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Review Article

Hormone use and stroke

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ARTICLE INFO

Article history:
Received 18 February 2016
Accepted 20 February 2016
Available online 14 March 2016

Keywords:
Stroke
HRT
OC
Estrogen
Progestin

ABSTRACT

Strokes are an important cause of disability and death among older women. Because many women use hormone therapy for the control of perimenopausal symptoms and to prevent osteoporosis after menopause, establishing whether such therapy has other health effects is of considerable clinical importance. Overall, 55% of strokes occur in women, and women account for nearly 60% of all stroke-related deaths. Women appear to be protected from heart disease and stroke before menopause. This is thought to be because of the protective effects of ovarian hormones, and this effect could provide clues on new paradigms to prevent stroke and ischemic vascular disease.

Strokes are an important cause of disability and death among older women. Because many women use hormone therapy for the control of perimenopausal symptoms and to prevent osteoporosis after menopause, establishing whether such therapy has other health effects is of considerable clinical importance.[1]

Stroke in women is a major public health problem. The incidence of stroke is strongly age-dependent.[2] In most age groups, the incidence of stroke is slightly higher in men than in women; however, women tend to live longer than men. This more than compensates for the difference in incidence, and more women have strokes each year than men. Overall, 55% of strokes occur in women, and women account for nearly 60% of all stroke-related deaths. Women appear to be protected from heart disease and stroke before menopause. This is thought to be because of the protective effects of ovarian hormones, and this effect could provide clues on new paradigms to prevent stroke and ischemic vascular disease.[3]

Estrogen has multiple recognized mechanisms of action in many different tissues. In a stroke perspective, some appear to be protective and some to increase the risk of stroke. In animal models, estrogen has been shown to protect neurons against ischemic damage by blocking glutamate injury, as well as antiapoptotic and antioxidant effects. Estrogen is further thought to mediate increased blood flow by a direct endothelium-dependent vasodilatation and by affecting the nitric oxide/endothelium ratio which leads to vasodilatation. On the other hand, estrogen appears to be proinflammatory and relates to increase C-reactive protein-levels. Estrogen affects hemostasis and an increase in risk of especially venous thrombosis is observed. The exact mechanism is not clear and progestogen may also contribute to the effect.[4]

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http://dx.doi.org/10.1016/j.apme.2016.02.007

1. Sources of sex hormones

The source of the hormones may be exogenous as well as endogenous. From menarche to menopause, the cyclic changes in hormone levels are seen as the consequence of pregnancy and surgery. Further, the time span in which the female is under influence of endogenous sex hormones depends on genetic factors as well as dietary and socio-economic factors. The sources of exogenous sex hormones are mainly oral contraceptives and hormone replacement therapy.

2. Endogenous hormones and the risk of stroke

Some have suggested that the lifetime exposure to ovarian estrogen affects the risk of stroke in such a way that longer lifetime exposure is protective, while early menarche increases the risk of stroke. This could, however, to some degree, represent socio-economic factors.

3. Exogenous sex hormones and the risk of stroke

As cerebrovascular disease as well as cardiovascular disease occurs at later ages in women, it has been suggested that women were protected against thrombo-embolic events by the high premenopausal estrogen levels. After menopause, hormone replacements therapy has been suggested as a potential protective agent. However, an association between oral contraceptives and ischemic stroke has been known for 40 years. The debate remains if this concern is related to dose or formulation, or is only relevant for women with other specific risk factor, e.g. factor V Leiden-mutations or hypertension. It has been suggested that estrogen reduces the risk of developing atherosclerosis in the pre-menopausal woman, while estrogen in the postmenopausal woman with established atherosclerosis increases the risk of vascular insults.[5,6]

4. Oral contraceptives (OC)

The OCs contain artificial estrogen and/or progestin, and a combination is the most commonly used. The combination may be monophasic, biphasic, that is three different doses in three-phase pill (3 months with one bleeding), transdermal formulations, or vaginal ring formulation. Four generations are described in OC depending on the type of progestin and estrogen dose. Levels of ethyl estradiol vary from 20 to 50 μg in 2nd and 3rd generation OCs. The effect of estrogen is to prevent the release of FSH and keeping the ovaries inactive, while progestin thickens the cervical mucus and prevents implantation in the uterus. The lowest expected failure rate is <2%, and typical expected failure rates are <3–5%. The estimated risk of death, mainly cardiovascular death, is 1/66,700. A large number of cohort and case–control studies have been published and shows a consistent increase in stroke risk in users of OC; however, the absolute risk in the population is small. A number of factors appear to affect the size of the risk including high estrogen dose, progestin generation, smoking, and hypertension. Migraine is a risk factor of ischemic stroke with a relative risk of 3. The combination of migraine, tobacco use, and OC prescription appears to be especially perilous as it increases the risk of ischemic stroke up to OR 35. However, the definition of OC users as well as the stroke diagnosis adjudication varies between studies, which may result in overestimation of stroke risk especially in the younger patients. No randomized controlled trials are available. Based on existing observational studies, the absolute risk of ischemic stroke – in an OC user with no other risk factors of stroke – may be estimated to be 0.0041%/year.[7]

5. Hormone replacement therapy (HRT)

HRT is used to diminish menopausal discomfort and has been suggested to reduce the risk of vascular disease based on the observation that this mainly occurs in later ages in women. Observational cohort studies in postmenopausal women have shown a consistent reduction in risk of ischemic heart disease with 50%; however, the results for stroke have been less clear. There are four randomized controlled trials that have investigated this subject, and none of these supports the theory that HRT reduces the risk of stroke or heart disease.

6. HERS study (heart and estrogen–progestin replacement study)

This was a randomized controlled trial of HRT (conjugated equine estrogen and medroxy progesterone acetate) vs. placebo in 2763 postmenopausal women, mean age 67 years. The mean observation time was 4.1 years and primary outcome was fatal and non-fatal stroke. 5% of the included women had 1 or more strokes. HRT did not significantly affect the risk of stroke; however, a non-significant increase was observed. This is a primary prevention study.[1]

Findings of HERS study did concur with many recent observational studies that reported no significant association between postmenopausal hormone therapy and stroke risk.[8–16] However, some studies examining the relation between postmenopausal hormone therapy and stroke have reported that hormone therapy decreases stroke risk[17–21] and the Framingham Heart Study reported that it increased risk of stroke, at least among smokers.[22]

7. WEST study (women's estrogen for stroke trial)

This was a randomized controlled trial of estradiol −17β vs. placebo in 64 postmenopausal with ischemic stroke or TIA within 90 days of the randomization. Mean age in the treatment group was 72 years and 71 years in the placebo group. The mean observation time was 2.8 years and primary outcome was stroke and secondary outcome TIA. A total of 89 deaths and 103 non-fatal strokes occurred during the trial. HRT