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RESEARCH ARTICLE

ENDOMETRIAL TUBERCULOSIS: AN IMPORTANT CAUSE OF INFERTILITY IN A DEVELOPING COUNTRY.

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Abstract

Background :Endometrial tuberculosis , important cause of secondary amenorrhoea and infertility where tuberculosis is endemic.**Materials and methods** : Random sampling of patients failing to conceive for a year included in study conducted in tertiary care hospital, where congenital abnormalities and problems regarding husband excluded.Tests conducted were routine blood examination with hormone assays, ultrasonography, hysterosalpingography and endometrial tissue biopsy. Endometrial tissue culture done in case of infections with PCR.**Results** : Among 100 female subjects;28 were hypothyroid,16 were hyperprolactinemic. Endometrial biopsy showed 47 cases of anovulation , 32 showed luteal phase defects and 5 showed features of endometrial tuberculosis confirmed by staining by Z-N method, culture and PCR study. **Conclusion** : Apart from hormonal imbalance; infections specifically tuberculosis can be an important cause of infertility and must be taken care of.

Introduction:-

Tuberculosis (TB) is one of the top three infectious killing diseases in the world: HIV/AIDS kills 3 million people each year, TB kills 2 million and malaria kills 1 million. In developing countries, like India, tuberculosis remains a major cause of infertility[1,2]. Endometrial TB is the second most common form of extrapulmonary TB (EPTB), after lymph node TB [2, 3]. 75% of women with endometrial TB are aged 20–45 years.Patients might present with constitutional symptoms or be asymptomatic, and can also present with symptoms similar to those of pelvic inflammatory disease, as genitourinary TB can cause Fitz-Hugh Curtis syndrome, a complication of pelvic inflammatory disease [1, 2, 3] .The endometrial tuberculosis (TB) PCR (Polymerase chain reaction) test is now commonly employed for the diagnosis of female genital TB, a common cause of infertility in India. [1-4]

Genital tuberculosis is typically asymptomatic and is usually diagnosed incidentally during infertility investigations. Symptomatic disease usually presents with infertility, pelvic pain, and/or menstrual irregularities .Infertility is typically caused by pathology in the endometrium and fallopian tubes and a blockage of ovum transport, and dysfunction of menstruation is largely attributed to endometrial caseation.[2] The antigonadotrophic effect of Mycobacterium tuberculosis may be responsible for the menstrual irregularities that take place in cases of active pulmonary tuberculosis without genital tract lesions.[2,3] In 2007, the World Health Organization (Global Tuberculosis Control) stated that in 92% of cases, diagnosis of genital tuberculosis is secondary to lesions found in the lungs, lymph nodes, urinary tract, bones, or joints.[1,3]

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The differential diagnosis of female genital tuberculosis includes chronic pelvic inflammation, mycotic infection, enterobiasis, lipid salpingitis, and carcinoma. The endometrium is involved in approximately 50–60% of women with genital tuberculosis. Hysteroscopy provides direct information about endometrial trophicity, and may reveal a scarred atrophic endometrial layer with adhesions varying from mild to severe, leading to Asherman's syndrome and secondary amenorrhea.[1-4] In developed countries, such as USA, Australia and Western European countries, the incidence of genital tuberculosis (GTB) is less than 1 per cent, but the incidence in some African countries is as high as 15-19 per cent. Various Indian studies have shown that tuberculousendometritis and salpingitis account for 4-9 per cent of all infertility cases.[2]

Routine laboratory values are of little value. A positive chest X-ray for healed or active pulmonary tuberculosis, contact history, elevated ESR and positive tuberculin test may indicate the need for further investigations.[3]Though absolute diagnosis cannot be made from characteristic features in hysterosalpingogram (HSG) or laparoscopy, laparoscopy is a valuable procedure for obtaining tissue for culture and histopathological examination.[3]

A definite diagnosis can be made by positive mycobacterial culture and by demonstrating specific histopathological lesion in the specimen. However, these methods have low detection rates and limitations as GTB is paucibacillary.[2,3] In recent years, polymerase chain reaction (PCR) technique has evolved as a useful and rapid technique for the diagnosis of pulmonary and extra-pulmonary tuberculosis. Any method that is used to diagnose GTB should be highly sensitive to diagnose the disease reliably in its early stage, so that treatment may improve the prospects of cure before the tubes are damaged beyond recovery.[1-3]

The present study was conducted to measure effects of genital tuberculosis as a cause of infertility in a rural population in India.

Materials and methods:-

This study was conducted in a tertiary care hospital in West Bengal in a time span of one year after taking approval from the ethical committee and informed consent from the patients.

Inclusion criteria: Women in reproductive age group unable to conceive within one year of unprotected sexual intercourse.

Exclusion criteria: Infertile women with diagnosis of congenital malformation of uterus and appendages, husband having abnormal semen analysis, women with history of malignancy, severe systemic, infective and metabolic disease.

Sampling was done by convenience sampling technique. On first appointment, particulars of the subject, chief complaints, personal history, family history, history of vaccination, history of past illness and treatment history of the subjects were carefully recorded. Clinical examinations and per vaginal were done. Adequate counseling was given to the couple.

Blood tests, i.e. hemoglobin, Total count, Differential count, Erythrocyte sedimentation rate, Post Prandial blood sugar, HIV screening, VDRL, were done. Vaginal discharge if present was further investigated by staining collected smears by PAP staining method to detect the cause.

Hormonal assay (FSH, LH, Progesterone), Transvaginal ultrasonography, Hyterosalpingography, Serum TSH, Prolactin levels, Testosterone, SHBG, DHEA, DHEAS, Laparoscopy, hysteroscopy, chromosomal karyotyping were done as per requirement. Endometrial samplings with interpretation of biopsy were carried.

Menstrual blood samples (in regularly menstruating women) were collected for histopathology, bacteriology, culture in Lowenstein- Jenson Media, Rapid antibody detection(test kit used, SEROCHEK-MTB) and PCR applied DNA detection for Mycobacterium Tuberculosis.[1-4] Hormone study done by enzyme linked immunosorbent study.
For histopathological studies, a portion of the endometrial tissue/tissue from the lesion over the tube was fixed in 10 per cent formalin; routine processing was done and stained with haemotoxylin and eosin. Presence of caseating granulomas surrounded by epithelioid cells, lymphocytes, plasma cells and giant cells were diagnostic of tuberculosis.

For microscopic examination of acid fast bacilli (AFB), biopsy material was ground well using homogenizer and the concentrated mix was taken for smear and was stained with Ziehl-Neilsenstain.For culture, the tissue sample was ground well with 5 ml of sterile distilled water. The specimen was centrifuged and the supernatant fluid was discarded. The deposit was decontaminated by 5 per cent $H_2SO_4$and added to selective Kirchner's liquid media and cultured for **Mycobacterium tuberculosis**. Since these extra-pulmonary lesions were paucibacillary in nature, their processing included milder decontamination and inoculation into multiple media. For the diagnosis of genital tuberculosis there is no absolute gold standard test available.

Therefore, based on the clinical profile and laparoscopic evaluation of patients, a diagnostic criteria were derived to suspect tuberculosis. A woman was said to be suspected of having genital tuberculosis if she has had findings suggestive of tuberculosis at laparoscopy with one or more of the following findings: A definite past history of tuberculosis, in the presence of active extra-genital tuberculosis, characteristic features on HSG, elevated ESR, positive Mantoux test, evidence of calcification/ complex adnexal mass by scan.

The specific diagnostic tests including culture, histopathological evaluation and polymerase chain reaction were evaluated against the newly derived diagnostic criteria using bivariate two by two tables.

Results:-

Among 100 female subjects, 28 were hypothyroid; 10 hypothyroid patients had metrorrhagia; 13 had oligomenorrhea and 5 had menorrhagia.16 patients had raised prolactin levels; 3 showed both increased TSH and raised prolactin levels. Among the 16 hyperprolactinemic subjects 13 had oligomenorrhea and 3 had metrorrhagia. In the rest of subjects, 20 patients showed regular cycles and 33 had irregular menstrual cycles (oligomenorrhea in 17, menorrhagia in 11; metrorrhagia in 5). Amongst 100 subjects ; 47 showed anovulatory cycles, 4 patients had polycystic ovarian disease, 32 showed evidence of luteal phase defects (coordinated delayed endometrial transformation in 18 cases , irregular ripening and altered stromo glandular synchrony in 14 cases) ; 5 patients were positive for genitourinary tuberculosis (confirmed by Z-N staining in tissue, culture and PCR study).

Discussion:-

Genital tuberculosis (GTB) is one of the major causes for severe tubal disease leading to infertility. Unlike pulmonary tuberculosis, the clinical diagnosis of GTB is difficult because in majority of cases the disease is either asymptomatic or has varied clinical presentation. The endometrial tuberculosis (TB) PCR test is now commonly employed for the diagnosis of female genital TB, a common cause of infertility in India. In the present study, 5 cases out of 100 females showed evidence of tubercular endometritis with positive bacterial and culture status. PCR was found to be useful in diagnosing early disease as well as confirming diagnosis in clinically suspected cases. False negative PCR is an important limitation. A combination of tests is needed to increase the detection rate. Treatment given solely on the basis of a positive PCR result can result in conception [1-4]. In the present study five women were found to have genitourinary tuberculosis among the hundred cases of infertility studied.

Infertile women without tubal or endometrial damage given early anti-tuberculosis treatment based on a positive endometrial TB-PCR test show an excellent chance of early spontaneous conception [1-4].Since laparoscopy, hysteroscopy other endoscopic procedures are associated with operative risks and may cause flaring of infection, and other conventional laboratory tests including histopathology have poor sensitivity, PCR-based detection of 65 kDa gene of M. tuberculosis in endometrial biopsy specimens could be a promising molecular diagnostic technique compared to conventional methods of diagnosis[1-4] .Patients with genital tuberculosis may have no documented history of tuberculosis or may have evidence of tubercular lesions elsewhere in the body. Abdominal and vaginal examinations may be normal.

A high erythrocyte sedimentation rate and a positive Mantoux test are nonspecific, and therefore cannot provide an accurate diagnosis of genital tuberculosis. Chest X-rays are normal in most cases; however, pelvic ultrasound and hysterosalpingography examinations may aid in the diagnosis. Histopathological evidence from biopsies of premenstrual endometrial tissue or the demonstration of tubercle bacilli in cultures of menstrual blood or endometrial curetting is necessary to provide a conclusive diagnosis of the disease .[5,6]

Newer techniques, such as polymerase chain reaction (PCR), can detect genital tuberculosis from clinical samples earlier and are less invasive. However, most of these techniques are too expensive and complicated to be of any

practical benefit to the vast majority of tuberculosis patients living in developing countries. It has been estimated that 5–10% of infertile cases are a result of female genital tuberculosis and even this rate is higher among patients with tubal factor infertility (39- 41%).[6,7] The most common genital organs involved are fallopian tubes (95-100%), endometrium (50–60%), and ovaries (20–30%) respectively.[7,8] It is important to note that if after treatment a patient conceives, there is an increased chance of an ectopic pregnancy as a consequence of chronic salpingitis and tubal damage. If pregnancy progresses, pre-term labour and abnormal placentation are possible complications. Importantly, timely therapy at an early stage of genital tuberculosis typically completely resolves the disease, resulting in successful pregnancy.[8,9,10]

In vitro fertilization with embryo transfer remains the most effective method of treatment associated with infertility here is a strong association between genital tuberculosis and secondary amenorrhea; therefore, genital tuberculosis would be more frequently diagnosed if this possibility was considered in the evaluation of every patient presenting with secondary amenorrhea in areas where tuberculosis is endemic.[9-11]

Conclusion:-

Apart from endometrial disorders and hormonal imbalances which play major role in infertility; specific granulomatous infections like genital tuberculosis which is common in India must be diagnosed early as proper conservative therapy prove useful.A combination of clinical and laparoscopic diagnoses, PCR applied DNA detection for Mycobacterium Tuberculosis, along with endometrial histopathologic studies, acid-fast bacillus culture, may prove useful in early diagnosis of genital tuberculosis in infertile women and may increase the chances of conception. .

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