OXFORD JOURNAL
OF STUDENT
SCHOLARSHIP

Estrogen-Based Therapies As A Potential Disease - Modifying Therapy In Multiple Sclerosis

Abiola Adejana
abi_faith@icloud.com

ABSTRACT

Although current disease-modifying therapies (DMT) can reduce inflammation and relapses in cases of Multiple Sclerosis (MS), they do not fully prevent neurodegeneration. MS typically impacts women more than men, and disease activity changes according to hormonal fluctuations in the body. Consequently, estrogen has emerged as a potential therapy. These therapies have been tested by combining traditional disease-modifying therapies with them. The effectiveness of this is possible in monoclonal antibodies, and oral drugs. Which could be treatment strategies for MS patients. Estrogen helps the body with neuroprotection, and immunomodularity. Significant amounts of estrogen stimulate myelin repair, protect axons from degeneration, and suppress inflammatory T-cells**.** This review examines whether estrogen-based therapies could effectively treat MS. Research suggests that estrogen can reduce inflammatory immune activity, and support remyelination. The decrease in relapse rates during pregnancy and the increase postpartum further support a correlation between estrogen and MS activity. Overall, estrogen-based therapies show potential as effective disease-modifying therapies for MS.

INTRODUCTION

MS is an autoimmune, heterogeneous, inflammatory, and demyelinating disease where the immune system attacks the myelin in the brain and spinal cord [1]. It affects approximately 2.9 million people worldwide, including nearly 1 million adults in the United States [2]. MS mainly affects people that are ages 20-40, mostly women [1]. Relapsing-remitting MS (RRMS) starts between 20-35 years old, and primary progressive MS (PPMS) usually starts at the age of 40, although 10% of patients experience their first demyelinating event during childhood or adolescence [1]. In MS immune cells attack the body mistakenly [1]. These immune cells include T cells (CD4+, Th1 and Th17), B cells, cytokines, macrophages, and antibodies that attack the myelin sheath [15]. These cells move past the endothelial cells and enter the BBB. The T cells will go to the brain, recognizing myelin proteins as foreign [15]. Releasing cytokines T cells that will promote deterioration of the BBB, increasing its permeability. This demyelination, and the axonal damage that occurs leads to a larger progression in symptoms [16].

Symptoms of MS rely on the location of the damage to the nervous system and its intensity [1]. MS impairs vision, throat function, the spinal cord, and patients have reduced cognitive abilities, paying attention, thinking, and decision-making [1]. The treatments that were approved for relapsing-remitting

MS (RRMS) were Interferon-β, Glatiramer Acetate, and Mitoxantrone, and monoclonal antibodies (Natalizumab, Alemtuzumab, and Rituximab) that are being used to mainly target the inflammatory processes of the disease [19]. This includes oral drugs that just finished their trials. Such as Cladribine, Fingolimod (FTY 72), Teriflunomide, Oral fumarate, and Laquinimod [3]. Currently these DMT's are useful but they do not save neurons from degeneration, and axonal loss. Once an axon is demyelinated, current therapies can not help restore it [5].

An unexplained female dominance occurs in MS [1]. A research conducted approximated that the amount of MS cases are 3.6 per 100,000 women, and only 2 per 100,000 in men [1]. The increased prevalence in women is possibly due to environmental risks that mainly affect women [9]. Globally, 1.89 million people live with MS, with over 62,000 new cases diagnosed in 2021 [8]. The frequency of MS cases globally is 23.9 cases per 100,000 population, with a steady incline over the last three decades [8]. Sex hormones most likely contribute to this female dominance [13]. Mainly seen in pregnancy, because during the third trimester estrogen levels increase rapidly, and then during the post-partum phase estrogen levels drop, leaving them more prone to MS. A lot of evidence supports this timeline. Epidemiological data demonstrates that annual relapse rates fluctuate and drop by up to 70% during a woman's third trimester of pregnancy. This is accompanied by a sharp 3 to 6 month postpartum rebound spike in relapses that directly begins the abrupt withdrawal of estrogen hormones [20]. These things suggest estrogen as a potential DMT because it correlates with changes in MS. Estrogen acts as a double-sided regulator for the immune system, primarily by modulating white blood cells. Estrogen regulates pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 [12] while increasing anti-inflammatory responses in the body. Estrogen expands regulatory T-cells and increases B-cell apoptosis, preventing the immune system from becoming overly aggressive [13]. Treatments with estrogen based therapies use estrogen receptors ER alpha and ER beta which are capable of providing disease protection [21]. This protection includes, but is not limited to, prevention of clinical disease, reduction of central nervous system (CNS) inflammation, protection against demyelination, and protection against axonal loss [21]. Although there is this potential for estrogen as a DMT, there is a lack of a unified consensus that proves this. This paper will explain why estrogen is a strong potential DMT.

METHODS

This paper is a qualitative literature review that looks at whether estrogen-based therapies could help treat MS. Instead of collecting data, information was reviewed from research that has already been published utilizing PubMed and Google Scholar to find research articles and reviews related to estrogen and MS. I researched a total of 40 studies, and I selected 24 of those studies. I excluded the other 16 studies because the information did not assist my paper well. The keywords used included "estrogen", "multiple sclerosis", "neurodegeneration", "pregnancy", "demyelination", "hormonal therapies", "neuroprotection", "immune system", and "white matter". Using research articles and review papers published between 2008 and 2025. The inclusion criteria was information regarding MS, estrogen, and how the therapy works on a cellular level and its benefits. I conducted searches June 24, July 6, July 9, and July 10 of 2026. The exclusion criteria was post-menopausal women since they can't get pregnant. The relevance of the paper

was determined after multiple reads, and each paper was judged on if they were strongly supportive of the research that had been done. A narrative approach was chosen because as a student there was a limited amount of what I could find from PubMed and Google Scholar for my research. I focused on research about how estrogen affects the immune system, inflammation, myelin, neuroprotection, pregnancy, and hormonal changes. Also, I compared information from the selected papers and used the findings that were most relevant to explaining the possible benefits of estrogen-based therapies for people with MS.

BACKGROUND/PATHOPHYSIOLOGY

Estrogen is a female sex hormone that influences major aspects of women's health [13]. There are several types of estrogen; the two main types are estradiol and estriol [11]. Estradiol is the primary form of estrogen in the body during your reproductive years. Estriol is the main form of estrogen in the body during pregnancy [11]. Estrogen acts as a powerful immunomodulatory and neuroprotective hormone that directly shapes MS development [16]. While women are roughly three times more likely to develop MS than men, fluctuating estrogen levels impact the severity of the disease over a lifespan [13].

On a cellular level, specific estrogens like estradiol and estriol actively protect the nervous system by using estrogen receptors (ER - Alpha and ER- Beta) that stimulate myelin repair, protect oligodendrocytes, and stop the production of toxic proteins [21]. However, managing these hormonal transitions (puberty, menstrual cycle, pregnancy, postpartum, and menopause) through therapies like hormone replacement therapy (HRT) remains a critical challenge in preventing physical and cognitive decline for MS patients [16]. Women between the ages 50-79 utilize menopausal hormone replacement therapy, which replaces declining estrogen levels to reduce menopausal symptoms, and inflammation. In women ages 18-50 HRT focuses on RRMS [3]. Rather than replacing hormones (estrogen) lost during menopause, it tries to reduce inflammatory disease activity. The relapse rate of MS is decreased during a woman's pregnancy, especially in the third trimester, and increases during the postpartum period. This is due to the rapid increase in estrogen levels during pregnancy, and then the drastic decrease in estrogen levels after pregnancy. Pregnancy is typically a stabilizing period in the clinical course of MS. In the third trimester of pregnant women with MS, the MS relapse rate can be 70% lower when compared with the time before pregnancy, but aggravation of the disease is common after delivery [14]. The immune system is suppressed by the shifting of the immune system from a damaging pro-inflammatory, such as Th1 and Th17 responses to a protective anti-inflammatory Th2 response, these low estrogen levels fast track the progression of disease [14]. The sudden drop in hormone levels when a woman is postpartum causes relapse rates to nearly double, while the permanent loss of estrogen during menopause is tightly linked to advanced MS symptoms such as brain volume loss, and spinal cord atrophy. This can lead to a faster transition into SPMS.

ESTROGEN AND IMMUNE REGULATION

The innate immune system plays a major role in causing inflammation when the body is dealing with an infection or tissue damage [17]. It uses pattern recognition receptors (PRRs) to recognize signals from

pathogens and damaged cells [17]. In MS, these early immune signals can activate cells that eventually attack the nervous system [6]. Many different immune and CNS cells are involved in MS. Dendritic cells, macrophages, microglia, oligodendrocytes, and autoreactive T cells all have important roles in the disease [1]. These cells can contribute to inflammation and damage within the CNS [6]. Dendritic cells help activate autoreactive T cells, which can cross the blood-brain barrier (BBB) and attack myelin, oligodendrocytes, and neurons [1]. Normally, the BBB controls which immune cells can enter the CNS, but inflammation in MS can make the barrier weaker and allow T cells to enter [1]. These processes may help explain why estrogen is being studied as a potential treatment for MS. Estrogen can affect immune and CNS cells by lowering inflammation, helping protect the BBB, protecting oligodendrocytes, and supporting OPC development and remyelination. Because of these effects, estrogen may help reduce myelin damage and support repair, making it a promising area of research for limiting neurological damage in people with MS [3].

GENETIC FACTORS AND ENVIRONMENTAL TRIGGERS

Scientists have identified more than 200 genetic factors that may increase the risk of developing MS, but none of these factors alone determine whether someone will develop the disease [18]. Instead, MS is thought to result from an interaction between genetic susceptibility and environmental factors [18]. Having these genetic risk factors does not mean a person will definitely develop MS. Rather, they can make someone more susceptible to the disease. Environmental factors, infections, and especially Epstein-Barr virus (EBV) may then act as triggers that contribute to MS development [10].

PRE, PERI, AND POST MENOPAUSE

Stages of MS during menopause involve specific hormonal shifts that directly impact the neurological functions in MS [16]. Pre-menopause brings stabilized estrogen before hormonal changes begin. It helps maintain immune regulation by promoting anti-inflammatory, protecting the BBB, and myelin function [16]. While peri-menopause has hormone drops that often cause temporary symptom flare-ups like fatigue and heat sensitivity from increased inflammatory activity and immune cells permeating into the CNS [16]. Declining estrogen levels dysregulate the immune system. Post-menopause marks stable low estrogen levels leading to accelerated neurodegeneration, reduced myelin function, and further symptom progression [16]. Where symptoms may settle or change due to natural aging.

THERAPUTIC IMPLICATIONS

Monoclonal antibodies that target CD20, CD52, and natalizumab have proven to be very effective at minimizing relapse rates and preventing the formation of new lesions [19]. The high efficiency of natalizumab treatment is a result of its blockade of the migration of many different inflammatory cell types [4]. These DMT’s either slow down or block movement of white blood cells into the central nervous systems [19]. Anti CD20 therapies have emerged as a therapy of choice for most patients. They target B cells and some T cells [19]. The effects of DMTs on lesion formation provide strong evidence that the

peripheral immune system is directly involved in relapsing MS activity. The success of anti-CD20 treatments targeting B cells also suggests that B cells have a more important role in MS development than previously believed. [19].

Estrogens show therapeutic potential in MS due to their immunomodulatory and neuroprotective properties [16]. Hormones like estriol and estradiol regulate both the innate and adaptive immune system by reducing Th1 and Th17 cells, promoting anti-inflammatory T cells, and suppressing cytokines can reduce spinal cord inflammation and protect the myelin coating of nerve fibers, potentially aiding in the development of future therapies for progressive forms of MS [13,16]. Studies suggest estrogen based therapies because they slow neurodegeneration, and improve myelin repair in progressive forms of MS [20].

RISKS

Although estrogen based therapy is potentially effective, it comes with increased risk of cardiovascular considerations including thromboembolism, as well as associations with certain hormone-sensitive cancers such as breast or endometrial. Hormone-sensitive cancers are single nucleotide polymorphisms (SNPs) related to MS [23] and a number of studies have suggested that MS can be associated with serious vascular complications, for which thromboembolism is a potentially lethal complication [24]. Researchers are trying to work around them using estriol, which has a different receptor-binding profile than estradiol and was specifically chosen in trials partly for this reason. HRT trials have been conducted that have tested estrogen compounds in MS patients directly. Estriol treatment in MS models was associated with reduced atrophy in the hippocampus and cerebral cortex [22].

CONCLUSION

Overall, the research suggests that estrogen-based therapies could be an effective treatment strategy for MS, but more research is needed before they can be considered a standard treatment. Estrogen has both immunomodulatory and neuroprotective effects, allowing it to influence immune cells positively, reduce inflammation, protect oligodendrocytes, and support remyelination [21]. The decrease in MS relapse activity during pregnancy and increase in relapses following the postpartum decline in estrogen also demonstrate a relationship between hormonal changes and MS activity [14]. Unlike current DMT's that primarily target inflammation, estrogen may have the additional benefit of protecting nervous tissue from damage and supporting myelin repair [3,19]. Therefore, estrogen-based therapies may have particular potential as a complementary strategy for limiting both inflammation and neurodegeneration. However, current evidence is not sufficient to establish estradiol estrogen therapy as a replacement for approved MS treatments. Estrogen-based therapies represent a future potential treatment strategy for MS that encourages further investigation.

REFERENCES

1. Filippi, M., Bar-Or, A., Piehl, F. *et al.* Multiple sclerosis. *Nat Rev Dis Primers* 4, 43 (2018). https://doi.org/10.1038/s41572-018-0041-4

2. Nelson LM, Wallin MT, Marrie RA, Culpepper WJ, Langer-Gould A, Campbell J, Buka S, Tremlett H, Cutter G, Kaye W, Wagner L, Larocca NG; United States Multiple Sclerosis Prevalence Workgroup. A new way to estimate neurologic disease prevalence in the United States: Illustrated with MS. Neurology. 2019 Mar 5;92(10):469-480. doi: 10.1212/WNL.0000000000007044. Epub 2019 Feb 15. PMID: 30770422; PMCID: PMC6442012.

3. Gold SM, Voskuhl RR. Estrogen treatment in multiple sclerosis. J Neurol Sci. 2009 Nov 15;286(1-2):99-103. doi: 10.1016/j.jns.2009.05.028. Epub 2009 Jun 18. PMID: 19539954; PMCID: PMC2760629.

4. Höftberger R, Lassmann H. Inflammatory demyelinating diseases of the central nervous system. Handb Clin Neurol. 2017;145:263-283. doi: 10.1016/B978-0-12-802395-2.00019-5. PMID: 28987175; PMCID: PMC7149979.

5. Tepavčević V, Lubetzki C. Oligodendrocyte progenitor cell recruitment and remyelination in multiple sclerosis: the more, the merrier? Brain. 2022 Dec 19;145(12):4178-4192. doi: 10.1093/brain/awac307. PMID: 36093726.

6. Miljković D, Spasojević I. Multiple sclerosis: molecular mechanisms and therapeutic opportunities. Antioxid Redox Signal. 2013 Dec 20;19(18):2286-334. doi: 10.1089/ars.2012.5068. Epub 2013 Apr 22. PMID: 23473637; PMCID: PMC3869544.

7. Cambron M, D'Haeseleer M, Laureys G, Clinckers R, Debruyne J, De Keyser J. White-matter astrocytes, axonal energy metabolism, and axonal degeneration in multiple sclerosis. J Cereb Blood Flow Metab. 2012 Mar;32(3):413-24. doi: 10.1038/jcbfm.2011.193. Epub 2012 Jan 4. PMID: 22214904; PMCID: PMC3293127.

8. Khan G, Hashim MJ. Epidemiology of Multiple Sclerosis: Global, Regional, National and Sub-National-Level Estimates and Future Projections. J Epidemiol Glob Health. 2025 Feb 10;15(1):21. doi: 10.1007/s44197-025-00353-6. PMID: 39928193; PMCID: PMC11811362.

9. Olsson T, Barcellos LF, Alfredsson L. Interactions between genetic, lifestyle and environmental risk factors for multiple sclerosis. Nat Rev Neurol. 2017 Jan;13(1):25-36. doi: 10.1038/nrneurol.2016.187. Epub 2016 Dec 9. PMID: 27934854.

10. Soldan SS, Lieberman PM. Epstein-Barr virus and multiple sclerosis. Nat Rev Microbiol. 2023 Jan;21(1):51-64. doi: 10.1038/s41579-022-00770-5. Epub 2022 Aug 5. PMID: 35931816; PMCID: PMC9362539.

11. Vegeto E, Benedusi V, Maggi A. Estrogen anti-inflammatory activity in brain: a therapeutic opportunity for menopause and neurodegenerative diseases. Front Neuroendocrinol. 2008 Oct;29(4):507-19. doi: 10.1016/j.yfrne.2008.04.001. Epub 2008 Apr 29. PMID: 18522863; PMCID: PMC2630539.

12. Zhang Y, Tan X, Tang C. Estrogen-immuno-neuromodulation disorders in menopausal depression. J Neuroinflammation. 2024 Jun 19;21(1):159. doi: 10.1186/s12974-024-03152-1. PMID: 38898454; PMCID: PMC11188190.

13. Maglione A, Rolla S, Mercanti SF, Cutrupi S, Clerico M. The Adaptive Immune System in Multiple Sclerosis: An Estrogen-Mediated Point of View. Cells. 2019 Oct 19;8(10):1280. doi: 10.3390/cells8101280. PMID: 31635066; PMCID: PMC6829884.

14. Airas L, Kaaja R. Pregnancy and multiple sclerosis. Obstet Med. 2012 Sep;5(3):94-7. doi: 10.1258/om.2012.110014. Epub 2012 May 29. PMID: 27582863; PMCID: PMC4989704.

15. Lopez, J.A., Denkova, M., Ramanathan, S., Dale, R.C. and Brilot, F. (2021), Pathogenesis of autoimmune demyelination: from multiple sclerosis to neuromyelitis optica spectrum disorders and myelin oligodendrocyte glycoprotein antibody-associated disease. Clin Transl Immunol, 10: e1316. https://doi.org/10.1002/cti2.1316

16. Hsu, S., Bove, R. Hormonal Therapies in Multiple Sclerosis: a Review of Clinical Data. *Curr Neurol Neurosci Rep* 24, 1–15 (2024). https://doi.org/10.1007/s11910-023-01326-7

17. Chelangarimiyandoab F, Lavoie JC, Flamand N, Cordat E, Breton S. Molecular mechanisms of acute inflammation: systemic responses and kidney-specific pathophysiology. Function (Oxf). 2026 Feb 1;7(1):e0872025. doi: 10.1152/function.087.2025. Epub 2025 Dec 8. PMID: 41401426; PMCID: PMC12790851.

18. Didonna A, Oksenberg JR. Genetic determinants of risk and progression in multiple sclerosis. Clin Chim Acta. 2015 Sep 20;449:16-22. doi: 10.1016/j.cca.2015.01.034. Epub 2015 Feb 4. PMID: 25661088; PMCID: PMC4524789.

19. Sabatino JJ Jr, Cree BAC, Hauser SL. New Horizons for Multiple Sclerosis Therapy: 2025 and Beyond. Ann Neurol. 2025 Aug;98(2):317-328. doi: 10.1002/ana.27270. Epub 2025 Jun 6. PMID: 40474602; PMCID: PMC12278195.

20. Voskuhl R, Momtazee C. Pregnancy: Effect on Multiple Sclerosis, Treatment Considerations, and Breastfeeding. Neurotherapeutics. 2017 Oct;14(4):974-984. doi: 10.1007/s13311-017-0562-7. PMID: 28766273; PMCID: PMC5722767.

21. Spence RD, Voskuhl RR. Neuroprotective effects of estrogens and androgens in CNS inflammation and neurodegeneration. Front Neuroendocrinol. 2012 Jan;33(1):105-15. doi: 10.1016/j.yfrne.2011.12.001. Epub 2011 Dec 24. PMID: 22209870; PMCID: PMC3616506.

22. Voskuhl R. All women with multiple sclerosis should start hormone replacement therapy at menopause unless contraindicated: Yes. Mult Scler. 2024 Aug;30(9):1107-1109. doi: 10.1177/13524585241255002. Epub 2024 Jun 22. PMID: 38907632; PMCID: PMC11363466.
23. Ghoshouni H, Shafaei B, Farzan M, Hashemi SM, Afshari-Safavi A, Ghaffary EM, Mohammadzamani M, Shaygannejad V, Shamloo AS, Mirmosayyeb O. Multiple sclerosis and the incidence of venous thromboembolism: a systematic review and meta-analysis. J Thromb Thrombolysis. 2023 Oct;56(3):463-473. doi: 10.1007/s11239-023-02848-0. Epub 2023 Jul 2. PMID: 37394561.
24. Liu Z, Fan T, Mo X, Kan J, Zhang B. Association between multiple sclerosis and cancer risk: A two-sample Mendelian randomization study. PLoS One. 2024 Mar 19;19(3):e0298271. doi: 10.1371/journal.pone.0298271. PMID: 38502664; PMCID: PMC10950213.