Menopause and ischaemic stroke: basic, clinical and epidemiological considerations. The role of hormone replacement

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Stroke is a leading cause of disability and death in women, despite progress in its prevention and treatment. As with coronary artery disease, the incidence of stroke rises after the menopause, in parallel with metabolic changes that add up to create an unfavourable risk factor profile for cardiovascular disease. The menopause metabolic syndrome, which includes weight gain and changes in lipids, insulin resistance, endothelial dysfunction, increased levels of homocysteine, lipoprotein (a) and several coagulation factors, may in part be attributable to estrogen deficiency, and may be reversible with hormone replacement therapy (HRT). As for blood pressure, a major detrimental risk factor for stroke, it is probably not affected by either the menopause per se or by HRT. Abundant experimental data exist indicating that estrogens have both anti-atherosclerotic and neuroprotective effects. The width or thickness of the carotid wall is a good indicator of carotid atherosclerosis; it increases after the menopause transition, and decreases with HRT. Estrogens may enhance cerebral blood flow and reduce vascular resistance. In animal models of stroke, estrogen induced anti-ischaemic effects. Several large-scale epidemiological studies have verified the concept of primary protection of stroke by HRT, though others have failed to do so. In light of these contradictory data, several recent reports were highly significant (Nurses’ Health Study, HERS Study, Cancer Prevention II Trial, WEST Trial). Despite the known neural and vascular benefits of estrogen, it is uncertain whether HRT is associated with stroke protection. At present, prevention of stroke should involve proven risk reduction strategies.

Key words: cerebrovascular disease/hormone replacement therapy/ menopause/stroke

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Menopause and risk of stroke

Stroke remains a leading cause of disability and death in women, despite progress in its prevention and treatment. A 50-year-old white woman in the USA has a 20% lifetime probability of developing stroke, and an 8% probability of dying from the condition (Grady et al., 1992). One study in the USA claimed that one in six American women would die from stroke (Bonita, 1992). Thus, although cerebrovascular diseases are as important as coronary artery disease and breast cancer in women’s health, they somehow have not received sufficient public attention in the context of menopause medicine, despite many articles on this issue.

Basically, stroke is a disease of old age, the incidence increasing from age 65 years onward (Brown et al., 1996; Manolio et al., 1996). Ischaemic stroke is rare in premenopausal women however, and the few cases of stroke in young women are mainly attributed to either embolism or haemorrhage. Before the age of 65 years, women demonstrate strikingly less cerebral atherosclerosis than men, but later on the incidence is comparable (Flora et al., 1968; Sacco et al., 1997). Interestingly, and very similar to coronary artery disease, once a woman has had a stroke, the course of the disease and her prognosis is worse than that in a
man (Bousser, 1999). The main risk factors for stroke in women, as in men, are age, hypertension and metabolic alterations that induce accelerated atherosclerosis (Bronner et al., 1995; Rosenthal and Oparil, 2000).

**Hypertension**

The lifetime risk for hypertension in a 50-year-old woman exceeds 60% (Cummings et al., 1989). Epidemiological studies agree that under the age of 40 years, systolic pressures are higher in men than in women, but by 60 years they are higher in women (Miall and Lovell, 1977; Sigurdsson, 1983; Landahl et al., 1986). Diastolic pressures increase less steeply, and to a similar degree, with age in both sexes (Wilson et al., 1985). Data on changes in blood pressure during the menopause transition are contradictory, but in summary there appears to be no interaction (Hjortland et al., 1976; Lindquist, 1982; Staessen et al., 1989). In a recent longitudinal study (Matthews et al., 2001), the systolic blood pressure and the pulse pressure increased significantly from the first to the fifth year post menopause, whereas a small increase in blood pressure from premenopause values to first year post menopause did not reach statistical significance. Hypertension is an important risk factor for stroke: according to the Framingham study, women with blood pressure values of 160/95 mmHg or higher had an age-adjusted relative risk of 2.9 for stroke (Elkind et al., 2001). Stroke risk is higher in cases with increased insulin resistance or hyperinsulinaemia without hyperglycaemia (Shinozaki et al., 1996). Indeed, the width or thickness of the carotid wall, which is considered to be a good indicator of carotid atherosclerosis, was may have been due to either the effect of ageing or of weight gain (Writing Group for the PEPI Trial, 1995). However, several small-scale studies were able to demonstrate favourable changes in blood pressure in hypertensive women taking HRT, either during exercise or in 24-h ambulatory blood pressure recordings (Mercuro et al., 1997; Pines et al., 1998). Apart from a suggestion of preference for the transdermal route in diabetic patients, a broad-based recommendation for the use of hormones in diabetics cannot be made (NAMS, 2000). However, both the Nurses’

**Diabetes mellitus**

Diabetes mellitus, a major risk factor for atherosclerosis and cardiovascular diseases in women, increases the risk for stroke by a factor of at least 2 to 3, especially in older women (Biller and Love, 1993). Stroke risk is higher in cases with increased insulin resistance or hyperinsulinaemia without hyperglycaemia (Shinozaki et al., 1996). In view of data showing that tight control of both glycaemia and blood pressure may reduce the vascular complications of diabetes, including stroke (UK PDS Group, 1998), and may decrease mortality rate after stroke (Wang et al., 2000), such measures are highly recommended (NAMS Consensus Opinion, 2000). In the Nurses’ Health Study, the relative risk for stroke in women with type 2 diabetes was 5.4, and was even higher in those who were also smokers (Manson et al., 1991). Ten years after cessation of smoking, the cardiovascular mortality risk was decreased to a value comparable with that in non-smoking diabetic women (Al-Delaimy et al., 2001).

**Menopause metabolic syndrome and hypercholesterolaemia**

In recent years, the concept of a ‘menopause metabolic syndrome’ has gained popularity (Spencer et al., 1997). This refers to a series of alterations, related to estrogen deficiency, which become evident in post-menopausal women and add up to create an unfavourable risk factor profile for cardiovascular disease. The main features of the syndrome include weight gain and changes in lipid profile [raised low-density lipoprotein (LDL) cholesterol; lowered triglycerides (TG)], insulin resistance, endothelial dysfunction, increased levels of homocysteine, lipoprotein (a) and several coagulation factors as well as fibrinolytic factors. Unlike the case with coronary artery disease, the relationship between serum cholesterol and stroke risk is unclear, and most data have so far shown no correlation (Prospective Studies Collaboration, 1995). Although an analysis of earlier studies on the effect of lipid-lowering medications on stroke risk showed no association (Herbert et al., 1995), recent studies on women with statins revealed some beneficial results, especially in patients with coronary artery disease (Amarenco, 2001).

The net result of all the above-mentioned metabolic changes is an increased risk for cardiovascular diseases and atherosclerosis. Indeed, the width or thickness of the carotid wall, which is considered to be a good indicator of carotid atherosclerosis, increases after the menopause. Premenopausal women have thinner intima-media values and fewer carotid focal plaques than their post-menopausal counterparts (Dobs et al., 1999). Women having an early menopause demonstrate thicker intima-media than women entering menopause at a relatively late age (Joakimsen et al., 2000). Others (Matthews et al., 2001) found that the increase in intima-media thickness observed between premenopause and the fifth year post menopause correlated with the cardiovascular risk factor profile of the study participants, mainly blood pressure, lipids, fasting glucose and body mass index.

**HRT and risk factors for stroke**

The overall effect of hormone replacement therapy (HRT) on blood pressure is considered to be negligible. A 3-year follow-up in the PEPI trial did not show any difference in blood pressure between the placebo group and the hormone group, although a small increase in blood pressure was recorded in all groups (this may have been due to either the effect of ageing or of weight gain) (Writing Group for the PEPI Trial, 1995). However, several small-scale studies were able to demonstrate favourable changes in blood pressure in hypertensive women taking HRT, either during exercise or in 24-h ambulatory blood pressure recordings (Mercuro et al., 1997; Pines et al., 1998). Apart from a suggestion of preference for the transdermal route in diabetic patients, a broad-based recommendation for the use of hormones in diabetics cannot be made (NAMS, 2000). However, both the Nurses’
As for the menopause metabolic syndrome, most of the metabolic changes related to menopause are reduced, or even reversed after the administration of estrogen (Manolio et al., 1993; Mendelsohn and Karas, 1999; Davidson et al., 2000). Estrogen treatment led to the lowering of LDL cholesterol and elevation of high-density lipoprotein (HDL) cholesterol, a decrease in insulin resistance, and an improvement in endothelial function (through both the vasodilatory and vasoconstrictory mediators). It should be mentioned that adverse metabolic changes might also occur, such as an increase in triglycerides. Concern has also been expressed about the prothrombotic effects of estrogen (Teede et al., 2000), and these could be relevant to the increase in incidence of stroke related to oral contraceptives (Gillum et al., 2000), or to a higher dosage of post-menopausal estrogen replacement (Grodstein et al., 2000). Nevertheless, most of the above estrogen-induced alterations and reactions seem beneficial and may be the basic explanation for a cardiovascular protective effect of estrogen.

**HRT and neuroprotection**

Abundant experimental data exist which indicate that estrogens have a neuroprotective effect (Hurn and Macrè, 2000; McEwen, 2001; Wise et al., 2001). Estrogen has both receptor-dependent and -independent brain actions, mainly affecting neuronal viability and cerebral blood flow. Estrogen has been mentioned in the context of maintaining memory, cognition and mood, and is believed to attenuate the extent of acute brain injury (i.e. during stroke). Recent data, however, have raised some doubts with regard to these effects (see below). Some studies have suggested that physiological concentrations of estradiol protect through estrogen receptor-dependent mechanisms that lead to the transcription of critical genes that ultimately promote cell survival. Estrogen receptor α has an important role (Dubal et al., 2001), although high-dose estradiol seems to protect neurons that do not express estrogen receptors. Among the potential mechanisms investigated in experimental models in the context of neuroprotection by estrogen were the following: endothelial effects that induce vasodilation; anti-oxidant activity; various signalling effects through estrogen receptors; interaction with the bcl-2 proto-oncogenes (involved in cell survival); interaction with neuronal growth factors; alteration of the glutamatergic and γ-aminobutyric acid (GABA) neuronal activity; stimulation of neuronal regeneration; and secretion of neurotransmitters.

In a middle-cerebral-artery-occlusion model, the volume of induced infarcts was smaller in fertile female rats with intact ovaries and normal estrogen secretion than that in castrated female rats or in male rats (Alkayed et al., 2000). The administration of low physiological levels of estradiol 1 week before permanent occlusion of the middle cerebral artery in ovariectomized rats, led to a dramatic decrease in the size of cortical infarction (Dubal et al., 1998). Higher doses of estradiol were equally efficient. The same effect was seen in young rats (3–4 months) and in middle-aged rats (9–12 months) (Dubal and Wise, 2001).

**HRT and carotid/cerebral blood flow**

A substantial volume of the brain mass consists of blood vessels. Numerous studies have determined that carotid and cerebral blood flows each react to estrogens in the same way, and via the same mechanisms as the coronary or peripheral arteries. Thus, the end result of estrogen deficiency states might be a decrease in flow and increase in resistance, whereas the effect of estrogen on the cerebral arterial tree is the opposite. The following are examples of such studies: comparing the ophthalmic artery blood flow and resistance in non-pregnant, pregnant and post-menopausal women showed a correlation with estrogen status, namely the lowest flow and highest resistance were recorded in the post-menopausal women, while highest flow and lowest resistance was seen in pregnancy (Belfort et al., 1995). In a small-scale study (Gangar et al., 1991), an association was demonstrated between time since menopause and carotid artery pulsatility index, a parameter which correlates negatively with blood flow. In the above two studies, after the initiation of estrogen supplementation, a significant positive effect on blood flow was recorded. On the other hand, drug-induced hypoestrogenism during GnRH therapy was not associated with any changes in carotid or middle cerebral artery flows (Penotti et al., 1996a). As for the effect of HRT on cerebral vasculature, many studies have indicated a clear vasoreaction. When long-term hormone users were compared with age-matched non-users, lower carotid vascular resistance was recorded in the users (Naessen and Bakos, 2001). Another group who measured whole cerebral and cerebellar blood flow by single-photon emission computed tomography were able to detect a significant increase in brain perfusion following several weeks of conjugated estrogen (Ohkura et al., 1995). Penotti and colleagues published several studies on the interaction of HRT and carotid/cerebral blood flow. In the first study (Penotti et al., 1993), it was shown that the pulsatility index was reduced in both arteries after 6 weeks of transdermal estradiol at 50 μg/day. Interestingly, cyclical medroxyprogesterone acetate supplementation (12 days per cycle, 10 mg per day) did not modify this positive effect. In a later study from the same investigators (Penotti et al., 1999), cyclical medrogestone acetate (12 days per month, at 5 mg/day) added to continuous conjugated equine estrogen at 0.625 mg/day gave similar results. These authors also demonstrated that the pulsatility index rapidly increased to pre-treatment values following the suspension of hormone therapy (Penotti et al., 1996b). Others (Darj et al., 1999) used a different hormonal combination consisting of oral estradiol and cyclical norethisterone acetate, but could not show any important differences in common, internal or external carotid blood flow between the treated women and a control group. In summary, it is possible that estrogens may enhance cerebral blood flow and reduce vascular resistance, though there are studies in which such an effect was either marginal or not present.

**HRT and carotid atherosclerosis**

The intima-media thickness, evaluated by B-mode ultrasonography, is considered a good marker for atherosclerosis. Many studies which have investigated stroke risk or myocardial infarction risk, used this parameter. The Healthy Women Study assessed a possible association between menopause and carotid
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artery atherosclerosis (Matthews et al., 2001). Women were followed from the premenopausal period until several years post menopause. Premenopausal values of blood pressure, lipids and body mass index predicted intima-media thickness and carotid plaque score 5–8 years after menopause. Two large surveys, one from the United States (Atherosclerosis Risk in Community) (Dobs et al., 1999) and the other from Norway (Joakimsen et al., 2000), demonstrated that menopause is associated with thickened carotid artery walls. The Norwegian study also showed an inverse relationship between age at menopause and carotid atherosclerosis, namely that women having a late menopause had relatively less atherosclerosis than women entering menopause at an early age. Clearly, this effect on the structure of the arterial wall was considered as another aspect of the vascular damage inflicted by estrogen deficiency. The importance of estrogen status has also been demonstrated while comparing hormone users with non-users. In all those studies, HRT was associated with thinner intima-media (Baron et al., 1998; Dobs et al., 1999; Joakimsen et al., 2000). In one study, the adjusted odds ratio for carotid atherosclerosis in ever-users of estrogen was 0.75 as compared with never-users, a very significant preventive effect (Joakimsen et al., 2000). A thinner intima-media was also observed in a cohort of women aged 65 years or older who used HRT (Manolio et al., 1993). The above data point to a protective effect of hormones, possibly through retardation of atheroma formation. The studies of Clarkson and colleagues on monkeys should also be mentioned in this respect (Clarkson et al., 2001). Animals were fed an atherogenic diet and developed arterial plaques that could be measured. Some were also given estrogen, and this resulted in a substantial decrease in plaque size. Interestingly, soy protein extract containing phytoestrogens had the same beneficial effect as estrogen. Few data exist on the effect of progestins. An early study containing phytoestrogens had the same beneficial effect. The lack of consistency in stroke endpoints, definition of HRT user, estrogen preparation, and influence of combined regimen might account in part for the unclear association between HRT and risk of stroke. Also, the definition of a cerebrovascular event usually includes ischaemic stroke, haemorrhagic stroke and subarachnoid bleeding. Those three entities are different in pathogenesis and risk factors, and therefore should be evaluated separately. Table I, which shows data from selected major studies on HRT and stroke risk, clearly demonstrates the inconsistency and wide variability in their methodology and results (Pfeffer, 1978; Wilson et al., 1985; Falkeborn et al., 1993; Finucane et al., 1993; Folsom et al., 1995; Pederson et al., 1997; Schairer et al., 1997; Petitti et al., 1998; Sourander et al., 1998; Fung et al., 1999; Godstein et al., 2000; Rodriguez et al., 2001).

A non-traditional approach was used in two recent relevant trials: the Cardiovascular Health Study performed brain magnetic resonance imaging (MRI) scans on 2100 healthy women aged over 65 years (Luoto et al., 2000). Although MRI scans identified infarcts (mostly small and asymptomatic) in about 30% of the cohort, the prevalence of MRI infarcts did not differ among current users, past users or never-users of hormones. White matter changes were associated with the score of the Mini Mental State Exam, but not with hormone use. Another study investigated a possible correlation between hormone use at the time of stroke and stroke severity (according to the Canadian Neurological Scale score) (Bushnell et al., 2001). The score was 10 for hormone users and 9.5 for matched non-users, interpreted by the authors as a non-significant trend toward lesser stroke severity in hormone users. However, multivariate analysis showed no independent effect of hormone therapy.

Secondary prevention of stroke by HRT

There is very little information available on this issue. In a trial of aspirin and HRT in women who suffered a transient ischaemic attack (TIA), hormone users had a RR for stroke of 0.23 compared with non-users (Persantine aspirin trial; The American-
Canadian Co-operative Study Group, 1986). Others (Viscoli et al., 2001) recently published data from the Women’s Estrogen for Stroke Trial (WEST). A total of 652 post-menopausal women with stroke/TIA within 90 days of entry were randomized to estradiol at 1 mg/day or placebo. The follow-up period was 3 years, and drug compliance was 76% at year 1. Non-fatal stroke, death rate and adverse events were similar for both groups. The relevant results on stroke obtained in the HERS trial (Simon et al., 2001) will be mentioned later, as this was a secondary prevention trial in women with known coronary artery disease at baseline, but no history of cerebrovascular disease. A recent Medline and web search on HRT in stroke patients was largely unproductive because of a paucity of information (Damczyk and Gardner, 2000). The authors concluded that there are no data available which specifically examine the value and safety of HRT use in women with a history of stroke.

Recent data from major epidemiological studies

It should be noted that the characteristics of a cohort, its sample size and methodology differed from study to study on stroke risk and HRT in the menopause, and this perhaps explains the diversity of results obtained in those trials. To resolve this uncertainty about a possible benefit of HRT in the prevention of cerebral events, one of the following two investigations would be needed: either a very long-term observational study on a very large cohort; or (preferably) a double-blind, placebo-controlled study. Fortunately, three reports have been published during the past 12 months, which may fit the above specifications.

The first summarizes the latest experience from the Nurses’ Health Study, which is a primary prevention observational trial (Grodstein et al., 2000). The data were derived from biennial questionnaires filled by more than 70,000 female nurses who were followed-up since 1976. This study is unique in its scope, as 767 strokes were identified during a 20-year follow-up. The main findings of the study were as follows:

1. Overall, there was little association between current use of hormone and stroke risk, but the relative risk for ischaemic stroke was 1.23.

2. Relative risk correlated with dosage of conjugated equine estrogen: 0.54 for the 0.3 mg daily dose, 1.35 for the standard 0.625 mg daily dose, and 1.63 for the 1.25 mg daily dose. This means that only the low-dose estrogen was protective, while most of the women were exposed to a higher risk of stroke because of HRT.

3. Relative risk for the use of estrogen only was 1.18, whereas relative risk for combined estrogen-progestin was 1.45. It should
be noted that the cardioprotective effect of estrogen was similar for both the small and standard doses.

The Cancer Prevention Study II addressed cardiovascular mortality in healthy post-menopausal women (Rodriguez et al., 2001). Women with significant diseases or incomplete data regarding their menopause were excluded. The cohort was huge (about 290,000 participants) and the follow-up period was 12 years. There were 12% ever-users of hormones and 22% past users. During follow-up, about 31,000 women died, 2390 from stroke; hormone use was associated with a 19% reduction in stroke risk.

The above two studies were primary prevention observational trials. A recent publication from the HERS Study, a secondary prevention double-blind, placebo-controlled trial, investigated women in late menopause with proven coronary artery disease during a follow-up period of 4.1 years (Simon et al., 2001). Women who were included in the hormone treatment arm were assigned to receive a continuous combined regimen of conjugated equine estrogen at 0.625 mg plus medroxyprogesterone acetate at 2.5 mg daily. A total of 149 women suffered a stroke, and 85% of the strokes were ischaemic. Although increasing age, hypertension, atrial fibrillation and current smoking were risk factors for stroke, HRT was not significantly associated with risk for stroke. However, there were six more fatal strokes and 10 more non-fatal strokes among hormone users, leading to a 2% absolute difference in stroke risk between the hormone and placebo groups. One additional study was of interest (Aingeja et al., 2001) in which the occurrence of in-hospital strokes immediately following acute myocardial infarction in women was examined. The cohort included 114,724 women aged 55 years or older, of whom 0.9% suffered an ischaemic stroke. When stratified by hormone use, the rate was similar for both users and non-users.

Conclusions

During the past year, the issue of post-menopausal hormone use and stroke risk was discussed in an overview (Paganini-Hill, 2001), an editorial (Tolbert and Oparil, 2001), and two statements from the American Heart Association (Goldstein et al., 2001; Mosca et al., 2001). All of these authors reached the same conclusions. It seems that, despite ample animal data being available on neuroprotection by estrogen, plus the beneficial effects of estrogen on risk profile for cardiovascular disease, plus the vasodilatory properties due to endothelial and non-endothelial mechanisms, the conclusion remains somewhat unclear, disappointing and confusing because of the non-uniform results in the major studies. In addition, there is a lack of high-quality, randomized, double-blind studies on this important issue. The data on primary prevention are derived from observational studies, which are subject to bias. Despite the large numbers of women evaluated in those studies, modern epidemiology is looking for results from evidence-based medicine. Although it is felt that observational trials are valuable, the paucity of controlled studies unfortunately leaves unanswered the question of whether HRT reduces the risk of stroke. At early stages, the development of carotid and cerebral atherosclerosis might be influenced by hormones, and so long-term hormone users might have fewer ischaemic strokes. Also, there is no clear basis for an assumption that HRT affects the progression of established carotid atherosclerosis or changes the risk in women who have already suffered cerebrovascular events. Recent studies on coronary artery disease and cerebrovascular disease point at a possible role for the type and dosage of hormone regimens. We support the current consensus of opinion that HRT should not be considered as a specific measure for primary or secondary prevention of stroke. Protection from ischaemic stroke should comprise proven risk reduction strategies, such as aggressive treatment of blood pressure, prescribing aspirin, tight glycaemic control and cessation of smoking (Goldstein et al., 2001).

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References


Menopause and ischemic stroke


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