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RESEARCH ARTICLE

Changing Trends of Tubercular Assault on Reproduction

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ABSTRACT

Background and Objectives. Genital tuberculosis (GTB) is a rare disease in developed countries but is an important cause of subclinical chronic pelvic inflammatory state and infertility in 1–18% of women, being as high as 18 % in India. What we are observing nowadays GTB is changing its way of assault to reproductive process less by infection but more by infestation of the genital tract and thereby leading to harmful molecular changes or may be immunomodulation locally. Reduction of infection may be due to increased surveillance, treatment or use of antibiotics for other reasons indiscriminately, which may make the bacteria dormant. It is being observed as a silent invader of the genital tract of both the female and male partners. It is to be kept in mind that mycobacteria, non- pathogenic to humans, may also cause molecular assault on reproduction. At present, our cohort of patients can be categorized in three groups a) Frank tuberculosis b) LGTB infection c) LGTB infestation There has been extensive research about the involvement of genital tuberculosis in female infertility. Various studies have been undertaken to screen and detect latent genital tuberculosis in apparently normal infertile couples intervening fertility at molecular level. The adverse effects of latent genital tuberculosis, as found in current researches, on the female and male reproductive process has been addressed in the current review.

Methods Endometrial aspirates at mid-luteal phase and samples of menstrual blood were collected aseptically from each of those women enrolled in this study and stored at -80°C for DNA-PCR (Polymerase chain reaction test) and cytokine study. Multiplex polymerase chain reaction (PCR) were performed. DNA-PCR test and sperm DNA fragmentation tests were carried out in semen samples, collected according to WHO guidelines, from male partners in question.

Observation. It is being observed that pro-inflammatory cytokines showed significantly different values in TB-PCR- positive and TB-PCR-negative groups. Sperm DNA fragmentation index also appears to be quite high in TB-PCR positive males.

Conclusion. LGTB infestation has been found to be responsible for unfavourable molecular changes in reproductive tract and thereby causing a negative impact on fertility.

Keywords: latent genital tuberculosis, infertility, cytokine, tubercular infestation, tuberculosis-polymerase chain reaction,

Abbreviations: latent genital tuberculosis – LGTB, tuberculosis-polymerase chain reaction -TB-PCR, DNA fragmentation index test – DFI, interleukin-6,10,2- IL-6; IL-10; IL-2, interferon gamma- IFNγ, tumor necrosis factor alpha-TNFα

Introduction

Genital Tuberculosis (GTB) is a major cause of infertility particularly in developing countries like India.[1,2] Although pulmonary TB (PTB) remains the commonest and the most infectious type of TB, extra-pulmonary TB (EPTB) is becoming more prevalent especially in young women throughout the world.[3] In recent years the nature of tubercular affection of the genital tract is changing. Tubercular infection either pulmonary or extra pulmonary are getting less and less due to improvement of health condition and standard of care. Instead, tubercular infestation that is mere presence of tubercular bacteria on the genital tract surface is increasing. This local presence of bacteria is small in number and difficult to detect by usual way of detection procedures like smears and culture. So, to identify them molecular diagnostics procedures like polymerase chain reaction (PCR) are undertaken. These sort of infestation often clinically cause latent genital tuberculosis (LGTB). Tubercular infection may cause major structural damage to the genital organs like tubal block, hydrosalpinx, destruction of endometrium leading to various grades of uterine synechia and ovarian abscess.[4] In another study TB endometritis was detected in 72.03%, tubal involvement in 34.03%, ovarian TB in 12.9% and cervical TB in 2.4% of the patients.[5] LGTB mostly cause molecular change of the endometrium or tubal surface leading to tubal block, non-receptive endometrium & diminished ovarian function etc. LGTB being noninfective passes unnoticed for long time and may cause local damage which is not that severe. It is observed in the literature that LGTB is associated with tubal block leading to infertility and ectopic pregnancy.[6,36] Endometrial infestation with MTB may cause implantation failure, early embryonic rejection and recurrent miscarriage.[3] LGTB may cause unexplained infertility. The association of LGTB and endometriosis is another cause of concern.[7] It is being observed as a silent invader of the genital tract of both the female and male partners. Male to female transmission of LGTB has been reported in literature.[8] It is to be kept in mind that those mycobacteria which are non- pathogenic to humans, may cause molecular assault on reproduction.

Depending on the virulence of organism and immune response generated by the host, the disease remains either active or becomes asymptomatic with latent infection persisting for many years.[9] Latent infected individuals contain dormant, yet viable bacilli, which may re-activate when the host response becomes low, and as a consequence, the disease may become active again. During the process of reactivation, the bacilli induce immune modulation within the local tissues, which mimics inflammatory reaction.[10] It is release of harmful cytokines like IL2, TNFa and IFNy. The final effect will depend upon how strongly the host tissue (ovarian tissue and endometrium) can resist this trauma.[11] If unable to resist, immune-modulatory impact will affect adversely on the endometrial receptivity. Once the adverse impact has been established on the delicate function of this reproductive organs, the consequences may continue to persist. Since definite physical symptoms are usually not present, the disease remains undiagnosed or specific investigations are not undertaken to rule out the problem.[12] It is a pauci-bacillary form of disease where cultures and smears are often negative.[13] The primary focus is rarely found outside the genital tract.[14] Routine screening tests for pulmonary tuberculosis like X-ray chest, tuberculin test and sputum examination are negative usually.[15]

At present, our cohort of patients can be categorized in the following group a) **Frank tuberculosis**, with symptoms and signs of tuberculosis with positive smear culture and histopathology from respective specimens, with permanent damage of genital organs; b) **LGTB infection** – asymptomatic patients, with or mostly without signs of tuberculosis and smear culture being positive, with conclusive or inconclusive histology, with positive Polymerase chain reaction for TB (TB-PCR positive)with or without some damage to the genital tract; c) **LGTB infestation –** asymptomatic patients with no signs, no damage caused, smear & culture tested negative, only TB-PCR test being positive. This group is more prevalent among infertile women.

Material & Methods

2036 patients of reproductive age group being 23yrs to 42yrs for women and 25yrs to 50 yrs for men were included in whole review. The individual number of participants and the criteria of selection are mentioned separately in individual research papers.

Collection of endometrial aspirates for DNA-PCR (Polymerase chain reaction test at mid-luteal phase of the menstrual cycle under aseptic conditions With pipelles or IUI canula, later being our preference. Another sample of menstrual blood has been taken during day 2 or day 3 of menses from those enrolled in this study aseptically and stored at -80°C.On the day of cytokine extraction samples were transferred to the 4°C to avoid the heat shock, subsequently brought to room temperature. DNA was extracted from samples using QIAamp Viral DNA Mini Kit (Qiagen, Hilden, Germany) and

eluted in 200 µl of elution buffer and was stored at −20°C for further study within 1-2 days. Multiplex polymerase chain reaction PCR were performed after genomic DNA extraction. DNA-PCR test and sperm DNA fragmentation tests were carried out in semen samples from male partners in question collected according to WHO guidelines. DNA extraction was performed using DNA Mini Kit.

Polymerase chain reaction (PCR) is a laboratory technique for rapidly producing (amplifying) millions to billions of copies of a specific segment of DNA, which can then be studied in greater details. PCR involves using short synthetic DNA fragments called primers to select a segment of the genome to be amplified, and then multiple rounds of DNA synthesis to amplify that segment. This technology is widely available at present commercially where single primer flakes are used. This leads to low detection rate of only pathogenic tubercle bacilli to humans. Even non-pathogenic bacilli may bring harmful immunomodulation in reproductive organs. To identify large number of them a multiplex PCR system was developed by Bhattyacharya et. al,[16] by modifying three individual PCR to one reaction condition.[17,18]

There is no good guideline as yet for treating asymptomatic subclinical tubercular involvement or otherwise *called tubercular infestation. Many authorities do not accept positive TB-PCR as a* standard parameter for diagnosing tubercular involvement and depending on that they deny to initiate any antitubercular treatment, as false positivity of TB-PCR rate is high. It is to be mentioned here with strict asepsis and multiple PCR testing, as it is performed here with more than one set of primer either from menstrual blood or endometrial sampling in case of females or semen in males, the error can be avoided. Any insidious, low-grade inflammation is quite likely to alter the function of fallopian tubes, uterus, and of the endometrium, as it happens in Mycobacterium tuberculosis (MTB) infestation. Such mechanism, however have not been studied or reported in the case of GTB. Mycobacterial presence may also alter endometrial receptivity and cause implantation failure[19] through mechanisms such as disturbed immunomodulation and cytokine overburden, endocrine disruption, activation of anti-phospholipid antibodies and micro thrombosis without the presence of overt clinical disease. Latent TB was also shown to be responsible for unexplained infertility[20] and repeated IVF failures.[21] LGTB in males may cause Oligoasthenospermia, Sperm DNA fragmentation & in rare cases obstructive Azoospermia.[28] There are multiple studies in literature which have highlighted a very high diagnostic specificity, sensitivity, and clinical correlation of TB-PCR with GTB. Even in normal pelvis detected by laparoscopy, tubercular infestation otherwise called latent TB detected by positive TB-PCR study can lead to infertility. Instituting antitubercular treatment improves pregnancy outcome.[22]

Cytokine Changes in LGTB

The concentration of cytokine in endometrium has been studied, which might influence reproductive performance.[23,24] Five cytokines have been studied to start with – IL-2, IL-10, IL-6, TNFa, and IFNy.[25] Of all these three cytokines showed reproducible results with statistically significant differences in positive and negative TB-PCR cases. The inflammatory cytokines such as IFNy and IL-2 are significantly high in TB-PCR-positive cases indicating hostility of endometrium, possibly leading to implantation failure. Many of the patients showed prolonged luteal phase followed by onset of period in ovulatory cycles which indicates possibility of micro miscarriage. The other two cytokines IL-10 and TNFa show bizarre concentration between positive and negative TB-PCR cases and could not be corroborated statistically. It is difficult to estimate the endometrial cytokines in day-to-day practice. What appears from the present study is that IFNy may come out as an important indicator of endometrial hostility. There is an established relation between interferon-gramma and TB, as evidenced in literature review. This interferon gamma can be detected in blood when the question is generalized infection comes. In case of infestation, as we suggest, IFNy can also become an indicator of local presence of MTB and their harmful influences. We believe that any form of MTB bacillus may influence the endometrial environment by mere presence and manipulate cytokine release.

EFFECTS OF LGTB ON HUMAN REPRODUCTION

Tubal damage

The fallopian tubes are the most common affected pelvic organs, followed by endometrium, ovary and cervix in female genital tuberculosis but the involvement may differ in LGTB. In developing countries, it is not cost effective to perform laparoscopy for all infertile women and HSG continues to be the preliminary investigation to detect the abnormalities of the uterus and fallopian tubes and their patency. During the past two decades, the clinicians have faced quite a number of cases of LGTB and its consequences such as infertility. Multiple HSG findings for diagnosis of tubercular infestation has been given by various authors such as tubal obstruction between the isthmus and the ampullary portion of the fallopian

tube, an everted or agglutinated fimbria with a patent orifice, slight or moderate dilatation of the ampullary portion of the fallopian tube. Small synechiae of the uterine cavity in the absence of clinical history of curettage or pelvic surgery may be due to LGTB. In our study 15.6% [26] of the patients were seen to have block in the isthmus or ampulla; 7.09% of the enrolled patients had cornual block and 26.9% of them had fimbrial block. 33.8% of the women had tubal kinking, convoluted or beaded tubes and 16.5% patients had tubal or cornual extravasation. In that study the following minor tubal defects were more common on laparoscopy like tubal kinks due to serosa-serosal adhesions, shortening of the tubal length but hydrosalpinx was less common. Tubal block due to mucosal edema or adhesions inside the fallopian tube can also be seen in LGTB. All these tubal defects can be corrected by laparoscopy if genital tract is free of tubercular bacilli.

Diminished Ovarian Function

LGTB exerts its deleterious effects by mere presence of bacilli and due to harmful cytokine secretion. The same mechanism may play a role in the ovary as harmful inflammatory cytokine might diminish ovarian function indicated by low AMH.[27] The retrograde menstruation is a normal phenomenon of most women. In PCR positive patient, this blood may come in contact with ovary, influencing the ill effects of inflammatory cytokine.[28] It has been evidenced that AMH level significantly lowered in TB-PCR positive group,[29] means patients with tubercular infestation of the genital tract. The ovarian reserve which controls the ovulatory process is usually determined by AMH level along with early follicular FSH and antral follicular count (AFC). AMH maintains static level throughout the cycle without showing much variation in follicular or luteal phases. Due to low AMH level, ovary responds sub-optimally during folliculogenesis, which becomes a feature for ovulatory failure in TB-PCR positive cases. The comparison of AMH level in PCR positive and negative cases also showed significant difference even where age-stratified values were studied. Statistically significant diminished ovarian reserve was found in affected cases. The fertile controls in whom AMH was estimated has been found that their level is better than infertile group, but much better than TB-PCR positive and little better than TB-PCR negative cases. We have estimated the AMH level after completion of antitubercular treatment. AMH level increased by 15% than pre-treatment value but that rise was not exceeding 25%. It is very interesting that this rise was not age specific. 6-month AMH value was better than 3 months value. As the fertility potential of a woman depends on its ovarian reserve vis-a-vis the AMH level, the latent tubercular involvement imparts a negative impact in female reproductive potential.[30]

Endometriosis

The clinical finding of association of endometriosis with LGTB is a recent one, as mentioned in a recent study.[25] The ill- effect of endometriosis on fertility has so long been discussed and well known. But the the presence of tubercular bacilli in genital tract along with endometriosis probably worsens the situation. This study indicates women with endometriosis has high level of IL-6 and TNF-a but IFN-γ was in normal range. These inflammatory mediators also contribute to sperm DNA fragmentation. This finding correlates with the study by chou CH et al which states that use of IFN-γ shorten the time to diagnosis of extra-pulmonary tuberculosis than conventional culture method. Low IFN-γ value occurs when there is clearance or resolution of infection.[24] The inflammatory component of endometriosis is probably exaggerated by presence of tubercular bacilli as during laparoscopy, tubal wall edema and inflammatory look of the pelvis is much more in the presence of LGTB. Though endometriosis induces aseptic inflammation of reproductive organs, the presence of LGTB exaggerates it, as it is indicated by the presence of IFN-γ and TNF- α together. Those patients who have endometriosis only without LGTB, the presence of TNF – α in high concentration is found and in association with LGTB, both IFN-γ and TNF – α are observed to be high. It is also interesting to find that in absence of endometriosis, the presence of LGTB induces rising levels of IFN-γ only.

Unexplained Infertility

In couples with unexplained Infertility the chance of a natural conception within 1 year is 30% or higher. Medically assisted reproduction (MAR) is one of the treatment for unexplained infertility so also tailored expectant management (TEM). MAR is no better than TEM for 6-12 months except those having poor Ovarian reserve.[31,32] Most often TEM is underutilised either due to failure in identifying couples who are eligible for TEM or couples do not undergo expectant management for lack of advice by medical professional. Latent genital tuberculosis is an important cause of subclinical chronic pelvic inflammatory disease and infertility which may remain unexplained due to failure of detection. In a study 28.6% of patients with apparently unexplained infertility were found to have LGTB[20] and 31.76% of them had conceived following treatment with ATD. In this study 36.54% cases with unexplained Infertility had LGTB and 34.15% patients, were diagnosed to have early

endometriosis stage I and II. Similarly, in the above-mentioned study, Minor tubal defects on laparoscopy were detected in as high as 43.56% in patients with LGTB and 29% without it.

Male To Female Transmission

It has been demonstrated that not only women but also their asymptomatic male partners have been affected with LGTB causing adverse reproductive outcome.[33,8] From same study, it been testified with statistically significant data analysis (p value<0.001) that poor DNA fragmentation index (DFI) i.e., high sperm DNA fragmentation in seminal fluid of male partners with LGTB, leads to either infertility or RPL. If the history of previous literature is carefully looked into, there are evidences of sexual transmission in case of extra pulmonary tuberculosis, though not generally regarded as being infectious, but may be due to transmission from one mucosal surface to another during intercourse which has been described in animal models.[34,35] Increased transmission of the disease has also been noted in infected marital couples.

Recurrent Early Pregnancy Loss

Repeated miscarriage appears to be a curse in a woman's reproductive career. It becomes difficult to form a work-up to detect the cause of recurrent pregnancy loss (RPL). Continuation of pregnancy involves many factors like genetic factors, anatomical factor (uterine cavity defect), hormonal causes or miscellaneous like infections and immunological factors. Among infective & immunological causes investigations are so many. A study has shown that PCR detection of tubercular infestation of the endometrium has come out to be a causative factor of RPL.[6] It has been observed that quite a large number of cases of RPL are affected with latent GTB or a tubercular infestation of the endometrium as a sole or strongly associated factor for the development of such an unfortunate situation. Patients with history of RPL with secondary infertility who otherwise had no other demonstrable cause of pregnancy loss other than latent FGTB, 29.36% of patients had conceived spontaneously during or within 12 months of ATD administration.

The evaluation of implantation markers is necessary to detect occult endometrial assault. The most offensive cytokine for the loss of pregnancy is TNF-a.[7] TNF-a, and anti-cardiolipin antibody levels are seen to be potential diagnostic markers and they exhibit significant role in prognosis of RPL patients. An increased prevalence of IFN-y has been shown in endometrial aspirate in TBPCR positive cases. Hence IFN y showed a possibility to become an important clinical indicator of endometrial hostility followed by IL2 and on treatment by ATD improved reproductive outcome indicating the ill effect is reversible, as in contrast to tubercular infection.

Ectopic Pregnancy

The association of infertility and ectopic pregnancy (ETP) is complex, as ETP has been observed to be a cause as well as a consequence of infertility and it can be presumed that they have common causal factors. Although many of these factors have always been screened and sometime the possible cause of ETP has been detected, in about 50% of cases the cause still remains unknown. Endometrial inflammation has been proved to be hostile for implantation and the movement of the embryo comes to a halt in the fallopian tube or it might as well move to the other tube by trans-uterine migration. In order to find out the cause in these patients with idiopathic ETP screening for LGTB using DNA-PCR test was undertaken.[36] Presence of tubercular bacilli is responsible for inflammation of the fallopian tubes resulting in presence of pro-inflammatory interleukins which might facilitate tubal implantation leading to ETP as seen in cases of Chlamydia trachomatis infection. Tubercular insult of the female genital tract is responsible solely or in association with other predisposing factors for ETP as documented by other authors. In the present study 31 to 59% patients treated with Anti-tubercular drugs (ATD) for FGTB conceived spontaneously and even those who had undergone IVF had live birth, spontaneous abortion or ectopic pregnancy. clinical pregnancy rate (CPR) has been seen to be statistically significant.

Conclusion

Genital tuberculosis is age old disease prevalent in Asia and Africa. In recent years the nature of its pathogenicity is changing due to upliftment of healthcare and nutritional status. More latent or dormant form of this disease is prevailing. The infective form of the disease often causes permanent structural damage of reproductive organs which are mostly irreversible leading to sterility. Latent form (LGTB) remain mostly on the surface of genital tract leading to molecular changes which causes reproductive failure like fallopian tubal defect, recurrent miscarriage, unexplained infertility, ectopic pregnancy, in association with endometriosis, poor ovarian function and male infertility due to seminopathy. Male to female transmission is also possible. All these damages are reversible by proper medical treatment with antitubercular drugs. Many of these bacteria may be non-pathogenic to humans but can cause harmful molecular changes. Screening for LGTB seems to become a routine procedure for infertile couple in near future particularly in developing countries.

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References

1. Punnonen R, Kiilholma P, Meurman L. Female genital tuberculosis and consequent infertility. Int J Fertil. 1983; 28(4):235-238.
2. Nogales-Ortiz F, Tarancón I, Nogales FF Jr. The pathology of female genital tuberculosis: A 31-year study of 1436 cases. Obstet Gynecol. 1979; 53(4):422-428.
3. Malik S. Genital tuberculosis and implantation in assisted reproduction. Reviews in Gynaecological Practice. 2003; 3(3):160-164.
4. de Vynck WE, Kruger TF, Joubert JJ, Scott F, van der Merwe JP, Hulme VA, Swart Y. Genital tuberculosis associated with female infertility in the western Cape. S Afr Med J. 1990;77(12):630-631.
5. Jahromi BN, Parsanezhad ME, Ghane-Shirazi R. Female genital tuberculosis and infertility. Int J Gynaecol Obstet. 2001; 75(3):269-272.
6. Chowdhury RG, Paine SK, Bhattacharjee B, Chatterjee S. Infestation of endometrium by mycobacterium tuberculosis bacilli-cause of reproductive failure. Al Ameen J Med Sci. 2010; 3(4): 322-331.
7. Mueller-Eckhardt G, Mallmann P, Neppert J, Lattermann A, Melk A, Heine O, Pfeiffer R, Zingsem J, Domke N, Mohr-Pennert A. Immunogenetic and serological investigations in nonpregnant and in pregnant women with a history of recurrent spontaneous abortions. German RSA/IVIG Study Group. J Reprod Immunol. 1994; 27(2):95-109.
8. Datta A, Gupta P, Bhattacharya B, Das A, Chatterjee S, Banerjee A. Evidence of sexual transfer of mycobacteria from male to female partners reporting to an IVF clinic. Trop Doct. 2022; 52(2):331-334.
9. Stead WW, Kerby GR, Schlueter DP, Jordahl CW. The clinical spectrum of primary tuberculosis in adults: Confusion with reinfection in the pathogenesis of chronic tuberculosis. Ann Intern Med. 1968; 68 (4):731-45.
10. Sharma JB, Sharma S, Sharma E, Dharmendra S, Singh S. Immune disturbances in female genital tuberculosis and latent genital tuberculosis. Am J Reprod Immunol. 2023; 89(2), e13632.
11. Raghupathy, R., Makhseed, M., Azizieh, F., Al-Azemi, M.M.K., Hassan, N.A., Bandar, A. Th1 and Th2 Cytokine Profiles in Successful Pregnancy and Unexplained Recurrent Abortions. In: Gupta, S.K. (eds) Reproductive Immunology. Dordrecht: Springer Netherlands. 1999; 149-158.
12. Bateman BG, Nunley WC Jr, Kitchin JD 3rd, Fechner RE. Genital tuberculosis in reproductive-age women: A report of two cases. J Reprod Med. 1986; 31(4):287-290.
13. Baum SE, Dooley DP, Wright J, Kost ER, Storey DF. Diagnosis of culture-negative female genital tract tuberculosis with peritoneal involvement by polymerase chain reaction. J Reprod Med. 2001; 46(10): 929-932.
14. Sutherland AM. Tuberculosis of the female genital tract. Tubercle. 1985; 66(2):79-83.
15. Purohit M, Mustafa T. Laboratory Diagnosis of Extra-pulmonary Tuberculosis (EPTB) in Resource-constrained Setting: State of the Art, Challenges and the Need. J Clin Diagn Res. 2015;9(4):EE01-6.
16. Bhattacharya B, Karak K, Ghosal AG, Roy A, Das S, Dandapat P, Khetawat D, Mondal DK, Bhattacharya S, Chakrabarti S. Development of a new sensitive and efficient multiplex polymerase chain reaction (PCR) for identification and differentiation of different mycobacterial species. Trop Med Int Health. 2003; 8(2):150-157.
17. Pao CC, Yen TS, You JB, Maa JS, Fiss EH, Chang CH. Detection and identification of Mycobacterium tuberculosis by DNA amplification. Journal of Clinical Microbiology. 1990; 28(9): 1877-1880.
18. Bhanu NV, Singh UB, Chakraborty M, Suresh N, Arora J, Rana T, Takkar D, Seth P. Improved diagnostic value of PCR in the diagnosis of female genital tuberculosis leading to infertility. J Med Microbiol. 2005; 54(10):927-931.
19. Subramani E, Madogwe E, Ray CD, Dutta SK, Chakravarty B, Bordignon V, Duggavathi R, Chaudhury K. Dysregulated leukemia inhibitory factor and its receptor regulated signal transducers and activators of transcription 3 pathway: a possible cause for repeated implantation failure in women with dormant genital tuberculosis?. Fertility and sterility. 2016; 105(4):1076-1084.
20. Chatterjee S, Bagchi B, Chatterjee A, Datta A. Latent Genital Tuberculosis – A Possible Explanation for Unexplained Infertility. Integr Gyn Obstet J. 2020; 3(1): 1–4.
21. Dam P, Shirazee HH, Goswami SK, Ghosh S, Ganesh A, Chaudhury K, Chakravarty B. Role

of latent genital tuberculosis in repeated IVF failure in the Indian clinical setting. Gynecol Obstet Invest. 2006; 61(4):223-227.

22. Jindal UN, Verma S, Bala Y. Favorable infertility outcomes following anti-tubercular treatment prescribed on the sole basis of a positive polymerase chain reaction test for endometrial tuberculosis. Hum Reprod. 2012; 27(5):1368-1374.
23. Datta A, Chaudhuri AR, Chatterjee S, Chowdhury RG, Bhattacharya B. Role of endometrial cytokines of the female genital tract tuberculosis in the context of infertility. BLDE University Journal of Health Sciences. 2018. 3(1): 24-30.
24. Chou CH, Hsu HL, Lee LN, Hsueh PR, Luh KT. Comparison of 2 interferon-gamma assays and Roche Cobas Amplicor Mycobacterium tuberculosis assay for rapid diagnosis of tuberculosis among patients with suspected tuberculosis in Taiwan. J Microbiol Immunol Infect. 2009; 42(3):251-257.
25. Datta A, Bagchi B, Chatterjee S, Chowdhury RG, Bhattyachariya B, Das A. Role of TH-I based Endometrial Cytokines in Latent Genital Tuberculosis and Endometriosis Causing Infertility. SF J In Vitro Fertil Embryo Res. 2020; 1(1): 1001.
26. Chatterjee S, Bagchi B., Chatterjee A, Datta A. Latent female genital Tuberculosis causes tubal defect leading to infertility. Glob J Reprod Med. 2020; 7(4): 5556718.
27. Rahman E. Positive correlation between latent female genital tuberculosis and low anti-mullerian hormone levels in young individuals. Int J Reprod Contracept Obstet Gynecol. 2023; 12(8):2403-2408.
28. Jirge PR. Ovarian reserve tests. J Hum Reprod Sci. 2011; 4(3):108-113.
29. Datta A, Chowdhury S, Chowdhury RG, Bhattyacharya B, Chatterjee S. Effect of Female Genital Tubercular Involvement on Anti-Mullerian Hormone Secretion in Latent Genital Tuberculosis Affected Women. J Reprod Med Gynecol Obstet. 2019; 4(1): 018.
30. Kulshrestha V, Kriplani A, Agarwal N, Singh UB, Rana T. Genital tuberculosis among infertile women and fertility outcome after antitubercular therapy. Int J Gynaecol Obstet. 2011;113(3):229-34.
31. Nandi A, Homburg R. Unexplained subfertility: diagnosis and management. The Obstetrician & Gynaecologist. 2016; 18(2): 107-115.
32. Custers IM, van Rumste MM, van der Steeg JW, van Wely M, Hompes PG, Bossuyt P, Broekmans FJ, Renckens CN, Eijkemans MJ, van Dessel TJ, van der Veen F, Mol BW, Steures P; CECERM. Long-term outcome in couples with unexplained subfertility and an intermediate prognosis initially randomized between expectant management and immediate treatment. Hum Reprod. 2012; 27(2):444-450.
33. Chatterjee S, Bhattacharya SM, Bagchi B, Chaudhuri AR, Datta A. Latent Genital Tuberculosis in Male - A Possible Cause of Reproductive Failure. J Reprod Med Gynecol Obstet. 2020; 5(4): 057.
34. Gondzik M, Jasiewicz J. Experimental study on the possibility of tuberculosis transmission by coitus. Zeitschrift fur Urologie und Nephrologie. 1979; 72(12): 911-914.
35. Gondzik M, Jasiewicz Z. Transmission of tuberculosis by sexual route in guinea pigs under experimental conditions. In *Annales Academiae Medicae Stetinensis*. 1979; 25: 505-521.
36. Chatterjee S, Bagchi B, Chowdhury RG, Dutta A. Latent Genital Tuberculosis–A Causative Factor for Ectopic Pregnancy-A Retrospective Analysis. J Clinical Research and Reports. 2020; 3(5): 1-6.