



HYSTEROSCOPY FOR DIAGNOSIS OF FEMALE GENITAL TUBERCULOSIS IN INFERTILE WOMEN: AN ESSENTIAL TOOL IN MINIMALLY INVASIVE ERA.

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ABSTRACT

INTRODUCTION: Female genital tuberculosis (FGTB) is difficult to diagnose due to asymptomatic presentation and paucity of definitive investigations. Hysteroscopy can be utilized for the diagnosis of genital tuberculosis in infertile women. This study was done to study the role of hysteroscopy in the diagnosis of genital tuberculosis.

METHODS: Prospective observational study was performed on 50 infertile women after basic evaluation of infertility. The women with tubal factors for infertility or unexplained infertility were selected for the study. Premenstrual endometrial biopsy (EB) was done for mycobacteria (AFB) detection. Hysteroscopy was performed in the next cycle if no AFB was detected on EB. ATT was given if genital TB was diagnosed on EB, and hysteroscopy was performed after completion of ATT. Hysteroscopic observations were compared with endometrial biopsy results.

RESULTS: A total of 4 (8%) cases were diagnosed as bacteriologically positive for genital tuberculosis in endometrial samples. They were given anti-tubercular treatment. On hysteroscopy, pale endometrium (16%), Intrauterine adhesions (46%), and ostial obliteration (18%) were the common abnormal observations. 12 patients had mild adhesions, 6 had moderate and 5 patients had severe adhesions. Overall, 26 (52%) patients had features of intrauterine fibrosis, like intra-uterine adhesions or ostial obliteration, which could be suggestive of chronic infection like tuberculosis. Hysteroscopic adhesiolysis was performed in 46% and the cavity was restored.

CONCLUSION: Endometrial Biopsy and Hysteroscopy are complementary procedures that together can help in the diagnosis of FGTB. Hysteroscopy is not only the gold standard for diagnosing uterine adhesions, distortion of the uterine cavity and tubal ostia, but it can also be a prognostic and therapeutic tool.

KEYWORDS : Female Genital Tuberculosis, Infertility, Hysteroscopy, Intra-uterine Adhesions.

INTRODUCTION:

The prevalence of Female genital tuberculosis (FGTB) is as high as 10-19% amongst Indian women as compared to less than 1% in developed countries^{1,2}. FGTB is mostly secondary infection acquired by hematogenous spread from an extra-genital source such as pulmonary or abdominal tuberculosis³. The initial involvement of endometrium is non-specific with irregular inflamed, patchy, shaggy endometrium and later ulceration, necrosis and fibrosis starts. This results in endometrial adhesions and Asherman's syndrome manifesting as secondary amenorrhoea and infertility⁴. The actual incidence of genital tuberculosis may be under reported due to asymptomatic presentation and paucity of definitive investigations.

The gold standard for diagnosis of Tuberculosis is mycobacterial (MTB) detection and isolation. The endometrial involvement of genital Koch's can be diagnosed by Acid Fast Bacilli (AFB) staining on microscopy, AFB Culture, histopathology, Polymerase chain Reaction (PCR) and GeneXpert (CBNAAT) of endometrium. While direct microscopy in AFB smear and culture by Lowenstein- Jensen medium (LJ) or BACTEC are great success in pulmonary TB, they are of lesser value in genital TB.⁵ Ziehl-Neelsen (ZN) staining for AFB requires 10^4 - 10^6 bacilli/ml of tissue or fluid specimens to give a positive result. The detection rate is generally under 10% for genital tuberculosis. Culture remains the standard for laboratory confirmation of MTB. A composition of 10-100 bacilli/ml of sample is required and it takes 2-6 weeks for the growth of Mycobacterium in culture. Traditionally, Lowenstein Jensen (LJ) culture has been used; in addition, the BACTEC MGIT™ (mycobacteria growth indicator tube) system has shortened the time to diagnosis to 2 weeks⁶. The BACTEC culture has been reported to have sensitivity of 40% with a specificity of 90%⁷.

The histopathology in initial stages might not show typical features like tuberculous granulomas with epithelioid cells, caseative necrosis and giant cells. The presence of chronic endometritis may be suggestive but not diagnostic of tuberculosis. Histopathology of EB in diagnosing genital tuberculosis has high specificity (100%), and Positive Predictive value (100%), but a low sensitivity (6.6%) and low negative predictive value (51.7%)⁸

Nucleic acid amplification tests are used to amplify deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) segments to rapidly identify the microorganisms in a specimen. Polymerase chain reaction (PCR), is one such test, often used but its major disadvantage is the inability to detect a difference between viable and nonviable organisms. It has a low sensitivity and specificity of 62.5% and 54%, respectively⁷. The Cartridge Based Nucleic Acid Amplification tests (CBNAAT/GeneXpert) is semiautomated, rapid molecular assay. 100% sensitivity and 46.6% specificity of CBNAAT for definite female genital tuberculosis has been reported⁹. This has the limitation of being sensitive to high temperature and humid conditions, which are quite prevalent in countries like India.

Endoscopic procedures like laparoscopy and hysteroscopy are widely used for investigation of infertile women. Hysteroscopy has been generally accepted as the gold standard for the evaluation of the uterine cavity because entire endometrial cavity is directly visualized to identify the pathological changes. In fact, it is an eye in the uterus. This advantage of hysteroscopy can be utilized for diagnosis of genital tuberculosis.

The advantages of combining hysteroscopy with laparoscopy include not only the exclusion of endometrial involvement but

also to do interventions such as lysis of synechiae¹⁰. (Fig. 1) This study was done with the aim to know the role of hysteroscopy in diagnosis of genital tuberculosis.

METHODS:

This prospective observational study was done, after clearance from institutional ethics committee, in 50 infertile patients. Infertile women with unexplained infertility or suspected tubal factor were selected after basic evaluation of infertility.

EXCLUSION CRITERION:

Patients with male factor infertility, infertility due to ovulatory factor, active pelvic inflammatory disease, patients who have taken ATT in the past (before enrolment in the study), or any proven gynaecological malignancy.

After a detailed history, clinical examination, and basic haematological investigations were performed. Specialized infertility investigations like semen analysis, hysterosalpingography, ultrasonography, hormonal profile, and follicular study were done as a part of infertility workup. They were enrolled for study if tubal factor was found or unexplained infertility was diagnosed. Premenstrual endometrial biopsy (EB) was done for mycobacterial detection/isolation by Histopathology / AFB staining / Culture in L. J. medium / GeneXpert (CBNAAT). Hysteroscopy was performed in next cycle if no AFB was detected. Anti-tubercular treatment (ATT) was given if MTB was detected in premenstrual EB and hysteroscopy was performed after completion of ATT. Hysteroscopy is not performed with active tuberculosis of endometrium, as it may result in the spread of mycobacterium to rest of abdominal organs.

Endometrium, uterine cavity and internal tubal ostia were examined on hysteroscopy. Findings like fibrosis, bands of adhesions, ridges and synechiae are suggestive of intrauterine adhesions. Internal ostia were observed for pinhole openings, periosteal fibrosis and blocks or obliterations. American Fertility Society's Classification¹¹ of intrauterine hysteroscopic findings was done. They were classified as mild (score 1-4), moderate (score 5-8) and severe (Score 9-12). Results of endometrial biopsy and hysteroscopy were analysed and compared.

RESULTS:

50 patients with infertility were included in the study after ruling out the male factors and ovulatory causes of infertility. The patients presented with both Primary Infertility (58%) and Secondary Infertility (42%) in our study. The duration of infertility ranged from 2-14 year. Besides infertility, 36% also had menstrual complaints, while chronic pelvic pain was seen in 14%. Most common menstrual complaint was hypomenorrhea (22%). Oligomenorrhea was seen in 14%, amenorrhea in 6% and menorrhagia in 2%.

On premenstrual EB samples, total 4 (8%) cases were diagnosed as bacteriologically positive for genital tuberculosis. Out of these 4, 1 case was diagnosed by both AFB Stain and CBNAAT. Rest 2 cases were diagnosed on AFB stain and 1 by CBNAAT alone on endometrial biopsy sample. MTB Culture by LJ medium was not positive in any patient.

2 endometrial samples showed features of chronic endometritis on histopathology, while typical features of Tuberculosis were not seen in any patient.

Hysteroscopy was performed to note the detailed features of endometrium, both ostia and any other abnormality in uterine cavity (Table No.1).

Table No. 1 : Comprehensive Observations Of Hysteroscopy (with Overlapping Features)

Hysteroscopy Findings	Frequency	Percent
Normal Hysteroscopy (with no abnormality)	24	48
Pale endometrium	8	16
Hyperplastic endometrium	3	6
Obliterated endometrial cavity	6	12
Intrauterine adhesions	23	46
Ostial Obliteration	13	26
Polypoidal	2	4
Chronic endometritis	2	4

Endometrium On Hysteroscopy: On examination of the endometrium on hysteroscopy, 24 (48%) patients had normal healthy endometrium, while pale endometrium suggestive of atrophic endometrium was the seen in 8 (16%) women. 3 patients showed hyperplastic endometrium, 2 had polypoidal and 2 patients had feature of chronic endometritis. 6 patients exhibited completely obliterated cavity with destroyed endometrium due to dense intrauterine adhesions.

Ostial Morphology On Hysteroscopy: Out of the 50 patients included in the study, 37 patients showed normal gross morphology of ostia. Fibrosed or obliterated ostia are visible as deep seated, pin hole to non-visualized, with pale intramural epithelium, fibrous adhesion bands and whitish deposits around it. The ostial abnormality in the form of pin hole ostia (Fig.2), blocked ostia or inability to see ostia, was observed in 13 (26%) patients. 9 (18%) demonstrated bilateral obliteration, while 4 (8%) had unilateral ostial obliteration.

Intrauterine Adhesions On Hysteroscopy: 12 patients had mild grade (AFS Grade 1-4), 6 had moderate (AFS Grade 5-8) and 5 patients had severe grade (9-12) of intrauterine fibrosis. The severe degree of adhesions mostly coexisted with ostial occlusion. In all the patients with adhesions (46%), hysteroscopic adhesiolysis was performed.

Out of these 26 patients, with features of intrauterine abnormality, 4 had a history of Dilatation and Curettage, performed for incomplete abortion, but all of these patients had flimsy adhesions at fundus. They were not associated with ostial obliteration and none of them had dense adhesions.

On comparing the menstrual history with the hysteroscopic findings, it was observed that 10 (90.1%) out of 11 patients presenting with hypomenorrhea had features suggestive of intrauterine fibrosis on hysteroscopy. While 5 patients (45.5%) out of these women with hypomenorrhea had atrophic endometrium with completely obliterated cavity on hysteroscopy

The findings of hysteroscopy were compared with AFB stain / CB-NAAT/ HPE of endometrial biopsy sample (Table No.2). In 2 out of 3 patients with positive AFB staining, had features suggestive of tuberculosis on hysteroscopy. None of the 2 patients who are positive on CBNAAT, had any features suggestive of genital tuberculosis on hysteroscopy. This could be because if MTB was detected on endometrial biopsy, a full course of ATT was given before hysteroscopy, and hence the changes of endometrium were prevented by treatment of disease. Both cases of chronic endometritis on histopathology were correctly diagnosed by hysteroscopy.

The difference in results of the hysteroscopic findings, as compared to EB results, was not statistically significant (p value >0.05) (Table No.2). Hence, hysteroscopy is complementary to endometrial biopsy and cannot replace the bacteriological confirmation of diagnosis by endometrial biopsy. Hysteroscopy helps in diagnosis as well as treatment of intrauterine fibrosis which could be due to genital tuberculosis.

Table No. 2: Comparison Of Hysteroscopy With Endometrial Sample Result

Endometrial Biopsy		Hysteroscopy		P-Value
		Intrauterine abnormality	Normal Cavity	
AFB Stain	Positive	2	1	0.60
	Negative	24	23	
Histopathology	Chronic Endometritis	2	0	0.133
	No abnormality	24	24	
CBNAAT	Positive	0	2	0.166
	Negative	26	22	

DISCUSSION:

The diagnosis of FG TB is challenging, as there is no single diagnostic test available. High degree of clinical suspicion, elaborate history taking, systemic examination, battery of tests to document *M. tuberculosis* as well as imaging methodologies for characteristic structural changes are essential for the diagnosis. Traditionally the gold standard being demonstration of mycobacteria on smear examination and culture.

The diagnosis of tuberculosis (TB) still offers big diagnostic challenges due to the detection limit of smear microscopy, long time to culture-confirmation and variable sensitivity of molecular tests. Hence diagnosis of FG TB for early institution of treatment is always challenging.

A retrospective study was conducted by J B Sharma et al¹, on 28 women, who underwent hysteroscopy and /or laparoscopy for infertility, with clinical suspicion of Asherman's syndrome. He reported that 57.6% of the women presented with normal menses, while hypomenorrhea, oligomenorrhea, secondary amenorrhea and menorrhagia were seen in 25 (30.1%), 3 (3.5%), 5 (5.9%), and 2 (2.4%) women respectively, with hypomenorrhea being the most common menstrual irregularity. He reported various grades of adhesions in all women on hysteroscopy. Grade I in 17.8%, grade II in 28.5%, grade III in 28.5% and grade IV in 17.5% women. Only four women (14.3%) had open ostia, while others had bilateral (28.5%) or unilateral (21.3%) blocked ostia or inability to see ostia (28.5%).

The symptom of hypomenorrhea and amenorrhea were most commonly associated with intrauterine adhesions (90.1%) in the present study. The destruction of the endometrium by tubercular endometritis may result in the failure of the end organ, i.e., uterus, which initially presents as oligomenorrhea or hypomenorrhea, and later as amenorrhea.

A combination of the morphology of cavity, extent of adhesions, and ostia according to the American Fertility Society's Classification of intrauterine adhesions was used to classify to see if the hysteroscopic findings are suggestive for FG TB or not. In our study, hysteroscopy revealed abnormal findings in 26 cases (52%). The severe degree of adhesions was more commonly associated with ostial fibrosis and often co-existed.

Endometrial biopsy gives the definitive bacteriological confirmation of FG TB, while hysteroscopic features can only be suggestive of chronic infections, if features like adhesions, ostial fibrosis or pale or inflamed endometrium are present. Only 2 out of the 4 patients with bacteriologically confirmed FG TB had abnormal features on hysteroscopy. This could be because if Tubercular endometritis was diagnosed on endometrial biopsy, a full course of ATT was given before Hysteroscopy. This also signifies the need for early diagnosis and treatment of FG TB, as there was absence of adhesions or other irreversible features of endometrial involvement in these women.

J B Sharma et al¹² analysed the records of 94 women who underwent diagnostic hysteroscopy for infertility where genital tuberculosis was diagnosed by laboratory studies of an endometrial biopsy and/or laparoscopic findings. 20.2% had no abnormality on hysteroscopy with a uterine cavity of normal size and shape and no adhesions and normal ostia. Grade 4 adhesions were the most common (31.9%) followed by grade 3 (21.27%), and then grade 2 (14.9%). Thus, they confirmed that genital TB is associated with a high rate of intrauterine adhesions in infertile women.

S. K. Mohakul¹³ did a study on 105 women with infertility. Hysteroscopy was done, and the endometrium was subjected to DNA-PCR testing for detection of Mycobacterium tuberculosis infection. Hysteroscopy features were compared in tuberculosis positive (39%) and negative (61%) cases for correlation. He demonstrated that only 2.86 % of had normal-looking endometrium on hysteroscopy. Ostial and peri-ostial fibrosis was associated with positive TB-PCR in 43.75 % and intrauterine fibrosis was associated with positive TB-PCR in 48.48 % of cases. This finding strongly suggests looking for the presence of *M. tuberculosis* in such types of hysteroscopic pictures in infertility. Although irregular cavity surface and spotted endometrium were associated with 66.67% and 100 % of positive TB-PCR, respectively, however, the number of patients were too minimal to derive any conclusion.

V J Arpitha⁵ performed hystero-laparoscopy on 69 infertile women, with positive endometrial TB PCR result on EB, as a part of infertility work up. Hysteroscopy revealed normal findings in 51 of patients (73.9%), there by implicating less than 50% endometrial involvement. 2 patients (2.9%) each had distorted ostia and fibrosis, poorly vascularised endometrium was seen in 8 patients (11.6%), bald areas were seen in 4 patients (5.8%), synechiae was seen in 1 patient (1.4%), cervical stenosis in 1 patient (1.4%). None of the patients had tubercles or calcification on hysteroscopy. They concluded that majority of the women have an asymptomatic presentation, hence a high degree of suspicion is needed in the evaluation of these patients.

Kumar A.¹⁴ performed total of 304 hysteroscopies in cases of infertility and reported appearance of endometrium as dirty, whitish, pale and covered with whitish caseous deposits, adhesions and ill-defined endometrial gland openings in cases of genital tuberculosis who responded well to ATT. They concluded that impregnated whitish deposits, over extremely flimsy very thin adhesion strands, is a valuable hysteroscopic marker of early endometrial TB with respect to a pregnancy after ATT. They suggested that early diagnosis of tubercular endometritis is possible by detecting the subtle hysteroscopic changes. Therefore, subtle changes like deep seated ostium, peri-ostial fibrosis and gross changes like fundal fibrosis, intrauterine fibrotic bands, atrophic endometrium and blocked ostia should all be taken into consideration for assessing the possible involvement of the endometrium.

Hysteroscopy has also been accepted as the optimum route to surgery aiming to restore the size and shape of the uterine cavity, normal endometrial function and fertility. In the present study, adhesiolysis was performed in 46%. and cavity was restored. The results of hysteroscopic adhesiolysis in Asherman's syndrome, as reported by Fernandez H, are encouraging (a high rate of resumption of menses, a pregnancy rate of up to 43.8% and a live birth rate of 32.8%)¹⁵.

The prognosis for fertility is very poor in women with severe degree of intrauterine adhesion due to genital TB, as the fallopian tubes are often blocked and scarring of the endometrial cavity affects the results of in vitro fertilization and embryo transfer.

The limitation of the study is that origin of intrauterine fibrosis on hysteroscopy cannot be ascertained as it is a late sequel of chronic infections or trauma and the organism cannot be isolated once these changes have already established. ATT was given to patients if tuberculosis was bacteriologically confirmed. If there is clinical suspicion of tuberculosis on hysteroscopy due to presence of intrauterine adhesions / fibrosis, it needs to be supported by bacteriological isolation. Moreover, it is not sure that the patients would benefit with ATT at this stage or not, as the organism has already done the damage. Hence there is a need of research in the field of investigations for early diagnosis of genital tuberculosis in endemic countries like India.

CONCLUSION:

A multi-pronged approach increases the chances of diagnosis of FG/TB. Early diagnosis, with timely administration of ATT, results in improvement of endometrial cavity and may give a significant advantage in improving the chances of conception.

Endometrial biopsy and hysteroscopy are complementary procedures which together can help in the diagnosis of Female Genital TB. Hysteroscopy is not only the gold standard for diagnosing uterine adhesions, distortion of the uterine cavity and tubal ostia, but it can also be a prognostic and therapeutic tool. All gynaecologists must carefully examine the uterine cavity during hysteroscopy in women with infertility. Hysteroscopy is an essential tool in this era of minimally invasive surgery and should be utilized in the workup of infertile couple specially in endemic country like India.

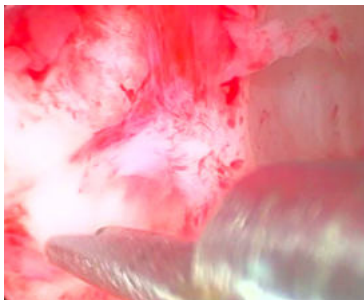


Fig.1: Lysis Of Intrauterine Adhesions By Sharp Scissors

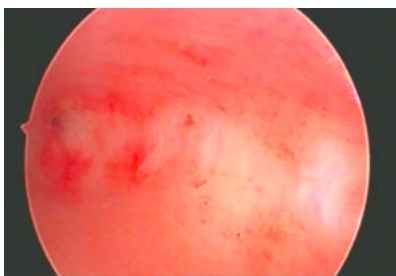


Fig.2: Deep Seated Ostia With Fundal Adhesions

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