Student's Journal of Health Research Africa
e-ISSN: 2709-9997, p-ISSN: 3006-1059
Vol. 5 No. 3 (2024): March2024 Issue
https://doi.org/10.51168/sjhrafrica.v5i3.1057
Narrative Article

INVESTIGATING INFECTION'S ROLE AS A CONTRIBUTING FACTOR IN THE GENETIC AND EPIGENETIC MECHANISMS OF ENDOMETRIOSIS: A NARRATIVE REVIEW.

Archana Jha
Associate Professor, Department of Obstetrics & Gynaecology, JLNMCH, Bhagalpur, Bihar, India.

ABSTRACT

Endometriosis is a chronic gynecological condition, characterized by the presence of endometrial-like tissue outside the uterus. It is associated with symptoms such as pelvic pain, dysmenorrhea, and infertility, significantly impacting women's quality of life. Despite its prevalence, the pathophysiology of endometriosis is not fully understood, with genetic, epigenetic, environmental, immunological, and hormonal factors all playing roles in its development. This review aims to systematically examine the evidence linking infections to the genetic and epigenetic mechanisms of endometriosis, highlighting how these interactions may contribute to the disease's development and progression. Recent research has identified a connection between genetic predispositions to endometriosis and an enhanced immune response to infections. Specific genetic markers associated with an increased risk of endometriosis have also been linked to heightened immune reactions to infectious agents, suggesting a complex interplay between endometriosis and infections. Variations in genes regulating the immune system and inflammatory processes, such as the Toll-like receptor 4 (TLR4), have been implicated in both endometriosis and the body's response to infections. Furthermore, infections can induce epigenetic changes that may influence the development and severity of endometriosis by altering gene expression related to inflammation, immune surveillance, and tissue repair. Understanding the relationship between infections, genetic predispositions, and epigenetic modifications in endometriosis opens new avenues for research into targeted therapies. Addressing the underlying genetic and immunological factors contributing to endometriosis could lead to more effective treatment strategies, potentially improving the quality of life for those affected by the condition. Clinicians should consider the potential role of infections in the exacerbation of endometriosis symptoms and the importance of comprehensive patient evaluations to identify and treat any concurrent infections. Future therapeutic strategies should also explore anti-inflammatory therapies and preventive measures against pathogens known to influence endometriosis progression.

Keywords: *Endometriosis, Infections, Genetic Predispositions, Epigenetic Modifications*
Submitted: 2024-03-01 Accepted: 2024-03-02

Corresponding Author*: Archana Jha**
Email: dr.archana.bgp@gmail.com
Associate Professor, Department of Obstetrics & Gynaecology, JLNMCH, Bhagalpur, Bihar, India.

INTRODUCTION

Endometriosis, a chronic gynecological condition characterized by the presence of endometrial-like tissue outside the uterus, affects an estimated 10% of women of reproductive age worldwide [1]. This condition is associated with a range of symptoms, including pelvic pain, dysmenorrhea, and infertility, significantly impacting the quality of life of those affected [2]. Despite its prevalence and the substantial burden it places on individuals and healthcare systems, the pathophysiology of endometriosis remains incompletely understood.

Recent advances in genetic and epigenetic research have begun to shed light on the complex mechanisms underlying endometriosis. Studies have identified several genetic loci and epigenetic modifications associated with the disease, suggesting that endometriosis has a strong heritable component [3]. However, the etiology of endometriosis is multifactorial, with environmental, immunological, and hormonal factors also playing crucial roles.

Among the various factors investigated, the role of infections as a potential cofactor in the development of endometriosis has garnered attention. Infections can induce inflammatory responses and immune system dysregulation, which are key features of endometriosis. Moreover, certain infections have been associated with epigenetic changes that could contribute to the disease's pathogenesis.

The review delves into the intricate relationship between infections and endometriosis, highlighting the influence of genetic and epigenetic mechanisms in disease progression. It reveals a link between genetic predispositions, such as Toll-like receptor 4 (TLR4) variants, and an augmented immune response to infections. Additionally, infections are shown to induce epigenetic changes that impact gene expression related to inflammation and immune surveillance, shaping the severity of endometriosis. The review stresses the significance of considering infections in both diagnosis and treatment, advocating for comprehensive patient evaluations. It suggests potential therapeutic strategies targeting inflammatory pathways activated by infections and underscores the importance of ongoing research to enhance patient care and outcomes.

This review aims to systematically examine the evidence linking infections to the genetic and epigenetic mechanisms of endometriosis, offering insights into how

Student's Journal of Health Research Africa
e-ISSN: 2709-9997, p-ISSN: 3006-1059
Vol. 5 No. 3 (2024): March2024 Issue
https://doi.org/10.51168/sjhrafrica.v5i3.1057
Narrative Article

these interactions may contribute to the disease's development and progression.

METHODOLOGY

To conduct a comprehensive review of the literature on the association between infections and the genetic and epigenetic mechanisms of endometriosis, we employed a systematic search strategy across multiple electronic databases. These included PubMed, Scopus, Web of Science, and Google Scholar. The search was designed to capture a broad range of studies published from 2010 to 2023, using a combination of keywords and MeSH terms such as "endometriosis," "infections," "genetic predisposition," "epigenetic modifications," "TLR4," and "immune response." The search was limited to articles published in English. Reference lists of identified articles were also scanned to capture additional studies not identified through database searches.

Studies were included in the review if they met the following criteria: (1) original research articles, including observational studies (cohort, case-control, and cross-sectional), case reports, and clinical trials, as well as systematic reviews and meta-analyses focusing on the relationship between infections and endometriosis; (2) studies that investigated genetic or epigenetic factors associated with endometriosis in the context of infections; and (3) studies that provided data on the immune response to infections in patients with endometriosis. Exclusion criteria encompassed articles that were not peer-reviewed, conference abstracts, editorials, and commentaries, as well as studies not directly addressing the role of infections in the pathogenesis of endometriosis.

Given the heterogeneity of study designs, populations, and outcomes, a narrative synthesis approach was adopted to summarize the findings. The synthesis focused on elucidating the connections between infections and endometriosis, particularly regarding genetic predispositions, epigenetic modifications, and immune responses. Where possible, thematic analysis was used to identify common themes across studies, and findings were grouped according to the type of infection, genetic and epigenetic mechanisms, and clinical implications.

THE ROLE OF INFECTION IN ENDOMETRIOSIS

Infections associated with Endometriosis

Research has identified several types of infections that may be associated with endometriosis. These include bacterial infections, such as those caused by *Escherichia coli*, which have been found in higher concentrations in the pelvic peritoneal fluid of women with endometriosis [4]. Viral infections, particularly those linked to human papillomavirus (HPV) and herpes simplex virus (HSV), have also been explored for their potential connections to endometrial tissue proliferation outside the uterus.

Studies have reported varying prevalence rates of infections in patients with endometriosis [5]. For instance, chronic pelvic inflammatory disease (PID), often resulting from sexually transmitted infections (STIs), has been observed at higher rates in women with endometriosis compared to those without the condition. This suggests a possible link between pelvic infections and the development or exacerbation of endometriosis.

Genetic Links

The intricate relationship between genetic predispositions to endometriosis and susceptibility to infections represents a burgeoning area of investigation within the realm of reproductive health research. Endometriosis has long been recognized for its multifactorial etiology, encompassing hormonal, environmental, and genetic factors. Among these, genetic predispositions play a pivotal role, not only in the direct risk of developing endometriosis but also in modulating the body's response to infections, which may exacerbate or influence the disease's progression.

Recent studies have begun to unravel the genetic underpinnings that link endometriosis with an enhanced immune response to infections. This connection is particularly evident in the identification of specific genetic markers associated with both an increased risk of endometriosis and a heightened immune reaction to infectious agents [6]. Such findings suggest that individuals with these genetic markers may be predisposed to both the development of endometriosis and an amplified inflammatory response to infections, potentially creating a vicious cycle that exacerbates the condition.

A key example of this genetic interplay is observed in the variations of the gene coding for Toll-like receptor 4 (TLR4). TLR4 is integral to the innate immune system, serving as a primary sensor for bacterial lipopolysaccharides (LPS) and playing a crucial role in initiating the immune response to bacterial infections. Variants of the TLR4 gene have been implicated in a range of inflammatory conditions, reflecting its central role in modulating the body's reaction to pathogens [7].

In the context of endometriosis, research has demonstrated that certain polymorphisms in the TLR4 gene are associated with an increased risk of developing the disease. These genetic variations may alter the expression or function of TLR4, leading to an exaggerated inflammatory response when encountering bacterial infections. This heightened inflammatory state could contribute to the establishment and proliferation of ectopic endometrial tissue, thereby exacerbating the symptoms and severity of endometriosis.

Furthermore, the association between TLR4 gene variants and endometriosis underscores the complex interplay between the immune system and endometriosis pathogenesis. It suggests that the immune system's dysregulation, influenced by genetic factors, maybe a critical component in the disease's development and progression [8]. This insight opens new avenues for research into targeted therapies that address the underlying genetic and immunological factors

Student's Journal of Health Research Africa
e-ISSN: 2709-9997, p-ISSN: 3006-1059
Vol. 5 No. 3 (2024): March2024 Issue
https://doi.org/10.51168/sjhrafrica.v5i3.1057
Narrative Article

contributing to endometriosis, potentially offering more effective treatment strategies for those affected by the condition.

The relationship between genetic predispositions to endometriosis and susceptibility to infections highlights the multifaceted nature of this gynecological condition. Understanding the genetic factors that influence both the risk of endometriosis and the immune response to infections is crucial for developing comprehensive approaches to treatment and management. As research in this area continues to evolve, it holds the promise of unveiling novel therapeutic targets and improving the quality of life for individuals living with endometriosis.

Epigenetic Modifications

Infections can induce epigenetic changes through various mechanisms, including DNA methylation, histone modification, and non-coding RNA expression. These changes can alter gene expression without modifying the DNA sequence, affecting the body's inflammatory and immune responses. For instance, bacterial infections can lead to the methylation of genes associated with immune regulation, potentially influencing the development of endometriosis by altering the local immune environment in the pelvis.

Epigenetic modifications induced by infections can have a profound impact on the development and progression of endometriosis. By altering the expression of genes involved in inflammation, immune surveillance, and tissue repair, these changes may contribute to the establishment and growth of endometrial-like tissue outside the uterus. Furthermore, epigenetic modifications can influence the severity of symptoms experienced by women with endometriosis, including pain and infertility.

MECHANISMS OF ACTION

Inflammatory Response

Inflammation is a fundamental component of endometriosis, contributing to the development and progression of the disease. The ectopic endometrial tissue characteristic of endometriosis is associated with increased production of pro-inflammatory cytokines, which facilitate the establishment and persistence of endometrial lesions. Chronic inflammation in the pelvic cavity promotes angiogenesis, nerve growth, and fibrosis, exacerbating pain and infertility associated with endometriosis [1, 9].

Infections can amplify the inflammatory response in endometriosis by stimulating the production of additional pro-inflammatory cytokines and chemokines. Bacterial endotoxins, for example, can activate macrophages and other immune cells, leading to a heightened inflammatory state that exacerbates the growth and invasiveness of endometrial lesions.

Immune System Dysregulation

The immune response to infections is altered in women with endometriosis. The disease is characterized by compromised immune surveillance that allows for the survival and implantation of ectopic endometrial cells. Infections further dysregulate the immune system, impairing the clearance of ectopic endometrial tissue and promoting an environment conducive to the progression of endometriosis.

Studies have documented various immune system alterations in endometriosis, including changes in the function and distribution of immune cells such as macrophages, natural killer (NK) cells, and T lymphocytes. These alterations contribute to an immunosuppressive pelvic microenvironment, facilitating the establishment of endometrial lesions [10].

Infections can induce hormonal changes that affect the progression of endometriosis. For instance, inflammatory processes triggered by infections can influence estrogen metabolism, increasing estrogen levels and enhancing the proliferation of ectopic endometrial tissue. Additionally, infections may impact the hypothalamic-pituitary-adrenal (HPA) axis, leading to alterations in cortisol levels that can further dysregulate immune function and inflammatory responses in endometriosis.

CLINICAL IMPLICATIONS

Diagnosis

The diagnostic process for endometriosis is notably challenging, compounded by the potential role of infections that can mimic or exacerbate the condition's symptoms. Infections such as pelvic inflammatory disease (PID) share common symptoms with endometriosis, including pelvic pain, dysmenorrhea, and infertility, which can lead to misdiagnosis or delayed diagnosis [11]. This overlap not only complicates clinical assessments but also underscores the necessity for healthcare providers to consider and rule out infectious processes when evaluating patients suspected of having endometriosis. Advanced diagnostic techniques, including laparoscopy, remain the gold standard for endometriosis diagnosis, yet the integration of biomarker testing for specific infections could refine diagnostic accuracy, enabling more targeted interventions.

The exploration of potential biomarkers indicative of an inflammatory response to infection presents a promising avenue for enhancing the diagnostic precision of endometriosis. Elevated levels of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), have been observed in both endometriosis and infectious conditions, suggesting their utility as biomarkers [12]. However, distinguishing between these underlying causes requires a nuanced understanding of their pathophysiological contexts. Ongoing research into the immunological and molecular landscapes of endometriosis may yield specific biomarkers that can differentiate endometriosis from

infectious processes, facilitating earlier and more accurate diagnoses.

Treatment and Management

Addressing infections within the context of endometriosis care is critical for effective management of the disease. The presence of bacterial infections can exacerbate endometriosis symptoms by intensifying the inflammatory environment within the pelvic cavity. Antibiotic therapy, aimed at eradicating bacterial infections, may alleviate some endometriosis symptoms by reducing inflammatory and immune responses. This approach highlights the importance of comprehensive patient evaluations to identify and treat any concurrent infections, thereby potentially mitigating the severity of endometriosis-related symptoms and improving patient outcomes.

The interplay between infections and endometriosis also opens new avenues for future therapeutic strategies. Anti-inflammatory therapies that specifically target the inflammatory pathways activated by infections could offer relief to patients with endometriosis. For instance, the use of non-steroidal anti-inflammatory drugs (NSAIDs) and immunomodulatory agents may be explored as adjunct therapies to address the inflammatory component of endometriosis exacerbated by infections [13]. Moreover, the development of vaccines or other preventive measures against pathogens known to influence endometriosis progression could represent a novel approach to reducing the incidence or severity of the disease. Such strategies would require a deep understanding of the specific mechanisms by which infections contribute to endometriosis pathogenesis, underscoring the need for continued research in this area.

The clinical implications of infections in the diagnosis and management of endometriosis are profound, necessitating a multidisciplinary approach to care that encompasses the identification and treatment of infectious processes alongside endometriosis-specific interventions. As research continues to unravel the complex relationship between infections and endometriosis, it is anticipated that new diagnostic markers and therapeutic strategies will emerge, offering hope for improved patient care and outcomes.

CONCLUSION

The review elucidates the intricate relationship between infections and endometriosis, emphasizing the role of genetic and epigenetic factors in the disease's pathogenesis. It reveals how infections contribute to inflammatory and immune dysregulation in endometriosis, suggesting the potential for targeted therapies that address these underlying mechanisms. The findings advocate for further research to develop advanced diagnostic and treatment strategies, aiming to improve outcomes for those with endometriosis. This work underscores the necessity of integrating genetic, immunological, and infectious disease perspectives for a holistic approach to endometriosis management.

Limitations

The review offers valuable insights into the relationship between infections and endometriosis but acknowledges limitations in individual studies. These include small sample sizes, potentially impacting generalizability, and retrospective designs prone to recall bias. Methodological variations across studies, such as diagnostic criteria and identification methods, could introduce heterogeneity. While the review highlights genetic and epigenetic factors, it may not encompass all relevant studies, potentially overlooking key findings. Addressing these limitations through larger, prospective studies with standardized methodologies could strengthen future research in this area.

Acknowledgment

We would like to express our sincere gratitude to all the researchers, clinicians, and participants whose work and contributions have made this review possible. Additionally, we extend our appreciation to the funding agencies and institutions that supported the research cited in this review. Finally, we thank the editors, reviewers, and staff involved in the publication process for their valuable insights and assistance.

List of abbreviations

PID: Pelvic Inflammatory Disease
STIs: Sexually Transmitted Infections
HPV: Human Papillomavirus
HSV: Herpes Simplex Virus
TLR4: Toll-like Receptor 4
LPS: Lipopolysaccharides
NK cells: Natural Killer cells
HPA axis: Hypothalamic-Pituitary-Adrenal axis
IL-6: Interleukin-6
TNF-α: Tumor Necrosis Factor-alpha
NSAIDs: Non-steroidal anti-inflammatory Drugs

Source of funding

No source of funding was received.

Conflict of Interest

The authors have no competing interests to declare.

REFERENCES

1. Laganà AS, Garzon S, Götte M, Viganò P, Franchi M, Ghezzi F, Martin DC. The pathogenesis of endometriosis: molecular and cell biology insights. International journal of molecular sciences. 2019 Nov 10;20(22):5615.
2. Gruber TM, Mechsner S. Pathogenesis of endometriosis: the origin of pain and subfertility. Cells. 2021 Jun 3;10(6):1381.

3. Borghese B, Zondervan KT, Abrao MS, Chapron C, Vaiman D. Recent insights on the genetics and epigenetics of endometriosis. Clinical genetics. 2017 Feb;91(2):254-64.
4. Koninckx PR, Ussia A, Tahlak M, Adamyan L, Wattiez A, Martin DC, Gomel V. Infection as a potential cofactor in the genetic-epigenetic pathophysiology of endometriosis: a systematic review. Facts, views & vision in ObGyn. 2019 Sep;11(3):209.
5. Hong YS, Park J, Kim H. Association of endometriosis with genital human papillomavirus infection in US women: a national population-based study. Scientific Reports. 2023 May 17;13(1):8020.
6. Miller JE, Symons LK, Marks RM, Tayade C. Endometrial immune-inflammatory gene signatures in endometriosis. Endometrial Gene Expression: An Emerging Paradigm for Reproductive Disorders. 2020:141-58.
7. Khan KN, Kitajima M, Hiraki K, Fujishita A, Sekine I, Ishimaru T, Masuzaki H. Toll-like receptors in innate immunity: role of bacterial endotoxin and toll-like receptor 4 in endometrium and endometriosis. Gynecologic and obstetric investigation. 2009 Apr 9;68(1):40-52.
8. Miller JE, Symons LK, Marks RM, Tayade C. Endometrial immune-inflammatory gene signatures in endometriosis. Endometrial Gene Expression: An Emerging Paradigm for Reproductive Disorders. 2020:141-58.
9. Burney RO, Giudice LC. Pathogenesis and pathophysiology of endometriosis. Fertility and sterility. 2012 Sep 1;98(3):511-9.
10. Herington JL, Bruner-Tran KL, Lucas JA, Osteen KG. Immune interactions in endometriosis. Expert review of clinical immunology. 2011 Sep 1;7(5):611-26.
11. Jacobson L. Differential diagnosis of acute pelvic inflammatory disease. American Journal of Obstetrics and Gynecology. 1980 Dec 1;138(7):1006-11.
12. Fassbender A, Burney RO, F O D, D'Hooghe T, Giudice L. Update on biomarkers for the detection of endometriosis. BioMed Research International. 2015 Oct;2015.
13. Tassinari V, Smeriglio A, Stillittano V, Trombetta D, Zilli R, Tassinari R, Maranghi F, Frank G, Marcoccia D, Di Renzo L. Endometriosis treatment: role of natural polyphenols as anti-inflammatory agents. Nutrients. 2023 Jun 30;15(13):2967.

Publisher details:

SJC PUBLISHERS COMPANY LIMITED

SJC Publishers Company Limited

Category: Non-Government & Non-profit Organisation
Contact: +256775434261(WhatsApp)
Email: admin@sjpublisher.org, info@sjpublisher.org or studentsjournal2020@gmail.com
Website: https://sjpublisher.org
Location: Wisdom Centre Annex, P.O. BOX. 113407 Wakiso, Uganda, East Africa.