hysteroscopic and laparoscopic findings in subfertile women suffering from proven endometrial tuberculosis. **Materials and methods:** 16,784 infertile women had a diagnostic hysterolaparoscopy between February 2014 and June 2021, among which 1084 patients were prescribed anti-tubercular medication based on the results of their findings; however, only 309 individuals had endometrial tuberculosis verified via positive on histopathology examination, AFB demonstration, Culture, and GeneXpert MTB/RIF. We retrospectively observed the diagnostic hysterolaparoscopy findings in those proven cases of subfertile women suffering from FGTB. **Results:** The major findings on hysteroscopy were periosteal fibrosis (209/309,67.63%), pale endometrium(179/309,57.92%), and micro polyp(138/309,44.66%). Other notable hysteroscopic findings were intrauterine adhesions (88/309,28.47%), endometrial tubercle (78/309,25.24%), endometrial polyp(54/309,14.88%), caseation(42/309,13.59%), focal hyperemia(29/309,9.38%) and diffuse hyperemia(18/309,5.82%). The most common finding on laparoscopy was abdominopelvic adhesions of various grades (297/309,96.11%). The major findings of laparoscopy were tubercle (155/309,50.16%), isthmo ampullary block (118/309,38.18%), tubal diverticula (116/309,37.54%), hydrosalpinx (97/309,31.39%) and TO mass (96/309,31.06%). 5.50% (17/300) had a normal appearance on hysteroscopy, and 1.29% (4/309) had a normal-looking pelvis on laparoscopy. **Conclusions:** In proven endometrial tuberculosis, significant hysteroscopic findings are periosteal fibrosis, pale endometrium, micro-polyp, and intrauterine adhesions, whereas major laparoscopic findings are various grades of abdominal pelvic adhesions, including perihepatic adhesions, miliary tubercle, isthmo ampullary block, tubal diverticula, caseous material, and hydrosalpinx. Tuberculosis should be considered if these signs are discovered during a diagnostic work-up in infertile people.

Introduction

In India, Africa, and other underdeveloped nations, female genital tuberculosis (FGTB) is a prevalent cause of infertility; however, accurate diagnosis is difficult to come by because of paucibacillary illness. Fifty percent of extrapulmonary tuberculosis(EPTB) cases in India were found in HIV-positive people, whereas the remaining 15 to 20% were in immune-competent patients. (1,2). Among these, 9% are FGTB in women's reproductive age group, adversely affecting their reproductive health. (1,2)Acid-fast bacilli on endometrial or peritoneal biopsy, epithelioid granuloma on biopsy, or a positive MTB gene Xpert on biopsy are all conventional techniques of diagnosis. There is a minimal chance of success with these, however. Due to the high rate of false positive results, a positive polymerase chain reaction (PCR) cannot be relied upon as diagnostic evidence on its own. When conventional TB tests are negative for a patient, diagnostic laparoscopy

and hysteroscopy may often reveal the presence of TB lesions. FGTB significantly affects women's chance of conception by distorting anatomically and pathophysiologically reproductive organs. (3–5) The presence of characteristic caseous granuloma, with or without Langerhans giant cells, is indicative of genital tuberculosis when exhibited on histology. (6) The crucial histologic finding to diagnose endometrial tuberculosis is the presence of epithelioid cell granulomas in different stages and multinucleated giant cells of both Langhans and foreign body type and lymphoid aggregate. (7,8) The ability to see acid-fast bacilli (AFB) and the discovery of caseation are two other findings. Those who identify these characteristics on endometrial biopsy are thus included in the study population. In addition, C cartridge-based nucleic acid amplification tests (CBNAAT/Xpert MTB/RIF assay) and liquid culture by mycobacterial growth indicator tube (MGIT) with phenotypic drug sensitivity testing (DST) are WHO-approved rapid diagnostic tests. (6,9)

Several observations made during laparoscopy and hysteroscopy have been mentioned in the published research relevant to FGTB.(6,10–12). In addition, treatment with anti-tubercular medication is started once that has been determined to be necessary. However, there is no such paper that discusses the results of laparoscopic and hysteroscopic examinations in female patients who have been diagnosed with subfertility and endometrial tuberculosis.

Material and Methodes

The subfertile women with positive findings in HPE, Culture, AFB, and Gene Xpert MTB/RIF were taken as diagnosed cases of endometrial tuberculosis, and we explored their hysteroscopy and laparoscopy findings. As a result, 16,784 infertile women had a diagnostic hysterolaparoscopy between February 2014 and June 2021. Despite the fact that only 309 individuals had endometrial tuberculosis verified via histological investigation, AFB, Culture, and GeneXpert MTB/RIF, all 1084 patients were prescribed anti-tubercular medication based on the results of their diagnostic hysterolaparoscopy. Therefore, only those infertile women with positive evidence of female genital tuberculosis on endometrial HPE and GeneXpert test taking their diagnostic hysterolaparoscopy finding retrospectively can clearly identify what all findings can be found in infertile women with proven endometrial tuberculosis. This article details a noteworthy discovery made during laparoscopic and hysteroscopic procedures for diagnosing TB in the uterus of subfertile women who had proven FGTB evident by HPE, AFB, Culture, and GeneXpert.

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Results

Diagnosis of genital TB was made by histopathological evidence of TB granuloma in 304 (98.38%) women, demonstration of acid-fast bacilli (AFB) on microscopy in 3(0.009%), positive AFB culture in 7 (0.22%), positive GeneXpert MTB/RIF assay in 3 (0.009%). Some of them had positive findings in more than a laboratory test. Surprisingly, 5.50% (17/300) of the 309 individuals with laboratory-proven TB had a normal appearance on hysteroscopy, and 1.29% (4/309) had a normal-looking pelvis on laparoscopy. Nonetheless, no individual presented with both unremarkable hysteroscopic or laparoscopic results. The major findings on hysteroscopy (Figure 1-3) were periosteal fibrosis (209/309,67.63%), and pale endometrium(179/309,57.92%) and micro polyp(138/309,44.66%). Other notable hysteroscopic findings were intrauterine adhesions (88/309,28.47%), endometrial tubercle (78/309,25.24%), endometrial polyp(54/309,14.88%), caseation(42/309,13.59%), focal hyperemia(29/309,9.38%) and diffuse hyperemia(18/309,5.82%). The most common finding on laparoscopy was abdominopelvic adhesions of various grades (297/309,96.11%).(Figure 4) The major findings of laparoscopy (Figure 5 to 9) were tubercle (155/309,50.16%), isthmo ampullary block (118/309,38.18%), tubal diverticula (116/309,37.54%), hydrosalpinx (97/309,31.39%) and TO mass (96/309,31.06%). Other considerable findings on laparoscopy were encysted fluid (64/309,20.71%), beaded appearing tubes(48/309,15.53%),

fimbrial agglutination(39/309,12.62%), omental caking(31/309,10.03%), thick cornu (27/309,8.73%), rigid tube(21/309,6.79%) and complete tubal destruction(5/309,1.61%).

Discussion

Fifty to sixty percent of FGTV patients will have endometrial tuberculosis. Hematogenous, lymphatic, or contagious transmission is the norm. Ulceration caused by tuberculosis may damage the uterine cavity's structure, especially in the disease's latter stages. (13) Epithelioid cell granuloma predominates as the primary histological finding in tuberculous endometritis. The granuloma may have a localized, limited size and prominence in the middle of the body. (13) Proliferative solid epithelioid granulomas, giant or beaded cells, dense polymorphonuclear cells, lymphocytic infiltrations, accumulation of plasma cell, and enlarged lymphoid cells are all histopathological findings indicative of chronic inflammation or lesions that are suggestive of tuberculosis. Goel et al. found that none of the currently available tests for genital tuberculosis could detect all cases, despite their use of a wide variety of diagnostic methods (including HPE, AFB smears, Lowenstein-Jensen (LJ) culture, BACTEC culture, and CBNAAT/ Xpert MTB/RIF assay) in diagnosing endometrial tuberculosis in infertile women. (14) Automatically detecting *M. tuberculosis* DNA in an endometrial sample and reporting rifampicin resistance is the goal of the gene-Xpert MTB/RIF, a nucleic acid amplification (NAA) test. (15) This test had 33-50 percent sensitivity and 100 percent specificity for diagnosing FGTV (16). Although there are no gold standard diagnostic methods for FGTV detection, traditional histopathology evidence, AFB on the microscope, and positive culture of *M. tuberculosis* are considered proven diagnostic methods for FGTV. (17) Molecular techniques, including PCR, LAMP, Xpert MTB/RIF, and line probe assays, have shown promise and are now being researched to enhance the diagnostic algorithm of FGTV; however, culture and HPE remain crucial contributors. (18) An evaluation of the Composite Reference Standard (CRS) for the diagnosis of FGTV that includes various clinicopathological findings have also been proposed by Sharma et al. (19) to make a diagnosis of FGTV more secure way.

On hysteroscopy, the most significant findings were periosteal fibrosis, pale endometrium, and micro-polyp, which are seen in over 30% of patients with positive evidence on histopathology. This is in contrast to most studies where major findings were intrauterine adhesions, shrunken cavities, and normal uterine cavities. (20–23). The most common site of tubercular Infection is in the fallopian tube; hence, foci of Infection remain in ostia more commonly than the endometrium, which every month shades during menstruation. This corresponds to our most common finding, periosteal fibrosis. In the event of endometrial destruction, the uterine cavity will fill up with formations that have the appearance of cotton and spread throughout the whole endometrial surface, leading to the development of pale endometrium. A prospective observational study by Sharma et al. that looked at hysteroscopic findings in patients with FGTV found that 54.31 % of women had a pale endometrial cavity. (22) Another common finding in our study of women with proven endometrial tuberculosis is the presence of endometrial micro polyps, defined as polyps measuring less than 1 mm in size. In our experience, they are linked to stromal edema, endometrial thickness, and periglandular hyperemia, all of which point to the presence of chronic endometritis. (24) Intrauterine adhesions (Figure 2) are a dreadful finding of tuberculosis as they often have poor fertility outcomes. (25,26) Infection of the endometrium occurs on many levels, including the basalis layer, which is destroyed by endometrial ulceration. As a result, the endometrium loses its regeneration capacity, and intrauterine adhesions form over time as the lesion heals with fibrosis. Intrauterine adhesions are present in 1 in 4 patients (25.24%) with proven endometrial tuberculosis, according to our study. According to the European Society for Hysteroscopy (ESH) classification of intrauterine adhesions type IIa (16/88, 18.18%) and type IV(16/88, 18.18%) was most common followed by type III(14/88,15.90%) and this findings are more or less similar to previous published literature.(20,21) We are aware that tubercle and caseation are two important diagnostic findings in tuberculosis(27) but are not usually encountered, and this is also true for patients with histopathological proven endometrial tuberculosis. In all the patients with caseation, caseous material was seen coming out through ostia. After prolonged Infection, considerable fibrosis arises in the uterus as a sequela leads to a shrunken uterine cavity that is difficult to distort with fluid media during hysteroscopy. In rare instances there

may be formation of dystrophic calcification. (Figure 10) According to a study conducted by Song et al., the presence of endometrial hyperemia, micro-polyps, adhesions, periosteal fibrosis, or endometrial interstitial edema during a hysteroscopic examination should raise suspicion for the presence of chronic endometritis; however, the overall accuracy of a hysteroscopic examination concerning the diagnosis of is only 67%. (28) An endometrial biopsy should be performed on women when a diagnosis of chronic endometritis or TB is suspected. Initiating anti-tubercular treatment (ATT) early improved the menstrual cycle and endometrial thickness and decreased the incidence of grade I adhesions; nevertheless, the prognosis is frequently poor for women with advanced endometrial involvement. (29)

The fallopian tubes are often impacted on both sides when genital tuberculosis is present. Salpingitis tuberculosis may affect the tubes in several different ways, such as endo salpingitis, exosalpingitis, interstitial salpingitis, or Salpingitis isthmica nodosa(SIN). Endosalpingitis caused by tuberculosis often spreads throughout the body through the hematogenous pathway and may also spread via other routes. The fallopian tube has become more extensive, thicker, and twisted. (30) Caseation in the tubal wall and collecting of cheesy like material in the lumen with blockage of both ends of fallopian tubes owing to fibrosis may cause pyosalpinx to develop unilaterally or bilaterally. A woman can be at increased risk for ectopic pregnancy and infertility if her endosalpinges are hyperplastic, edematous, or wholly destroyed, or if there is a fusion of papillae in the endo salpinx. (30,31) In tuberculous exosalpingitis, the disease spreads from the intestines or peritoneum and begins in the muscularis mucosa layer of the tube. The fallopian tubes, ovaries, and peritoneum of the Douglas pouch are initially hyperemic, with weak adhesions and miliary tubercles on their surface. (Figure 5) Beaded tubes, characterized by calcification and tubal blockage, tubo-ovarian masses because of peri oophoritis, hydrosalpinx, pyosalpinx, or extensive adhesion development, occur later. (6,30) In our study, most of the patients (96.11%) with proven endometrial tuberculosis had abdominal-pelvic adhesions ranging from mild scattered adhesions to severe adhesions that can give rise to a frozen pelvis. Fitz-Hugh-Curtis syndrome or perihepatitis (Figure 4), i.e., inflammation of the liver capsule, without the involvement of the liver parenchyma resulting in adhesion formation, is a chronic manifestation of pelvic inflammatory disease (PID)(32) and often seen in patients with tuberculosis. Miliary tubercle, encysted fluid collection, caseous material, and isthmo-ampullary junction block are considered a major endoscopic findings to establish the diagnosis of FGTB, but they are not easy to find. (27,33) In the present study, the tubercle (Figure 6) was seen almost half of the cases of biopsy-proven endometrial tuberculosis, and around one-third of patients had the isthmo-ampullary block, encysted fluid collection, and caseous material. Nodular growth in the isthmic section of the fallopian tube is called salpingitis isthmica nodosa (SIN) (34), which is often endoscopically seen as an isthmo-ampullary block or nodule. It is common in underdeveloped countries and is caused by TB, which invades the isthmic region of the fallopian tube directly between the lumen and the serosa, affecting the muscularis layer. Hydrosalpinx was present in 31.39% of patients in our study, and after anti-tubercular therapy, if hydrosalpinx is present often managed by salpingectomy or delinking. A comparative study of laparoscopic findings before and after anti-tubercular therapy (ATT) showed that ATT improves most laparoscopic findings like pyosalpinx, beaded tube, and non-visualization of tubes, but no improvement on advanced lesions like agglutinated or destructed fimbria. (35) Ovarian tuberculosis may manifest as a variety of findings, including tubo-ovarian cyst or mass (TO mass) (Figure 8), adhesions, and caseation formation(Figure 7). TO mass of various sizes (from 2.7 cm to 13.4 cm; mean size 4.67cm) was seen in 31.07% of patients with proven endometrial tuberculosis. We prefer not to do any intervention for TO mass and only give ATT; unless the TO mass is associated with pain, fever, or any obstructive symptoms. It is widely considered that tuberculosis decreases ovarian blood flow, and involvement of the cortex decreases ovarian reserve. A study was done to know the effect of anti-tubercular therapy (ATT) on ovarian function, such as ovarian reserve, ovarian dimensions, and ovarian stromal blood flow showed that a significant increase in AMH (2.68 ± 0.97 ng/ml to 2.8 ± 1.03 ng/ml) pre- to post-ATT, nonsignificant increase in FSH (7.16 ± 2.34 mIU/ml to 7.26 ± 2.33 mIU/ml) post-ATT, significant increase in mean AFC (7.40 ± 2.12 - 8.14 ± 2.17), PSV in the right ovary (6.015-6.11 cm/s) and left ovary (6.05-6.08 cm/s). (36) In women with genital TB, ATT enhances ovarian function (AMH and AFC) and ovarian blood flow. (36,37) Endo-ovarian tissue biopsy can also be used to diagnose FGTB. A study showed that MTB DNA was observed in 49.5% of endometrial biopsies and 33.17% of ovarian tissue biopsies on the same sample. (13) In rare instances, the disease may

completely destroy the ovary and tubes. (Figure 10)

Conclusions

In proven endometrial tuberculosis, significant hysteroscopic findings are periosteal fibrosis, pale endometrium, micro-polyp, and intrauterine adhesions, whereas major laparoscopic findings are various grades of abdominal pelvic adhesions including perihepatic adhesions, miliary tubercle, isthmo ampullary block, tubal diverticula, caseous material, and hydrosalpinx. If these abnormalities are observed following diagnostic endoscopy in infertile female tuberculosis should be strongly suspected.

Author's roles

R.M. studied and managed the reported cases, designed the article, reviewed the literature, made the table and figures, and wrote the paper. P.B. operated on the patients and reviewed the manuscript. N.J. edited and structured the manuscript.

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Consent

It is our institutional policy to take written consent from each patient undergoing any procedure and a part of it may reproduce or publish only for academic purpose. Written informed consent was obtained from each patient for publication of images without disclosing their personal details. It is retrospective study and all patient had consent for the same.

Ethical approval

The study received ethical approvals from Bansal Hospital Institutional Human Ethics Committee on 20/3/21.

Funding

No funding is associated with this study.

Data availability

The data that support the findings of the study are available from the corresponding author upon reasonable request.

Conflict of interest

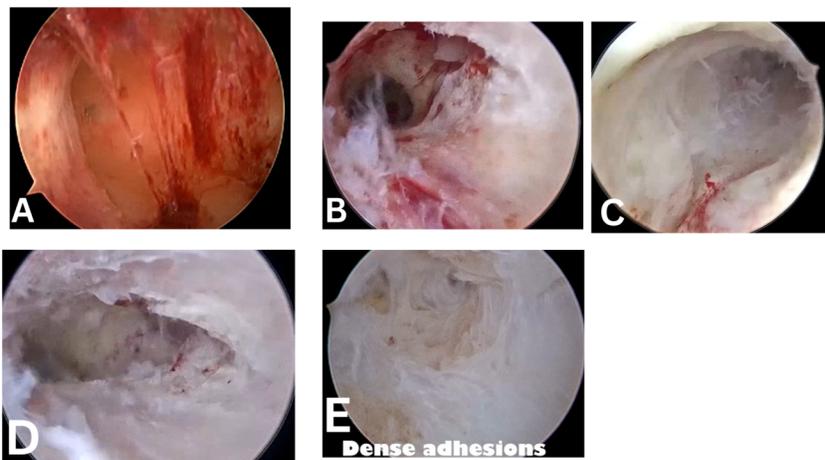
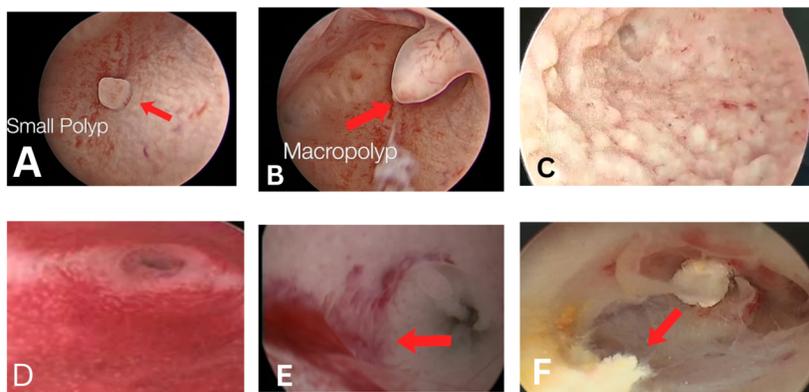
We do not have any conflicts of interest to declare and also no competing interests.

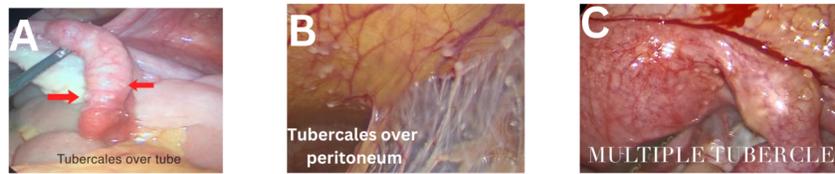
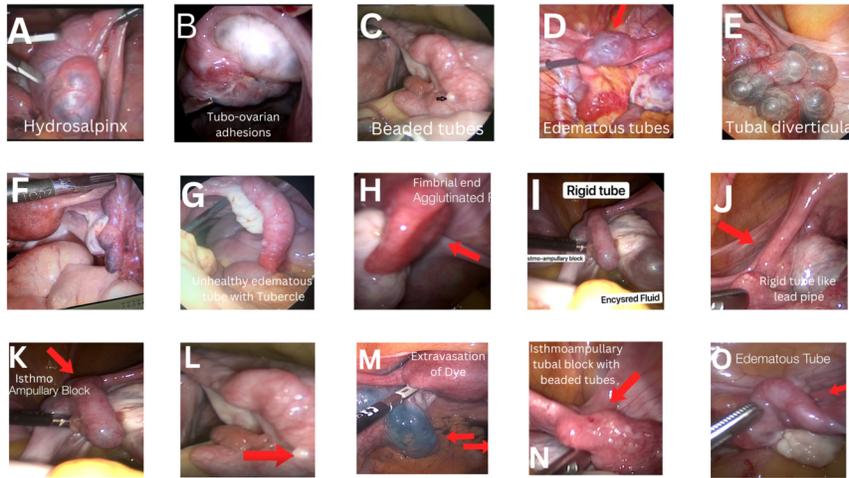
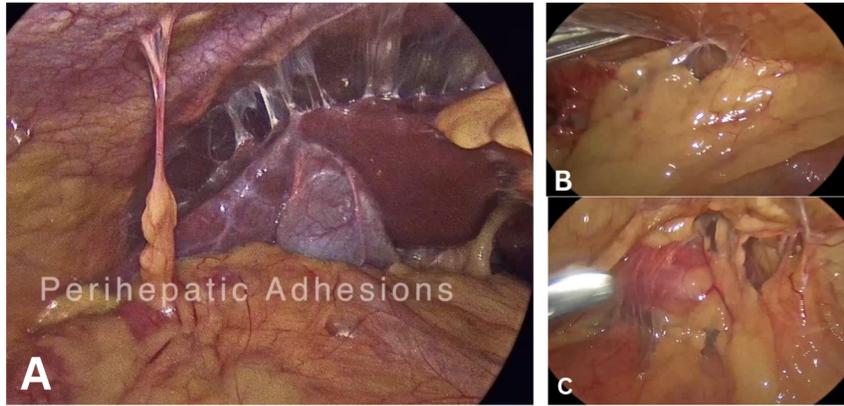
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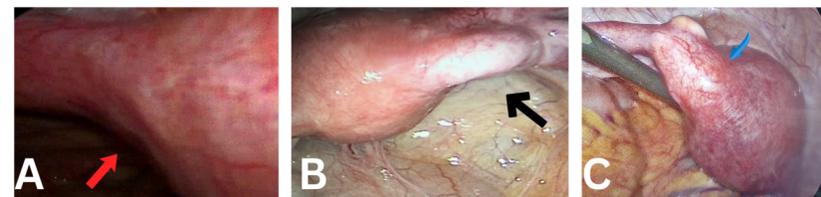
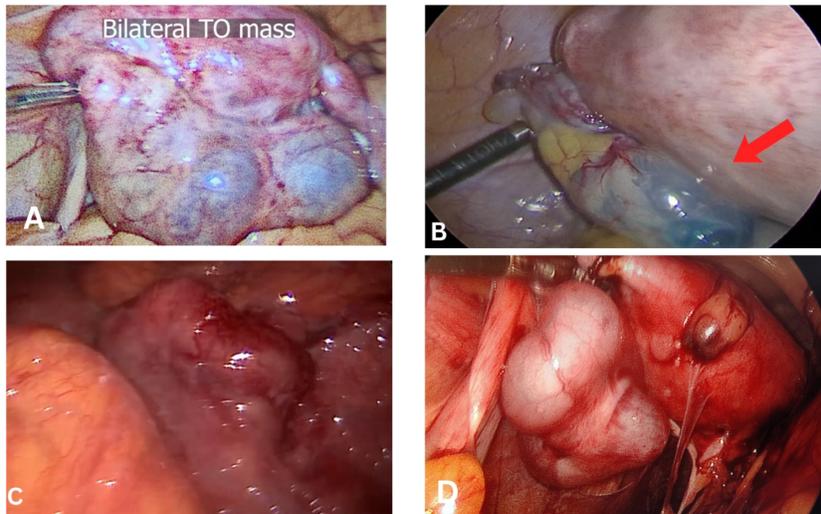
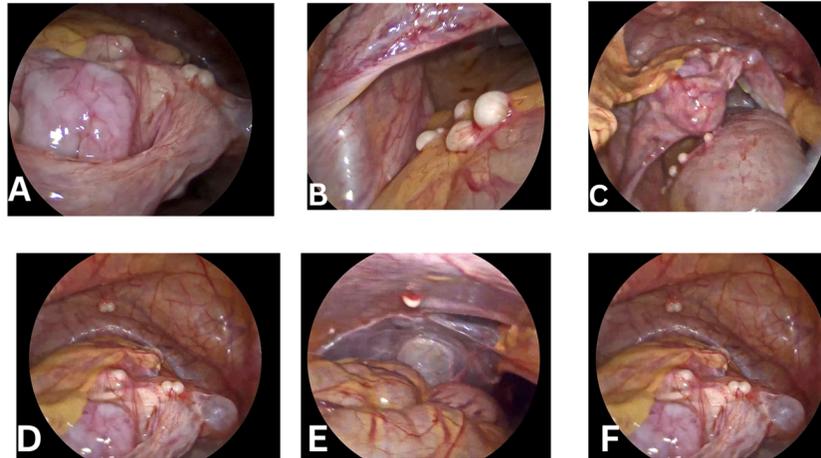
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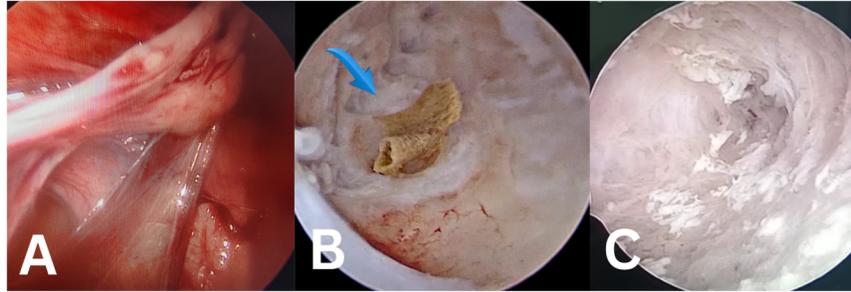
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Table 1. Hysterolaparoscopic findings in proven cases of FGTB.docx available at <https://authorea.com/users/502862/articles/623108-hysteroscopic-and-laparoscopic-finding-in-infertile-women-with-proven-endometrial-tuberculosis>

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Table 2 European Society for Hysteroscopy (ESH) 1989, classification of IUA and our result according to available at <https://authorea.com/users/502862/articles/623108-hysteroscopic-and-laparoscopic-finding-in-infertile-women-with-proven-endometrial-tuberculosis>