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CHRONIC NICHE INFLAMMATION IN ENDOMETRIOSIS-ASSOCIATED INFERTILITY: CURRENT UNDERSTANDING AND FUTURE THERAPEUTIC STRATEGIES.

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Abstract:
It is defined as the formation of endometrial tissue outside the urine cavity in estrogen-dependent inflammation condition is known as endometriosis that affects 10% of females at childbearing age and contributes up to 50% cases of infertility. It has an awful association with assisted reproductive technology inclusive low implantation and pregnancy rates. To treat infertility originated with endometriosis required a deep understanding of its pathology. In this article we have discussed the chronic niche inflammation in endometriosis development, targeting inflammation for treatment of endometriosis-associated infertility, and stem cell therapy. Moreover, mesenchymal stem cell-based treatments are highlighted as potential endometriosis therapy.

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INTRODUCTION:

It is defined as the formation of endometrial tissue outside the urine cavity in estrogen the dependent inflammation condition is known as endometriosis. Approximately, 5-10% of females at childbearing, 80% experienced pelvic pain, and 21-50% of females with infecund. Endometriosis is associated with more complications such as pelvic pain, dysmenorrhea, menorrhagia, dyspareunia, and dyschezia. Affected females are at greater risk to develop ovarian cancer and endometrial cancer, patients are more prone to cardiovascular disease, autoimmune, and allergic diseases.[1] However, to relief the pain and treatment of infertility is the main objective of current therapy of endometriosis. The treatment of suspected patients proceeded through empirical therapy using inflammatory drugs, gonadotrophin-releasing hormone agonists, progestogens, and hormonal contraceptive, instead of diagnosis based on presented symptoms of endometriosis.[3] Thereafter, if empirical treatment shows inadequate response, laparoscopic exploration, and excision will be considered as curative treatment.[2] Interesting, the emergence of conventional medical treatment has an abundant role to cure endometriosis-associated infertility using the assisted reproductive technology but it is illustrated that pretreatment with gonadotrophin-releasing hormone agonists can ameliorate the pregnancy rate 4-folds. Medical therapies are very effective in the reduction of pain in patients of endometriosis, on the other hand, medical or hormonal treatments are insufficient to treat infertility in patients with endometriosis. Thus, these treatments subdue the ovarian function and develop the contraceptive condition.[4]

Moreover, it is difficult to understand all the causes of endometriosis that impaired the normal reproduction organ in women while distorted pelvic anatomy due to adhesions, ovarian dysfunction, abnormal peritoneal function, and impaired endometrial receptivity are the various causes that have been explored by researchers.[5] Here, we will discuss the dysregulated niche immune modulation and focused on therapies helpful in the reduction of infertility faced by endometriosis patients.

Chronic Niche Inflammation in Endometriosis Development

The chronic niche inflammation was specifically found in the peritoneal cavity, ovaries, and uterus.

i. Peritoneal Cavity

The abnormality in the peritoneal cavity due to chronic inflammation may lead to developing infertility in patients with endometriosis. The amount of peritoneal fluid was greater in patients with endometriosis than the normal fertile women. Endometriosis bring changes in the immune system such as inhibit the T-cells mediated cytotoxicity to endometrial cells, reduced the activity of natural killer cells, and escalate the activated macrophages.[6] These alterations assist the endometriotic implants to survive by providing the suitable immune-tolerant microenvironment. The specific secretions were secreted by the endometriotic implants including estradiol, progesterone, vascular endothelial growth factor, and many other factors that promote the endometriosis development.[7]

ii. Ovaries

The alteration of ovarian function through the local effect in case of endometriomas. Endometrioma contain cystic fluid is an ample source of pro-inflammatory cytokines, growth factors (TGF-β, and matrix metalloproteases) and reactive oxygen space. This fluid can diffuse to surrounding tissue and impose a bad effect on the function of the adjacent ovary.[8] The structural changes were observed in the surrounding tissue of ovarian endometriomas such as impaired follicular density, higher fibrosis, and reduction in the cortex-specific stroma. Local inflammatory reaction in endometriomas ovarian cortex enhanced the oxidative stress, growth factor, and reactive oxygen species encourage fibrosis and profibrotic gene expression of plasminogen activator inhibitor-1. Alteration of the structure is the reason for ovarian stroma loss and impose the deleterious effects on folliculogenesis as a repercussion of this reduction of blood supply to follicles and lowering the number of growth factors secreted through the stroma cells.[9]

iii. Uterus

Various clinical publications identified the reduction rate of implantation during in vitro fertilization in patients with endometriosis and 26 studies based on meta-analysis illustrated that substantial reduction of implantation numbers and lowering the clinical pregnancy rate in patients with acute endometriosis.[11] In a prospective study without considering the factors involved in oocyte and embryo quality demonstrated that patients with endometriosis were found with lesser implantation pregnancy rates than control group patients.[10] There was no difference in reproduction rate was found for females of the age group of 35 to 40 years while it is elusive to figure out the exact percentage of effects of endometriosis on implantation.[11]

Targeting Inflammation for Treatment of Endometriosis-Associated Infertility

i. **Immunomodulators**

In a study of the animal model demonstrated that pentoxifylline decrease endometriotic lesion and meliorate the fertilization process but lack of evidence was found which support the use of pentoxifylline for infertility in women with endometriosis.[13] Luflunomide and Loxoribine are also immunomodulators, decrease the size of the endometriotic implants with the enhancement of dendritic cells, and lowing the number of natural killer cells. In preclinical studies, limited development of endometriosis lesion was identified with the use of drugs namely rosiglitazone and pioglitazone which were previously used in diabetes treatment as insulin sensitizer.[14]

ii. **Anticytokine Treatment**

Proinflammatory cytokines are amply found in peritoneal fluid. A study shows the decrease of formation of an inflammatory cytokine through the inhibition of tumor necrosis factor (TNF) α-mediated pathways. Although controversy was a notice in studies for the use of anti-TNF-α treatment to ameliorate the pain induced by endometriosis. Currently, clinical pregnancy and birth rate has been increased in patients of endometriosis treatment with anti-TNF-α along with assisted reproductive technology (ART).[15] Tocilizumab based therapy significantly reduced the lesion size of endometriosis and targeted delivery of anti-inflammatory cytokine IL-4 diminish the ectopic lesion formation.[16]

iii. **Statins**

Stains used as inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme-A (HMG-CoA) reductase. The various study attempted that statins decline the chemokine production which lower the immune cell migration and adhesion, also decrease the activated T-cells by changing the lipid raft and dwindle the major histocompatibility complex molecules. A clinical therapy demonstrated that statins also exhibited anti-inflammatory effects.[17]

Cell-Based Therapy for Endometriosis Treatment

Stem Cells in Endometriosis Pathogenesis

The research on stem cells present in the endometrium is feasible because endometrial tissue has the potential to regenerate during each menstrual cycle. Researchers stated that there is a relationship between adult stem cells and endometriosis development. The endometrial stem cell is recognized as clonogenic cells in human endometria.[18] The segregation of endometrial mesenchymal stem cells can be achieved with the use of different markers such as PDGFRβ and SUSD2. Results of many studies show that endometrial mesenchymal stem cells have a greater involvement for octamer-binding transcription factor 4 (OCT4) with an effective response to niche cytokines ultimately impose healthy control to endometrial tissues.[19] Stem cell therapy has been used for the treatment of infertility specifically Asherman's syndrome elucidated by endometrium adhesion and fibrosis in patients with infection or absence of menstruation.[20] The key point of stem cell treatment is to decrease the inflammation after adhesiolysis. In an animal-based model study, stem cell transplantation ameliorates ovarian function especially in premature ovarian insufficiency, reducing the apoptosis of granulosa cells with modulation of cytokine expression.[21]

DISCUSSION:

The study of menopause women with a history of endometriosis revealed that 43 patients of age range from 35 to 60 years, 40 patients had a history of endometriosis which was confirmed through the laparoscopic excision and presented symptoms of menorrhagia, infertility pelvic pain while 3 patients had not diagnosed with premenopausal endometriosis history. 36 patients undergo to surgical therapy.[3]

In another study patients of age range 48 to 55 presenting the symptoms such as mid-right side lower abdominal pain, urinary frequency, constipation for two months and having a medical history of pelvic endometriosis, left ovarian endometriosis, adenomyosis, and surgical menopause, clearly diagnosed with carcinomas cell in endometriosis of the retro-peritoneum had treated through the surgery and 22 months of radiation therapy.[22]

A study on patients of the age group of 60, 57, and 54 years were suffering from the right side abdominal pain for four years and experienced the cramp-like discomfort in the abdomen and postmenopausal bleeding, diagnosed with widespread endometriosis in the ovary and clinician offered the surgery along with aromatase inhibitors and surgery plus chemotherapy.[23]

CONCLUSIONS:

Long and last medical care of endometriosis patients mainly focused to overcome the pain, symptoms, and improve the quality of life. According to an estimation, almost 5 to 59% of patients face inadequate treatment, and 17-35% of patients suffered from recurring symptoms after a few months of treatment. Therefore, novel strategies being targeting the dysregulated immune system that distinguishes the endometriosis but not proven to be effective to use in standard management. Cell-based therapy provided an option to address the issues of endometriosis linked

with infertility due to its immunomodulatory response. This method is effectively used in the diagnosis of Asherman's syndrome and premature ovarian failure

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