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# IS THERE ANY ROLE OF ATT AND INTERFERON GAMMA IN SEVERE ENDOMETRIOSIS?


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## ABSTRACT

**Introduction:** One of the main causes of infertility and disability in women is endometriosis, which is brought on by the presence of inflammatory endometrial implants in extrauterine regions. As part of the immune response as the illness develops, a number of chemokines, such as interferons (IFNs), may play a role in the pathogenesis of endometriosis. **Objective:** The aim of this study was to investigate if Anti tubercular therapy (ATT) has a role in endometriosis and to hypothesize if ATT drugs act by the same mechanism of downregulation of interferon gamma acting as immunomodulators in severe endometriosis similar to Kochs. **Material and Methods:** In this study a total of 10 subjects were studied, 5 of group A who received LHRH in combination with ATT drugs and group B who received only LHRH depot. Only patients of Stage III and 1V endometriosis were studied. Group A received ATT drugs along with LHRH depot prior to IVF while Group B received only LHRH depot. After the IVF various parameters like number of oocytes, embryos and blastocysts were compared among both the groups. **Results:** After 6 months of treatment, subjects underwent IVF in which there was significant difference observed in the number of oocytes, embryos and blastocyst with p- values of 0.0045, 0.0088 and 0.0037 respectively. With Group A, a considerably larger proportion of spontaneous pregnancies occurred during or within 6 months of the completion of ATT than in Group B. **Conclusion:** Our results point to a strong anti-endometriotic action of ATT medicines, providing support for their prospective use in the treatment of DIE (Stage III and IV), which should be validated in upcoming preclinical and clinical investigations. This study will help infertile women with FGTB and severe endometriosis have better reproductive health and increase their chances of getting pregnant if the disease is discovered early, when permanent damage to the reproductive organ has not yet occurred.


**KEYWORDS :** Endometriosis, Anti tubercular drugs, interferon gamma, DIE

## INTRODUCTION:

Endometriosis is a chronic estrogen-driven gynecological disorder in which ectopic endometrium-like epithelial and stromal cells exist that affect women during their reproductive years. The estimated prevalence rate is around 10%, although it can be as high as 25%-40% in situations of subfertility.[1,2]

This condition is characterized by the presence of endometrial-like tissue outside of the uterus, most typically affecting the pelvic and ovarian linings.[3]

Tubal obstruction, hydrosalpinx, and adhesions can all coexist with severe endometriosis. It is challenging to pinpoint the precise contribution of each cause to the ultimate functional impairments because inflammation underlies all of these disorders, causing them to commonly overlap and be connected.[4]

The symptoms can vary, but for many women, it is a crippling condition that lowers their quality of life. There are currently no cures and conflicting data support the course of the disease. Three types of endometriosis can be distinguished: surface endometriosis, ovarian endometrioma, and deeply infiltrating endometriosis (DIE), which has a 1% incidence. The disease can damage the colon, bladder, and ureters in addition to the rectovaginal lesions that 90% of DIE patients have.[2,5,6]

DIE is a subtype of the same disease that also includes endometrioma and peritoneal lesions. The bladder is located in the anterior compartment, while the vagina, uterosacral ligaments, rectum, and ureters are located in the posterior compartment.[7]

Endometriosis symptoms vary depending on where the illness is located, but dysmenorrhea, persistent pelvic discomfort, deep dyspareunia, tiredness, and subfertility are the most common symptoms.[8]

If the urinary system is involved, symptoms include frequent urination, nocturia, bladder spasms, and haematuria. DIE affecting the recto-vaginal septum (RVS) is associated with more severe types of dyschezia and dyspareunia.[7]

A pelvic examination reveals severe endometriosis in the form of restricted organ motion and sensitive nodularity in the posterior vaginal fornix, indicating severe endometriosis. Endometriotic vaginal lesions are visible on per speculum examination and are linked with pressure on the ovaries or uterine ligaments elicited during palpation.

As the initial processes may be influenced by the anatomical distribution of endometriotic lesions, the pathophysiology of severe endometriosis and deep infiltrating endometriosis (DIE) is unclear and undoubtedly complex. Although there are numerous theories and explanations for endometriosis, the role of the fallopian tubes (FT) is rarely emphasised. The FT may have a role in the development of endometriotic tissue, the choice of sites for the production of ectopic lesions, and the transmission of proinflammatory media in all clinical and symptomatic manifestations of endometriosis.[2]

Severe endometriosis most frequently affects the uterosacral

ligaments (USL), recto-sigmoid colon, recto-vaginal septum (RVS), vagina, and bladder. Pathogenesis of endometriosis is depicted in **figure 1**.

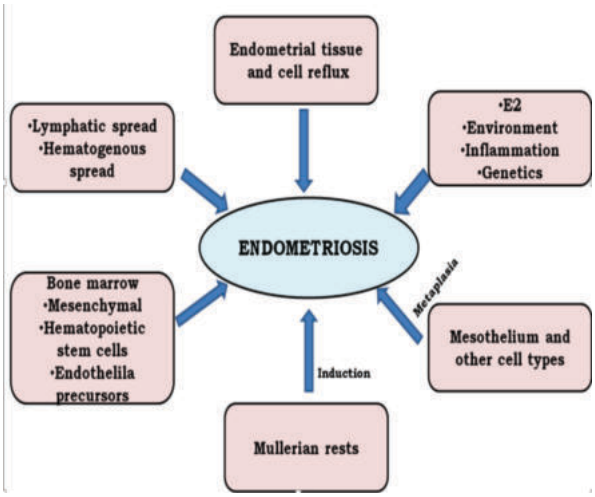


**Figure 1**-Endometriosis pathogenesis and pathophysiology

Immunologic pathways have also been hypothesized as contributing to endometriosis pathogenesis, implying an inflammatory hypothesis. [9] A cytokine imbalance has been linked to the immune system's alleged malfunction in women with endometriosis. In this context, it has been emphasised how crucial interferon gamma (IFN-γ) is to understanding the pathophysiology of endometriosis. IFN-γ mRNA expression has been found to be much higher in endometriosis than in eutopic endometrium. They are already resistant to apoptotic signals when endometriotic cells from the uterine cavity move into the pelvic cavity during retrograde menstruation. (10) Although the precise mechanism underlying these cells' resistance to IFN-induced apoptosis is unknown, the fact that they have IFN-γ receptors shows that endometriotic stromal cells' intracellular signaling pathways are dysregulated.[11]

It's interesting to note that IFN-γ has been proven to activate the EGF system and change how EGF activates downstream signaling pathways. All of these factors convinced us that IFN-γ expression, which is crucial for the etiopathogenesis and progression of endometriosis via modulation of the EGF system, is the link between the retrograde menstruation theory and the inflammatory hypothesis.

Last but not least, future endometriosis treatment efforts may want to focus on the IFN- γ signal transduction pathway.[12]

The World Health Organization declared tuberculosis, a contagious illness that is common in the Indian subcontinent, a "global emergency" in 1993.[13]

For a definitive diagnosis of tuberculosis, the pathogenic organism, Mycobacterium tuberculosis, must be shown by acid-fast staining and/or growth of the organism on Lowenstein-Jensen medium from a diagnostic specimen. In contrast to culture, which only needs 100 organisms per milliliter of sample, microscopic analysis of acid-fast bacilli requires at least 10,000 organisms.[14]

Female genital tuberculosis (FGTB) is a chronic inflammatory disease that almost invariably results from an initial infection in another part of the body. Young infertile women who are affected by FGTB may experience irreversible, permanent fallopian tube damage that is challenging to treat medically and surgically.

The predominant pelvic factor in infertility is believed to be tuberculosis of the genital tract, which is typically asymptomatic.[15,16]

The function of the Fallopian tubes, as well as the ovaries and endometrium in rare instances, is lost due to the fibrosis and scarring that develop as a result of the healing process. Therefore, it is preferable to identify and treat GTB as soon as possible during the subclinical stage in order to prevent or at least limit damage to the genital organs.[17]

M. tuberculosis may remain latent in the basal endometrium before developing into active tuberculosis, and it is still not detected with the current gold standard tests. A hysterosalpingogram and laparoscopy are required for the diagnosis of active genital Koch's, whereas molecular testing are required for the diagnosis of latent FGTB. A specific DNA genomic sequence can be amplified using the PCR process in very little amounts.[14]

The antitubercular regimen included 4 months of isoniazid and rifampicin, followed by 2 months of isoniazid, rifampicin, ethambutol, and pyrazinamide. Because modern ATT has a low risk of teratogenicity, it is not recommended that women utilize contraception while undergoing treatment. Following ATT, women are monitored for at least 6 months.[18]
Additionally, a positive endo-TB-PCR test signals the presence of latent, subclinical, or prior tuberculosis, all of which are treatable with antitubercular drugs (ATT). This is supported by the few observations made for both genital and other types of TB in a number of recent research.[19,20,21]

Short-term chemotherapy is an effective treatment for symptomatic GTB. Infertile women with GTB, on the other hand, will need to use assisted reproduction techniques (ARTs) to get pregnant. It is believed that TB DNA in endometrial reliably identifies subclinical disease and that subclinical GTB causes infertility that can be treated with enough ATT before damage to the pelvic organs develops. These days, there are several immunomodulating medications on the market, and antibiotics are commonly used with them. It has been extensively studied, especially with regard to antibacterial medications, how antimicrobial compounds can affect the host system on their own. Antimicrobial medicines can alter the immune response in a variety of ways. Figure 2 shows how the ATT drugs which are antimicrobial in nature also act for immunomodulating. Due to immune-modulation, cytokine overload, endocrine disturbance, and other causes, Mycobacterial infection can also alter endometrial receptivity and result in implantation failure. Without any obvious clinical disease, antiphospholipid antibody activation and micro thrombosis occur. ATT has antibacterial properties, but it also possesses immunomodulatory properties. Immunomodulatory pathways of ATT are shown in **Figure 2**.

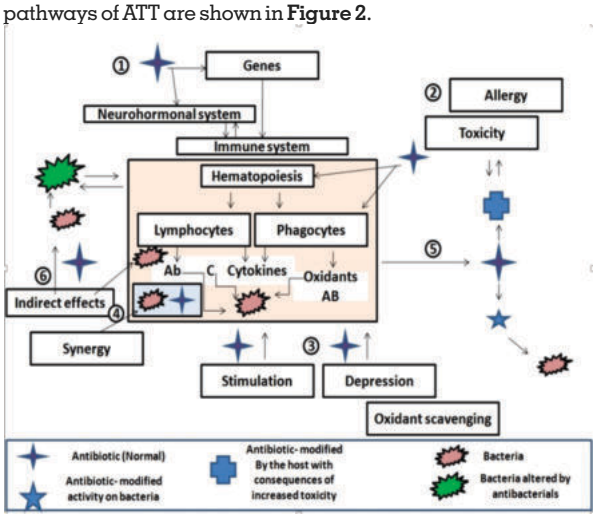


**Figure 2.** Antimicrobial agents' immunomodulatory mechanism.

(1) Immune-related gene or immune function-regulating neurohormonal system modulation.
(2) Consequences that are toxic or immunotoxic (allergic responses or immune effector destruction, for example, neutropenia).
(3) Direct modulation of immune effectors (phagocytes, lymphocytes), including oxidant scavenging.
(4) Killing of intra- or extracellular pathogens through host mechanisms.
(5) Change of an antimicrobial agent's antimicrobial action or its propensity for toxic or immunotoxic effects due to host factors (enzymes, oxidants).
(6) The drug's indirect effects on the pathogen include changes in sensitivity to host factors and the release of harmful substances.e.g. lipopolysaccharides).

Ab: Antibody; AB: Natural antibiotics of phagocytes; C: Complement.

After being exposed to the same pathogen repeatedly, or after reinjection, pathogen clearance may proceed more quickly due to protective immunity and immunological memory. Data from preclinical and clinical research suggest that the inflammatory cytokine IFN- plays a significant role in the pathogenesis of bacterial infections, including tuberculosis. IFN-γ has a well-established protective role in bacterial infections. Immunosuppression, inflammation, and tissue damage are all potential pathogenesis factors in chronic viral infections.[23]

Chemokines, such as interferons, are one of the elements involved in the immune response during pregnancy. IFNs may have a role in the pathophysiology of endometriosis. [24]

Endometriosis is associated with angiogenesis, lymph angiogenesis, and neurogenesis, all of which can be sparked by the activation of inflammatory cells and support the formation of ectopic endometrial tissue. According to growing research, endometriosis appears to be a common type of chronic inflammatory disease with an immunological origin. The presence of numerous immune cells, including mast cells, neutrophils, dendritic cells, natural killer cells, and macrophages, in the peritoneal fluids of people with endometriosis suggests that macrophage activity is significant in this condition.. Contrarily, these immune-associated cells are unable to identify and eliminate ectopic endometrial cells, suggesting that they are not functioning properly. [25]

The immunologic changes seen in women with endometriosis, it has been suggested that future treatments should also include immunomodulators associated with GnRH analogues or danazol.[26]

Important roles for IFNG are initiation of endometrial vascular remodeling, angiogenesis at implantation sites, and maintenance of the decidual (maternal) component of the placenta.[27]

As these literatures suggest that interferon plays a crucial role both in Kochs as well as in endometriosis and by administration of ATT drugs which act as both antimicrobial and immuno-modulatory in function, they cause downregulation of interferon in Kochs. We want to hypothesize if the same mechanism occurs in the endometriosis and will the ATT drugs downregulate the immunological factors in endometriosis.

**Methodology:**

The study was carried out in the Medical Health and Research Institute, Hyderabad, Telangana state in the southern region of India from 2020-2022. It's an observational, prospective, unicentric study in which women of age less than 40 years with severe endometriosis (stages III and IV) who had infertility and underwent laparoscopy were enrolled after obtaining their informed consent. Women with severe endometriosis from all couples seeking treatment for infertility were screened for inclusion in the study. The existence of endometriosis was documented based on laparoscopic examination. The initial diagnosis of endometriosis, evaluated by a clinician at the time of laparoscopy, was confirmed in all cases by histopathological examination. The biopsy samples were stained with hematoxylin and eosin and analyzed with a light microscope in all cases by an experienced pathologist at 10X and 40X **(Figure 3)**. The severity of the disease was determined according to the revised American Society for Reproductive Medicine (rASRM) classification (American Society for Reproductive Medicine, 1996).

Based on the treatment modalities, the individuals were separated into two groups. The subjects in group A consisting of 5 patients who received a luteinizing hormone-releasing hormone (LHRH) depot along with anti-tubercular treatment (ATT drugs-2 months of isoniazid H-300mg, rifampicin -R 450-600mg, ethambutol E-800-1200mg, and pyrazinamide-Z- 12-00-1500 mg, followed by 4 months of isoniazid and rifampicin) and have constituted the study group . For the treatment of endometriosis, subjects in group B which consisted of 5 patients in the control group were administered LHRH depot. Prior to IVF, both groups received treatment for 6 months. Ultrasound was carried out at the end of each month and the treatment response was observed. Following IVF, we evaluated and compared the number of oocytes, embryos and blastocysts in both groups.

**RESULTS:**

In this study a total of 10 subjects were studied, 5 of group A who received LHRH in combination with ATT drugs and group B who received only LHRH depot. There was no significant difference observed in the ages of both groups. Only patients of Stage III and 1V endometriosis were studied. The endometriosis stages were confirmed by laparoscopy and histopathology of the biopsy samples **(Figure 3,4)**.

After 6 months of treatment, subjects underwent IVF in which there was significant difference observed in the number of oocytes, embryos and blastocyst with p- values of 0.0045, 0.0088 and 0.0037 respectively **(Table 1, Figure 5).** With Group A, a considerably larger proportion of spontaneous pregnancies occurred during or within 6 months of the completion of ATT than in Group B.

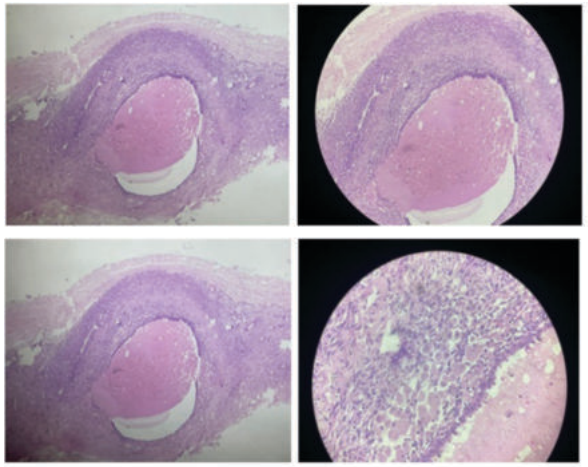

**Figure 3**- a) H & E X 10 section shows the endometrial gland surrounded by endometrial stroma and hemosiderin-laden macrophages. b) H & E X 40 showing endometrial gland surrounded by endometrial stroma and hemosiderin laden macrophages

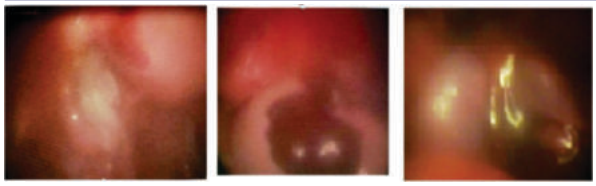

**Figure 4-** Laparoscopy images showing Endometriosis stage III,IV with chocolate cyst.

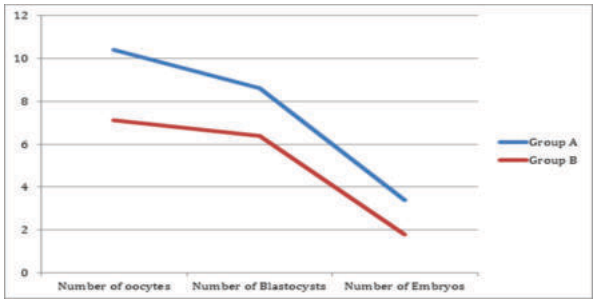


**Figure 5:** Statistical values of various parameters evaluated in group A and B.
*P value <0.01 is considered significant.

**Table 1:** Statistical values of various parameters evaluated in group A and B.

| Parameters | Group A (LHRH +ATT) | Group B (LHRH depot) | P - value |
|---|---|---|---|
| Patient's Age | 26.62 ± 6.2 | 29.12 ± 6.06 | 0.5371 |
| Stage of Endometriosis | 3 ± 0.63 | 2.8 ± 0.74 | 0.6576 |
| No.of oocytes | 10.4 ± 1.01 | 7.1 ± 1.6 | 0.0045* |
| No.of embryos | 8.6 ± 1.01 | 6.4 ± 1.01 | 0.0088* |
| No.of blastocysts | 3.4 ± 0.48 | 1.8 ± 0.74 | 0.0037* |

## DISCUSSION:

PID is more likely to occur in endometriosis-affected women (Pelvic Inflammatory Disease). Additionally, endometriosis-affected women are said to experience more severe and prolonged pelvic infections than endometriosis-free women. (28) With a prevalence of 43 percent in women with tubal endometriosis and a higher risk for women with severe sickness, a cross-sectional investigation found a link between tubal endometriosis and a noticeably raised risk of hydrosalpinx or hematosalpinx.[2]

There is significant expression of various neuro angiogenesis pathways in DIE (nerve growth factors, vascular endothelial growth factor, and intercellular adhesion molecule).[7]

The aggressive nature of the disease may be attributed to the poor apoptosis, along with other immunological components (peritoneal macrophages, natural killer cells, and lymphocytes) that are drastically changed in DIE. Treatment methods include surgical removal of lesions or the use of oral contraceptives, progestins, agonists of gonadotropin-releasing hormone (GnRH), androgenic medications to pharmacologically suppress ovulation and end menstruation. In most cases, conservative surgery can lessen pain, but the alleviation is only temporary.[29]

A study showing that ATT can lead to high conception rates found that the cumulative chance of spontaneous pregnancy in a trial nearly reached 90% within the first year of treatment, compared to a more evenly distributed pregnancy occurrence throughout time in the control group. It demonstrates that a sizeable portion of instances in which early ATT for infertility was restored based purely on a positive endo-TB-PCR in the endometrium and no other established cause. It could be suggested that early treatment is necessary for sub-clinical GTB that only manifests as infertility and can be identified by TB DNA PCR in the endometrium.[17]

For more than 20 years, clinical trials have investigated the therapeutic effectiveness of IFN-γ against tuberculosis. Controlled clinical studies and additional research are needed to understand how IFN can treat tuberculosis and combat antibiotic resistance.[22] According to a study by Bao et al., after less than 3 months on ATT, 44.4% of patients with active TB changed their QFT-GIT results from positive to negative. This is thought to be the result of ATT's bactericidal impact on M. tuberculosis, which reduces the production of antigens, which in turn boosts the production of IFN-γ. The investigators believed that rather than the immunomodulatory effects of these medications, large fluctuations in IFN-γ were connected to treatment results.[30,31,32] In the search for innovative methods to combat medication resistance in patients with MDR TB, the function of IFN as an immunomodulator in the complex treatment of TB was examined.[33]

A key cytokine in tuberculosis immunity is interferon-gamma (IFN-γ) (TB). In people with active tuberculosis, M. tuberculosis (M. tb) has been demonstrated to suppress the surface expression of IFN-γ on macrophages and peripheral blood mononuclear cells (PBMCs) (TB). Many M. tb antigens also lower macrophage IFN-γ levels as compared to healthy controls.

It follows that careful control of the calcium response is essential for preserving IFN-R levels on macrophage surfaces since this downmodulation is regulated by the TLR (Toll-like receptor) signalling pathway, second messengers like calcium, and cellular kinases like PKC and ERK-MAPK. In order to ensure its longevity and thwart host defense, the TB virus may thus exploit host machinery to adjust IFN-γ levels as part of an essential immune suppressive strategy. [34] During the implantation window, the endometrium of women with endometriosis has significant IFN γ expression. [35]

Some research suggested that human recombinant IFN could be used to treat endometriosis because of its immunomodulatory and anti-proliferative effects.[36]

Treatment for endometriosis is challenging, particularly for aggressive forms like DIE that impair women's fertility and quality of life. Furthermore, the development and progression of endometriosis may be influenced by immune dysfunction. The potential use of IFN in the treatment of DIE is supported by a number of preliminary findings, which will be confirmed in follow-up preclinical and clinical research. [29]

The IFN-gene (CA)n repeat polymorphism was found to be associated with endometriosis susceptibility in the Japanese and South Korean populations.[37,38]

Similar numbers of endometriosis patients in both groups had advanced stages of the disease (stage-III/IV rates were 71.9 percent and 79.9 percent, respectively). It's possible that South Korea's population is genetically different from Japan's. The IFN-γ gene polymorphism and risk of endometriosis have only been investigated in one study so far.[37]

Traditionally, ovarian suppression has been used to treat endometriosis; however, mounting evidence indicates that endometriosis is a disorder involving immunological malfunction. Despite the fact that we did not examine changes in IFN-γ levels based on genotype, a better understanding of the function of IFN-γ or its polymorphism would allow for the use of inflammation modulation as an alternative to traditional endometriosis treatments. Future studies on the variations in IFN- levels in relation to endometriosis genotype and stage may provide a critical cue for understanding the

etiology of the condition.[38]

We have carried out the study on patients with stage III and IV endometriosis who had infertility. Endometriosis was confirmed by performing laparoscopy and histopathology of the biopsy samples obtained from the patients. The Group A patients have shown better results in terms of pregnancies after the IVF was performed in both groups. We have observed better results in terms of number of oocytes, embryos and blastocysts in patients receiving ATT drugs along with LHRH depot when compared to patients who received LHRH depot alone. This will help us to understand that ATT drugs definitely play a role in patients with severe endometriosis and give better results in terms of successful pregnancies.

## CONCLUSION:

Our results point to a strong anti-endometriotic action of ATT medicines, providing support for their prospective use in the treatment of DIE (Stage III and IV), which will be validated in upcoming preclinical and clinical investigations. The advancement of research in this area will help us treat the condition and give us a better knowledge of the aetiology and pathophysiology of how these medications actually operate in endometriosis. This study will help infertile women with FGTB and severe endometriosis have better reproductive health and increase their chances of getting pregnant if the disease is discovered early, when permanent damage to the reproductive organ has not yet occurred.

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## Conflict of Interest:

No authors have conflicts of interest.

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