Is there a link between gynecologic surgeries and Alzheimer disease?

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In 2001, an Institute of Medicine report concluded that "being male or female is an important fundamental variable that should be considered when designing and analyzing basic and clinical research."[1] The extent to which gender- and sex-specific factors influence the risk of Alzheimer disease (AD) is a matter of profound importance.[2] Sex refers to biological characteristics of men and women such as chromosomal differences (e.g., XX vs XY chromosomes), hormonal differences (e.g., effects of estrogen), or reproductive differences (e.g., pregnancy or breastfeeding). By contrast, gender refers to social, political, and cultural differences (e.g., access to education or to certain jobs). The burden of AD is particularly great in women, and gender-associated differences in educational attainment may explain part of the differences in AD risk. In addition, exposures to gonadal steroids are linked to differences in Alzheimer-related pathology in animal models, although implications for human disease remain controversial.[3]

In this issue of *Neurology*®, Bove et al.[4] report the results of a cohort study on the association between surgical menopause and cognitive decline and AD pathology. They found that earlier age at surgical menopause was associated with faster decline in global cognition, specifically in domains of episodic memory and semantic memory. Among women who underwent autopsy after death, earlier age at surgical menopause was also associated with increased burden of AD neuropathology, in particular neuritic plaques. Hormone replacement therapy initiated within 5 years of the surgery and continued for at least 10 years was associated with a lesser decline in global cognition, supporting the view that the effect of surgical menopause on cognitive decline was mediated by the early loss of ovarian hormones. These associations were not observed for women who underwent natural menopause.

The study was based on 2 large, well-characterized cohorts: the Religious Orders Study and the Memory and Aging Project.[4] Strengths of the study include the long duration of follow-up, the detailed assessment of cognitive functions, and the large number of autopsies. Weaknesses include the lack of information needed to separate several different gynecologic surgeries that were analyzed together as surgical menopause (exposure misclassification, if the primary exposure of interest is the abrupt loss of ovarian hormones), the lag time between surgery and enrollment in the study ("left truncation" in epidemiologic terminology of women who may have developed early AD before cohort inception), and the reliance on self-reported information about gynecologic surgeries (exposure misclassification) and about age at menopause (information bias).

The term surgical menopause as used in this study included several distinct endocrine situations: women with hysterectomy without oophorectomy, women with hysterectomy with one ovary preserved, and women with bilateral oophorectomy with or without hysterectomy. Only the women who underwent bilateral oophorectomy are believed to experience an abrupt decline in circulating estrogens and progesterone, as well as a decline in testosterone, which is derived in part from the ovarian stroma. The effects of removing only the uterus on the remaining ovaries, or the effects of removing one ovary on the other ovary, remain largely unknown.[5,6]

The study by Bove et al. is the first to confirm and extend the findings from the Mayo Clinic Cohort Study of Oophorectomy and Aging in a North American population. In 2007, the Mayo Clinic study suggested that women who undergo unilateral or bilateral oophorectomy before the onset of menopause are at increased risk of cognitive impairment or dementia.[7] The risk increased with younger age at oophorectomy, did not vary by indication for the oophorectomy, and was eliminated by hormone replacement therapy initiated after the surgery and continued up to age 50 years or longer. In most of the women, oophorectomy was performed at the time of hysterectomy.[7]

The findings from the Mayo Clinic study were replicated in studies from Denmark in 2010 and from China in 2011,[6,8,9] but other studies have not confirmed

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the associations.[10] The biological basis for the importance of the timing of the oophorectomy is the drastic reduction of ovarian function with menopause (occurring naturally at a mean age of 51 years). An oophorectomy performed before the onset of natural menopause has more extreme endocrine consequences than an oophorectomy performed after the onset of menopause. Although the beneficial or harmful effects of estrogen on the brain of women who experienced natural menopause remain an area of major scientific debate, it appears that estrogen is protective against cognitive decline when administered to women who underwent oophorectomy before menopause.[5]

We hope that the study by Bove et al.[4] will stimulate further research on the links between menopause, oophorectomy, gonadal steroids, cognitive aging, and dementia. More broadly, we hope that in an era of increasingly personalized medicine, the consideration of risk and protective factors in men and women separately may accelerate the progress of discovery and translation in AD, other forms of dementia, and other neurologic diseases.[1,2]

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DISCLOSURE

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