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Review

Multiple sclerosis at menopause: Potential neuroprotective effects of estrogen

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ABSTRACT

Multiple sclerosis (MS) is an autoimmune demyelinating and neurodegenerative condition of the central nervous system that preferentially afflicts women more than men. Low estrogen states such as menopause and the postpartum period favor exacerbations of multiple sclerosis in women with the disease. Existing and emerging evidence suggests a role for estrogen in the alleviation of symptoms and reversal of pathology associated with MS. While clinical evidence is sparse regarding the benefit of estrogen therapy for women at risk for MS exacerbations, scientific data demonstrates that estrogen potentiates numerous neuroprotective effects on the central nervous system (CNS). Estrogens play a wide range of roles involved in MS disease pathophysiology, including increasing antiinflammatory cytokines, decreasing demyelination, and enhancing oxidative and energy producing processes in CNS cells.

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1. Introduction

Multiple sclerosis (MS) is an autoimmune demyelinating and neurodegenerative condition of the central nervous system that affects women up to three times more often than men [1–3]. The clinical presentation typically involves a constellation of symptoms, with common deficits including optic neuritis, gait ataxia, limb weakness, paralysis, cognitive impairment and fatigue [1]. The disease course often occurs in a relapsing remitting, primary progressive or secondary progressive manner [2].

While much remains to be uncovered regarding the precise etiology of MS, research has suggested several candidate pathophysiological mechanisms for the disease. Two major processes have been identified as critical for disease onset: T-cell medi-

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ated inflammation coupled with subsequent demyelination and neurodegeneration. The extent that neurodegeneration versus demyelination impacts the pathophysiology of MS is an issue of debate, given that some MS lesions can occur in the absence of inflammation [4,5]. Demyelination is a key inflammatory event that disables salutatory conduction and neuronal function and has been principally implicated in MS pathophysiology [6]. Demyelinated plaques in the CNS of MS patients are thought to be due to an autoimmune-mediated phagocytosis of myelin sheaths by macrophages in the presence of activated T lymphocytes [7,8]. Additional evidence suggests a role for oligodendrocyte apoptosis and activated microglia in the absence of inflammation as a means for the CNS damage seen in MS [8,9].

Current treatment modalities for MS include immunomodulating and anti-inflammatory agents, such as interferon-B and glatiramer acetate. These agents function primarily to palliate rather than reverse the demyelination, neurodegeneration, and T-cell mediated inflammatory changes seen in MS [6,10,11]**.** In addition to these agents, existing and emerging evidence suggests a role for sex steroid hormones, specifically estrogen, in the alleviation of symptoms and reversal of pathology associated with MS. Furthermore, clinical and molecular evidence suggests that low estrogen states, such as those observed during the postpartum period and during menopause, potentially result in exacerbations of symptoms in women affected by MS. To date, there is a paucity of evidence and prospective research examining whether estrogen therapy can ameliorate the documented increase in MS exacerbation that occurs in low estrogen states. This review will examine the current evidence that estrogen therapy can have a beneficial neuroprotective effect on MS.

2. The reproductive years and MS: Insight to the benefit of estrogens

Pregnancy is noted as a time when MS symptoms may actually improve, and this benefit may be due to increased estrogen levels. Studies suggest that the frequency of MS flares decrease during the second and third trimester of pregnancy [3,12–15]. However, during the subsequent postpartum period, the frequency of MS flares increases—an observation that is thought to be estrogen-mediated [3,12,14–20]. Miller et al. observed an increased incidence of postpartum relapse in 170 pregnant women with MS [12,16]. These early findings were later reaffirmed in other observational studies examining the effect of pregnancy on MS, with an improvement in MS symptoms noted during pregnancy and a worsening of symptoms postpartum (Table 1). Among an analysis of several such studies which included over 1000 patients, the authors noted MS exacerbations in 11% of women during pregnancy and 29% of women postpartum [12].

In recent years, a multicenter prospective European study examined rates of MS relapse in 254 pregnancies. They found a reduction of patient-reported MS flares during pregnancy, an increase in the pueripartum, and a subsequent return to baseline pre-pregnancy relapse rates at approximately three months post-partum [3]. A similar prospective European study of 227 pregnant women, Pregnancy in Multiple Sclerosis (PRIMS), demonstrated that in the last three months of the 3rd trimester of pregnancy, a state with the highest circulating levels progesterone and estrogen, there is a decrease in MS relapse rate [14]. This was in contrast to postpartum, where the decline in estrogen was associated with a two to three fold increase in relapse rate [3,14,15,18]. The possible therapeutic benefit of estrogen and progesterone derivatives for prevention of relapse in the postpartum period is currently under examination in the POPART'MUS trial (Prevention of Post-Partum Relapses with Progestin and Estradiol in Multiple Sclerosis) [14,19].

While the mechanism behind this phenomenon has yet to be clearly elucidated, molecular evidence of the physiological changes which occur during pregnancy lend support to the theory of an estrogen-mediated protection. Demyelination and plaque creation in the CNS is believed to be the result of Th1 cell-mediated neuroinflammation. The resultant cytokines these activated T-cells release include IL-2, TNF-B, and IFN-y. Late pregnancy, however, is a Th2 cell dominated state, which enables fetal growth and development. Estrogen is a key player in mediating this Th2 shift during the third trimester of pregnancy [18,20,21].

In contrast to studies of MS in pregnancy, there is less clear evidence for disease flares during other stages of a woman's reproductive lifespan. Current literature suggests a general trend for worsening of MS disease and symptom severity in association with low estrogen states like that at menses or menopause [22–29]. If true, supplementation of sex steroid hormones during these periods of hormone depletion should diminish MS flare frequency and symptom severity. Evidence in support of this theory, however, is sparse and inconclusive at best. In a small retrospective survey of disease severity and frequency, 11 premenopausal women (mean age of 35.8) with MS were surveyed to evaluate for worsening of MS symptoms and disability pre-menstrually using the Kurtzke Disability Status Scale. Among these women, 82% reported a worsening of symptoms pre-menstrually (mean score change +1.9, SD 3.18), thus implying that the withdrawal of estrogen may be associated with worsening of MS [15]. It is therefore reasonable to postulate that estrogen replacement may have the opposite effect, resulting in improvement in MS symptoms. Estrogen via oral contraceptive pills (OCPs) has been studied to evaluate possible protective and therapeutic effects in the premenopausal population with MS with conflicting results. One study revealed the mean age of onset of MS symptoms was delayed in users of combined oral contraceptive pills (COCs) (26 vs 19 years old, $P < 0.01$) [24]. Contrary to these findings, evaluation of the Nurse's Health Study population found no link between OCP use and risk of developing MS [25]. In a study of OCP use among women with MS, a majority of respondents (66.7%) reported no change in symptom severity while on this treatment [26]. A small trial of 10 women aged 28–50 with MS examined the use of oral estriol treatment (8 mg/day) in improving symptoms for six months duration. On subsequent brain imaging with MRI, treatment with estriol decreased the number and volume of lesions. When treatment was stopped, lesions increased to pretreatment levels; however, with re-initiation of estriol, the treatment benefit resumed [27]. These findings support the hypothesis that estrogen has a beneficial neuroprotective effect in premenopausal women with MS. Despite promising work in postpartum and premenopausal women with MS, a paucity of prospective data exists examining whether the declining estrogen state associated with menopause results in a worsening of MS disease severity. In a small retrospective survey of nineteen women, 54% reported a worsening of MS-related disability following menopause. With hormone therapy (HT), 75% of these women reported an improvement in their symptom severity [15]. Another larger retrospective Swedish study of 128 women investigated whether MS symptoms change in relation to menopause and use of hormone therapy (HT). Among menopausal women surveyed, 39.3% reported an increase in MS symptoms after menopause, however among those taking HT, 96.6% reported either no change or worsening of MS symptoms while only 3.4% reported an improvement [26].

The treatment of menopausal women with MS with estrogen has not been formally studied in a randomized prospective manner. Given that menopause and MS share many overlapping clinical features, it is interesting this has not been evaluated more comprehensively. Common symptoms shared between menopause and MS include fatigue, urologic, affective, cognitive, and vasomo-