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A Prospective Study of Estrogen Replacement Therapy and the Risk of Developing Alzheimer's Disease: The Baltimore Longitudinal Study of Aging

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The incidence of Alzheimer's disease (AD) is increased in women compared with men, presumably because of increased life expectancy. Several studies have investigated the role of estrogen in the development of AD, but the results have been inconclusive, partly because of study design and the lack of prospective clinical data. Nonetheless, some authors advocate the use of estrogen replacement therapy (ERT) in mitigating the cognitive losses associated with AD. The purpose of this study was to investigate prospectively the use of ERT and the risk of developing AD using the Baltimore Longitudinal Study of Aging (BLSA).

The BLSA began enrolling women in 1978 and data regarding ERT have been gathered since that time. For the current study, 514 women were eligible for enrollment, with a mean age of 61.5 years. The women were all similar regarding education (63 percent had college or graduate degrees) and race (92 percent were white), and the mean age at menopause and menarche were 46.4 +/- 6.5 and 12.7 +/- 1.5 years, respectively. Under the protocol of BLSA, the women participated in a 2.5-day evaluation every 2 years. For this study, the women who used either oral or transdermal ERT were considered users and they were subsequently assigned to a category regarding length of time of ERT use: <6 months, 7 months to 1 year, etc. Dementia was determined from neurological examination and laboratory and imaging studies. The relative risk (RR) of developing AD in association with ERT use and duration of use was determined, and the individual variables of age at menopause and menarche, years of natural cyclic estrogen exposure, duration of menopause, and surgical menopause were also analyzed. Additionally, the use of nonsteroidal anti-inflammatory drugs (NSAIDs) was analyzed as a time-dependent binary covariant.

When ERT users were compared with nonusers, the RR for the development of AD was 0.457 (95 percent CI, 0.209-0.997). There did not seem to be any appreciable protective effect with increased duration of ERT use. The other variables analyzed had no significant effect on the outcome of this study. The model that included NSAID use yielded a RR for ERT use of 0.49 (95 percent CI, 0.23-1.07) and for the development of AD, 0.45 (95 percent CI, 0.21-0.98).

(Readers of the Survey may recall that I previously reviewed an article emanating from Columbia University indicating that the incidence of Alzheimer's disease was reduced and the age of onset of the disease in those women who eventually were afflicted was greater in those postmenopausal women taking estrogen as part of a hormone replacement therapy regimen compared with a matched group of women who did not take estrogen (M Tang et al., Lancet 1996;348:429). Part of the impetus for that study was research findings in rodents published by Toran-Allerand and her associates, also from Columbia University, indicating that neurons from the central nervous system grew more luxuriantly and sent out more dendritic processes when cultured in the presence of estrogen than in its absence. This group previously had found that estrogen receptors co-localized with low affinity nerve growth factor receptors in neurons of the basal forebrain (CD Toran-Allerand et al., Proc Natl Acad Sci USA 1992;89:4668). Another noted neuroscientist, Bruce McEwen, and his associates also had observed that gonadal steroids regulate dendritic density (E Gould et al., J Neurosci 1990;10:1286; CS Noolley, BS McEwen, J Neurosci 1994;14:7680). There was, therefore, a scientific basis for clinical investigators attempting to determine whether estrogens would have salutary effects on the occurrence of Alzheimer's disease.

In the present study, advantage was taken of data from the Baltimore Longitudinal Study of Aging, a prospective study of normal aging conducted by the National Institute of Aging. It has the advantage of permitting prospective studies of the impact of a given variable or group of variables on a particular disease entity or on mortality or all-cause morbidity, as compared with case-control studies. In this report, the authors assessed the risk of developing Alzheimer's disease in the presence or absence of estrogen replacement therapy (ERT). They classified women who had used oral or transdermal estrogen at any time as ERT users. About 45 percent of the women in the cohort had used ERT. There were 34 incident cases of Alzheimer's disease during follow-up, of whom nine were estrogen users. The relative risk for Alzheimer's disease after adjusting for education was 0.46, with a 95 percent confidence interval of 0.209 to 0.997, thus indicating a reduced risk for Alzheimer's disease. Probably because the study was observational, the data did not demonstrate an effect relevant to the duration of hormone usage.

This report lends added support for the concept that ERT is protective against Alzheimer's disease. So, too, are studies that demonstrated cognitive and affective improvement in women with Alzheimer's disease who received ERT (e. g., H Fillit et al., Psychoneuroendocrinology 1986;11:337; H Honjo et al., Horm Metab Res 1995;27:204).

In addition to the effects of estrogen on neuronal growth, estrogen can exhibit antioxidant activity (E Niki, M Nakuno, Methods Enzymol 1990;186:330), inhibit circulating apolipoprotein E concentrations (S Asthana et al., Abstract Soc Neurol 1996;22:200) and affect other processes that may favorably impact on Alzheimer's disease (NR Smolheiser, Neurology 1996;47:809).

Taken together, these studies point to a beneficial effect on the incidence and management of Alzheimer's disease. It's one more factor in balancing the risks and benefits of ERT in post-menopausal women.-RBJ)