Caspian Journal of Neurological Sciences
"Caspian J Neurol Sci"
Journal Homepage: http://cjns.gums.ac.ir

Review Paper: Effects of Estrogen and Progesterone on Different Immune Cells Related to Multiple Sclerosis

Aryan Rafiee Zadeh[1*], Keyvan Ghadimi[1], Banafsheh Mohammadi[2], Hamidreza Hatamian[3], Seyed Navid Naghibi[4], Ali Danaeiniya[5]

1. Department of Neurology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran
2. Gynecologist, Department of Gynecology and Obstetrics, School of Medicine, Ahvaz Jondishapur University of Medical Sciences, Ahvaz, Iran
3. Department of Neurology, Poursina Hospital, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran
4. Kashani Comprehensive Epilepsy Center, Kashani Hospital, Department of Neurology, School of Medicine, Isfahan University of Medical Science, Isfahan, Iran
5. MSc. in Physiology, Department of Biology, Isfahan Payam-e-Noor University, Isfahan, Iran

Use your device to scan and read the article online

Citation: Rafiee Zadeh A, Ghadimi K, Mohammadi B, Hatamian H, Naghibi SN, Danaeiniya A. Effects of Estrogen and Progesterone on Different Immune Cells Related to Multiple Sclerosis. Caspian J Neurol Sci. 2018; 4(2):83-90.

Running Title: Estrogen and Progesterone and Different Immune Cells and MS

doi:

Funding: See Page 43

Bullet Points:

- Estrogen and progesterone both have affect on cellular immunity in MS.
- The role of estrogen and progesterone in MS can be considered as a potential therapeutic opportunity.

Article info:
Received: 30 Oct 2017
First Revision: 10 Nov 2017
Accepted: 08 Feb 2018
Published: 01 Apr 2018

ABSTRACT

Multiple Sclerosis (MS) is a chronic autoimmune disease of young adults with an unknown etiology, but cellular immune responses and inflammation has a pivotal role in this regard. The higher incidence of MS among women indicates the possible involvement of female sex hormones on the disease course. Progesterone and estrogen are the most important sexual hormones in women. They exert different immunomodulatory effects through both nuclear and membrane associated receptors present in different immune cells. The immunological effects include shifting the immune response towards Th2, stimulating Treg production, inhibiting pro-inflammatory cytokine production, prohibiting cell migration into Central Nervous System (CNS), suppressing proinflammatory immune cells, stabilizing the neuronal environment, and promoting neuronal survival, all of which might ameliorate the condition in women suffering from MS. Some clinical trials have reported a correlation between the use of Oral Contraceptives (OCs), which contain estrogen and progesterone, and MS among women. Some of these studies show a positive effect of OC usage on the onset and severity of the disease while others have found no significant impact. In this review, we collected articles published between 1995 and 2017 from PubMed Central and Google Scholar for evaluating effects of estrogen and progesterone on different immune cells related to MS.

Keywords: Multiple Sclerosis, Estrogen, Progesterone, Immune cells

*** Corresponding Author:**
Aryan Rafiee Zadeh, MD
Address: *Department of Neurology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran*
Tel: *+98 (938) 068 6777,* ***Fax:*** *+98 (31) 37323079*
E-mail: *rafieezadeh.a@gmail.com*

Caspian Journal of Neurological Sciences

Introduction

Multiple Sclerosis (MS), a chronic autoimmune disease in which myelin sheaths of Central Nervous System (CNS) is targeted by self-immune cells, is a leading cause of neurological disability in young adults [1]. Despite the efforts to determine the causes and aggravating factors of the disease, along with the pivotal role of the immune system, the exact etiology remains unknown [2]. Since women have two- to three-times higher MS incidence compared to men [3], it is plausible that female sex hormones such as estrogen and progesterone affect the progression and development of MS. Furthermore, MS symptoms are significantly ameliorated during the last trimester of pregnancy during which the levels of estrogen and progesterone are at the highest [4].

Oral Contraceptives (OCs) containing estrogen and progesterone are known to influence some aspects of autoimmune diseases including MS. Accumulating epidemiological evidence has shown controversial results regarding the role of OCs in the advancement of MS. In addition, studies on experimental models of MS such as Experimental Autoimmune Encephalomyelitis (EAE) have shown that both estrogen and progesterone affect different aspects of the immune system, which might influence the disease in women who suffer from MS. Some studies have also studied the possibility of antagonism between estrogen and progesterone when taken simultaneously. While Mannella and colleagues [5] claimed no antagonism between the two hormones, Yao et al. [6] believed that the effects of estrogen were inhibited by progesterone or synthetic progestins. In this review article, we assessed the effects of estrogen and progesterone on the immune system, as well as the different aspects of immune cells in the pathogenesis of MS.

Estrogen

Estrogen, the major constituent of OCs, is a steroid hormone mainly synthesized in the ovaries, and to a much lesser extent in the adrenal glands as well as in the testes in males. The biosynthesis of estrogen is a multistep process initiated from cholesterol and is regulated at each step by hormones, such as Adrenocorticotropic Hormone (ACTH) and Luteinizing Hormone (LH), which controls the first enzymatic steps. In addition, the P-450 enzyme complex aromatase also plays a crucial role in estrogen biosynthesis and is a highly regulated enzyme [7]. Ghayee et al. have shown that estrogen consists of three endogenous biologically different compounds; estradiol, estriol, and estrone [8, 9].

As with all other regulatory substances, estrogen action is mediated by its specific receptors. So far, two distinct intracellular receptors; Estrogen Receptors α (ERα) and β (ERβ) and one membrane-associated Receptor (mER) are known. Nuclear estrogen receptors are known to regulate gene transcription in different target cells while membrane receptors control non-genomic actions such as calcium reflux and some other signaling pathways [10].

Gustafsson et al. reported that ERα is mainly localized in the uterus and mammary glands, while ERβ is predominant in the central nervous system, cardiovascular and immune system [11]. In addition, ERα is expressed in different types of immune cells, including CD4+ and CD8+ T cells, B cells, Natural Killer (NK) cells, and macrophages [12, 13]. Recent studies have reported therapeutic effects of estrogen in autoimmune diseases, especially MS. For instance, MS symptoms are ameliorated in the last trimester of pregnancy during which the estrogen levels are the highest and relapse within 3-6 months after delivery with the ebbing of the hormone levels [14]. Experiments on animal MS models (i.e. EAE) have shown that estrogen treatment led to a significant remission of the severity of EAE symptoms [15], even when administered after disease onset [16]. Estrogen is known to have a wide range of effects on the immune system and CNS such as cell differentiation, cytokine production, inhibition of cell migration in CNS, and neuroprotective actions on axons and myelin. We have reviewed these aspects in the sections below.

Lymphocytes

Bone marrow and thymus are both affected by estrogen due to the expression of estrogen receptors [11] that makes lymphocytes primary mediators of the protective effects of estrogen. Reduction in the number of lymphocytes is one of the several effects of estrogen during pregnancy. In fact, reversible ERα-dependent thymic atrophy is a consequence of estrogen therapy and pregnancy, as determined by the loss of all thymocytes and the CD4+CD8+ population [17]. Furthermore, Singh and colleagues found that estrogen agonists mediated immunosuppression through T-cell apoptosis via activation of the Fas/FasL pathway [17]. Many studies suggest that estrogen and estrogen agonist therapy shifts the T-cell population towards the Th2 phenotype [18] and promotes Treg cells [19]. Studies show that a dominant Th1 population is associated with abortion [20] and autoimmune diseases [21] due to the proinflammatory cytokines like Interferon (IFN)-γ, Tumor Necrosis Factor (TNF)-α, IL-1 and IL6 produced by this cell type.

In contrast, a Th2 dominant phenotype results in the secretion of anti-inflammatory cytokines such as IL-4, IL-5, and Transforming Growth Factor-β3 (TGF-β3) [22]. Experimental studies on the EAE model show that estrogen mediates the amelioration of symptoms via upregulation of FoxP3 (forkhead box P3) gene, which is related to the development of CD4+ and CD25+ Treg cells. Increased number of Treg cells has been observed both during pregnancy and estrogen therapy which suggest that fetal tolerance is significantly correlated with high estrogen levels during pregnancy [19, 23, 24]. Different stages of B-cell development, such as differentiation, proliferation, and viability, are also negatively affected by estrogen leading to a reduction in the number of B-cell precursors [25]. The effects of estrogen are observed not only in bone marrow but also in the peripheral lymphoid organs.

Macrophages and dendritic cells

Macrophages and monocytes [13], as well as Dendritic Cells (DCs) [26], are also targeted by estrogen due to the expression and processing of estrogen receptors in these cells. Anti-CD3-stimulated mixture of cytokines released by lymphocytes can reduce the number of macrophages and dendritic cells in estrogen-treated animals by stimulating the expression of inducible Nitric Oxide Synthase (iNOS) and production of nitric oxide in these cells [26]. A shift towards the Th2 dominant T-cell population is responsible for decreased secretion of IL-2 and INF-γ, and increased secretion of IL-10, which suppresses Th1 development. These findings indicate that estrogen reduces the number of macrophages and DCs by altering cytokine production [27].

In contrast, Soldan et al. reported that the number of macrophages and monocytes remained intact after oral estriol treatment [28]. Another protective effect of estrogen that has been observed in the EAE animal model is the reduced ability of DCs to present antigen to myelin basic protein-specific T cells [27], which likely ameliorates the MS-like symptoms. The decreased number of dendritic cells is declared to occur with the means of p38 MAPKs due to the expression of CD40, a co-stimulatory molecule playing a significant role in the immune response of effector cells [29]. Decreased expression of TNF-α, IFN-γ, and IL-12 mRNA in DCs following estradiol treatment is another factor in improving MS [27].

Cytokines

Marked reduction in proinflammatory cytokines and increased anti-inflammatory cytokines have been observed after estrogen therapy [30, 31], mediated via the shift to the Th2 phenotype, which is also observed during pregnancy and is essential for fetal tolerance [28, 32]. Palaszynski and colleagues [19] showed that estriol treatment inhibited the secretion of IFN-γ, TNF-α, IL-2, and IL6. INF-γ is released by different cell types such as CD8+ and CD4+ T cells as well as NK cells and affects cell-mediated immunity, antiviral activity, inflammation, and autoimmune diseases [21].

Taken together, these results elucidate the impact of estrogen in shifting cytokine production towards a Th2 dominant phenotype, which suppresses cell-mediated immune response and activates the antibody-mediated immune response instead [33]. This cytokine shift is also responsible for reduced proliferation and development of T-cells, macrophages, DCs and NK cells. On the other hand, as Matejuk et al. declared, considerably suppressed expression of chemokines Regulated on Activation, Normal T Cell Expressed and Secreted (RANTES), Macrophage Inflammatory Protein (MIP)-1a, MIP-2, Induced Protein (IP)-10, and Monocyte Chemoattractant Protein (MCP)-1, chemokine receptors C-C Chemokine Receptor (CCR)1, 2, and 5 are truly responsible for decreased inflammatory cell population [34].

Neuroprotection

Estrogen has also been shown to be a neuroprotective agent [35] which can promote growth and development of neurons. The developmental effects of estrogen on adult neurons are activated post brain damage. Arvanitis et al. showed the presence of membrane-associated estrogen Receptor (mER) in the oligodendrocyte plasma membrane and within the myelin sheath [36, 37]. Furthermore, estrogen therapy rescued oligodendrocyte cytotoxicity and accelerated oligodendrocyte process formation [38, 39]. Khan and Ansar Ahmed [40]evaluated the effects of estrogen on autoimmune diseases such as MS and Systemic lupus erythematosus and concluded that estrogen had a different effect on autoimmune disease, wherein they hypothesize that estrogen does not affect immune cells.

Progesterone

Progesterone, which is a component of some OCs, is an immunomodulatory effector during pregnancy along with cortisol, vitamin D, estrogens, Early Pregnancy Factor (EPF), α-Fetoprotein, etc. Progesterone is synthesized in ovaries and placenta in females, and in the testes and adrenal cortex in males. The mitochondrial cytochrome P450scc enzyme is essential for progesterone biosynthesis and helps synthesize pregnenolone from cholesterol. Afterwards, 3b-Hydroxysteroid Dehydrogenase (3b-HSD), which is located in mitochondria and

endoplasmic reticulum, converts pregnenolone to progesterone [41].

Along with its immunomodulatory and anti-inflammatory roles via its effects on immune cells, progesterone also has neuroprotective effects. These effects are mediated by specific receptors that are present in many immune cells such as lymphocytes, monocytes, macrophages and DCs. Like estrogen, progesterone also has nuclear receptors which allow it to enter the nuclei and bind to specific Progesterone Response Elements (PREs) within the promoter region of target genes to regulate transcription. Furthermore, some membrane Progesterone Receptors (mPRs) have been recognized such as the Gamma-Aminobutyric Acid (GABA) receptor system, which also modulates the chloride ion channels [42, 43].

Thomas and Pang [44] have shown mPRs to have seven trans-membrane domains which act through cyclic Adenosine Monophosphate (cAMP). These mPRs, including mPRα, mPRβ, mPRγ, mPRδ, and mPRε, are present on the neurons in the brain [44, 45] while the nuclear receptors are selectively but not ubiquitously distributed within the brain. Studies have also indicated a beneficial impact of progesterone on CNS post injury [46]. The immunomodulatory effects of progesterone include inhibiting DCs and NK cells and steering T-cells towards a Th2 dominant phenotype [47]. The effects of progesterone on the immune and nervous system are explained in more detail in the sections below.

Lymphocytes

Th1 lymphocytes and their cytokines play major roles in many autoimmune diseases, mainly by causing inflammation. Shifting of the Th1/Th2 balance moves towards the Th2 dominant phenotype diminishes inflammation and reduces cell migration into CNS due to increased levels of anti-inflammatory cytokines. The main effects of progesterone on lymphocytes are suppression of CD4+ T-cell differentiation, modulation of the Th1/Th2 balance and increase in Treg production [48]. These effects are mediated via of the Progesterone-Induced Blocking Factor (PIBF), which shifts the Th1/Th2 balance to Th2 instead of a Th1 predominant population. PIBF targets the phospholipase A2 enzyme and inhibits arachidonic acid release that also influences NK activity and cytokine balance [49]. The Th2 cells activated by the PIBF are also responsible for the production of anti-inflammatory cytokines [50]. Progesterone also triggers the production of asymmetric antibodies by B-cells which block the binding of functional antibodies to their antigens [50, 51].

DCs and NK cells

Progesterone can modulate CD83+ DC differentiation by altering cytokine secretion. It diminishes pro-inflammatory cytokine secretion by the DCs, thereby, reducing inflammation and decreasing cell migration to CNS. Specifically, progesterone administration suppresses IL-23 secretion by the monocyte-derived DCs, and stimulates them to secrete the anti-inflammatory IL-10, IL-27, IL-8 and IL-13, which in turn block IL-12 production and stimulate the Th2 or antibody-mediated immune responses [31, 52, 53]. NK cell activity is also directly or indirectly inhibited by progesterone [47]. During pregnancy, the placenta produces high amounts of progesterone that diminishes NK-cell activity and IFN-γ production via PIBF and Major Histocompatibility Complex (MHC) I, G (HLA-G) [54, 55]. NK bustle is also significantly decreased due to PIBF which alters cytokine balance by influencing T-cell phenotype. Lower IL-12 production and secretion is correlated with PIBF production, resulting in lower NK activity [56].

Cytokines

As already mentioned, the balance between pro-inflammatory and anti-inflammatory cytokines play a crucial role in immune responses, and can be targeted to relieve the symptoms of autoimmune diseases. Progesterone induces PIBF production in lymphocytes [54, 57], which stimulates the production of Th2 dominant cytokines and promotes antibody-mediated immune response [58]. Hudi and colleagues [59] showed that lower serum concentration of PIBF and IL-10 and a higher level of proinflammatory cytokines is associated with higher risk of preterm labor. Furthermore, progesterone shifts the cytokine production in monocyte-derived DCs towards the anti-inflammatory spectrum. The inhibitory effects of progesterone on NK-cell activity and INF-γ secretion are likely due to increased IL-10 production. Munoz-Cruz et al. [58] have shown that lipopolysaccharide induced nitric oxide biosynthesis and secretion of pro-inflammatory cytokines by macrophages are inhibited by progesterone. Taken together, these findings show a highly significant function of progesterone in altering cytokine balance, which suppresses inflammation and cell migration into CNS in MS patients, and results in less myelin destruction.

Neuroprotection and Myelination

One study showed that progesterone decreased the lesion volume of cerebral brain ischemia or Traumatic Brain Injury (TBI), and also prevented the death of facial motor neurons after nerve transection [60]. It is hypothesized that the neuroprotective effects of progesterone in

Table 1. Effects of estrogen and progesterone on immune cells

Immune Cells	Contraceptives	
	Estrogen	Progesterone
Lymphocytes	Th2 dominant cell types in the immune system are resulted by sex hormones including estrogen resulting in secretion of anti-inflammatory mediator.	Th2 lymphocytes production instead of a Th1 predominant population
Dendritic cells	Reducing dendritic cells capacity to present antigen to myelin basic protein-specific T cells	Inhibition and modulation of CD83+ DC differentiation via cytokine secretion changes
Cytokines	Marked reduction in proinflammatory cytokines (TNFα, IFN-γ, and IL6) and increased anti-inflammatory cytokines (IL-4, IL-5 and TGF-B3) and inactivation of cell-mediated immune response and activated antibody-mediated immune response instead	Progesterone alters the cytokine production via monocyte-derived dendritic cells toward anti-inflammatory cytokine production (higher IL-10, IL-27, IL-8 and IL-13 along with lower IL6, IL-12 and IL-23 production).
Neuroprotection	Regulation of cholinergic neurons and regulation of synaptogenesis resulting in increased the density of dendritic spines of hypothalamic and hippocampal neurons	The presence of membrane progesterone receptors or the GABA receptor is thought to mediate some neuroprotective signaling pathways such as higher expression Bcl-2, regarded as an anti-apoptotic protein.

mammalian brain tissue is mediated either directly via the neurons or indirectly via the glial cells. The presence of membrane progesterone receptors or the GABA receptor can also trigger some neuroprotective signaling pathways, such as upregulation of the anti-apoptotic B-cell lymphoma 2 (Bcl-2) protein [61].

Progesterone is known to influence the function of glial cells that are important mediators of neuronal survival. Labombarda and colleagues have reported decreased proliferation of astrocytes and microglia by progesterone [62]. Myelination is a major defense action against MS and is controlled by various mediators. Progesterone has also been shown to activate NG2+ and O4+ Oligodendrocyte Precursor Cells (OPCs) which are the fundamental cells in myelination and myelin repair [63, 64]. Furthermore, Ghoumari et al. reported increased levels of the Myelin Basic Protein (MBP) and the mature oligodendrocyte marker 2',3'-Cyclic-Nucleotide 3'-Phosphodiesterase (CNPase) in the slice cultures of cerebellum (mixed glial cells and organotypic) in the presence of progesterone, indicating that accelerated myelination is mediated by progesterone [65].

Consistent with these reports, Hughes [66] demonstrated that low levels of progesterone would enhance IFN-α pathways in SLE which further aggravate the symptoms. Taken together, progesterone can suppress MS and rheumatoid arthritis by inhibiting the Th1 and Th17 pathways and inducing an anti-inflammatory effect. The effects of estrogen and progesterone on immune cells were summarized in Table 1.

Conclusion

Estrogen and progesterone are able to shift the immune response towards an antibody-mediated one, inhibit pro-inflammatory cytokine production, prohibit cell migration into CNS, suppress different pro-inflammatory immune cells, stabilize neuronal environment and inhibit neural death. As MS is primarily an inflammatory disease in which NK cells, cytotoxic T cells, DCs and macrophages play pivotal roles, therefor estrogen and progesterone can play role in MS. This concept can be considered as a potential therapeutic opportunity.

Ethical Considerations

Funding

This research did not receive any specific grant from funding agencies in public, commercial or not-for-profit sectors

Conflict of interest

The authors declared no conflict of interest.

References

[1] Goverman J. Autoimmune T cell responses in the central nervous system. Nat rev Immunol. 2009; 9(6):393-407. [DOI:10.1038/nri2550] [PMID] [PMCID]

[2] Hoglund RA, Maghazachi AA. Multiple sclerosis and the role of immune cells. World J Exp Med. 2014; 4(3):27-37. [DOI:10.5493/wjem.v4.i3.27] [PMID] [PMCID]

[3] Koch-Henriksen N, Sorensen PS. The changing demographic pattern of multiple sclerosis epidemiology. The Lancet

Neurol. 2010; 9(5):520-32. [DOI:10.1016/S1474-4422(10)70064-8]

[4] Jalkanen A, Alanen A, Airas L. Pregnancy outcome in women with multiple sclerosis: Results from a prospective nationwide study in Finland. Mult Scler J Exp Transl Clin. 2010; 16(8):950-5. [DOI:10.1177/1352458510372629] [PMID]

[5] Mannella P, Sanchez AM, Giretti MS, Genazzani AR, Simoncini T. Oestrogen and progestins differently prevent glutamate toxicity in cortical neurons depending on prior hormonal exposure via the induction of neural nitric oxide synthase. Steroids. 2009; 74(8):650-6. [DOI:10.1016/j.steroids.2009.02.011] [PMID]

[6] Yao J, Chen S, Cadenas E, Brinton RD. Estrogen protection against mitochondrial toxin-induced cell death in hippocampal neurons: antagonism by progesterone. Brain Res. 2011; 1379:2-10. [DOI:10.1016/j.brainres.2010.11.090] [PMID] [PMCID]

[7] Kipp M, Amor S, Krauth R, Beyer C. Multiple sclerosis: Neuroprotective alliance of estrogen-progesterone and gender. Front Neuroendocrinol. 2012; 33(1):1-16. [DOI:10.1016/j.yfrne.2012.01.001] [PMID]

[8] Ghayee HK, Auchus RJ. Basic concepts and recent developments in human steroid hormone biosynthesis. Rev Endocr Metab Disord. 2007; 8(4):289-300. [DOI:10.1007/s11154-007-9052-2] [PMID]

[9] Airas L. Hormonal and gender-related immune changes in multiple sclerosis. Acta Neurol Scand. 2015; 132(S199):62-70. [DOI:10.1111/ane.12433] [PMID]

[10] Micevych PE, Kelly MJ. Membrane estrogen receptor regulation of hypothalamic function. J Neuroendocrinol. 2012; 96(2):103-10. [DOI:10.1159/000338400]

[11] Gustafsson JA. Novel aspects of estrogen action. J Soc Gynecol Invest. 2000; 7(1 Suppl):S8-9. [DOI:10.1016/S1071-5576(99)00060-X] [PMID]

[12] Mor G, Sapi E, Abrahams VM, Rutherford T, Song J, Hao XY, et al. Interaction of the estrogen receptors with the Fas ligand promoter in human monocytes. J Immunol. 2003; 170(1):114-22. [DOI:10.4049/jimmunol.170.1.114]

[13] Lang TJ. Estrogen as an immunomodulator. Clin Immunol. 2004; 113(3):224-30. [DOI:10.1016/j.clim.2004.05.011] [PMID]

[14] Voskuhl R, Wang H, Elashoff RM. Why use sex hormones in relapsing-remitting multiple sclerosis?–Authors' reply. Lancet Neurol. 2016; 15(8):790-1. [DOI:10.1016/S1474-4422(16)00129-0]

[15] Polanczyk M, Zamora A, Subramanian S, Matejuk A, Hess DL, Blankenhorn EP, et al. The protective effect of 17β-estradiol on experimental autoimmune encephalomyelitis is mediated through estrogen receptor-α. Am J Pathol. 2003; 163(4):1599-605. [DOI:10.1016/S0002-9440(10)63516-X]

[16] Cunningham M, Gilkeson G. Estrogen receptors in immunity and autoimmunity. Clin Rev Allergy Immunol. 2011; 40(1):66-73. [DOI:10.1007/s12016-010-8203-5] [PMID]

[17] Singh NP, Singh UP, Nagarkatti PS, Nagarkatti M. Prenatal exposure of mice to diethylstilbestrol disrupts T-cell differentiation by regulating Fas/Fas ligand expression through estrogen receptor element and nuclear factor-κB motifs. J Pharmacol Exp Ther. 2012; 343(2):351-61. [DOI:10.1124/jpet.112.196121] [PMID] [PMCID]

[18] Soldan SS, Retuerto AIA, Sicotte NL, Voskuhl RR. Immune modulation in multiple sclerosis patients treated with the pregnancy hormone estriol. J Immunol. 2003; 171(11):6267-74. [DOI:10.4049/jimmunol.171.11.6267] [PMID]

[19] Palaszynski KM, Liu H, Loo KK, Voskuhl RR. Estriol treatment ameliorates disease in males with experimental autoimmune encephalomyelitis: Implications for multiple sclerosis. J Neuroimmunol. 2004; 149(1-2):84-9. [DOI:10.1016/j.jneuroim.2003.12.015] [PMID]

[20] Dunn SE, Steinman L. The gender gap in multiple sclerosis: intersection of science and society. JAMA Neurol. 2013; 70(5):634-5. [DOI:10.1001/jamaneurol.2013.55] [PMID]

[21] Young HA, Bream JH. IFN-gamma: Recent advances in understanding regulation of expression, biological functions, and clinical applications. Curr Top Microbiol Immunol. 2007; 316:97-117. [DOI:10.1007/978-3-540-71329-6_6] [PMID]

[22] Laffont S, Garnier L, Lélu K, Guéry J-C. Estrogen-mediated protection of experimental autoimmune encephalomyelitis: Lessons from the dissection of estrogen receptor-signaling in vivo. Biomed J. 2015; 38(3):194-205. [DOI:10.4103/2319-4170.158509] [PMID]

[23] Polanczyk MJ, Carson BD, Subramanian S, Afentoulis M, Vandenbark AA, Ziegler SF, et al. Cutting edge: Estrogen drives expansion of the CD4+CD25+ regulatory T cell compartment. J Immunol. 2004; 173(4):2227-30. [DOI:10.4049/jimmunol.173.4.2227]

[24] Polanczyk MJ, Hopke C, Huan J, Vandenbark AA, Offner H. Enhanced FoxP3 expression and Treg cell function in pregnant and estrogen-treated mice. J Neuroimmunol. 2005; 170(1-2):85-92. [DOI:10.1016/j.jneuroim.2005.08.023] [PMID]

[25] Nordqvist J, Bernardi A, Islander U, Carlsten H. Effects of a tissue-selective estrogen complex on B lymphopoiesis and B cell function. Immunobiol. 2017; 222(8):918-23. [DOI:10.1016/j.imbio.2017.05.013] [PMID]

[26] You HJ, Kim JY, Jeong HG. 17 beta-estradiol increases inducible nitric oxide synthase expression in macrophages. Biochem Biophys Res Commun. 2003; 303(4):1129-34. [DOI:10.1016/S0006-291X(03)00477-7]

[27] Liu HY, Buenafe AC, Matejuk A, Ito A, Zamora A, Dwyer J, et al. Estrogen inhibition of EAE involves effects on dendritic cell function. J Neurosci Res. 2002; 70(2):238-48. [DOI:10.1002/jnr.10409] [PMID]

[28] Soldan SS, Alvarez Retuerto AI, Sicotte NL, Voskuhl RR. Immune modulation in multiple sclerosis patients treated with the pregnancy hormone estriol. J Immunol. 2003; 171(11):6267-74. [DOI:10.4049/jimmunol.171.11.6267]

[29] Xie H, Hua C, Sun L, Zhao X, Fan H, Dou H, et al. 17beta-estradiol induces CD40 expression in dendritic cells via MAPK signaling pathways in a minichromosome maintenance protein 6-dependent manner. Arthritis Rheum. 2011; 63(8):2425-35. [DOI:10.1002/art.30420] [PMID]

[30] Ito A, Bebo BF, Jr., Matejuk A, Zamora A, Silverman M, Fyfe-Johnson A, et al. Estrogen treatment down-regulates TNF-alpha production and reduces the severity of experimental autoimmune encephalomyelitis in cytokine knockout

mice. J Immunol. 2001; 167(1):542-52. [DOI:10.4049/jimmunol.167.1.542]

[31] Whitacre CC. Sex differences in autoimmune disease. Nat Immunol. 2001; 2(9):777-80. [DOI:10.1038/ni0901-777] [PMID]

[32] Whitacre CC, Reingold SC, O'Looney PA. A gender gap in autoimmunity. Sci. 1999; 283(5406):1277-8. [DOI:10.1126/science.283.5406.1277] [PMID]

[33] Formby B. Immunologic response in pregnancy. Its role in endocrine disorders of pregnancy and influence on the course of maternal autoimmune diseases. Endocrinol Metab Clin North Am. 1995; 24(1):187-205. [PMID]

[34] Matejuk A, Adlard K, Zamora A, Silverman M, Vandenbark AA, Offner H. 17 beta-estradiol inhibits cytokine, chemokine, and chemokine receptor mRNA expression in the central nervous system of female mice with experimental autoimmune encephalomyelitis. Journal of neuroscience research. 2001;65(6):529-42. [DOI:10.1002/jnr.1183] [PMID]

[35] Czlonkowska A, Ciesielska A, Joniec I. Influence of estrogens on neurodegenerative processes. Med Sci Monit: Int Med J of Exp and Clin Res. 2003; 9(10):RA247-56. [PMID]

[36] Arvanitis DN, Wang H, Bagshaw RD, Callahan JW, Boggs JM. Membrane-associated estrogen receptor and caveolin-1 are present in central nervous system myelin and oligodendrocyte plasma membranes. J Neurosci Res. 2004; 75(5):603-13. [DOI:10.1002/jnr.20017] [PMID]

[37] Offner H. Neuroimmunoprotective effects of estrogen and derivatives in experimental autoimmune encephalomyelitis: therapeutic implications for multiple sclerosis. J Neurosci Res. 2004; 78(5):603-24. [DOI:10.1002/jnr.20330] [PMID]

[38] Takao T, Flint N, Lee L, Ying X, Merrill J, Chandross KJ. 17beta-estradiol protects oligodendrocytes from cytotoxicity induced cell death. J Neurochem. 2004; 89(3):660-73. [DOI:10.1111/j.1471-4159.2004.02370.x] [PMID]

[39] Zhang Z, Cerghet M, Mullins C, Williamson M, Bessert D, Skoff R. Comparison of in vivo and in vitro subcellular localization of estrogen receptors alpha and beta in oligodendrocytes. J Neurochem. 2004; 89(3):674-84. [DOI:10.1111/j.1471-4159.2004.02388.x] [PMID]

[40] Khan D, Ansar Ahmed S. The immune system is a natural target for estrogen action: Opposing effects of estrogen in two prototypical autoimmune diseases. Front Immunol. 2016; 6:635. [DOI:10.3389/fimmu.2015.00635] [PMID] [PMCID]

[41] Cherradi N, Chambaz EM, Defaye G. Organization of 3 beta-hydroxysteroid dehydrogenase/isomerase and cytochrome P450scc into a catalytically active molecular complex in bovine adrenocortical mitochondria. The Journal of steroid biochemistry and molecular biology. 1995; 55(5-6):507-14. [DOI:10.1016/0960-0760(95)00199-9]

[42] Bixo M, Johansson M, Timby E, Michalski L, Bäckström T. Effects of GABA active steroids in the female brain with focus on the premenstrual dysphoric disorder. J Neuroendocrinol. 2018; 30(2):e12553. [DOI:10.1111/jne.12553]

[43] Runyon SP, Rogawski M, Cook E, Kepler J, Navarro H, Kaminski R, et al. Androstane and pregnane steroids with potent allosteric GABA receptor chloride ionophore modulating properties. [Internet]. 2014 [Updated 2014 April 03]. Available from: http://www.freepatentsonline.com/20140094619.pdf

[44] Thomas P, Pang Y. Membrane progesterone receptors: evidence for neuroprotective, neurosteroid signaling and neuroendocrine functions in neuronal cells. Neuroendocrinol. 2012; 96(2):162-71. [DOI:10.1159/000339822] [PMID] [PMCID]

[45] Pang Y, Dong J, Thomas P. Characterization, neurosteroid binding and brain distribution of human membrane progesterone receptors delta and {epsilon} (mPRdelta and mPR{epsilon}) and mPRdelta involvement in neurosteroid inhibition of apoptosis. Endocrinol. 2013; 154(1):283-95. [DOI:10.1210/en.2012-1772] [PMID] [PMCID]

[46] Stein DG. Brain damage, sex hormones and recovery: A new role for progesterone and estrogen? Trends Neurosci. 2001; 24(7):386-91. [DOI:10.1016/S0166-2236(00)01821-X]

[47] Szekeres-Bartho J, Halasz M, Palkovics T. Progesterone in pregnancy; receptor-ligand interaction and signaling pathways. J Reprod Immunol. 2009; 83(1-2):60-4. [DOI:10.1016/j.jri.2009.06.262] [PMID]

[48] Munoz-Cruz S, Togno-Pierce C, Morales-Montor J. Non-reproductive effects of sex steroids: their immunoregulatory role. Curr Top Med Chem. 2011; 11(13):1714-27. [DOI:10.2174/156802611796117630] [PMID]

[49] Lu J, Reese J, Zhou Y, Hirsch E. Progesterone-induced activation of membrane-bound progesterone receptors in murine macrophage cells. J Endocrinol. 2015; 224(2):183-94. [DOI:10.1530/JOE-14-0470] [PMID] [PMCID]

[50] Druckmann R, Druckmann MA. Progesterone and the immunology of pregnancy. J Steroid Biochem Mol Biol. 2005; 97(5):389-96. [DOI:10.1016/j.jsbmb.2005.08.010] [PMID]

[51] Ivanova-Todorova E, Kyurkchiev DS, Nalbanski A, Timeva T, Shterev A, Kyurkchiev SD. Production and characterization of a novel monoclonal antibody against progesterone-induced blocking factor (PIBF). Journal of reproductive immunology. 2008; 78(2):94-101. [DOI:10.1016/j.jri.2007.12.001] [PMID]

[52] Verthelyi D. Sex hormones as immunomodulators in health and disease. Int Immunopharmacol. 2001; 1(6):983-93. [DOI:10.1016/S1567-5769(01)00044-3]

[53] Ivanova E, Kyurkchiev D, Altankova I, Dimitrov J, Binakova E, Kyurkchiev S. CD83 monocyte-derived dendritic cells are present in human decidua and progesterone induces their differentiation in vitro. Am J Reprod Immunol. 2005; 53(4):199-205. [DOI:10.1111/j.1600-0897.2005.00266.x] [PMID]

[54] Szekeres-Bartho J, Wegmann TG. A progesterone-dependent immunomodulatory protein alters the Th1/Th2 balance. J Reprod Immunol. 1996; 31(1-2):81-95. [DOI:10.1016/0165-0378(96)00964-3]

[55] Carosella ED, Gregori S, Rouas-Freiss N, LeMaoult J, Menier C, Favier B. The role of HLA-G in immunity and hematopoiesis. Cell Mol Life Sci. 2011; 68(3):353-68. [DOI:10.1007/s00018-010-0579-0] [PMID]

[56] Kumar A, Begum N, Prasad S, Aggarwal S, Sharma S. Oral dydrogesterone treatment during early pregnancy to prevent recurrent pregnancy loss and its role in modulation of cytokine production: a double-blind, randomized, parallel, placebo-controlled trial. Fertil Steril. 2014; 102(5):1357-63.e3. [DOI:10.1016/j.fertnstert.2014.07.1251]

[57] Par G, Bartok B, Szekeres-Bartho J. Cyclooxygenase is involved in the effects of progesterone-induced blocking factor on the production of interleukin 12. Am J Obstet Gynecol. 2000; 183(1):126-30. [DOI:10.1067/mob.2000.105742]

[58] Piccinni MP, Giudizi MG, Biagiotti R, Beloni L, Giannarini L, Sampognaro S, et al. Progesterone favors the development of human T helper cells producing Th2-type cytokines and promotes both IL-4 production and membrane CD30 expression in established Th1 cell clones. J Immunol. 1995; 155(1):128-33. [PMID]

[59] Hudic I, Fatusic Z, Szekeres-Bartho J, Balic D, Polgar B, Ljuca D, et al. Progesterone-induced blocking factor and cytokine profile in women with threatened pre-term delivery. Am J Reprod Immunol. 2009; 61(5):330-7. [DOI:10.1111/j.1600-0897.2009.00699.x] [PMID]

[60] Gibson CL, Gray LJ, Bath PM, Murphy SP. Progesterone for the treatment of experimental brain injury; a systematic review. Brain. 2007; 131(2):318-28. [DOI:10.1093/brain/awm183] [PMID]

[61] Nilsen J, Brinton RD. Impact of progestins on estrogen-induced neuroprotection: synergy by progesterone and 19-norprogesterone and antagonism by medroxyprogesterone acetate. Endocrinol. 2002; 143(1):205-12. [DOI:10.1210/endo.143.1.8582] [PMID]

[62] Labombarda F, Gonzalez S, Lima A, Roig P, Guennoun R, Schumacher M, et al. Progesterone attenuates astro- and microgliosis and enhances oligodendrocyte differentiation following spinal cord injury. Exp Neurol. 2011; 231(1):135-46. [DOI:10.1016/j.expneurol.2011.06.001] [PMID]

[63] Ghoumari AM, Baulieu EE, Schumacher M. Progesterone increases oligodendroglial cell proliferation in rat cerebellar slice cultures. Neurosci. 2005; 135(1):47-58. [DOI:10.1016/j.neuroscience.2005.05.023] [PMID]

[64] Zawadzka M, Franklin RJ. Myelin regeneration in demyelinating disorders: new developments in biology and clinical pathology. Curr Opin Neurol. 2007; 20(3):294-8. [DOI:10.1097/WCO.0b013e32813aee7f] [PMID]

[65] Ghoumari AM, Ibanez C, El-Etr M, Leclerc P, Eychenne B, O'Malley BW, et al. Progesterone and its metabolites increase myelin basic protein expression in organotypic slice cultures of rat cerebellum. J Neurochem. 2003; 86(4):848-59. [DOI:10.1046/j.1471-4159.2003.01881.x] [PMID]

[66] Hughes GC. Progesterone and autoimmune disease. Autoimmun Rev. 2012; 11(6-7):A502-A14. [DOI:10.1016/j.autrev.2011.12.003] [PMID] [PMCID]