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PERSPECTIVE ARTICLE

Is vagus nerve-mediated regulation of immunity an etiological target for therapeutic intervention in endometriosis?

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Abstract

Endometriosis is a complex chronic neuro-inflammatory disorder, affecting roughly 10% of reproductive-age women. It is characterized by the presence of endometrial-like tissue outside the uterus, which induces a chronic inflammatory reaction. This disease can present a wide range of symptoms, including chronic pain and infertility. Despite extensive research, the exact pathogenesis of endometriosis remains incompletely understood. New strategies and paradigms on pathogenesis and treatment are needed. Schematic factors contributing to the development of endometriosis lesions include genetic, hormonal, and immunological factors. Although genetics may contribute to the epidemiologically suggested heritability of endometriosis, epigenetics has gained an increasing consideration in research. Remarkably, microbiota dysbiosis, acting as a catalyst for the main acknowledged epigenetic etiologies (locally produced estradiol, pro-inflammatory cytokines, and hypoxic stress) demands further attention. Indeed, over the past 10 years, it has become clear that the vagus nerve, the fastest component of the microbiota-gut-brain axis, can efficiently control inflammation through the cholinergic anti-inflammatory pathway. Therefore, stimulation of the vagus nerve could be a good candidate for modulating the severity of endometriosis. The detrimental consequences of microbiome dysbiosis and the estrobolome activity on the initiation of the disease as well as counterpart dysfunctions in the central nervous system will be focused on, both supporting a key role of the vagus nerve since the early stage of endometriosis. Consequently, the rationale for using non-invasive vagus nerve stimulation will be discussed, introducing a fruitful shift of paradigm in this still enigmatic disease.

Keywords: Endometriosis; Pathophysiology; Epigenetics; Immunity; Microbiota-gut-brain axis; Non-invasive vagus nerve stimulation

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1. Introduction

Endometriosis, a very common but complex chronic disorder affecting young women worldwide,[1] is classically defined as the presence of endometrial-like glands and stroma outside the uterine cavity, leading to chronic pelvic pain and infertility. With the advent of a validated non-invasive saliva-based diagnostic microRNA signature,[2-4] histopathological confirmation may not soon remain essential for the diagnosis of endometriosis. Thus, an earlier diagnosis is likely to open new avenues to improve the prognosis and the quality of life of the patients, provided an etiological and equally non-invasive treatment can be rapidly initiated.

At the beginning of 2024, a group of international experts called for a full revision of the pathogenesis and pathophysiology of endometriosis.[5] This reassessment is a rare opportunity to question an upstream unifying rationale underpinning this seemingly heterogeneous chronic disease. This review aims to pave the way for an innovative, scientifically proven therapeutic option: Non-invasive vagus nerve stimulation (VNS).

Having a family member with endometriosis noticeably increases a woman's chances of developing it as well.[6] A 2023 meta-analysis,[7] including 60,674 cases and 701,926 controls, identified 42 genome-wide significant loci comprising 49 distinct association signals with endometriosis. A significant genetic correlation between endometriosis and 11 pain conditions (including migraine), as well as inflammatory conditions was shown in this meta-analysis. Moreover, multitrait genetic analyses identified substantial sharing of variants associated with endometriosis and migraine. Nevertheless, the identified genetic signals only explained up to 5.01% of endometriosis variance and regulated not only expression but also methylation (hence epigenetic mechanisms) of genes in endometrium and blood.[7] Besides, three programmed cell death-related genes have recently been identified as key biomarkers of endometriosis, through machine learning and Mendelian randomization.[8] Actually, the results revealed marked upregulation of the expression of TNFSF12 and PDK2 in endometriotic samples, coupled with a significant downregulation of the expression of AP3M1, emphasizing, once more, the importance of the epigenetic mechanisms in this disease.

Thus, the main determinants of endometriosis (and main therapeutic targets to focus on) are likely to be epigenetic ones, resulting in altered expression of genetic material, independent of the modification of the genetic sequence itself.[9-11] Three driving microenvironmental cues modulating the expression of genes for the development of endometriosis have been identified: Locally produced steroid hormones, pro-inflammatory cytokines, and hypoxic stress.[11,12] Remarkably, the gut microbiota is a major regulator of circulating estrogens (through the estrobolome,[13] the collection of genes of the gut microbiota responsible for estrogen metabolism, in particular, the β-glucuronidase gene coding for an enzyme that deconjugates estrogens into their active forms),[14] immune response[15,16] and stress[17] (including hypoxic stress)[18] as well. Therefore, gut microbiota dysbiosis, acting as a catalyst of the main epigenetic cues, appears as the most interesting therapeutic target to focus on in endometriosis.

After reviewing the detrimental consequences of microbiome dysbiosis on endometriosis pathogenesis, we will underscore brain dysfunctions underpinning endometriosis pathophysiology before focusing on vagus nerve dysfunction, a pivotal, yet underappreciated, target for endometriosis progression. Consequently, non-invasive VNS appears as an innovative therapy, naturally connecting the central and peripheral nervous systems[19] and gathering the necessary conditions to provide a safe, global, and long-lasting maintenance of homeostasis regarding endometriosis.

2. Targeting microbiota dysbiosis as a potential strategy to prevent endometriosis

During homeostasis, a balance between the microbiota and the immune system maintains immune quiescence. Dysbiosis is defined as the perturbances to microbiota resulting from alterations in the bacteria, immune system, or local environment.

The issue of the involvement of microbiota dysbiosis and the estrobolome in endometriosis has been reviewed lately, confirming their importance in the physiopathology of the disease.[20] Altered microbiota have been reported in the genital tract of infertile patients with chronic endometritis or endometrial polyps[21] and in women with histology-proven stage 3/4 endometriosis.[22] A complete absence of *Atopobium* in the vaginal and cervical microbiota of the case group, as well as an increase of *Gardnerella*, *Streptococcus*, *Escherichia*, *Shigella*, and *Ureaplasma*, in the cervical microbiota of the endometriosis group were found. Besides, an enrichment of *Shigella*/*Escherichia* was found in the stool microbiome of the endometriosis group.[22] Peritoneal microbiota is also modified in endometriosis,[23,24] and this dysbiosis probably accounts for local inflammation and pelvic pain.[25]

Noteworthily, a growing body of recent evidence also suggests the existence of gut dysbiosis (notably gut dysbiosis-derived β-glucuronidase, *i.e.*, the estrobolome), promoting the development of endometriosis,[26-29] underscoring a potential similar role of microbiota in endometriosis and irritable bowel syndrome (IBS) conditions[30] and even inflammatory bowel disease (IBD). IBS is a common functional bowel disorder (abdominal pain and distension with an altered bowel movement), whereas IBD refers to inflammation in the gastrointestinal tract, traditionally categorized into ulcerative colitis and Crohn's disease. Actually, IBD, more than IBS (because of the absence of histologic lesions), shares a similar pathophysiology with endometriosis. A positive association between endometriosis and IBD has been confirmed in a systematic review.[31] Unfortunately, a meta-analysis on this topic is currently not possible due to the heterogeneity of the groups and because information on the temporal sequence of endometriosis and IBD is not available in several studies. A large-scale genome-wide association study has confirmed an increased risk of developing IBD after endometriosis, but not *vice versa*.[32]

Finally, two Mendelian randomization studies (assessed by two different teams) using huge consortium databases on gut microbiota (MibioGen, including 18,340 cases from 24 cohorts, mainly from Europe) and endometriosis (FinnGen, including data from 77,257 European participants) supported the causal relationship between gut microbiota and endometriosis without bidirectional causal effects.[33,34] More precisely, some families (*Prevotellaceae*, genus *Anaerotruncus*, genus *Olsenella*, genus *Oscillospira*) and order Bacillales were identified as risk factors for endometriosis, while others (Melainabacteria and genus *Eubacterium ruminantium* group) were protective factors.[33] Therefore, it seems that gut microbiota modification can trigger the onset of endometriosis, but any gut microbiota dysbiosis cannot promote endometriosis. Subsequently, gut microbiota dysbiosis that favors endometriosis is likely to also favor IBD, depending on the concomitance of other risk factors. Indeed, similarly, gut microbiota dysbiosis, especially a decrease in the abundance and diversity of specific genera (reduction in *Faecalibacterium prausnitzii*; *Alistipes*, *Collinsella*, and *Ruminococcaceae*), has been suggested as a trigger for IBD-initiating events.[35] Similarly, the onset of IBD is likely to be more strongly influenced by environmental factors, especially gut microbiota, than by genetic factors.[36]

Besides, gut dysbiosis triggers inflammation through recruitment and/or activation of immune cells,[37] as well as through modulation of the vasoactive intestinal peptide (VIP) signalling.[38,39] Because of the altered composition of the intestinal microbiota, a significant number of Gram-negative bacteria translocate and infiltrate outside the intestinal cavity, resulting in the destruction of intestinal tight junctions and the reduction of tight junction protein 2 (ZO-2) expression,[40] leading to the infiltration of a significant amount of Gram-negative bacteria outside the intestine.[41] According to Harada *et al.*[41] lipopolysaccharide can activate the macrophage TLR4 in innate immunity, leading to the production of significant levels of tumor necrosis factor alpha and interleukin 8 and the development of an inflammatory environment.[42] Otherwise, VIP is a non-cholinergic non-adrenergic neurotransmitter mainly expressed in the nerve terminals of the digestive tract, the genitourinary tract, the adrenal glands, and the central nervous system,[43] playing a key role in controlling the balance of pro- and anti-inflammatory cytokines[44] and in angiogenesis,[45] notably through alternative splicing.[46] VIP expression is upregulated in women with endometriosis and chronic pelvic pain,[47] concomitantly with inflammation, and the increase in nerve fiber density within ectopic endometrial tissue.[48] Moreover, dysfunction of VIP signaling could be involved in genital barrier disruption,[49] allowing endometriotic cell migration, as well as impacting gut[50,51] and brain barrier permeability,[52] supporting the recent insight that endometriosis is "no longer a pelvic disease."[53]

3. Brain and vagus nerve dysfunction in endometriosis

In addition to peripheral alterations provoked by endometriosis, such as peritoneal inflammation and angiogenesis, central repercussions, such as stress, pain, anxiety, depression,[54] and even bipolar and panic disorder[55] have been described, supported by experimental studies. Alteration in gene expression and electrophysiology in distinct brain regions,[56] upregulation of the expression of glial markers (GFAP and IBA-1) as well as morphological changes in glial cells in the spinal cord,[57,58] the hippocampus and the hypothalamus[59] were found in mice with endometriosis. Moreover, in a murine model, endometriosis lesions were shown to develop in the central nervous system, as endometriosis-derived cells were able to migrate and engraft to the brain.[60] Several teams have suggested chronic stress as a central, top-down mechanism exacerbating endometriosis by triggering the dysregulation of the hypothalamic-pituitary-adrenal axis, ending up with a release of inflammatory mediators in the circulatory system.[61,62] Endometriosis-linked central stress could also influence the desynchronization of both the Hypothalamic-pituitary-gonadal axis and the circadian system,[61] underpinning the occurrence of several comorbidities. Indeed, night shift work has been significantly associated with an increased risk of endometriosis as well as an increased risk of estrogen-influence diseases (namely breast cancer and adverse coronary events) and menstrual disruption.[63]

Whether endometriosis results from a top-down neuroinflammation[61] or a bottom-up activation of microglia by peripheral inflammatory mediators[59] remains an elusive question. Regarding the current validated level of knowledge in the pathophysiology of endometriosis, this distinction is rather ambitious, since endometriotic lesion can grow very slowly and the diagnosis is often delayed. Nevertheless, as the bidirectional microbiota-gut-brain axis is known to involve the vagus nerve[19,37,64-66] and as severe endometriosis leads to a reduced vagal tone in women,[67] the rationale for using non-invasive VNS in endometriosis is very much appealing.

4. Rationale for using VNS in endometriosis

In a nutshell, gut dysbiosis and estrobolome activity seem to be essential to initiate endometriosis.[20,33,34,68] Although preliminary, antibiotic and probiotic treatments have demonstrated efficacy in treating endometriosis,[13] modulating the gut and/or genital microbiota by other means, potentially including non-invasive VNS, has been suggested as a novel therapeutic strategy to improve outcomes in patients with chronic endometriosis.[29,69,70] Indeed, minimally or non-invasive VNS is already known to mitigate gut dysbiosis[71] and is currently advocated for managing both IBS[72] and IBD.[73-76]

VNS appears particularly promising to help delay or even prevent severe endometriosis, since in a mouse model, vagotomy has been shown to promote the progression of endometriosis, whereas VNS could relieve it.[67] Actually, besides mitigation of gut dysbiosis and estrobolome activity, non-invasive VNS is likely to be helpful to several therapeutic mechanisms: (i) decreasing local and systemic inflammation (by stimulating alpha 7 nicotinic receptors (α7nAChR),[77,78] involved in the cholinergic anti-inflammatory pathway,[79-84] which are significantly reduced in endometriotic lesions);[85] (ii) counteracting VIP-induced increase of intestinal and brain barrier permeability;[86-88] (iii) decreasing the central symptoms of endometriosis, *i.e.*, stress, pain, anxiety, and depression;[89-92] (iv) protecting from hypoxia;[93,94] (v) acting through epigenetic regulatory mechanisms (histone deacetylation, micro-RNA and methylation of DNA),[11,95-98] and (vi) finally modulating the downstream MAPK or NF-κB pathways signaling pathways, which are known to be involved in endometriosis.[98-100]

Traditionally, VNS was achieved through surgical implantation. In 2017, however, non-invasive approaches that involve stimulating the cervical vagus nerve and the auricular branch of the vagus nerve were approved by the U.S. Food and Drug Administration (FDA) for cluster headache and abdominal pain, respectively. Since then, numerous new indications have been cleared by the FDA, and remarkably for the treatment and the prevention of migraine attacks[101,102] (this is of highest importance since multitrait genetic analyses identified substantial sharing of variants associated with endometriosis and migraine)[7] as well as in case of threatening inflammation with Emergency Use Authorization from the FDA in July of 2020 for patients with known or suspected coronavirus disease 2019 (COVID-19).[103] We are seeing a paradigm shift in our understanding of how disease is modulated by infection and/or inflammation across numerous disorders from the use of electroceuticals in the treatment of IBD[75] and rheumatoid arthritis[104] to the treatment of cytokine storm associated with COVID-19.[105]

The benefits of non-invasive VNS are potentially plethora for women with endometriosis. First and foremost, non-invasive VNS can provide a significant reduction of side effects, compared to the actual drugs (from non-steroidal anti-inflammatory drugs whose anticipated side effects are relatively mild to progestins whose prolonged use has been linked with a malignant transformation of ovarian endometrioma).[106] Indeed, non-invasive VNS has proven to be very well tolerated[107] and is likely to be more ethical for young ladies than dienogest.[108,109]

Second, most current drugs merely alleviate symptoms without reversing the progression of endometriosis. Guo[110] even stated in 2014 that "no blockbuster drug for endometriosis seems to be on the horizon yet", probably because interdisciplinary clinical research, fully funded by non-industrial sources, is lacking.[111] The same author has even called for a paradigm shift in drug research and development in endometriosis lately.[112] Remarkably, non-invasive VNS has all the requisites to become an all-in-one tool (both etiological and symptomatic) in endometriosis (that is the main aim of this article). Indeed, non-invasive VNS has already been successfully used in different types of chronic pain[113] (chronic pain being an interdisciplinary clinical research field by essence), has shown promising results not only in chronic pelvic pain,[114] but also in a wide array of comorbidities of endometriosis (FDA-approved for preventing migraine attacks, stress, anxiety, and depression), and has the potential to reverse the several pathophysiologic mechanisms involved in endometriosis. Non-invasive VNS does not modify one but a variety of factors, both peripherally and centrally, and has demonstrated an expanded scope and value for holistic therapy.[19] This ability relies mainly not only on the widespread innervation of the vagus nerve but also on its ability to shift the body and brain from a sympathetic to a parasympathetic dominance. Indeed, another therapeutical approach (a fluid therapy comprising adenosine, lidocaine, and magnesium) allowing a similar shift from sympathetic to parasympathetic tone has been intitled "Revolution in sepsis: a symptoms-based to a systems-based approach?" as it enables to "maintain cardiovascular-endothelial glycocalyx coupling, reduce inflammation, correct coagulopathy, and maintain tissue O_2 supply" all by itself.[115]

Last but not least, non-invasive VNS, which is easier and more sustainable than pharmacological (hormonal[116] or anti-inflammatory[117]) options or microbiota transplants,[118] could even prevent the spontaneous occurrence of cancers linked to endometriosis. Indeed, ovarian cancer is the most important associated cancer, wherein a direct clonal relationship between endometriosis and cancer has been made.[119] A recent large cohort from Utah (including 78,893 women with endometriosis and those without endometriosis, in a 1:5 ratio) confirms a marked increase of ovarian cancer risk (multiplied by 4.2 in average, but up to 7.48, depending on the histological type of cancer) in women with ovarian and/or deep infiltrating endometriosis.[120] Moreover, although research has not found a direct link between endometriosis and breast cancer, so far, women with hormone-sensitive breast cancers should not be subjected to hormonal regulation of their endometriosis. On the contrary, an increased vagal tone, notably induced through non-invasive VNS, is correlated with a better prognosis in breast cancer[120] as well as in cancer in general.[108,109] Non-invasive VNS thus appears as a promising candidate for primary as well as secondary prevention of endometriosis. Thus, non-invasive VNS could be a potential lifelong innovative therapeutic solution for endometriosis, since the early phase of symptom manifestation, as it improves compliance.[121]

5. Conclusion

Merging both top-down and bottom-up mechanisms, vagus nerve-mediated regulation of immunity emerges as an etiological therapeutic intervention in endometriosis, offering patients a convenient therapeutic strategy to improve their quality of life as well as their prognosis. It is necessary to conduct clinical trials assessing the efficiency and tolerability of the very early use of this disruptive approach to tackle, particularly, pain, inflammation, and even the onset of endometriosis.

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Conflict of interest

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Ethics approval and consent to participate

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