International Journal of Women's Health

Dovepress
open access to scientific and medical research

Open Access Full Text Article

REVIEW

Impact of Menopause in Patients with Multiple Sclerosis: Current Perspectives

Lorena Lorefice[1], Maurizio Nicola D'Alterio[2], Davide Firinu[3], Giuseppe Fenu[4], Eleonora Cocco[1]

[1]Multiple Sclerosis Center, Binaghi Hospital, ASL Cagliari, Department of Medical Sciences and Public Health, University of Cagliari, Cagliari, Italy; [2]Division of Gynecology and Obstetrics, Department of Surgical Sciences, University of Cagliari, Cagliari, Italy; [3]Clinical Immunology, Department of Medical Sciences and Public Health, University of Cagliari, Cagliari, Italy; [4]Department of Neurosciences, ARNAS Brotzu, Cagliari, Italy

Correspondence: Lorena Lorefice, Multiple Sclerosis Center, Binaghi Hospital, ASL Cagliari, Department of Medical Sciences and Public Health, University of Cagliari, via Is Guadazzonis 2, Cagliari, 09126, Italy, Email lorena.lorefice@hotmail.it

International Journal of Women's Health downloaded from https://www.dovepress.com/
For personal use only.

Abstract: Given the aging population, with a peak age-specific prevalence that is shifting beyond the age of 50, several women currently living with MS are very close to menopause. Menopause is usually characterized by several specific symptoms with adverse impacts on different aspects of a woman's quality of life, such as fatigue, and cognitive, mood and bladder disorders, which overlap with symptoms of MS. Generally, after this biological transition, women with MS appear to be subject to less inflammatory activity. However, several studies have reported an increase of disability accumulation after menopause, suggesting that it is a turning point to a more progressive phase of the disease. This may be attributable to the hormonal and immunological changes associated with menopause, with several effects on neuroinflammation and neurodegeneration increasing due to the immunosenescence of aging. This review summarizes the hormonal and immunological changes associated with menopause, detailing the effects on MS symptoms, outcomes, and the aging process. Furthermore, possible interventions to improve patients' quality of life are evaluated. In fact, it is increasingly necessary to improve the global management of MS women, as well as their lives, at this multifaceted turning point.

Keywords: multiple sclerosis, menopause, hormone therapy, aging, best practice

Introduction

Multiple sclerosis (MS) is an inflammatory demyelinating and neurodegenerative disease of the central nervous system (CNS) whose pathogenesis is notoriously determined by genetic predisposition, environmental exposure, sex hormones and lifestyle.[1] A ubiquitous finding in epidemiological studies is the increased prevalence of MS in women as compared to men, in line with the female preponderance observed in a variety of other autoimmune diseases.[2] Several studies have shown that the higher female-to-male sex ratio declines with increasing age at MS onset, despite increased rates of late-onset MS having been found among women.[3,4] In addition to susceptibility to the disease, sex differences may play a role in the course of MS, as the most severe disability outcomes and progression occur in men.[5] This may reflect how sex differences influence both the immune response and neurodegeneration.[6] However, it should be noted that the mechanisms underlying sex differences in MS are many and complex, and the hormonal aspects only explain a part of them.[7] Sex hormones, fluctuations of their levels during the different physiological stages of the reproductive lives of women (puberty, fertile life, pregnancy, puerperium and menopause) and men (puberty, fertile life and andropause) appear to influence MS progression and prognosis.[8] However, while several studies have evaluated the risk and prognosis of MS in women during menarche, pregnancy and the postpartum period,[9–11] few studies have investigated the effects of menopause.

Menopause is a physiological event during a woman's life that marks the end of reproductive competence. Given the high numbers of MS women among the aging population, it is extremely important to understand the effects of menopause, and how it interacts with MS. To this end, this review summarizes the hormonal and immunological changes associated with menopause, detailing the effects on MS symptoms and outcomes, and evaluating possible interventions for the optimal management of women who cross this biological turning point.

Received: 30 August 2022
Accepted: 18 January 2023
Published: 25 January 2023

© 2023 Lorefice et al. This work is published and licensed by Dove Medical Press Limited. The full terms of this license are available at https://www.dovepress.com/terms.php and incorporate the Creative Commons Attribution – Non Commercial (unported, v3.0) License (http://creativecommons.org/licenses/by-nc/3.0/). By accessing the work you hereby accept the Terms. Non-commercial uses of the work are permitted without any further permission from Dove Medical Press Limited, provided the work is properly attributed. For permission for commercial use of this work, please see paragraphs 4.2 and 5 of our Terms (https://www.dovepress.com/terms.php).

Biological Changes in Menopause and Symptoms

Natural menopause is the irreversible interruption of menstruation and the latter phase of ovarian physiology, representing a period when the reproductive function is lost due to the total decline of the limited ovarian follicle supply.[12] It occurs in the sixth decade of life in the general population, with the median age around 51 years.

The menopausal transition, also known as perimenopause, is based on a changing pattern of ovulation and anovulation in the years preceding menopause. While the underlying process of menopause is linked to ovarian senescence, the hypothalamic-pituitary ovarian-uterine axis changes with time in several ways,[13] until post-menopausal condition that results in high level of FSH and an ovarian reserve ranging from very low to undetectable.[14] The revolutionary hormone research of the Study of Women's Health Across the Nation (SWAN) have previously investigated reproductive hormone variations, menstrual cycles, and symptom characteristics throughout menopausal transitions.[13] This transition starts with an erratic increase in estradiol secretions,[15] then the ovary becomes less sensitive to gonadotropin stimulation, resulting in lower estradiol production. Next to this, LH stimulation is attenuated and insufficient for ovulation, resulting in progestogen loss.[14] The estradiol declines, that begin two years prior and continuing for two years following the final menstrual period,[16] are frequently associated with a variety of symptoms impacting various aspects of a woman's quality of life.[17] Menopause is usually marked by vasomotor symptoms, including hot flashes, sweating, tremors and a sense of coldness.[18] The primary proposed mechanism driving vasomotor symptoms is the change in thermoregulation due to the brain's stress reaction to the hormonal cycle's transitions, with changes in the activity of noradrenergic and serotoninergic pathways.[19] Mood and cognitive disorders, as well as migraines, are also frequent during perimenopause. The estradiol-dependent stimulation of estrogen receptors in the hippocampus and prefrontal cortex can affect the synthesis and secretion of neurotransmitters (such as serotonin, dopamine, and gamma-aminobutyric acid equilibrium) and synaptic activity.[20,21] Moreover, several human and animal studies have previously demonstrated the protective effects of estrogen on neuronal survival,[22] with the evolution of neurodegenerative processes such as brain atrophy occurring as their levels drop.[23] Despite a significant reduction in estrogen levels, the menopausal ovary keeps producing high androgen levels for years following menopause, with several systemic effects, including the deposition of body fat.[24] Estrogen deficiency after menopause also facilitates the onset of osteoporosis, with decreased bone mineral index and changed bone architecture.[25] In the end, urogenital symptoms such as vaginal dryness, dyspareunia, vulvar itching and burning, dysuria, urine frequency and urgency, and recurrent lower urinary tract infections are common after menopause.[26]

Finally, a separate discussion should be devoted to surgical menopause (iatrogenic menopause) that happens when both ovaries are removed before the natural "switching off" of their function. Premature ovarian insufficiency may emerge with a menopause that occurs before the age of 40. Surgical menopause is also associated with a sudden reduction of ovarian sex steroid production rather than a gradual decrease as is the case in natural menopause, with more rapid hormonal, immunological and clinical changes.[27]

Immunosenescence and Immunological Effect of Menopause

During aging the immune system undergoes notable changes that collectively are known as immunosenescence. This is characterised by a decline in the immune response, with a decrease in the number of naive T and B cells, NK cells, and a disruption of the pro- and anti-inflammatory balance.[28] This is associated with a chronic inflammatory process with persistent production of proinflammatory mediators – the "inflamm-aging"- that increases the risk for morbidity and mortality related to age, affecting responses to infections and autoimmunity.[29]

Biological transitions, of which menopause is a primary example, can mark the ageing of the immune system, which is also conditioned by a series of other factors (chronic disorders, lifestyle, environmental, epigenetic factors, and infections).[30] Besides age, in postmenopausal women, the immunological changes are driven by estrogen deprivation, resulting in increased pro-inflammatory serum markers, an increasing response of the body's cells to cytokines, a decrease in CD4 T, B lymphocytes and cytotoxic activity of NK cells with higher susceptibility to pathogenic invasion and infection. In addition, postmenopausal women show higher chronic levels of pro-inflammatory cytokines MCP1, TNFα, and IL-6.[31] Among these, IL-6 is also a key factor in bone reabsorption by osteoclast activation, and is related to other diseases particularly common in menopause, ie diabetes, atherosclerosis and cardiovascular diseases.[32] Therefore, inflammatory states further shape T cell responses, resulting in CD4+T cell subset reductions in menopausal women,

inversion in the CD4/CD8 ratio, which is indicative of aging and associated with increased oxidative stress.[33] In addition, during aging it is also observed that immune systems decline to mount an effective response against neoplastic cells due, in particular, to a deficiency in adaptive immunity.[34] An increased susceptibility to tumors related to aging is therefore observed, facilitated also by immunological changes related to menopause.[35]

Effect of Menopause on MS Course and MS Symptoms

Menopause is associated with a series of biological hormonal and immunological changes that can affect the pathogenetic mechanisms of MS, influencing the susceptibility as well as the course of the disease.[36] On the other hand, while MS does not affect the onset of menopause, some MS immunotherapies have been identified as associated with this risk.[37] Among these, the FEMIMS (FErtility and Mitoxantrone In MS) study showed that the probability of permanent amenorrhea or menopause was proportionally related to the age of patients at mitoxantrone administration and that it also increased with the cumulative dose of this drug.[38] This raised the important issue of the impact of this, as well as of other immunosuppressive drugs previously extensively used for MS (ie cyclophosphamide), on fertility, hormonal balance, ovarian functioning, and the biological transitions of treated MS women.[38]

Focusing on menopause transitions, little is known about the risk of developing MS in relation to this biological phase, while the effects of this reproductive transition on the evolution of the disease have been more explored.[39–42] Bove at al. showed that, in comparison to MS onset prior to 50, in MS onset after 50, the disease trajectories of women are more similar to those of men, suggesting a possible effect associated with age (and perhaps menopause).[43] Several observational studies have also indicated a reduction in the sex differences of disability progression, usually more marked in males, in individuals with MS after age 50. Thus, the course of the disease after menopause appears to be more similar to the course of the disease in men in which MS is notoriously more aggressive. An extensive study including 3028 men and 6619 women showed that MS women have more inflammatory disease activity in terms of relapses than men up to the age of menopause, with a weighted female: male relapse rate ratio of 1.16 (95% CI: 1.10 to 1.22). After the age of 50 years the difference disappears, and the evolution of disability worsens, becoming more similar in the two sexes.[44] Regarding disease activity, after menopause a significantly decreasing annualized relapse rate (ARR) (from 0.21±0.31 to 0.13± 0.24; $p = 0.005$) was reported by Baroncini et al, while disability was found to worsen, with EDSS score increasing by 0.2 ± 0.6 points before the final menstrual period and by 0.4 ± 0.7 points afterwards ($p = 0.014$).[39] Therefore, these findings are in line with preliminary research involving 124 women followed for a mean of 10.4 years through their menopausal transition, that has revealed a mild worsening of disability after menopause, with the rate of EDSS change increasing from 0.051 units per year before menopause, to 0.13 units per year after menopause (difference of 0.076 units; 95% CI: 0.010, 0.14, $p = 0.024$).[40] Consistent with these findings, menopause is identified by some authors as associated with an increase in the accumulation rate of disability, suggesting that it is a turning point to a more progressive phase of MS. This is believed to be attributable to a worsening of neurodegenerative processes rather than to the inflammatory activity of MS. However, the effects of menopause on the neuroradiological parameters of MS have been insufficiently explored. With regard to this latter point, a longitudinal study involving women with MS and healthy controls has recently shown that the anti-Mullerian hormone (AMH), typically considered to be an objective indicator of ovarian aging, is associated with greater total gray and cortical gray matter loss, independent of chronological age and disease duration.[45] This may be attributable to accelerated neurodegenerative processes and a decrease of the repair mechanisms resulting from the loss of ovarian estrogen,[46] in addition to other age-related determinants of disease evolution, and unrelated MS factors, such as comorbidities.[47,48] Contrary to studies that support the hypothesis of menopause as a turning point, Ladeira et al followed a longitudinal cohort of 37 MS women older than 44 years and obtained a picture of stable neuroradiological disability during menopause and a reduction of the annualized relapse rate.[41] On the other hand, the disability trajectories (change in annual EDSS) of 77 women in a Barcelona CIS cohort followed longitudinally did not change significantly during the menopausal transition.[42] These recent findings, therefore, fuel the debate on the impact of menopause on MS evolution, raising attention to other modifying factors, such as general health and lifestyle.

Several studies have reported a worsening of MS symptoms at menopause, by using several tools (questionnaires, online patient platforms, qualitative interviews).[49,50] A Swedish study investigated MS women's perceptions of severity

after menopause, by using an ad hoc questionnaire. They reported a worsening of MS symptoms in 40%, no change of symptoms in 56%, and decreased symptoms in 5% of cases.[49] However, Bove R. et al investigated the patient-reported impact of menopause by using a large online research platform. They found that the postmenopausal state was associated with a worsening of patient-reported severity scores on seven functional areas based on the MS Rating Scale, even those not typically overlapping with menopausal symptoms.[50] Among the most increased symptoms in post-menopause, was fatigue, affective disorders (anxiety and depression), urologic (bladder irritability and incontinence) and sexual symptoms.[8] Commonly in MS, fatigue tends to increase in severity and frequency during menopause, often limiting daily activities. Therefore, this symptom can be amplified by vasomotor menopausal symptoms, triggering Uhthoff's phenomenon and often co-existing with other symptoms, thus complicating their interpretation for the clinician who may view them as pseudo-relapses. It has also been noted that perimenopause is a period of vulnerability, often associated with the onset or worsening of affective symptoms (anxiety and depression), and effects on functioning in several areas, with detrimental consequences on patients' lives.[51] Analogously, with menopause, women may report changes in attention, memory, and cognitive performance, symptoms already frequent in people who age with MS.[52] Thus, menopausal and MS symptoms, as well as their overlapping effects, may impact the quality of life (QoL) of patients who are already enduring a stressful period, with multifaceted implications for their lives. Moreover, the postmenopausal period leads to an increased susceptibility to several comorbidities (ie osteoporosis and vascular comorbidities), which make this phase even more fragile,[53] and brain damage more enhanced.[47,48]

HRT Use in MS

Hormone replacement therapy (HRT) consists of estrogen therapy or combined estrogen–progestogen therapy, administered either orally, vaginally or trans-dermally.[54] HRT has been proven to alleviate many menopausal symptoms, with a reasonably good safety profile and positive effects on health-related QOL in symptomatic menopausal women. Improvement in MS symptoms and quality of life (QOL) was found in postmenopausal MS patients receiving HRT.[55] In particular, HRT is effective for menopause-related vasomotor symptoms, an overactive bladder, and symptoms of vulvar and vaginal atrophy. Additional effects on bone mineral density, and a reduction of the risk of osteoporotic fractures have also been described.[54] Recently, systemic HRT use was associated with a better physical QOL in postmenopausal MS women, with significantly better patient-reported physical functioning scores.[55] In particular, HT users had higher points than non–HT users in a physical functioning evaluation measured by means of the 10-item physical functioning assessment (PF10) subscale of the 36-Item Short Form Health Survey, with the longer duration of HT use associated with higher performances.[55,56] The current recommendation from the North American Menopause Society (NAMS) is that individualized HRT treatment be considered on the basis of a patient's risk profile, and to treat symptoms for the shortest possible duration and at the lowest possible dose.[57] In fact, there are several risks, such as breast cancer, when progestogens are given with estrogens, and venous thrombosis, despite a reduced risk of cardiovascular disease, has been reported.[58] More careful considerations are to be made for patients with MS, whose risk profile may be different from that of the general population. Consideration should be given to the history of disease modifying treatments and related risks, as well as to the patient's susceptibility to other comorbidities.[59] All aspects that increase the complexity of MS management in women need to be assessed with appropriate screening.

While the effects of HRT on overlapping menopause and MS symptoms have been evaluated, little is known about its effects on the course of MS and long-term outcomes. A neuroprotective effect of HRT has recently been hypothesized in healthy women, as indicated by a study showing improved cognition when HRT was started within a 5-year window of the final menstrual period.[60] Exogenous hormones may impact the disease course via their effects on neurodegeneration and neuroprotection,[61] although research has been limited in aging populations. HRT may also delay immunosenescence, partially reversing the deleterious effects of aging on the immune system.[62] In line with this point, a higher number of B-cells and improved T-cell function are described in HRT users, as well as the reduced plasma levels of several pro-inflammatory cytokines.[63] However, the choice of HRT use in MS women must necessarily weigh the benefits in terms of QOL and aspects related to safety, after an attentive discussion by a gynecologist and neurologist.

Conclusions

Given that the aging population, with peak age-specific prevalence in Europe and Northern America, is increasing from 40 years onwards,[64] there are several women who currently live with MS and who are very close to menopause. It is, therefore, urgent to understand the impact of menopause on the course of MS, and of how it interacts with this disease. As described, growing evidence indicates a worsening of disability and neurodegenerative aspects in postmenopausal MS women, although both phenomena are worsened by aging. Further studies are needed to evaluate and discriminate the clinical, neuroradiological and immunological effects related to menopause, with those induced by aging, as well as the effects of sex on aging with MS, immunosenescence, and brain resilience. The comprehensive care of postmenopausal MS women, including lifestyle optimization, a thoughtful choice of HRT that considers benefits and risks and the history of disease modifying treatments, and treatments of other age-related and menopausal-related comorbidities, is increasingly necessary to improve the global management of MS women, as well as of their lives at this multifaceted turning point.

Disclosure

The authors report no conflicts of interest in this work. Eleonora Cocco reports grants, personal fees, and non-financial support from Biogen and Merck; personal fees and non-financial support from Novartis; grants from Roche; and personal fees from Genzyme, outside the submitted work.

References

1. Filippi M, Bar-Or A, Piehl F., et al. Multiple sclerosis. *Nat Rev Dis Primers*. 2018;4(1):43. doi:10.1038/s41572-018-0041-4
2. Whitacre CC. Sex differences in autoimmune disease. *Nat Immunol*. 2001;2:777–780. doi:10.1038/ni0901-777
3. Koch-Henriksen N, Thygesen LC, Stenager E, et al. Incidence of MS has increased markedly over six decades in Denmark particularly with late onset and in women. *Neurology*. 2018;90(22):e1954–63. doi:10.1212/WNL.0000000000005612
4. Prosperini L, Lucchini M, Ruggieri S, et al. Shift of multiple sclerosis onset towards older age. *J Neurol Neurosurg Psychiatry*. 2022;jnnp-2022–329049.
5. Kalincik T, Vivek V, Jokubaitis V, et al. Sex as a determinant of relapse incidence and progressive course of multiple sclerosis. *Brain*. 2013;136:3609–3617. doi:10.1093/brain/awt281
6. Ramien C, Taenzer A, Lupu A, et al. Sex effects on inflammatory and neurodegenerative processes in multiple sclerosis. *Neurosci Biobehav Rev*. 2016;67:137–146. doi:10.1016/j.neubiorev.2015.12.015
7. Golden LC, Voskuhl R. The importance of studying sex differences in disease: the example of multiple sclerosis. *J Neurosci Res*. 2017;95(1–2):633–643. doi:10.1002/jnr.23955
8. Bove R, Chitnis T. The role of gender and sex hormones in determining the onset and outcome of multiple sclerosis. *Mult Scler*. 2014;20(5):520–526. doi:10.1177/1352458513519181
9. Azimi A, Hanaei S, Sahraian MA. Age at menarche and risk of multiple sclerosis (MS): a systematic review and meta-analysis. *BMC Neurol*. 2019;19(1):286. doi:10.1186/s12883-019-1473-5
10. Lorefice L, Fronza M, Fenu G. Effects of Pregnancy and Breastfeeding on Clinical Outcomes and MRI Measurements of Women with Multiple Sclerosis: an Exploratory Real-World Cohort Study. *Neurol Ther*. 2022;11(1):39–49. doi:10.1007/s40120-021-00297-6
11. Zuluaga MI, Otero-Romero S, Rovira A, et al. Menarche, pregnancies, and breastfeeding do not modify long-term prognosis in multiple sclerosis. *Neurology*. 2019;92(13):e1507–e1516. doi:10.1212/WNL.0000000000007178
12. Santoro N. The menopausal transition. *Am J Med*. 2005;118(Suppl12B):8–13. doi:10.1016/j.amjmed.2005.09.008
13. Santoro N, Crawford SL, El Khoudary SR, et al. Menstrual cycle hormone changes in women traversing menopause: study of women's health across the nation. *J Clin Endocrinol Metab*. 2017;102(7):2218–2229. doi:10.1210/jc.2016-4017
14. Harlow SD. Executive summary of the stages of reproductive aging workshop +10: addressing the unfinished agenda of staging reproductive aging. *Menopause*. 2012;19:387–395. doi:10.1097/gme.0b013e31824d8f40
15. Davis SR. Menopause. *Nat Rev Dis Primers*. 2015;1:15004. doi:10.1038/nrdp.2015.4
16. Randolph JF, Zheng H, Sowers MR, et al. Change in follicle stimulating hormone and estradiol across the menopausal transition: effect of age at the final menstrual period. *J Clin Endocrinol Metab*. 2011;96:746–754. doi:10.1210/jc.2010-1746
17. Monteleone P, Mascagni G, Giannini A, et al. Symptoms of menopause - global prevalence, physiology and implications. *Nat Rev Endocrinol*. 2018;14(4):199–215. doi:10.1038/nrendo.2017.180
18. Woods NF, Mitchell ES. Symptoms during the perimenopause: prevalence, severity, trajectory, and significance in women's lives. *Am J Med*. 2005;118:14–24. doi:10.1016/j.amjmed.2005.09.031
19. Freedman RR. Hot flashes: behavioral treatments, mechanisms, and relation to sleep. *Am J Med*. 2005;118:124–130. doi:10.1016/j.amjmed.2005.09.046
20. Genazzani AR, Pluchino N, Luisi S, et al. Estrogen, cognition and female ageing. *Hum Reprod Update*. 2007;13:175–187. doi:10.1093/humupd/dml042
21. Gordon JL, Girdler SS, Meltzer-Brody SE, et al. Ovarian hormone fluctuation, neurosteroids, and HPA axis dysregulation in perimenopausal depression: a novel heuristic model. *Am J Psychiatry*. 2015;172(3):227–236. doi:10.1176/appi.ajp.2014.14070918

22. Spence RD, Voskuhl RR. Neuroprotective effects of estrogens and androgens in CNS inflammation and neurodegeneration. *Front Neuroendocrinol*. 2012;33(1):105–115. doi:10.1016/j.yfrne.2011.12.001
23. MacKenzie-Graham AJ, Rinek GA, Avedisian A, et al. Estrogen treatment prevents gray matter atrophy in experimental autoimmune encephalomyelitis. *J Neurosci Res*. 2012;90(7):1310–1323. doi:10.1002/jnr.23019
24. Davis SR. Understanding weight gain at menopause. *Climacteric*. 2012;15:419–429. doi:10.3109/13697137.2012.707385
25. Cosman F, de Beur SJ, LeBoff MS, et al. National Osteoporosis Foundation. Clinician's guide to prevention and treatment of osteoporosis. *Osteoporos Int*. 2014;25(10):2359–2381. doi:10.1007/s00198-014-2794-2
26. Levine KB, Williams RE, Hartmann KE. Vulvovaginal atrophy is strongly associated with female sexual dysfunction among sexually active postmenopausal women. *Menopause*. 2008;15:661–666. doi:10.1097/gme.0b013e31815a5168
27. Pillay C, O, Manyonda I. The surgical menopause. *Best Pract Res Clin Obstet Gynaecol*. 2022;81:111–118. doi:10.1016/j.bpobgyn.2022.03.001
28. Lee KA, Flores RR, Jang IH. Immune Senescence, Immunosenescence and Aging. *Front Aging*. 2022;3:900028. doi:10.3389/fragi.2022.900028
29. Santoro A, Bientinesi E, Monti D. Immunosenescence and inflammaging in the aging process: age-related diseases or longevity? *Ageing Res Rev*. 2021;71:101422. doi:10.1016/j.arr.2021.101422
30. Gameiro C, Romao F. Changes in the immune system during menopause and aging. *Front Biosci*. 2010;2(4):1299–1303. doi:10.2741/e190
31. Ghosh M, Rodriguez-Garcia M, Wira CR. The immune system in menopause: pros and cons of hormone therapy. *J Steroid Biochem Mol Biol*. 2014;142:171–175. doi:10.1016/j.jsbmb.2013.09.003
32. Goetzl EJ, Huang MC, Kon J, et al. Immunosenescence and inflammaging in the aging process: age-related diseases or longevity? *Ageing Res Rev*. 2021;71:101422.
33. Larbi A, Franceschi C, Mazzatti D, et al. Aging of the immune system as a prognostic factor for human longevity. *Physiology*. 2008;23:64–74. doi:10.1152/physiol.00040.2007
34. Pawelec G. Immunosenescence and cancer. *Biogerontology*. 2017;18(4):717–721. doi:10.1007/s10522-017-9682-z
35. Einstein MH, Levine NF, Nevadunsky NS. Menopause and Cancers. *Endocrinol Metab Clin North Am*. 2015;44(3):603–617. doi:10.1016/j.ecl.2015.05.012
36. Bove R, Gilmore W. Hormones and MS: risk factors, biomarkers, and therapeutic targets. *Mult Scler*. 2018;24(1):17–21. doi:10.1177/1352458517737396
37. Østensen M, Khamashta M, Lockshin M, et al. Anti-inflammatory and immunosuppressive drugs and reproduction. *Arthritis Res Ther*. 2006;8(3):209. doi:10.1186/ar1957
38. Cocco E, Sardu C, Gallo P, et al. Frequency and risk factors of mitoxantrone-induced amenorrhea in multiple sclerosis: the FEMIMS study. *Mult Scler*. 2008;14(9):1225–1233. doi:10.1177/1352458508094882
39. Baroncini D, Annovazzi PO, De Rossi N, et al. Impact of natural menopause on multiple sclerosis: a multicentre study. *J Neurol Neurosurg Psychiatry*. 2019;90(11):1201–1206. doi:10.1136/jnnp-2019-320587
40. Bove R, Healy BC, Musallam A, et al. Exploration of changes in disability after menopause in a longitudinal multiple sclerosis cohort. *Mult Scler*. 2016;22(7):935–943. doi:10.1177/1352458515606211
41. Ladeira F, Salavisa M, Caetano A, et al. The Influence of Menopause in Multiple Sclerosis Course: a Longitudinal Cohort Study. *Eur Neurol*. 2018;80(3–4):223–227. doi:10.1159/000496374
42. Otero-Romero S, Midaglia L, Carbonell-Mirabent P, et al. Menopause does not modify disability trajectories in a longitudinal cohort of women with clinically isolated syndrome and multiple sclerosis followed from disease onset. *Eur J Neurol*. 2022;29(4):1075–1081. doi:10.1111/ene.14782
43. Bove RM, Healy B, Augustine A, et al. Effect of gender on late-onset multiple sclerosis. *Mult Scler*. 2012;18(10):1472–1479. doi:10.1177/1352458512438236
44. Magyari M, Koch-Henriksen N. Quantitative effect of sex on disease activity and disability accumulation in multiple sclerosis. *J Neurol Neurosurg Psychiatry*. 2022;93(7):716–722. doi:10.1136/jnnp-2022-328994
45. Graves JS, Henry RG, Cree BAC, et al. Ovarian aging is associated with gray matter volume and disability in women with MS. *Neurology*. 2018;90(3):e254–e260. doi:10.1212/WNL.0000000000004843
46. Correale J, Ysrraelit MC. Multiple sclerosis and aging: the dynamics of demyelination and remyelination. *ASN Neuro*. 2022;14:17590914221118502. doi:10.1177/17590914221118502
47. Jakimovski D, Gandhi S, Paunkoski I. Hypertension and heart disease are associated with development of brain atrophy in multiple sclerosis: a 5-year longitudinal study. *Eur J Neurol*. 2019;26(1):87–e8. doi:10.1111/ene.13769
48. Lorefice L, Frau J, Coghe G, et al. Assessing the burden of vascular risk factors on brain atrophy in multiple sclerosis: a case- control MRI study. *Mult Scler Relat Disord*. 2019;27:74–78. doi:10.1016/j.msard.2018.10.011
49. Holmqvist P, Wallberg M, Hammar M, et al. Symptoms of multiple sclerosis in women in relation to sex steroid exposure. *Maturitas*. 2006;54(2):149–153. doi:10.1016/j.maturitas.2005.10.003
50. Bove R, Healy BC, Secor E, et al. Patients report worse MS symptoms after menopause: findings from an online cohort. *Mult Scler Relat Disord*. 2015;4(1):18–24. doi:10.1016/j.msard.2014.11.009
51. Harsh V, Meltzer-Brody S, Rubinow DR, Schmidt PJ. Reproductive aging, sex steroids, and mood disorders. *Harv Rev Psychiatry*. 2009;17(2):87–102. doi:10.1080/10673220902891877
52. Brochet B, Ruet A. Cognitive impairment in multiple sclerosis with regards to disease duration and clinical phenotypes. *Front Neurol*. 2019;20(10):261. doi:10.3389/fneur.2019.00261
53. Weber MT, Rubin LH, Maki PM. Cognition in perimenopause: the effect of transition stage. *Menopause*. 2013;20(5):511–517. doi:10.1097/gme.0b013e31827655e5
54. Davis SR, Baber RJ. Treating menopause - MHT and beyond. *Nat Rev Endocrinol*. 2022;18(8):490–502. doi:10.1038/s41574-022-00685-4
55. Bove R, White CC, Fitzgerald KC, et al. Hormone therapy use and physical quality of life in postmenopausal women with multiple sclerosis. *Neurology*. 2016;87(14):1457–1463. doi:10.1212/WNL.0000000000003176
56. Bove R, Vaughan T, Chitnis T, Wicks P, De Jager PL. Women's experiences of menopause in an online MS cohort: a case series. *Mult Scler Relat Disord*. 2016;9:56–59. doi:10.1016/j.msard.2016.06.015
57. North American Menopause Society. The 2012 hormone therapy position statement of: the North American Menopause Society. *Menopause*. 2012;19(3):257–271. doi:10.1097/gme.0b013e31824b970a

58. Manson JE, Chlebowski RT, Stefanick ML, et al. Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials. *JAMA*. 2013;310(13):1353–1368. doi:10.1001/jama.2013.278040
59. Magyari M, Sorensen PS. Comorbidity in Multiple Sclerosis. *Front Neurol*. 2020;21(11):851. doi:10.3389/fneur.2020.00851
60. Bove R, Secor E, Chibnik LB, et al. Age at surgical menopause influences cognitive decline and Alzheimer pathology in older women. *Neurology*. 2014;82(3):222–229. doi:10.1212/WNL.0000000000000033
61. MacKenzie-Graham AJ, Rinek GA. Estrogen treatment prevents gray matter atrophy in experimental autoimmune encephalomyelitis. *J Neurosci Res*. 2012;90(7):1310–1323.
62. Porter VR, Greendale GA, Schocken M, Zhu X, Effros RB. Immune effects of hormone replacement therapy in post-menopausal women. *Exp Gerontol*. 2001;36(2):311–326. doi:10.1016/S0531-5565(00)00195-9
63. Vural P, Akgul C, Canbaz M. Effects of hormone replacement therapy on plasma pro-inflammatory and anti-inflammatory cytokines and some bone turnover markers in postmenopausal women. *Pharmacol Res*. 2006;54(4):298–302. doi:10.1016/j.phrs.2006.06.006
64. Trojano M, Kalincik T, Iaffaldano P, Amato MP. Interrogating large multiple sclerosis registries and databases: what information can be gained? *Curr Opin Neurol*. 2022;35(3):271–277. doi:10.1097/WCO.0000000000001057

International Journal of Women's Health Dovepress

Publish your work in this journal

The International Journal of Women's Health is an international, peer-reviewed open-access journal publishing original research, reports, editorials, reviews and commentaries on all aspects of women's healthcare including gynecology, obstetrics, and breast cancer. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit http://www.dovepress.com/testimonials.php to read real quotes from published authors.

Submit your manuscript here: https://www.dovepress.com/international-journal-of-womens-health-journal