The Role of Neuron Growth Factor and Interleukin-10 in Pain Development in Adenomyosis: A Narrative Review

Agus Heriyanto,[1] Dian Tjahyadi,[1] Anita Rachmawati,[1] Luky Adlino[2]
[1]Subdivision of Fertility and Endocrinology, Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Padjadjaran – Dr. Hasan Sadikin General Hospital, Bandung, Indonesia
[2] Siloam Hospitals Purwakarta, Purwakarta, Indonesia.
Correspondence: Agus Heriyanto, Email: agus10020@mail.unpad.ac.id

Abstract
Introduction: Adenomyosis, a non-malignant uterine condition characterized by endometrial tissue within the myometrium, leads to uterine enlargement, infertility, dysmenorrhea, and heavy menstrual bleeding. While its precise etiology remains unknown, delayed pregnancy may contribute to its rising incidence among infertile women. This condition primarily affects women who have given birth and is also linked to higher rates of early miscarriage. Although immune dysregulation in endometriosis is well-documented, comparable research on adenomyosis is limited.
Objective: This review aims to examine the roles of Interleukin-10 (IL-10), an anti-inflammatory cytokine, and Neuronal Growth Factor (NGF), a neuroimmune factor, in adenomyosis.
Discussion: Elevated IL-10 levels in ectopic endometrial tissue indicate a possible immunosuppressive mechanism that may worsen symptoms. NGF is also involved in the pain and inflammation related to adenomyosis. Gaining a deeper understanding of how IL-10 and NGF interact could provide important insights into the inflammatory processes and pain mechanisms of this condition.
Conclusion: This review suggests IL-10 as a potential inflammatory biomarker and NGF as a pain marker in adenomyosis, opening doors for future research into new therapeutic targets. Clarifying these pathways could lead to treatments that focus on reducing inflammation and easing related symptoms of adenomyosis.

Keywords: adenomyosis, neuronal growth factor, interleukin-10, pelvic pain .

Peran Neuron Growth Factor (NGF) dan Interleukin-10 (IL-10) dalam Pembentukan Nyeri pada Adenomyosis : Sebuah Review Naratif

Abstrak
Pendahuluan: Adenomyosis, suatu kondisi rahim jinak yang ditandai dengan adanya jaringan endometrium di dalam miometrium, menyebabkan pembesaran rahim, infertilitas, dismenore, dan perdarahan menstruasi yang berat. Meskipun etiologi pastinya masih belum jelas, kehamilan yang tertunda kemungkinan berkontribusi pada peningkatan insidennya di kalangan wanita infertil. Kondisi ini, yang sebagian besar memengaruhi wanita multipara, juga dikaitkan dengan tingkat keguguran dini yang lebih tinggi. Meskipun disregulasi imun pada endometriosis telah didokumentasikan dengan baik, penelitian serupa pada adenomyosis masih terbatas.
Tujuan: Tinjauan ini bertujuan untuk mengeksplorasi peran Interleukin-10 (IL-10), sitokin anti-inflamasi, Faktor Pertumbuhan Saraf (NGF) dan faktor neuroimun dalam adenomyosis.
Diskusi: Peningkatan kadar IL-10 dalam jaringan endometrium ektopik menunjukkan mekanisme imunosupresif potensial yang dapat memperburuk gejala. NGF juga berperan dalam nyeri dan peradangan yang terkait dengan adenomyosis. Pemahaman yang lebih dalam tentang interaksi antara IL-10 dan NGF dapat memberikan wawasan penting mengenai sifat inflamasi dan mekanisme nyeri dari kondisi ini.
Kesimpulan: Tinjauan ini mengusulkan IL-10 sebagai biomarker inflamasi potensial dan NGF sebagai penanda nyeri pada adenomyosis. Hal tersebut membuka jalan bagi penelitian lebih lanjut untuk target terapeutik baru. Menguraikan jalur-jalur ini dapat mengarah pada perawatan yang berfokus pada mitigasi peradangan dan mengurangi gejala adenomyosis.

Kata kunci: adenomiosis; interleukin-10; *neuronal growth factor*; nyeri pelvis.

 DOI:10.24198/obgynia.v8i3.931

Introduction

Adenomyosis is a non-malignant uterine condition characterized by the growth of ectopic endometrial glands and stroma within the myometrium, along with reactive hyperplasia of the adjacent smooth muscle cells.[1] Adenomyosis can cause an enlarged uterus, which may be either symmetrical or asymmetrical, and is associated with infertility, dysmenorrhea, and menorrhagia. The causes and pathological mechanisms of adenomyosis remain unclear. The prevalence of newly diagnosed adenomyosis among women with infertility is expected to increase as more women delay their initial pregnancies into their 30s and 40s.[2]

Furthermore, adenomyosis is considered a significant contributor to infertility in women of reproductive age,[3] and it is more prevalent in parous women and linked to a high rate of early miscarriage. Numerous studies suggest that immune system changes may contribute to the pathogenesis of endometriosis.[3,4] However, there have been no reports so far examining the inflammatory features of adenomyosis, particularly in relation to immunosuppression.

Interleukin-10 (IL-10) is an important immunomodulatory cytokine synthesized by various cell types. Originally identified as a cytokine synthesis inhibitory factor for T lymphocytes, it is produced by T helper 2 (Th2) cell clones and has been shown to inhibit interferon-g synthesis in Th1 cell clones.[5] Research shows that IL-10 is a key anti-inflammatory cytokine involved in multiple chronic inflammatory diseases and cancers. Uterine IL-10 has a dual effect on human leukocyte antigen expression in trophoblast cells, promoting the expression of human leukocyte antigen G while reducing classical class I and class II antigens.[5] We suggest that IL-10 expression might help establish and maintain immunosuppression, which could explain the persistence of ectopic foci within the peritoneal cavity or myometrium that the host's immune system fails to eliminate in women with endometriosis or adenomyosis. Studies indicate that peritoneal IL-10 levels are significantly higher in women with endometriosis compared to healthy women.[5] Wang et al. previously noted that this cytokine is produced in sizable amounts by the epithelial cells of both ectopic and eutopic endometrium in women diagnosed with adenomyosis.

Interleukin-10 (IL-10) in the uterus acts as a mediator in various intrauterine regulatory processes, including those involving progesterone, catecholamines, and prostaglandins.[6] The IL-10 signaling pathway includes two receptor complexes: IL-10 receptor 1 (IL-10R1) and IL-10 receptor 2 (IL-10R2). The formation of these receptor complexes plays a crucial role in modulating the immune response by triggering signals that inhibit the synthesis of cytokines and cellular receptors such as TNF-a, IL-1, and IL-6, which are important in the pathogenesis and persistence of adenomyosis.[6]

Neuronal growth factor (NGF) is the first identified neurotrophic factor and is essential in the mechanisms of pain production, neural plasticity, immune cell aggregation, and the release of inflammatory factors.[7] NGF is a neurotrophic protein that plays a vital role in the growth, differentiation, and survival of sympathetic and sensory afferent neurons during development. NGF is synthesized by neuronal cells (especially in the cerebral cortex), as well as by various other cell types such as astrocytes, fibroblasts, epithelial cells, endothelial cells, smooth muscle cells, and hepatocytes. NGF influences the neuronal phenotype by modulating axonal guidance, gene transcription, neurotransmitter release, and synaptic plasticity. Additionally, NGF plays an important role in regulating nociception in adulthood. The level of NGF expression has been found to correlate with the severity of adenomyosis. Increased

expression of endometrial stromal cell aromatase is associated with NGF levels. Meanwhile, elevated NGF levels and their receptors have been linked to inflammation and increased innervation in uterine adenomyosis.[7]

However, there are few reports showing the connection between IL-10 and NGF expression in adenomyosis. This review aims to clarify the role of IL-10 as a biomarker for inflammation and NGF in pain development related to adenomyosis. It also serves as a supplementary resource and preliminary study to explore the relationship between IL-10, an inflammatory marker, and NGF, a pain marker, in adenomyosis.

Sources of Evidence

This article is presented as a narrative review. Relevant literature was identified through purposive searches of international databases, including PubMed, Scopus, and the Cochrane Library. Search terms included "adenomyosis," "interleukin-10," "nerve growth factor (NGF)," and related synonyms. Additional references were obtained from the bibliographies of key articles to ensure comprehensive coverage of influential studies.

Since this review is narrative, the goal was not to provide complete coverage but to synthesize and interpret the most relevant evidence regarding the roles of NGF and IL-10 in adenomyosis-related pain. Priority was given to peer-reviewed studies published in English that reported molecular, immunological, or clinical findings related to NGF and/or IL-10 in the context of adenomyosis. Case reports and correspondence were excluded from the review.

From this process, 14 studies were identified as the most relevant. These studies serve as the foundation for the following discussion of mechanistic insights and clinical implications.

Pathogenic Mediators

The main mechanisms linked to adenomyosis include abnormalities in sex steroid hormones, cell proliferation and fibrosis, inflammation, and mediators of neuroangiogenesis (Figure 1).[8] These factors help explain the clinical signs of pain, abnormal uterine bleeding (AUB), and infertility.

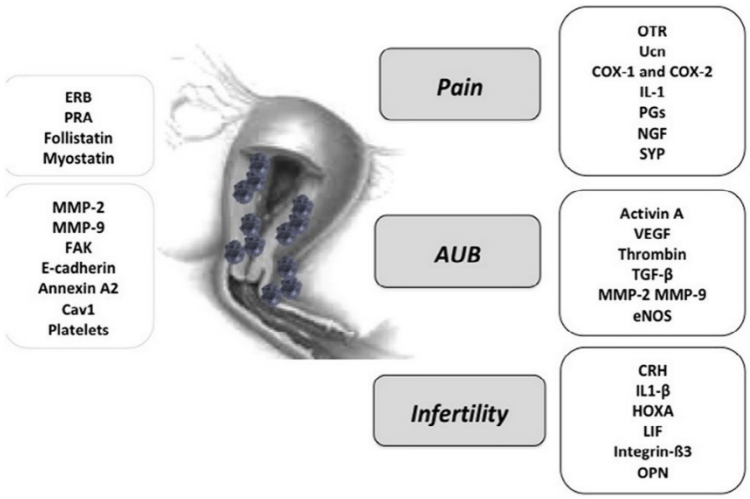

Figure 1 Pathogenetic mediator of adenomyosis.[8] (Adapted from Vannuccini et al., 2023)

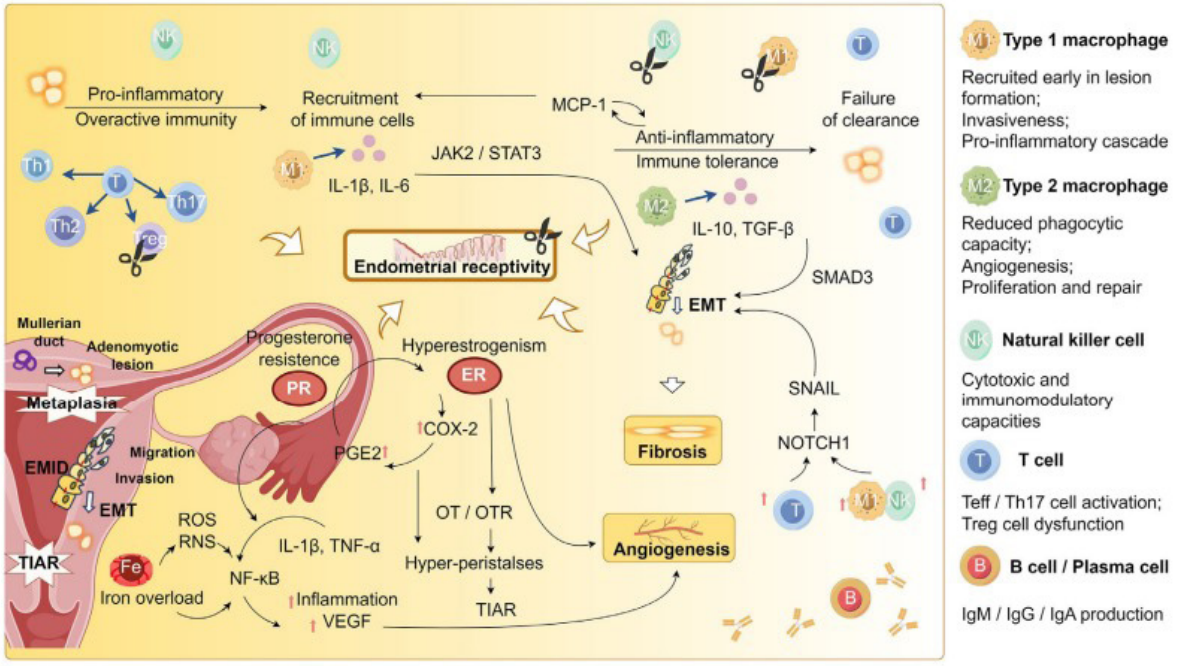

Figure 2 Immune system involvement in the pathophysiology of adenomyosis.[11] (Adapted from Cao et al., 2023)

Adenomyosis symptoms and immune changes

Adenomyosis is primarily associated with pain, abnormal uterine bleeding, and subfertility. The immune changes seen in these women may not only play a role in the pathogenesis of adenomyosis lesions but also contribute to the clinical symptoms. While the exact mechanisms causing pain in adenomyosis are not fully understood, a common explanation for dysmenorrhea involves the overproduction of COX-2 and prostaglandins. This excess may lead to abnormal myometrial hypercontractility, vasoconstriction, and increased sensitivity of pain fibers, which worsens pain symptoms (Figure 2). Adenomyosis shows increased levels of nerve growth factor (NGF) in both eutopic and ectopic cells. NGF is crucial for neural plasticity and the release of inflammatory factors related to pain.[9] Furthermore, other pro-inflammatory signals, such as NF and the number of macrophages, appear to be directly and positively related to the severity of dysmenorrhea in affected women.[10]

Pelvic Pain

Uterine contractility and oxytocin receptors

Women experiencing symptomatic adenomyosis show increased uterine contractility associated with dysmenorrhea.[12] In uterine smooth muscle, the contractile amplitude and oxytocin receptor (OTR) levels were significantly higher in women with adenomyosis, correlating with the severity of dysmenorrhea.[12] As a result, a hyperactive uterus, characterized by abnormal peristalsis during menstruation and increased innervation, is sufficient to cause dysmenorrhea.

Alterations in the expression or activity of potassium channels in uSMCs may cause insufficient membrane depolarization,

which can lead to abnormal uterine activity. Abnormal uterine smooth muscle contractility may disrupt uterine microcirculation, resulting in the build-up of inflammatory mediators that harm the endometrium and worsen pain symptoms.[12]

Inflammatory peptides and prostaglandins

The observation of elevated levels of IL-1B, CRH, and UCN in adenomyotic nodules suggests that inflammation plays a significant role in the pathogenesis of adenomyosis (Figure 3). The increased expression of CRH and UCN may serve as a local response to invading endometrial cells. Mast cells activated by CRH and UCN could contribute to inflammation in adenomyosis. Evidence that supports this is that CRH/UCN activate COX-2 in other tissues. Therefore, the higher levels of CRH and UCN in adenomyosis may lead to increased prostaglandin synthesis.[6]

The hypothesis that NF is essential to the development of adenomyosis is supported by evidence showing increased expression of the NF-k p65 subunit in both the eutopic endometrium and adenomyotic nodules.[9] Hyperestrogenism has been shown to boost the production of IL-10, a cytokine known for its immunosuppressive effects. Higher levels of IL-10 were found in both the eutopic and ectopic endometrium of women with adenomyosis. This finding may explain the persistence of ectopic foci within the myometrium, despite the immune system's efforts to eliminate them.[13]

Neurogenic Factors

The myometrium receives innervation from a subserosal plexus and a plexus located at the endometrial-myometrial junction.[13] The functional layer of the endometrium is mainly innervated by sensory unmyelinated C nerve fibers, which may be activated or sensitized by inflammatory mediators released from the endometrium. This process results in neurogenic inflammation. Additionally, prostacyclin and norepinephrine released from adrenergic fiber endings can further sensitize sensory C fibers.[14]

Nerve growth factor (NGF) plays a role in pain development, neural plasticity, immune cell aggregation, and the release of inflammatory factors. In a mouse model of adenomyosis, levels of NGF-B and its receptors in the uterus and dorsal root ganglia were significantly higher in older mice

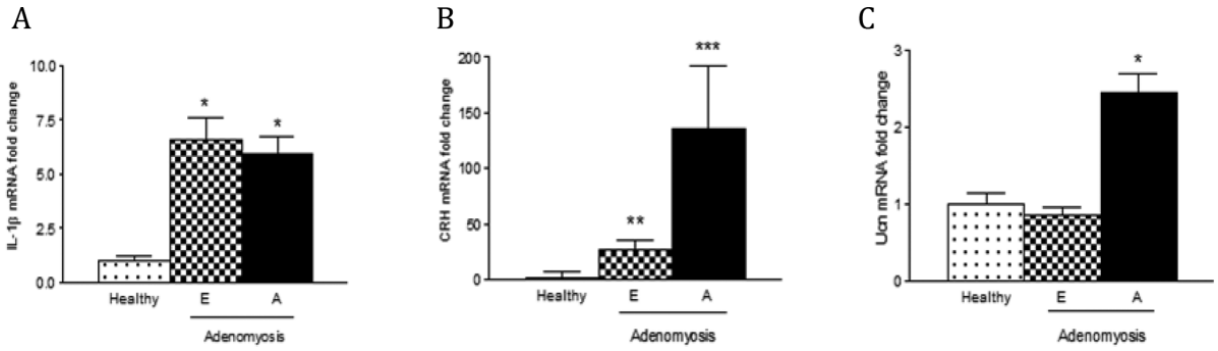

Figure 3 Inflammatory mediator mRNA expression in adenomyosis. Interleukin 1b (A), Ucn (B), CRH (C) mRNA levels in healthy controls (Healthy), eutopic endometrium of women with adenomyosis (E), and adenomyotic nodules (A). Fold change (y-axis) shows mRNA expression normalized to HPRT. *P < .05; **P < .01; ***P < .001. CRH stands for corticotropin-releasing hormone; mRNA means messenger RNA; Ucn is urocortin; HPRT is hypoxanthine phosphoribosyltransferase.[10] (Adapted from Carrarelli et al., 2017)

with adenomyosis compared to the control group. The increasing levels of NGF-B and its receptors correlate with disease severity, indicating NGF-B's involvement in the development of adenomyosis.[9] The elevated levels of NGF, synaptophysin (SYN), and MAP2 mRNAs in adenomyotic nodules suggest that neurogenesis may contribute to adenomyosis and associated pain (Figure 4). Immunofluorescence analyses confirmed the protein expression of CRH, NGF, and SYN in adenomyotic nodules. Urocortin-induced NGF mRNA expression in cultured human ESCs establishes a link between inflammatory and neurogenic pathways.[15]

Consequently, NGF serves as a marker for the severity of adenomyosis. As a multifunctional cytokine and growth factor, the overexpression of NGF may influence various biological processes in multiple ways. NGF is essential for the development of sympathetic and small fiber sensory neurons that function as nociceptors.[15] In adenomyosis, which is also characterized by an increased density of nerve fibers in the uterus of symptomatic patients, this suggests that nerve growth factor (NGF) may contribute to this abnormal innervation.[16] NGF is crucial in the development of pain and hyperalgesia in both severe acute and chronic pain conditions. It enhances the excitability of primary afferents by modifying ion channels or neurotransmitter synthesis.[16,17] NGF acts as a chemoattractant for granulocytes and mast cells, boosting immune responses and promoting the degradation of mast cells, thereby facilitating the release of pain-inducing substances.[18] Consequently, the increased effects of NGF in severe adenomyosis may play a role in worsening the pain associated with this condition.

NGF has been associated with various autoimmune and inflammatory diseases, including allergic conditions where elevated NGF levels closely relate to disease severity.[19] Adenomyosis is often linked to different autoimmune phenomena in humans. The rise in NGF may result from inflammatory conditions, subsequently influencing or regulating the immune response. As a result, the infiltration and growth of ectopic endometrium, along with uterine inflammation and localized estrogen, may increase NGF production and promote neural plasticity, local inflammation, and pain.[20]

Inflammatory Marker

The expression of the inflammatory marker IL-10 during the secretory phase is significantly

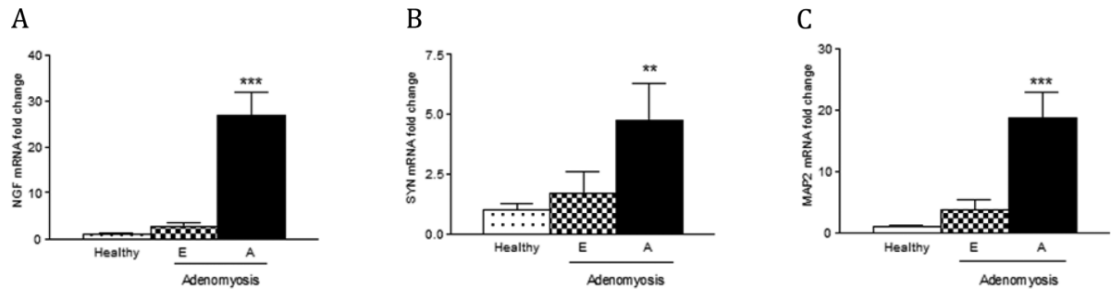

Figure 4 Neurogenic factors' mRNA expression in adenomyosis. Nerve growth factor (A), SYN (B), and MAP2 (C) mRNA levels in healthy controls (Healthy), eutopic endometrium of women with adenomyosis (E), and adenomyotic nodules (A). Fold change (y-axis) shows mRNA levels normalized to HPRT. **P < .01, ***P < .001. MAP2 stands for microtubule-associated protein 2; mRNA is messenger RNA; NGF is nerve growth factor; SYN is synaptophysin49; HPRT is hypoxanthine phosphoribosyltransferase.[10] (Adapted from Carrarelli et al., 2017)

H score values for epithelial IL-10 expression in the endometrium.

	No. of samples	H score (mean ± SEM)		P
Normal endometrium	30	4.29	0.52	
Proliferative phase	10	0.73	0.11	
Secretory phase	20	6.07	0.35	<.01[a]
Eutopic endometrium	34	31.39	1.03	<.01[b]
Proliferative phase	13	25.47	0.92	
Secretory phase	21	35.05	0.86	<.01[c]
Adenomyosis	34	34.39	0.08	.08[d]

[a] Normal secretory endometrium versus normal proliferative endometrium.
[b] Eutopic endometrium versus normal endometrium.
[c] Eutopic secretory endometrium versus normal proliferative endometrium.
[d] Adenomyosis versus eutopic endometrium.

Wang. IL-10 in adenomyosis. Fertil Steril 2009.

Figure 5 H score values for expression of IL-10 in the endometrium.[6] (Adapted from Wang et al., 2009)

higher than in normal endometrium. The role of IL-10 has been studied in various cancers, showing that IL-10 has diverse biological effects that help create an immunosuppressive microenvironment (Figure 5).[21]

Additionally, in certain chronic inflammatory diseases, IL-10 can suppress the secretion of cytokines from Th1 cells.[22] While there is no direct evidence for IL-10's role in immune response regulation in adenomyosis patients, its increased expression may help promote immune tolerance in both ectopic and eutopic endometrium. Furthermore, before infiltrating the myometrium, the eutopic endometrium may develop the ability to evade host immune surveillance by expressing IL-10. If it has already infiltrated the myometrium, it also uses IL-10 to improve its chances of survival within the myometrium, thus avoiding destruction by the immune system.[23]

Estrogen increased the intracellular expression of IL-10 at both the mRNA and protein levels. In women with adenomyosis, both eutopic and ectopic endometrial tissues show expression of aromatase and estrone sulfatase, enzymes responsible for the local production of estrogen.[24] Adenomyosis is an estrogen-dependent disease, and IL-10 expression may be regulated by cyclic variations in estrogen levels, potentially boosting IL-10 production as well.[25]

Strengths and Limitations of the Evidence

The available studies on NGF and IL-10 in adenomyosis vary significantly in design and quality. Most are cross-sectional or laboratory analyses of surgical specimens, often with limited sample sizes and diverse patient groups. While these studies offer important mechanistic insights, the absence of randomized controlled trials (RCTs) or large prospective studies lowers the overall strength of evidence. Conversely, animal studies provide controlled mechanistic data but may not fully reflect human disease. This results in the current evidence being rated as moderate to low in the hierarchy, emphasizing the need for higher-quality clinical research.

Clinical Implications

From a clinical perspective, the consistent association of NGF with increased innervation and pain indicates its potential as both a biomarker and a therapeutic target.

Anti-NGF agents, which have already been studied in chronic pain syndromes, could be examined for use in adenomyosis. In contrast, the role of IL-10 remains unclear: although typically anti-inflammatory, its dysregulated expression might contribute to ongoing immune activation. This uncertainty highlights why IL-10 is not yet ready to be used as a therapeutic target. Overall, incorporating neuro-immune markers like NGF and IL-10 into clinical practice could eventually lead to more personalized management of adenomyosis-related pain, but current evidence is still preliminary.

Future Directions

Future research should explore the correlation between IL-10/NGF levels and pain severity using standardized clinical scales (e.g., VAS). Long-term cohort studies are necessary to determine if these markers can predict disease progression or response to treatment. Additionally, interventional trials targeting NGF pathways, which have already been tested in chronic pain conditions, may provide translational opportunities in adenomyosis.

Conclusions

In conclusion, existing evidence shows that IL-10 and NGF levels are increased in both eutopic and ectopic endometrial tissues of patients with adenomyosis, compared to normal endometrium. Previous studies, such as Wang (2009) and Li (2015), have documented these molecular changes, and our review expands on this by examining their roles within the broader context of adenomyosis-related pain. The data suggest that IL-10 and NGF may play important roles in developing and sustaining pain through neuro-immune interactions. More research is necessary to understand the molecular mechanisms, establish causality, and evaluate these markers as potential diagnostic tools or treatment targets.

Declaration of Conflicting Interest

The authors declare that they have no conflicts of interest.

Funding Statement

The authors declare that this study did not receive external funding.

Author Contributions Statement

AH, DT, and AR conceived the idea. AH and DT conducted the literature search and initially drafted the manuscript. AR and LA reviewed, revised, and edited the manuscript. All authors approved the final draft for publication.

References

1. Ferenczy A. Pathophysiology of adenomyosis. *Hum Reprod Update* 1998; 4: 312–22.
2. Matalliotakis IM, Katsikis IK, Panidis DK. Adenomyosis: what is the impact on fertility? *Curr Opin Obstet Gynecol* 2005; 17: 261–4.
3. Gianetto-Berrutti A, Feyles V. Endometriosis related to infertility. *Minerva Ginecol* 2003; 55: 407–16.
4. Lebovic DI, Mueller MD, Taylor RN. Immunobiology of endometriosis. *Fertil Steril* 2001; 75: 1–10.
5. Viganò P, Somigliana E, Mangioni S, et al. Expression of interleukin-10 and its receptor is up-regulated in early pregnant versus cycling human endometrium. *J Clin Endocrinol Metab* 2002; 87: 5730–6.
6. Wang F, Li H, Yang Z, et al. Expression of interleukin-10 in patients with adenomyosis. *Fertil Steril* 2009; 91: 1681–5.
7. Barker PA, Mantyh P, Arendt-Nielsen L, Viktrup L, Tive L. Nerve Growth Factor Signaling and Its Contribution to Pain. J

Pain Res. 2020;13:1223-1241. Published 2020 May 26. doi:10.2147/JPR.S247472.
8. Vannuccini S, Tosti C, Carmona F, Huang SJ, Chapron C, Guo SW, Petraglia F. Pathogenesis of adenomyosis: an update on molecular mechanisms. Reprod Biomed Online. 2023;46(1):7–20. doi:10.1016/j.rbmo.2022.09.012.
9. Li Y, Zou S, Xia X, et al. Human Adenomyosis Endometrium Stromal Cells Secreting More Nerve Growth Factor: Impact and Effect. *Reprod Sci* 2015; 22: 1073–82.
10. Carrarelli P, Yen C-F, Funghi L, et al. Expression of Inflammatory and Neurogenic Mediators in Adenomyosis. *Reprod Sci* 2017; 24: 369–375.
11. Cao Y, Yang D, Cai S, Yang L, Yu S, Geng Q, Mo M, Li W, Wei Y, Li Y, Yin T, Diao L. Adenomyosis-associated infertility: an update of the immunological perspective. Reprod Biomed Online. 2023;47(2):169–182. doi:10.1016/j.rbmo.2023.06.003
12. Carrarelli P, Yen C-F, Arcuri F, et al. Myostatin, follistatin and activin type II receptors are highly expressed in adenomyosis. *Fertil Steril* 2015; 104: 744–52.e1.
13. Li B, Chen M, Liu X, et al. Constitutive and tumor necrosis factor-α-induced activation of nuclear factor-κB in adenomyosis and its inhibition by andrographolide. *Fertil Steril* 2013; 100: 568–77.
14. Li Y, Zhang S, Zou S, et al. Accumulation of nerve growth factor and its receptors in the uterus and dorsal root ganglia in a mouse model of adenomyosis. *Reprod Biol Endocrinol* 2011; 9: 30.
15. Reis FM, Petraglia F, Taylor RN. Endometriosis: hormone regulation and clinical consequences of chemotaxis and apoptosis. *Hum Reprod Update* 2013; 19: 406–18.
16. Brawn J, Morotti M, Zondervan KT, et al. Central changes associated with chronic pelvic pain and endometriosis. *Hum Reprod Update* 2014; 20: 737–47.
17. McKinnon BD, Bertschi D, Bersinger NA, et al. Inflammation and nerve fiber interaction in endometriotic pain. *Trends in Endocrinology & Metabolism* 2015; 26: 1–10.
18. Morotti M, Vincent K, Brawn J, et al. Peripheral changes in endometriosis-associated pain. *Hum Reprod Update* 2014; 20: 717–36.
19. Wang G, Tokushige N, Russell P, et al. Neuroendocrine cells in eutopic endometrium of women with endometriosis. *Hum Reprod* 2010; 25: 387–91.
20. Gori M, Luddi A, Belmonte G, et al. Expression of microtubule associated protein 2 and synaptophysin in endometrium: high levels in deep infiltrating endometriosis lesions. *Fertil Steril* 2016; 105: 435–443.
21. Ferrari A, Petraglia F, Gurpide E. Corticotropin releasing factor decidualizes human endometrial stromal cells in vitro. Interaction with progestin. *J Steroid Biochem Mol Biol* 1995; 54: 251–5.
22. McEvoy AN, Bresnihan B, FitzGerald O, et al. Cyclooxygenase 2-derived prostaglandin E2 production by corticotropin-releasing hormone contributes to the activated cAMP response element binding protein content in rheumatoid arthritis synovial tissue. *Arthritis Rheum* 2004; 50: 1132–45.
23. Petraglia F, Imperatore A, Challis JRG. Neuroendocrine mechanisms in pregnancy and parturition. *Endocr Rev* 2010; 31: 783–816.
24. Anaf V, Simon P, El Nakadi I, et al. Hyperalgesia, nerve infiltration and nerve growth factor expression in deep adenomyotic nodules, peritoneal and ovarian endometriosis. *Hum Reprod* 2002; 17: 1895–900.

25. Fan Y, Liu Y, Chen H, et al. Serum level concentrations of pro-inflammatory cytokines in patients with adenomyosis. *Biomedical Research* 2017; 28: 1809–1813.