Hormone replacement in menopausal women with multiple sclerosis

Looking back, thinking forward

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In this issue of *Neurology*®, Bove et al.[1] address whether hormone replacement therapy in the early menopausal years may be associated with better quality of life in women with multiple sclerosis (MS). There may be worsening of disabilities during menopause in women with MS,[2] and functional networks of working memory circuitry are influenced by menopausal status.[3] Estrogen replacement therapy administered after surgical menopause has shown beneficial effects on verbal memory,[4] and a window of opportunity of estrogen treatment for neuroprotection has been proposed.[5] In this retrospective analysis of data acquired from the Nurse's Healthy Study including 248 MS cases, the authors determined whether hormone use for at least 12 months was associated with better scores on the 10-item physical functioning assessment (PF10) subscale of the 36-Item Short Form Health Survey (quality of life). Surveys completed between 3 and 10 years after the final menstrual period were assessed (147 MS cases). They found that there was an association between better PF10 scores and estrogen use (mainly Premarin use; Pfizer, New York, NY). Also, duration of hormone treatment was associated with higher PF10 scores. An association between better PF10 scores and hormone use in women without MS was not found, suggesting that hormone treatment may uniquely benefit physical functioning in women with MS.

These findings are valuable because hormone replacement therapy is used less than it once was, reducing the ability to examine this issue. The authors' rigorous attention to detail regarding definitions of menopausal types and stages, as well as their focus on women treated no more than 10 years after menopause onset was important, since women who have been hormone deficient for many years are less likely to experience benefits of hormone treatment.

Regarding limitations, a potential confound was that hormone users had shorter MS disease duration than nonusers at the time of assessment, and shorter disease duration could influence quality of life. The authors managed this confound by including this variable in their statistical adjustments. Also, use of the survey instrument in other MS cohorts previously showed that better scores were associated with better objective assessments. However, direct objective evidence of better physical functioning remains lacking in this cohort. For example, if hormone treatment improved mood, then this may have influenced answers to questions on the PF10. Such limitations are inherent to retrospective studies analyzing data from surveys, thereby warranting caution in their interpretation and underscoring the need for blinded clinical trials of hormone vs placebo treatment using objective outcome measures in women in early menopausal with MS.

Causality is always difficult to show in retrospective studies, but here the data suggested lack of causality. As the authors state, poorer physical functioning could make participants less likely to seek general health care, including hormone treatment for menopause. Therefore, the authors cleverly assessed PF10 in the same participants at an earlier, premenopausal time point to address causality. The difference in PF10 scores between treated and untreated participants at the premenopausal time point (figure 1B) was similar to the difference between treated and untreated at the postmenopausal time point (figure 1A).[1] This suggested that higher PF10 scores post menopause were not caused by hormone treatment during menopause. On the positive side, the data established that hormone use during the first 10 years of menopause in women with MS was not associated with worse PF10 scores. Since Premarin was generally the hormone used, these safety data are useful to clinicians using Premarin to manage menopausal symptoms in MS women.

Looking forward, these results suggest that a different estrogen type or dose may be needed to induce better physical quality of life in menopausal women with MS. Regarding an alternative, estriol has been used for decades throughout Europe and Asia to treat menopausal symptoms in healthy women at an oral dose of 1 to 2 mg per day. It is considered one of the safest estrogens,[6,7] binding to estrogen receptor beta (ER-β) with higher affinity than ER-α, with ER-α mediating deleterious effects of other estrogens on breast and uterus.[8] In the recently completed multicenter, placebo-controlled, phase 2 trial of estriol treatment in younger women with relapsing-remitting MS,[9] the primary outcome of reducing relapses was reached as powered, but this is less

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germane in this population since relatively few menopausal women with MS have relapses. Instead, effects on exploratory outcomes were most relevant to menopausal women with MS. There was improvement in fatigue as measured by the Modified Fatigue Impact Scale in the estriol-treated group compared to the placebo-treated group. An effect of estriol treatment on fatigue could improve quality of life in menopausal women, since fatigue is common. However, an estriol dose of 8 mg per day was used in the phase 2 trial, which is higher than the dose usually used for menopausal symptoms. Dose is likely important, since other exploratory data in the phase 2 trial showed that higher estriol levels correlated with improved cognitive performance on tests of processing speed. Thus, a standard estriol dose of 1 to 2 mg per day for treatment of menopausal symptoms may not be enough to improve cognition in menopausal women with MS. It remains unknown whether a low dose of estriol could improve fatigue in this group. Dose-finding and validation trials of estriol treatment are needed with fatigue, cognition, or quality of life as possible primary outcome measures, particularly given the known neuroprotective properties of estrogens in other systems.[10] To this end, a clinical trial using the 8-mg dose of estriol in women with MS aged 18 to 55 years with cognitive testing as the primary outcome measure is ongoing (clinicaltrials.gov/NCT01466114).

The risk–benefit ratio of hormone treatment in healthy women with menopausal symptoms is different than that in women with MS who have worsening of MS symptoms. It is time to harness what has been learned from the past Women's Health Initiative studies[11] with regard to the timing, dose, and type of estrogen for optimal design of a clinical trial in menopausal women with MS. Bove et al. may not have shown causal effects of Premarin treatment on quality of life in menopausal women with MS, but they have elegantly addressed issues that will be important in future clinical trial designs.

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