

# **ROLE OF GENITAL TUBERCULOSIS IN SUB-FERTILE WOMEN**

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#### ABSTRACT

**OBJECTIVE:** To evaluate the role of Acid fast bacilli culture (AFB) in sub-fertile women undergoing laparoscopy and dye test with endometrial biopsy.

**METHODS:** This cross-sectional study was conducted from 1<sup>st</sup> January 2020 to 30<sup>th</sup> April 2021, on 108 cases of subfertility, enrolled through non-probability consecutive sampling technique, for the diagnostic laparoscopy & dye test with endometrial biopsy for AFB culture. We included all women of reproductive age with  $\geq$ 2 years of subfertility, normal menstrual history, hormonal assay and normal male-factor. All women with comorbidities, women having contraindications for anaesthesia & couple with male-factor subfertility were excluded. Data analysis was done by SPSS version-20.

**RESULTS:** Seventy-two (66.7%) women had primary and 36 (33.3%) had secondary subfertility. Duration of subfertility was >5 years in 63 (58.3%) cases. Ninety-seven (89.8%) patients had bilateral patent tubes. Majority of patients (n=46/108; 42.6%) were aging 32-38 years. Endometrial biopsy of 22 (20.4%) cases were positive for AFB culture. Out of AFB-positive cases, 17 (77.3%) had primary and 5 (22.7%) had secondary sub-fertility. All AFB-positive cases had patent tubes (unilateral n=5/22; bilateral n=17/22). Common laparoscopic findings were tortuous tubes (n=30; 27.8%) and clumped end fimbrial (n=24, 22.2%).

**CONCLUSION:** In our study, endometrial sampling of 20.4% cases were positive for AFB culture. Although female genital tuberculosis constitutes a small proportion of extra-pulmonary tuberculosis, but it has an immense effect on fertility. Thus without challenging the superiority of laparoscopy, AFB culture could be considered a judicious part of subfertility workup in low resource countries carrying high burden of disease.

**KEYWORDS:**Tuberculosis (MeSH); Mycobacterium tuberculosis (MeSH); Acid Fast Bacilli culture (Non-MeSH); Tuberculosis, Female Genital (MeSH); Endometrial Biopsy (Non-MeSH); Biopsy (MeSH); Sub-Fertility (Non-MeSH); Infertility (MeSH).

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## **INTRODUCTION**

uberculosis (TB) is a common disease, affected 10.6 million people across the globe in 2021, an increase of 4.5% from 2020. India (28%), Indonesia (9.2%), China (7.4%), the Philippines (7.0%) and Pakistan (5.8%) are the top high TB burden countries.<sup>1</sup> Although it is an immense health issue globally but in developing countries especially in Africa and Asia, 75% patients have laid a great economic and social burden on the family and the country.<sup>23</sup> Pulmonary Kocks is considered the most infectious & commonest type of tuberculosis. Extra-pulmonary TB has been rising globally, higher among females as compared to males, reflecting the observation of different research studies from South Asia. Among all extra-pulmonary TB cases, genital tract of woman is markedly affected system of the body.<sup>2,3</sup>

In female genital tuberculosis, the affected women undergo fibrotic changes & scarring as a phenomenon of healing which may result in grievous problem of sub-fertility by affecting the

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structural & functional configuration of genital organs.<sup>4</sup> The precise incidence of genital TB in females is difficult to estimate as its under reported due to asymptomatic cases and lack of reliable confirmatory investigation.<sup>5</sup> World Health Organization estimates that 60-80 million couples worldwide suffering from subfertility, with female factor contributing 40-55% and male factor 30-40%.<sup>6</sup> Around 10% of cases involve both partners whereas 10% cases remain unexplained.<sup>7</sup>

The average incidence of female genital TB is 5-10% throughout the world with wide spectrum of variation from 0.69% in Australia to 17.4% in India. About 80-90% of women are between 20-40 years of age at the time of diagnosis which is why it is described as the disease of young women.<sup>®</sup> The frequency of genital tuberculosis is 2-10% in Pakistan as reported by different research studies,<sup>9,10</sup> whereas frequency of subfertility found in 42.5% of cases with genital tuberculosis.<sup>11</sup>

Diagnostic laparoscopy is considered the gold standard among subfertility workup for assessment of internal pelvic organs. Direct visualisation of the abdomino-pelvic organs permits the diagnosis. In cases where clinical evaluation & imaging techniques remain inconclusive, direct inspection of abdomino-pelvic organs helps the explorer to reach a logical end as well as the definitive diagnosis.<sup>12</sup> So, diagnostic laparoscopy is deemed the most reliable tool to diagnose tuberculosis of internal pelvic organs i.e. tubal, ovarian & peritoneal disease.<sup>13</sup> The practice committee of American Society of Reproductive Medicine suggests, "Laparoscopy must be considered before embarking upon aggressive empirical treatment as it involves significant cost and potential risks."<sup>14</sup>

Diagnosis of genital tuberculosis requires multimodal approach of investigations but challenges persist despite technical advances. There exists a lot of diagnostic dilemma for genital tuberculosis, in available research studies "no single test is found confirmatory except for wet culture and histopathology positivity."15As per World Health Organization, the diagnosis of extra-pulmonary TB should be made on the basis of one culture positive specimen, or the histopathology or strong clinical evidence consistent with active extrapulmonary tuberculosis.<sup>16</sup>

Endometrial aspirates, Dilatation and Curettage or endometrial biopsy in secretory phase is advisable to diagnose the genital tuberculosis. Cyclical shedding of the Endometrium leads to inadequate granuloma formation and the sampling site may not contain the tubercle bacilli and classic giant cell.17 However negative AFB culture does not exclude the Female Genital TB as only 50-60% of cases shows signs of tuberculous endometritis despite the ongoing disease process, reason could be pauci bacillary nature of mycobacteria in the endometrial samples or sample site may not be the infected site. Moreover, sampling error, technical failure on processing biopsy, period of sampling collection with respect to the stage of disease may be responsible for it."

In low resource countries where tuberculosis is considered a major health issue, the possibility of female genital Tuberculosis should not be ignored in women presenting with subfertility. So, clinical evaluation, laparoscopy, histopathology and culture could be supplementary to each other in diagnosing female genital tuberculosis. High index of suspicion will drive the gynaecologist towards a least expensive policy of work up, earlier diagnosis & due treatment. This strategy of timely management would be beneficial in preventing progression of the disease & irreversible damage to the reproductive organs which will put an end to the concerned subfertility & social stigmata of the disease.

### **METHODS**

This prospective cross sectional study was carried out from 1<sup>st</sup> |an 2020 to 30<sup>th</sup> April 2021. Total of one hundred and eight cases with subfertility fulfilling the selection criteria were enrolled for the study. Sample size<sup>19</sup> was calculated by Open epi, taking 20 % prevalence of genital TB, 95 % confidence interval and 7.6% margin of error. Non-probability consecutive technique was utilized for sample collection. Informed consent was obtained before embarking upon diagnostic laparoscopy and dye test with endometrial biopsy for AFB culture. Laparoscopic findings were noted &endometrial curetting were obtained for AFB culture.

All women of reproductive age group with subfertility of  $\geq$ 2years requiring diagnostic laparoscopy and dye test for tubal factor assessment, normal male factor, normal menstrual history and hormonal assay were enrolled for study. All women with co-morbid, morbid obesity, women having contraindications for anaesthesia and couple with male factor in fertility were excluded from this study. The data collection was started after the approval of synopsis from Ethical committee of the institution.

After complete evaluation including detailed history, examination and mandatory investigations, they were explained about the procedure in details and informed consent was obtained. Anesthesia fitness acquired, patients were asked for being nil per oral a night before surgery. In operation room laparoscopy was performed in routine manner after administration of general anesthesia. Findings of direct visualization of internal organs were noted and 60 ml of methylene blue was instilled into the uterine cavity to assess the tubal patency. At the end of Laparoscopy thorough curettage was done, endometrial curetting obtained, normal saline was added to the specimen and sent for AFB culture. All procedures were done by qualified senior gynaecologist and the specimen were tested by the same laboratory with known standards. Patient were discharged with advice of follow-up after 8 weeks with culture report.

Confounders and bias were controlled by strictly following exclusion criteria. All the information including age, parity, type of subfertility, duration of subfertility and AFB culture findings were recorded in a predesigned proforma. Data was analysed using Statistical Package for social sciences (SPSS) version 20.

### RESULTS

In our study 108 women of reproductive age were included among them 18 (16.7%) women were between 18-24 years of age, 44 (40.7%) were 25-3 | years of age and 46 (42.6%) were between 32-38 years. Most of the women (n=72: 66.7%) presented with primary infertility with different period of sub-fertility from 2-5 years (41.7%), 6-10 years (47.2%) and 11-15 years (11.1%). All of 108 women had normal menstrual cycles and hormonal assay and their laparoscopy showed bilateral patent tube in 89.8% (n=97) cases, right patent tube in 6.5% (n=7), and left patent tube in 3.7% (n=4) cases. Endometrial biopsy of 22 (20.4%) cases were positive for AFB culture. Common laparoscopic findings were tortuous tubes (n=30; 27.8%) and clumped end fimbrial (n=24, 22.2%), bilateral dilated tubes (n=12; 11.1%)and unilateral dilated tubes (n=9;8.3%). Adhesions were present in 9 (8.3%) cases (Table I).

Out of 22 AFB-positive cases, 17 (77.3%) had primary and 5 (22.7%) had secondary sub-fertility (Table II). Adhesions were observed in 9.1% of AFB positive cases. All AFB-positive cases had surprisingly patent tubes either bilateral (n=21/22, 95.5% or unilateral (n=1/22, 4.5%). This depicts that tubal patency is not the only parameter ensuring fertility. In short anatomical escape from catastrophic event can't reflect the physiological status of an organ which becomes infirm as a result of destruction at cellular level.

On the basis of clinical findings and culture reports women were offered

#### TABLE I:DEMOGRAPHIC AND CLINICAL PROFILE OF THE STUDY SUBJECTS

Variables		Frequency (n=108)	Percentage
Age (years)	18 – 24	18	16.7
	25 – 31	44	40.7
	32 – 38	46	42.6
Types of infertility	Primary	72	66.7
	Secondary	36	33.3
Duration of Subfertility (years)	2 – 5	45	41.7
	6 - 10	51	47.2
	11 – 15	12	11.1
Tubal Assessment Status	Bilateral Tubal Patency	97	89.8%
	Right Tubal Patency	7	6.5%
	Left Tubal Patency	4	3.7%
Adhesions Status	Present	9	8.3%
	Absent	99	91.7%
AFB Culture Status	Positive	22	20.4
	Negative	86	79.6
Laparoscopic Findings of Tubal Morphology	Tortous tubes	30	27.8%
	Bilateral dilated tubes	12	11.1%
	Unilateral dilated tubes	9	8.3%
	clumped end fimbrial	24	22.2
	Clubbed fimbrial end	6	5.6%
	Normal looking	6	5.6%
	Polycystic ovaries	6	5.6%
	Convoluted pale white ovary	5	4.6%
	Hydrosalpings	5	4.6%
	Inflamed tubes	3	2.8%
	Vesicles	2	1.85%
	Fixed tubes	I	0.9%
	Tubo-ovarian mass	I	0.9%
	Endometrioma	I	0.9%
	Left tube absent, Right tube with clubbed end	I	0.9%
	Left tube convoluted with adhesion	I	0.9%

AFB=Acid Fast Bacilli, PID=Pelvic Inflammatory Disease

anti-tuberculous treatment (ATT), in turn three women of the treated cases got pregnant during our study period.

### DISCUSSION

In our study, around two third of women had primary subfertility. About 60 percent of patients had more than five years of Subfertility. About 20.4% cases were positive for AFB culture. Bilateral tubal patency was observed in 95.5% of AFB positive cases and 88.4% of AFB negative cases. Common laparoscopic findings were tortuous tubes/dilated tubes (47.2%) and clumped end fimbrial (22.2%).

In our study primary and secondary subfertility was observed in 66.7% and

33.3% cases respectively. Sub-fertility is the most common reason for women of reproductive age to visit the gynecologist. There is a small but steady rise in prevalence of subfertility the prevalence of unexplained fertility is 45% with 25% primary and 20% secondary subfertility respectively.<sup>20</sup> In our study, among AFB positive cases 77.3% women were with primary subfertility and 22.7% had history of secondary subfertility.

Tuberculosis demonstrates a substantial role in gynecological morbidity. Population of South East Asia is 26% of the world with overall 44% incidence of tuberculosis whereas the incidence of female genital tuberculosis varies from 5 to 15% in South East Asian countries.<sup>21</sup> In our country the incidence of tuberculosis is 263/100,000 population<sup>22</sup> and 41% of the total cases reported in female population of reproductive age. According to available data from evaluation cohorts reported rate of female genital tuberculosis among sub fertile women is between 3 to 3.5%.<sup>23</sup> In developing countries including Pakistan genital tuberculosis is a separate entity in the etiology of tubal factor subfertility. In female genital tuberculosis, isolated oophoritis is rarely observed but 25% of tuberculous oophoritis is seen combined with peritonitis and other pelvic organ tuberculosis. Fallopian tubes are affected in 90% of cases followed by endometrial involvement in 70% cases of genital tuberculosis. subfertility is observed in about 42.5% of cases diagnosed with genital tuberculosis.24

Primary genital tuberculosis is very rare, a history of extra-pulmonary tuberculosis is found in 25% to 50% of patients.<sup>21</sup> Almost always there is a primary focus elsewhere in the body. responsible for genital tuberculosis in women which might be the result of lymphatics, hematogenous and / or direct spread through abdominal route.25 Early diagnosis and stage of disease dictates the prognosis but early diagnosis is still a challenge due to subclinical nature, varied clinical presentation, limited sensitivity and specificity of imaging modalities, laparoscopy, histopathological, serological and bacteriological tests.<sup>26</sup>

Our study shows 20.4% women with positive acid fast bacilli culture and all the cases were diagnosed on endometrial samples hence the higher incidence of endometrial tuberculosis might be explained in our study, as almost all the specimen were endometrial curetting for diagnostic work up in sub fertile women.

Patel S, et al,<sup>27</sup> conducted a similar study and reported that endometrium is the most common affected site and 14.28% cases had positive AFB culture which is comparable to our study. Other studies conducted by Kayshap et al<sup>28</sup> and Jha A et al<sup>29</sup> who reported AFB culture positivity to diagnose female genital tuberculosis, their results are consistent with that of our study. In contrast to our study

	AFB POSITIVE		AFB NEGATIVE		Total
FINDINGS	Frequency (n=22)	%age	Frequency (n=86)	%age	(n=108)
Primary Infertility	17	77.3	55	64	72
Secondary Infertility	5	22.7	31	36	36
Bilateral patency	21	95.5	76	88.4	97
Unilateral Patency	I	4.5	10	11.6	
Tortous / Dilated tubes	12	55.5	39	45.3	51
Normal Looking	3	13.6	3	3.5	6
Adhesions	2	9.1	7	8. I	9
Hydrosalpings	I	4.5	4	4.7	5
Inflammation / inflamed	0	0	3	3.5	3
Vesicles	I	4.5	I	1.2	2
Other abnormality	5	22.7	36	41.9	41

#### TABLE II: DIFFERENT FINDINGS OF THE STUDY IN RELATION TO AFB CULTURE

AFB = Acid Fast Bacilli

Sharma R, et al $^{30}$  concluded the low incidence of female genital tuberculosis in their research study.

Female genital tuberculosis is a disease of young age with 80 to 90% patients diagnosed between 20 and 40 years of age and most of them present with subfertility.<sup>26</sup> Our study showed 42.6% women between 32 to 38 years of age followed by 40.7% women between 25 to 31 years of age with lowest number below 24 years. Reetu Sharma et al<sup>30</sup> reported the similar observations regarding age groups. In contrast to our study Patel S, et al<sup>27</sup> observed the comparatively younger age group in their research study however the impression of female genital tuberculosis occurring in younger age group still sustained.

With respect to duration of subfertility, our study showed 6 to 10 years in 47.2% cases followed by 2 to 5 years in 41.7% cases. A study conducted by Mahamood et al<sup>31</sup> reported that the incidence of endometrial tuberculosis was 13.6% in women with primary subfertility and 2.25% in women with secondary subfertility. Sharma |B et al<sup>32</sup> reported 72.9% and 17% of cases with primary and secondary subfertility respectively. In this study 18.8% cases were diagnosed with genital tuberculosis out of which 12.9% were diagnosed on endometrial biopsy and 5.9% cases by laparoscopic biopsy.

Laparoscopy is an important tool for subfertility in female genital

tuberculosis, since it possesses the dual benefit of internal pelvic organs inspection and biopsy for laboratory investigation concomitantly.<sup>33</sup> Our study explored a spectrum of different findings on laparoscopy from normal anatomy to frozen pelvis due to adhesions.

As far as tubal status is concerned, our study showed bilateral patent tubes in 89.8% where as 10.2% cases had unilateral patent tubes. In all cases with tubal blockade, culture done on their endometrial tissue turned out negative for AFB, however cases with negative culture had other Laparoscopic visual findings suggestive of tuberculosis. In fact, only tubal sparing from blockade doesn't exclude the destructive effects of tuberculosis on reproductive organs.

Study done by Grace et al<sup>25</sup> declared the laparoscopic visual inspection to be superior where as Deepti et al<sup>17</sup> and Arpitha et al<sup>26</sup> concluded that diagnostic laparoscopy supplemented with pertinent laboratory investigations could be promising for diagnosis of genital tuberculosis as compared to the laboratory investigation alone. Similarly, Neena Malhotra et al<sup>34</sup> suggested that one-time Laparoscopy is better than initiating anti-tuberculous treatments only on the basis of laboratory results. Briefly in face of subfertility these two diagnostic tools should proceed hand in hand.

For a gynaecologist serving in a low resource setting of the developing

country, it is essential to contemplate about the propensity of female gentle tuberculosis in sub-fertile women. Ignoring the possibility of female genital tuberculosis results in undue and ineffective treatment so it is advocated to get an AFB culture done on endometrial tissue in addition to Laparoscopy and dye test as a part of subfertility work up.

#### LIMITATIONS OF THE STUDY

It is a single centered small study which restricts the generalization of its inferences. Another limitation of the study is that it was merely the endometrial tissue which was biopsied for diagnosis of tuberculosis. Despite the optimistic aspect of early diagnosis associated with good prognosis the pessimistic aspect of the challenges in diagnostic pathway still exist due to subclinical nature of the disease, limited sensitivity and specificity of different diagnostic tools.

# CONCLUSION

Diagnostic laparoscopy is justifiably the principle modality of diagnosing genital tuberculosis. Nevertheless, a complete history supplemented by suggestive clinical and laboratory findings with histopathological inference and AFB culture play a supportive role in the diagnosis and timely treatment of tuberculosis which in turned halts and prevents further damage to the genital organs hence subfertility. In our study endometrial sampling of 20.4% cases turned out positive for AFB culture.

# RECOMMENDATIONS

Apparent tubal patency doesn't exclude the tubal factor because tubal patency alone could not be the representative of normal functional status of the Fallopian tubes. Structural damage affecting the anatomy could be assessed by laparoscopy whereas functional damage could be evaluated by microscopic studies. Hence, laparoscopy should be considered as the first line investigation for the cases of prolonged sub fertility combined with endometrial sampling for bacteriological (AFB) study. This combined approach would build up the prognostic sketch in the management of future fertility of an individual.

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# **AUTHOR'S CONTRIBUTION**

Following authors have made substantial contributions to the manuscript as under:

**NK:** Acquisition, analysis and interpretation of data, drafting the manuscript, critical review, approval of the final version to be published.

**BR:** Concept and study design, analysis and interpretation of data, drafting the manuscript, critical review, approval of the final version to be published

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

#### **CONFLICT OF INTEREST**

Authors declared no conflict of interest

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#### **DATA SHARING STATEMENT**

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



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