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Lower threshold for hormone therapy in women with multiple sclerosis

PERSPECTIVES

CECILIA SMITH SIMONSEN

cecsim@vestreviken.no
Cecilia Smith Simonsen, specialist in neurology and senior consultant at the Department of Neurology, Drammen Hospital, and postdoc at the Department of Neurology, Oslo University Hospital
The author has completed the ICMJE form and declares the following conflicts of interest: she has received speaker and consultancy fees from Biogen, Sanofi, Merck and Novartis.

METTE HAASE MOEN

Mette Haase Moen, specialist in obstetrics and gynaecology at the Department of Neurology, Oslo University Hospital, and professor emerita at the Department of Clinical and Molecular Medicine, Norwegian University of Science and Technology (NTNU)
The author has completed the ICMJE form and declares the following conflicts of interest: she has received speaker and consultancy fees from Gedeon Richter, Besins, Ferring, Astellas, Exeltis and Merck.

ELISABETH GULOWSEN CELIUS

Elisabeth Gulowsen Celius, specialist in neurology and senior consultant at the Department of Neurology, Oslo University Hospital, and Professor of Neurology at the Institute of Clinical Medicine, University of Oslo and the Department of Clinical and Molecular Medicine, Norwegian University of Science and Technology (NTNU)
The author has completed the ICMJE form and declares the following conflicts of interest: she has received speaker fees and fees for participation in scientific advisory boards from Biogen, BMS, Janssen, Sanofi, Merck, Novartis, Roche and Teva. Her department has received independent research funding from Biogen, Novartis, Merck and Genzyme.

We believe that hormone replacement therapy should be considered earlier and more frequently in women with multiple sclerosis.

For women already burdened with a chronic neurodegenerative disease, the benefits of alleviating menopausal symptoms and potentially slowing neurodegeneration should be given considerable weight. Menopause entails a dramatic reduction in the female sex hormone oestrogen, which may contribute to neurodegeneration (1). Despite this, hormone replacement therapy (HRT) tends to be overlooked in women with multiple sclerosis (MS).

Overlapping symptoms

MS is an autoimmune disease characterised by inflammation and neurodegeneration in the central nervous system (2). Neuroinflammation is most pronounced in younger age groups but decreases with age as neurodegeneration increases (3). An MS relapse refers to the onset of new symptoms or worsening neurological dysfunction resulting from focal inflammation and demyelination in the central nervous system.

Menopause is defined as the permanent cessation of menstruation. The time preceding menopause is referred to as perimenopause and the time following it as postmenopause. The average age of menopause in Norway is 51 years, with a range from 40 to 60 years (4).

One-third of people with MS are peri- or postmenopausal women. Women with MS often report that menopause exacerbates subjective symptoms such as fatigue, cognitive difficulties and urinary problems (5). In our experience, middle-aged women with MS are referred to neurological outpatient clinics for evaluation of disease activity or medication side effects, when the symptoms are actually due to menopause. Our research showed that 30 % of women started, changed or discontinued immunomodulatory therapy in the year they reached self-reported menopause. We also found a longer time to diagnosis from symptom onset in women who reach menopause before being diagnosed with MS. One possible explanation is that MS symptoms are confused with menopausal problems (6). Women with MS often face a complex disease burden, and it is crucial to acknowledge the significance of oestrogen's role in this context.

> ***«Women with MS often face a complex disease burden, and it is crucial to acknowledge the significance of oestrogen's role in this context»***

Most peri- and postmenopausal women experience hot flushes, and in women with MS, increased body temperature can temporarily exacerbate existing neurological symptoms, known as Uhthoff's phenomenon (7). Menopause can

lead to depression, anxiety, fatigue, sleep disturbances, urinary problems, sexual dysfunction, brain fog and cognitive difficulties – symptoms that are also common in MS (Figure 1) (8).

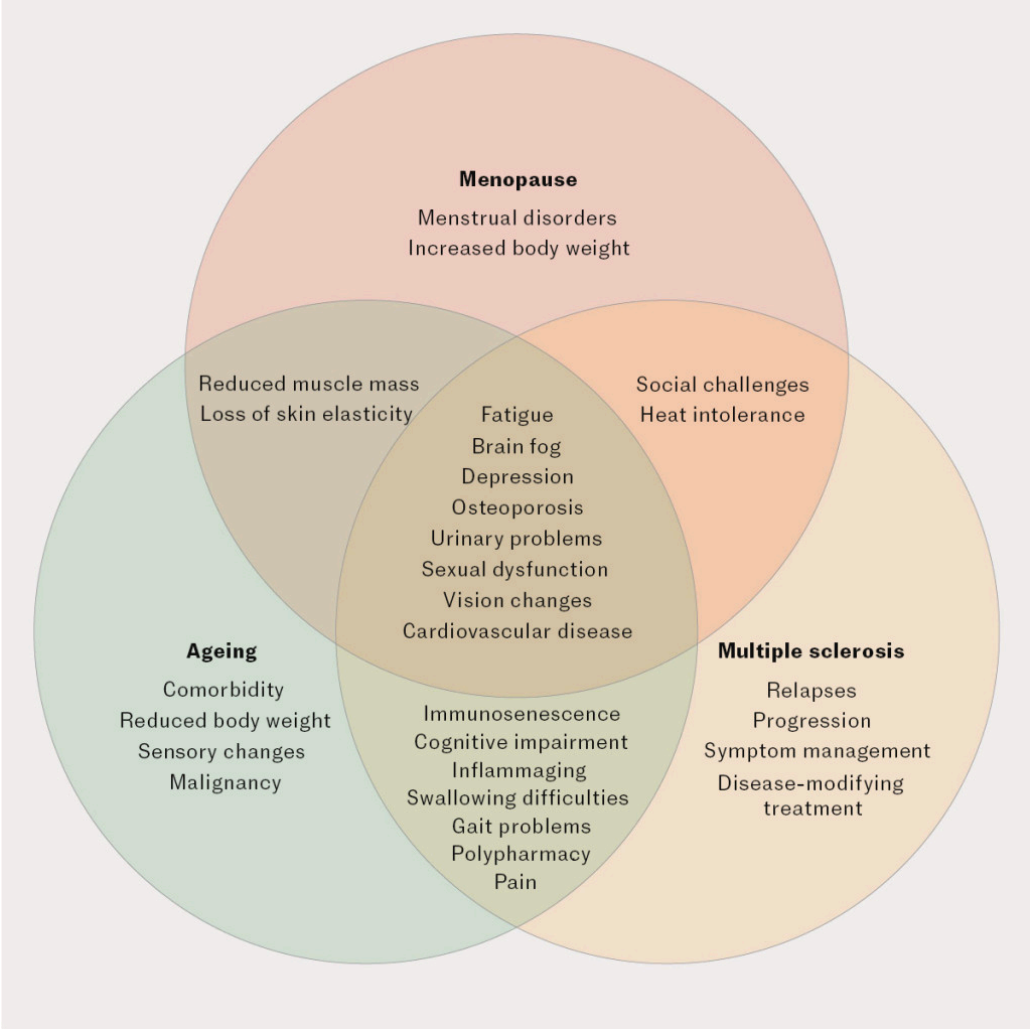

Figure 1 The association between multiple sclerosis, ageing and menopause, modified from Bove et al. (8). Inflammaging = a term introduced by immunologist Claudio Franceschi that describes chronic, low-grade inflammation that develops with age and contributes to age-related diseases.

Oestrogen, neurodegeneration and inflammation

Oestrogen is believed to have neuroprotective properties in relation to reducing inflammation, promoting myelin repair, protecting neurons from oxidative stress and enhancing neuroplasticity (9). Early menopause increases the risk of neurological diseases, cognitive decline and neurodegeneration (10–12). Some studies suggest that menopause accelerates functional decline in women with MS, while other studies find no changes in post-menopausal disease progression (6, 13–15). Even if measuring instruments with a focus on gait show no clear changes, biological studies show that neurodegeneration in the brain increases with menopause (1).

High oestrogen levels have an anti-inflammatory effect, while low levels promote inflammation (16). High oestrogen levels during pregnancy protect against relapses in women with MS, but the risk increases in the first months

after childbirth, when levels are low (17). Disease activity could therefore be expected to increase during menopause, when oestrogen levels drop dramatically. However, studies show that neuroinflammation decreases with age. This suggests that age, and not oestrogen level, has the greatest impact on relapse rates (14), due to age-related weakening of the immune system and chronic low-grade inflammation (3). A registry study found that women had more inflammatory relapses than men before the age of 50, with no difference observed after that age (18). Our study of 559 postmenopausal women with MS found no significant difference in the pre- and post-menopausal relapse rate (6).

Hormone replacement therapy

Use of HRT saw a sharp decline worldwide following the Women's Health Initiative study (19), which showed an increased incidence of heart disease, breast cancer and stroke among women receiving HRT. More recent research supports a more individualised approach to HRT. Women who start taking modern hormone formulations at an early stage of menopause can experience significant health benefits with an acceptable level of risk (20).

> ***«Women who start taking modern hormone formulations at an early stage of the menopause can experience significant health benefits with an acceptable level of risk»***

Animal models and some human studies suggest that exogenous oestrogen may have anti-inflammatory and neuroprotective effects in women with MS (21, 22). One issue is that earlier studies examined higher doses and formulations of oestrogen that are no longer in use. Optimisation of sleep, mood and hot flushes improved mental health in menopausal women with MS (23). One study showed that using HRT for less than five years does not affect the progression of MS (24).

To optimise its neuroprotective effects, HRT should ideally be initiated as soon as possible following the onset of menopause (10). Determining the optimal time to start HRT is challenging, as hormone tests are unreliable (25). Symptoms such as hot flushes and irregular menstruation indicate declining oestrogen levels, and HRT should be considered.

The principles of treatment are the same

The Norwegian clinical gynaecology guidelines include up-to-date information on treatment principles and long-term effects of HRT for all women (26). In Norway, oestradiol is the most commonly used oestrogen in HRT, and transdermal application is preferred as it does not seem to increase the risk of thrombosis or stroke. Oestrogen can stimulate abnormal growth of the endometrium, which could potentially lead to endometrial cancer, and must

therefore be combined with either natural progesterone or synthetic progestin. Long-term oestrogen therapy, especially when combined with progestin, increases the risk of breast cancer. However, this elevated risk is low when oestrogen is combined with natural progesterone or used alone in women who have had a hysterectomy (27). A history of breast cancer and thrombophilia are contraindications.

> ***«HRT has beneficial effects for hot flushes, quality of life, sleep, fracture risk, the onset of diabetes and overall mortality»***

HRT has beneficial effects for hot flushes, quality of life, sleep, fracture risk, the onset of diabetes and overall mortality (26). The impact of HRT on the risk of ischemic heart disease remains uncertain, but initiating treatment at an early stage of the menopause protects against cardiovascular disease (28). HRT should therefore be initiated before the age of 60 and no later than ten years after menopause (26). In the case of contraindications, non-hormonal treatments (selective serotonin and norepinephrine reuptake inhibitors (SSRIs/SNRIs), gabapentin, oxybutynin, fezolinetant) and local oestrogen can be prescribed for urogenital symptoms. In principle, there is no limitation on how long HRT can be used (26).

Little reason for scepticism

Doctors have likely been sceptical about using HRT in women with MS due to the pro-inflammatory effect of low-dose oestrogen on neuroinflammation and the belief that menopause protects against disease activity. A literature review from 2024 concluded that HRT should not be ruled out for women with MS, but more longitudinal studies are needed to assess the potential neuroprotective effects of oestrogen (29).

Most women experience menopause-related symptoms, and for those with MS, these add to the existing disease burden they already face. All clinicians treating women with MS, including general practitioners, neurologists and gynaecologists, should be better informed about this topic. Women with MS who are nearing menopause should be given detailed information about treatment options, including HRT (30, 31). Given the potential neuroprotective effect of oestrogen, the threshold for prescribing HRT should be low, while still adhering to established treatment guidelines.

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