Could estrogen protect younger menopausal women from stroke?


The findings from seven recent observational studies, from a 2011 Women’s Health Initiative report and from a UK study challenge the consensus that estrogen is invariably a risk factor for ischemic stroke.

The hypothesis that estrogen might be protective for younger women but might become neutral, or even harmful, for older women has been proposed for both cardiovascular disease and dementia [1,2]. When referring specifically to the benefits or risks of estrogen therapy (ET), this hypothesis has been called the window of opportunity, window of vulnerability, or timing hypothesis. For simplicity, we will call it the timing hypothesis. It remains unclear whether the timing hypothesis applies to stroke in general or to ischemic stroke (IS) in particular.

The general consensus has been that estrogen is invariably a risk factor for IS, probably because of its short-term prothrombotic and proinflammatory effects. For example, the experimental data from the Women’s Health Initiative (WHI) clinical trials and the observational data from the Nurses’ Health Study (NHS) indicate, with remarkable consistency, that estrogen is a risk factor for IS when administered orally to women older than 50 years of age, alone or in combination with a progestin (primarily conjugated equine estrogens at a dose of 0.625 mg/day) [3–5]. The same conclusion was reached by three meta-analyses of clinical trials of ET and risk of stroke [6–8].

However, in the past 5 years, newer observational studies have challenged this simple conclusion. In a review of observational studies of the association of premature or early menopause with stroke or IS, published in English from 2006 through to 2010, we found seven studies providing evidence for a protective role of estrogen in younger women [9].

More recent evidence on the effects of estrogen before the age of 50 years

A direct way of testing the effects of estrogen in young women is to study women who underwent bilateral oophorectomy before reaching natural menopause. These women experience an abrupt drop in circulating estrogen and other ovarian hormones unless they receive ET after the surgery. To mimic the natural time course of hormonal changes, estrogen should be administered for replacement until the age of natural menopause, which occurs at an average age of 51.4 years in the USA [10].

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Three cohort studies showed an increased risk of all stroke in women who underwent bilateral oophorectomy before 50 years of age compared with women who conserved their ovaries: the Mayo Clinic Cohort Study of Oophorectomy and Aging [11]; the NHS [12]; and a Swedish nationwide cohort study [13]. In the NHS, ET taken after the surgery eliminated the increased risk of stroke, suggesting that
estrogen deprivation is involved in the association. The NHS also showed that the association of bilateral oophorectomy with increased risk of stroke is not due to confounding by the usual cardiovascular risk factors or by genetic predisposition [12]. The Swedish study showed that the association is not due to confounding by socioeconomic factors [13].

Four additional observational studies showed an association of all stroke or IS with the early onset of menopause or with a shorter lifespan of ovarian function: the Japan Collaborative Cohort Study [14]; a Spanish study [15]; the Framingham Heart Study [16]; and a second Japanese study [17]. Three of the studies were cohort studies, and the Spanish study was a case–control study [15]. The Japanese cohort study by Baba et al. showed that the increased risk of stroke was not explained by confounding due to the usual cardiovascular risk factors [17].

Stoke is generally classified as ischemic, the most common type including embolic and thrombotic mechanisms, or hemorrhagic, including subarachnoid or intracerebral locations [9]. Not all of the studies described above distinguished IS from hemorrhagic stroke. In three of the seven studies, estrogen deficiency was associated specifically with increased risk of IS, suggesting that the protective effects of estrogen on stroke overall are mediated by mechanisms underlying ischemic lesions.

In the studies published so far, younger age at menopause was more important than the type of menopause (natural vs induced) in increasing the risk of stroke, suggesting that age at onset of hormonal deprivation may be a key factor. However, we remain concerned that the abrupt drop in circulating estrogen and other hormones caused by bilateral oophorectomy may further increase the risk compared with a premature or early menopause occurring less abruptly via natural mechanisms [9]. In summary, new data suggest that estrogen, naturally produced by the ovaries or given as a replacement therapy before the age of 50 years, may protect younger women from stroke.

More recent evidence on the effects of estrogen after age 50 years

In 2011, LaCroix et al. reported new analyses from the WHI, which included a post-intervention phase of follow-up [18]. In contrast to the initial WHI clinical trial reports, the authors showed that unopposed estrogen taken orally at a dose of 0.625 mg/day for a median of 5.9 years in women who had undergone hysterectomy was not associated with an increased risk of stroke or any other adverse outcomes after 10.7 years of follow-up [18]. The risk of stroke was particularly low among women who initiated treatment in the age group of 50–59 years. Approximately 40% of the women in this arm of the WHI trial had undergone bilateral oophorectomy along with hysterectomy. These new findings suggest that estrogen is not a risk factor for

IS in women aged 50–59 years who are treated with estrogen alone.

A recent case–control study based on a large sample of UK general practices (UK General Practice Research Database) showed that estrogen alone or estrogen plus progestogen given to women aged 50–79 years is not a risk factor for stroke if the estrogen is administered transdermally and at low doses. By contrast, the risk of stroke was increased when the hormonal treatment included estrogen administered transdermally at higher doses or orally at any dose [19]. This observational study suggests that both the dose and the route of administration of hormone therapy may modify the risk of stroke. In summary, new analyses from the WHI study combined with the findings from a UK study suggest that estrogen, given pharmacologically as part of hormone therapy after 50 years of age, may not actually increase the risk of stroke.

Interpretation

The findings from seven recent observational studies, from a 2011 WHI report and from a UK study challenge the consensus that estrogen is invariably a risk factor for IS. The contradiction between protective effects in younger women and deleterious effects in older women can be reconciled by a unifying timing hypothesis. We hypothesize that estrogen is protective for IS before the age of 50 years and may become a risk factor for IS after the age of 50 years or, more likely, after the age of 60 years, particularly if given orally at high doses [9]. The beneficial effects of estrogen on blood vessels probably occur throughout the lifespan of women, so that an adequate amount of endogenous or exogenous estrogen early in life may change the trajectory of atherosclerosis and vascular aging, and may reduce the risk of IS 30 or 40 years later (long-term protective effects). By contrast, the deleterious effects of estrogen therapy after the age of 50 years appear to be related to prothrombotic and proinflammatory effects, which tend to be more proximate or contemporary to the ischemic event (short-term deleterious effects) [1,9]. These deleterious effects may be avoided using lower doses and transdermal preparations.

Clinical implications

These findings have two major clinical implications. First, women who are considering bilateral oophorectomy before the age of natural menopause should be counseled about the increased risk of IS as part of the discussion of the risks and benefits of the surgery [11,12,20]. Second, women who experienced an early estrogen deficiency, approximately before 45 years of age, may consider taking hormone therapy unless there is a clear contraindication.

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women who receive hormone therapy between the ages of 50 and 59 years remains unclear, and may depend on the type of treatment (estrogen alone vs estrogen plus progestogen), on the route of administration (oral vs transdermal), on the dose (lower vs higher), and on the presence or absence of known risk factors for stroke.

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References

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Editorial

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