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Role of Interleukin-6 in Diagnosis of Endometriosis: A Review Article

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ABSTRACT

Background: Endometriosis, a prevalent inflammatory condition marked by the presence of endometrial glands and stroma outside the uterine cavity, affects a significant proportion of women in their reproductive years.

Objective: This review article aims to assess the significance of IL-6 levels in the peritoneal fluid and serum of individuals with endometriosis and evaluate its utility as a non-invasive diagnostic marker for the condition.

Methods: We searched Google Scholar, Science Direct, PubMed and other online databases for endometriosis and interleukin 6. The authors also reviewed references from pertinent literature, however only the most recent or comprehensive studies from 2010 to February 2023 were included. Documents in languages other than English were disqualified due to lack of translation-related sources. Papers such as unpublished manuscripts, oral presentations, conference abstracts, and dissertations that were not part of larger scientific studies were excluded.

Conclusion: IL-6 plays a critical role in the inflammatory processes associated with endometriosis, demonstrated by elevated levels in the peritoneal fluid of affected individuals. The correlation of IL-6 with disease presence and severity underscores its potential as a biomarker for non-invasive diagnosis, offering a promising avenue for research and clinical application. Further studies are warranted to validate the diagnostic accuracy of IL-6 in endometriosis and explore its implications for patient management and treatment strategies.

Keywords: Endometriosis, Interleukin-6, IL-6, Non-invasive Diagnosis, Cytokines, Peritoneal Fluid, Uterosacral Ligaments.

INTRODUCTION

Endometriosis is a prevalent reproductive disorder characterized by the extrauterine location of endometrial glands and stroma; it impacts between 6 and 10 percent of women during their reproductive years. The spectrum of symptoms is extensive, although painful periods, pelvic pain, pain during intercourse, and infertility are among the most prevalent [1].

The clinical diagnosis of endometriosis presents difficulties due to the vague nature of its symptoms. Though ultrasound and MRI can help detect endometriosis, their diagnostic accuracy varies widely. Currently, the most reliable method of diagnosing endometriosis involves laparoscopy followed by histological examination, but this process is invasive. Therefore, there's a significant need for developing a less invasive diagnostic technique to improve endometriosis care [1].

Endometriosis is recognized as a chronic inflammatory disease driven by oestrogen, with numerous studies pointing out the essential role of cytokines in the growth, activation, adhesion, and implantation of endometrial cells. Specifically, IL-1b is shown to support the adhesion and multiplication of these cells. Peritoneal mesothelial cells have been observed to secrete IL-6 in response to elevated levels of IL-1b and TNF-a, thereby exacerbating the inflammation that is characteristic of endometriosis [2].

Cytokine IL-6, which plays a multitude of functions in immune and growth-related mechanisms, is significantly increased in the peritoneal fluid of endometriosis patients. Through an examination of IL-6's presence in the peritoneal fluid and serum of individuals diagnosed with endometriosis, this article investigates the protein's potential as a non-invasive diagnostic marker for the disease [2].

Endometriosis:

Endometriosis is a pathological condition characterized by the presence of endometrium-like tissue (glands and stroma) that has developed abnormally and is situated in an area other than the uterine lining (cavity and musculature). Endometriosis mainly targets the pelvic organs and peritoneum, with common sites being the ovaries, ligaments, and fallopian tubes for intra-peritoneal locations, and areas like the cervical portio and abdominal scars for extra-peritoneal locations. It infrequently affects extra abdominal organs such as the lungs and urinary system [3].

The pathogenesis of endometriosis remains unclear and is likely multifactorial, involving mechanisms such as coelomic metaplasia, where pelvic peritoneal cells transform metaplastically, the transport theory; suggesting uterine endometrium transplantation to ectopic sites via various means, the induction theory; proposing that substances from shed endometrium induce the formation of endometriotic tissue, and the transplantation theory; supported by the phenomenon of retrograde menstruation [4].

Additionally, immunological factors, with changes in cell-mediated and humoral immunity promoting disease progression, genetic predispositions enhancing susceptibility, hormonal influences with oestrogen dependence, and environmental factors have all been implicated. Despite advances in understanding, no single theory comprehensively explains all aspects of endometriosis, reflecting its complex aetiology and the need for further research [4].

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Endometriosis predominantly affects women of reproductive age, with diagnosis commonly between 25 to 29 years. Although rare in premenarchal girls, it is notably present among adolescents with pelvic pain or dyspareunia. The condition is also observed in postmenopausal women, particularly those on estrogen therapy, and carries a risk of recurrence and potential for malignant transformation in some cases. Factors increasing risk include early menarche, short menstrual cycles, and possibly genetics, given its familial occurrence. Conversely, multiple pregnancies and long-term use of oral contraceptives may lower risk. Despite its considerable morbidity, endometriosis's exact prevalence in the general population is estimated to be around 10% [5].

Endometriosis manifests through a variety of symptoms, including infertility and pelvic pain, but can also be asymptomatic. Infertility affects 20%-40% of women with endometriosis, with pain ranging from dysmenorrhea and dyspareunia to general abdominal discomfort. The disease's impact on fertility and pain involves distorted pelvic anatomy, inflammation, and impaired reproductive functions. Additionally, endometriosis may present extra pelvic symptoms based on its location, such as gastrointestinal issues or urinary tract symptoms. Despite these varied symptoms, clinical examinations often appear normal, although specific signs like bluish cystic vaginal or cervical lesions can suggest the presence of endometriosis [6].

In early menstruation, when implants are at their largest and most tender, a physical examination for endometriosis is most effective. Emphasis should be placed on detecting any indications of a fixed, retroverted uterus, tenderness in the adnexa and uterus, pelvic masses, or nodules. Many women, notwithstanding these efforts, manifest normal pelvic findings, thereby necessitating laparoscopy as the final diagnostic procedure. A future may see a reduction in the necessity for surgical confirmation due to a combination of biochemical markers and clinical evaluations, although no single laboratory test has yet demonstrated diagnostic reliability [7].

Diagnosis relies on laparoscopy, which is considered the gold standard despite its invasive nature. This procedure allows for direct visualization of endometriosis lesions, which can vary widely in appearance, making the surgeon's ability to recognize these signs crucial. Lesions can range from blue-black “powder burn” spots to non-pigmented or atypical ones, each varying in colour and stage of disease **(Figure 1)**.

Ovarian endometriosis may present as superficial implants or as endometriomas, known for their chocolate-syrup-like contents. Despite advancements, accurately diagnosing endometriosis often requires this invasive approach to identify manifestations of the disease accurately [8].

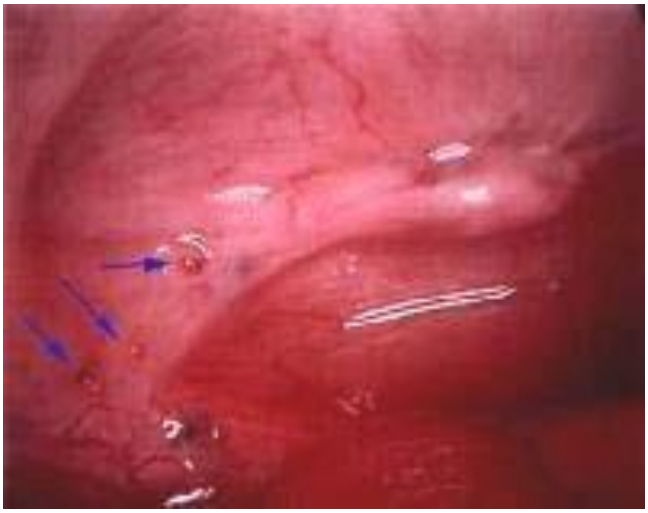

Figure 1: Typical appearance of minimal endometriosis on the uterosacral ligaments [8]

CA-125, a serum marker initially linked to ovarian cancer, has also been associated with endometriosis, showing elevated levels in affected women. Despite its use in monitoring disease progression, CA-125's limitations in sensitivity and specificity make laparoscopy the preferred diagnostic method. Other potential markers, like CA 19-9 and interleukin 6, offer additional research avenues but currently lack the precision for effective screening or diagnosis. The ongoing exploration of biomarkers like placental protein 14 and endometrial antibodies highlights the quest for non-invasive diagnostic tools, yet none have definitively proven reliable in clinical practice for endometriosis diagnosis or monitoring [9].

The FOATI classification, developed by the Endometriosis Study Group in 1994, categorizes endometriosis based on the involvement of peritoneal foci (F), ovarian (O), adhesions (A), and tubal (T), with a specific consideration for inflammatory aspects (I) due to their impact on fertility. This system also accounts for lesion depth (D) and side (R or L for right or left). The classification highlights the complexity of endometriosis manifestations and aids in understanding the disease's potential impact on fertility [10].

Endometriosis treatment varies from medical management, aiming to modify hormonal levels and mimic states like pseudopregnancy or pseudo menopause, to surgical interventions for symptom relief and fertility enhancement. Medications include combined oral contraceptives, danazol, progestogens, and GnRH agonists, each with specific effects and side effects, such as bone density loss with GnRH agonists necessitating add-back therapy. Surgery, ranging from conservative to radical, is often preferred for severe cases or when fertility is a concern, with laparoscopic methods offering potential benefits. Despite these treatments, recurrence is common, underlining the chronic nature of endometriosis and the need for a personalized treatment approach based on symptom severity, disease extent, and patient fertility goals [11].

Cytokines:

Cytokines are signalling proteins crucial for immune system regulation, including chemotaxis, cell growth, and angiogenesis. Produced locally by cells like macrophages and monocytes, they operate through specific receptors on target cells. Cytokines are key in diseases like endometriosis, where they promote ectopic endometrium growth and attachment. With over 200 types, including interleukins and interferons (IFN), their function is diverse, involving both synergistic and antagonistic actions. Elevated cytokine levels in endometriosis patients underscore their role in the disease's development and progression [12].

Cytokines interact with high-affinity and specificity to various classes of receptors on cell membranes, including those with enzymatic tyrosine kinase activity, G-protein-coupled receptors, and others that bind to intracellular adaptor proteins. These interactions mediate and regulate immune and inflammatory responses, with cytokine production triggered by new gene transcription, reflecting their transient nature and unstable mRNA. Cytokines, known for their pleiotropy, can affect multiple cell types and exhibit diverse interactions, including antagonism, additive effects, or synergy [13]. Their actions often overlap, leading to cascades of biological effects, and are regulated by inhibitors that can block cytokine activity through various mechanisms. Cytokines initiate slow cellular responses that typically require new mRNA and protein synthesis and can regulate cell division as growth factors. Their effects are mediated through autocrine, paracrine, or endocrine actions, depending on the proximity of the target cell to the cytokine source [14].

Cytokines are classified based on their three-dimensional structure, receptor similarity, biological activity, and the immune response they evoke. The largest receptor family, type I (hematopoietic receptor family), includes receptors with enzymatic tyrosine kinase activity. Type II receptors are part of the immunoglobulin superfamily, including all interferon receptors. Type III cytokine receptors bind to the IFN family, while class IV includes the IL-1 receptor accessory protein and related proteins [15].

Cytokines can be further grouped by their effects on T-cell function, B-cell actions, their role in both B and T-cell functions, modulation of inflammation, hematopoietic colony stimulation, and the chemokine family. These classifications reflect the diverse roles of cytokines in immune regulation, including their involvement in diseases like endometriosis, where they contribute to the growth and inflammatory behaviour of the condition. The complex network of cytokines modulates endometriosis through implant proliferation, angiogenesis, and leukocyte recruitment, highlighting their intricate role in immune responses [16].

Interleukin-6:

T cells and macrophages secrete IL-6, a crucial pro-inflammatory cytokine, which functions as an immune response mediator in response to tissue damage and trauma. It also functions as a myokine, produced in muscles during contraction, and is involved in bone metabolism by stimulating osteoclast formation. IL-6 stimulates the production of acute phase proteins (APPs) in the liver, mobilizes energy in muscle and fat tissue, and induces fever and the acute phase response [17].

These APPs, such as C-reactive protein (CRP) and serum amyloid A (SAA), enhance innate immunity and protect against tissue damage. The IL-6 receptor's presence on various cell types facilitates its wide-ranging effects, including promoting cell proliferation and regulating immune responses. Additionally, IL-6 influences the synthesis of proteins involved in inflammation, coagulation, and the systemic acute phase response, highlighting its central role in inflammation and immune regulation [18].

Interleukin-6 (IL-6) is a critical factor in the early stages of T-cell differentiation, specifically by promoting the transition of CD4 cells to Thelper2 cells. It is essential for the proliferation and development of progenitor cells in the thymus and bone marrow, as well as the activation of T-cells and natural killer (NK) cells. For B-cells, IL-6 is vital in stimulating their differentiation and proliferation, acting as a growth factor for plasma cells and promoting the release of IgG and IgA antibodies [19].

IL-6 is involved in a wide array of bodily functions beyond the immune response, including bone metabolism, reproductive processes, and even in the aging process, where its levels correlate with aging-related disorders. Increased levels of IL-6 have been associated with a range of ailments, including metabolic and cardiovascular disorders, autoimmune diseases such as rheumatoid arthritis, and endometriosis, in which it plays a role in the immunoinflammatory mechanisms. [20].

Critical for IL-6 effect mediation, the IL-6 receptor lacks independent signaling capability, indicating that IL-6's actions are mediated by other molecular mechanisms. Elevated levels of IL-6 in the peritoneal fluid of individuals with endometriosis highlight its involvement in the development of the disease. Research indicates that IL-6, along with other cytokines, fosters a peritoneal environment conducive to the implantation and growth of endometriotic cells, highlighting its significance in endometriosis and other inflammatory and autoimmune diseases [21].

Interleukin-6 (IL-6) levels can be influenced by various factors, both increasing and decreasing its concentration in the body. Factors that increase IL-6 levels include exposure to ultraviolet light, which induces IL-6 production in keratinocytes; hypoglycaemia, high levels of insulin, which stimulate IL-6 release from adipocytes, angiotensin II, which promotes oxidative stress and inflammation, epinephrine infusion, which acutely raises IL-6 levels, nicotine, which stimulates central nicotinic receptors to

increase IL-6, unstable angina, where IL-6 acts as a mediator of systemic inflammation, Graves' disease, cocaine use, cigarette smoking, catecholamines, growth hormone, and diseases like rheumatoid arthritis and other conditions characterized by increased bone resorption, where IL-6 plays a role in the inflammatory process [22].

Conversely, IL-6 levels can be decreased by higher physical activity, which may modulate the anti-inflammatory response, vitamins E and C, which reduce the IL-6 response to exercise, levosimendan infusion in heart failure patients, which decreases proinflammatory cytokines, micronized 17β-estradiol (E2), which lowers inflammation markers; growth hormone, which IL-6 inhibits, methylene bisphosphonic acid derivative; acting as an IL-6 production inhibitor, glucocorticoids, which suppress IL-6 production, and curcumin; known for its anti-inflammatory and antioxidant properties. These factors highlight the complex regulation of IL-6 and its significant role in inflammation, immune response, and various disease processes [23].

CONCLUSION

Presently, considerable research attention is devoted to investigating the potential non-invasive diagnostic utility and pathogenic mechanism of endometriosis via interleukin-6 (IL-6). In patients with endometriosis, elevated levels of IL-6 in the peritoneal fluid and serum indicate that the protein is involved in the inflammatory processes that underlie the condition. This review underscores the potential of IL-6 as a biomarker for the non-invasive diagnosis of endometriosis, offering a promising alternative to invasive diagnostic methods. The correlation of IL-6 with disease presence and severity suggests its utility not only in diagnosis but also in understanding disease mechanisms and guiding therapeutic interventions. Future research should aim to further elucidate the diagnostic accuracy of IL-6, explore its relationship with disease stages, and assess its potential role in personalized treatment approaches for endometriosis.

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