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Review paper

Hormone Replacement Therapy – Is There a Place for Its Use in Neurology?

Vlasta Vuković[1], Arijana Lovrenčić-Huzjan[1], Vesna Vargek Solter[1], Veljko Đorđević[2] and Vida Demarin[1]

[1] Department of Neurology, University Hospital »Sestre milosrdnice«, Zagreb, Croatia
[2] Department of Psychiatry, University Hospital Center »Zagreb», Zagreb, Croatia

A B S T R A C T

Stroke remains the third leading cause of mortality in developed countries despite declining tendency over the past decades. As the leading cause of disability and second cause of dementia, primary prevention should be the main way to fight the disease, since therapy is not efficient enough. Several observations pointed to estrogen as a protective agent that may reduce stroke risk, however, studies have shown conflicting data. There is no strong evidence that hormone replacement therapy (HRT) increases stroke risk. Several studies have shown that HRT may reduce the risk of fatal stroke. Conflicting results have been found for Alzheimer's disease and HRT as well. An association between higher serum concentration of estradiol and decreased risk of cognitive decline has been found in some studies, supporting the hypothesis that estrogen concentration may play a significant role in brain protection. Having in mind results of recent randomized trials, it is suggested that HRT should not be recommended on general basis for the primary or secondary prevention of cardiovascular/cerebrovascular diseases or for primary prevention of degenerative diseases such as Alzheimer's disease. Osteoporosis, cognitive decline and climacteric symptoms that are likely to impact on quality of life, speak in favor for recommendation of HRT use. On the other side, family history of breast carcinoma, mastopathy, thromboembolism, in certain cases gallbladder disease, will discourage the commencement of HRT. Respecting the patient's preferences and having benefits and risks in mind as well as science advisory statements, individual counseling regarding HRT should be the leading concept in the healthcare of postmenopausal women.

***Key words**: hormone replacement therapy, stroke, postmenopause*

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Introduction

The ovaries produce estradiol and progesterone on a cyclic schedule from puberty to menopause. These hormones have significant influence not only on sexual target organs such as the uterus, breast, vagina and skin, but also on the brain, urinary tract, kidneys, liver, bones, myocardium and arterial walls. Human ovaries stop secreting hormones when women are approximately 50 years of age. However, more than 50% of these postmenopausal women are able to synthesize estradiol outside the ovaries and do not experience the full consequences of estradiol deprivation[1–3].

Symptoms that occur during the climacteric phase of a woman's life may begin premenopausally or long before her last menstrual period. The onset of these symptoms fluctuates between the early forties and late fifties. The hormonal treatment of menopausal women has been controversial: what to give, when to start and for how long are the questions that physicians still need answers for.

Since the 60s, efforts have been made to identify and offer exogenous replacement of ovarian estradiol to women at risk of estrogen deficiency. Hormone replacement therapy aims to restore physiological levels of estrogen, in order to prevent estrogen deficiency symptoms and diseases resulting from the menopause. The benefits of estrogen replacement may be modified by the addition of progesterons, which are necessary to protect the endometrium in a woman with an intact uterus. In recent years, an increasing number of different estrogen formulations and doses have become available.

The need for improving the quality of life for postmenopausal women has become a serious matter in medical care. Longevity has naturally improved, and with it, quality has become considerably more important.

Although HRT has been available for 50 years, the indications for its use have gradually widened from relief of current menopausal symptoms to prevention of future osteoporotic fractures or coronary heart disease.

Benefits attributed to the use of HRT:

1. Menopausal symptoms – a positive effect of estrogen treatment on symptoms such as hot flushes, sleep disturbances, asthenia, mood instability, vaginal dryness and urinary tract infection can be expected

2. Bones – important part of preventive medicine in reducing bone loss in the short term and risk of fracture in the long term; the benefits appear to be restricted only to current users, since never and past users had similar fracture risks 5–10 years after HRT was stopped[4].

3. Plasma lipids – estrogens induce increase of HDL cholesterol and decrease of LDL cholesterol[5], estrogen reduces plasma levels of apolipoprotein E.

4. Artery intima-media thickness (IMT) – intima media thickness can be measured by high-resolution ultrasound, changes are correlated with atherosclerotic progression. HRT may influence the IMT in women over 65 years[6,7]. However, recent data are conflicting. A trial of postmenopausal women with increased IMT showed that treatment with estrogen (with or without progestin) had no effect on the progression of carotid IMT despite significant beneficial effects on LDL and fibrinogen[8].

5. Plaque formation may also be reduced by the modification of the inflammatory response by estrogen, via its effects of interleukin 6, a cytokine postulated to participate in plaque formation[9]. Estrogen has also been found to have antioxidant properties via its action on free radicals[10]. Estrogen prevents platelet aggregation by influencing the production

of prostacyclin, which opposes thromboxane.

6. Cardiovascular system – a 50% reduction in the relative risk of almost all vascular events has thought to be associated with HRT, however, recent studies found no significant decrease in the risk of coronary events[11]; this may be related to the fact that these studies used conjugated equine estrogens (CEE) + medroxyprogesterone acetate (MPA).

7. Vasomotor effects – vascular benefits include re-establishing the physiological vasoactive response to ischemia, exercise or cold; estrogen may also exert antihypertensive effects in premenopausal women; other studies have revealed that it increases both cerebral blood flow and cerebral glucose utilization[6].

8. Mood – estrogen influences brain functions that potentially impact mood and behavior, in general having a positive effect. Older postmenopausal women who use estrogen typically report fewer depressive symptoms than non-users. Beneficial effects of estrogen replacement on mood are most often reported in healthy women without diagnosed depression. Among postmenopausal women in randomized trials, active treatment reduced depressive scores and had a substantial beneficial influence on the quality of life[12]. Other controlled studies, however, reported no effect on mood[13].

Stroke and HRT

Stroke remains the third leading cause of mortality in developed countries and the first cause of mortality in Croatia[14]. Furthermore, stroke is the second cause of dementia and the leading cause of long -term disability. About 80% of strokes are ischemic, 15% hemorrhagic and 5% of other etiologies. Because stroke is often fatal and the impact of treatment on prognosis is limited, control of the disease should be through primary prevention.

Experimental studies have shown improvement in stroke outcome in animals treated with hormones-estrogen seems to exert neuroprotective effects[15]. After experimental carotid occlusion, female rats have shown decreased cerebral infarcts and less tissue damage than age-matched male rats[16]. Additionally researchers found that pretreatment of ovariectomized rats with estradiol significantly reduced infarct volume following middle cerebral artery occlusion, although acute treatment had not[17]. Recent evidence suggests that estrogen acts, in part, by increasing nitric oxide (NO) in the cerebrovascular endothelium; NO is produced by the enzyme endothelial nitric oxide synthase (eNOS) to cause vasodilatation and inhibit platelet aggregation[18].

Since observational studies have shown that HRT has been associated with a 35% reduction in risk of chronic heart disease (CHD), it has been suggested that HRT may reduce stroke risk through modification of intervening risk factors in the similar way as it reduces the risk of CHD as stroke and CHD share many risk factors[19].

In the past 25 years, 26 observational studies (in 37 articles) have evaluated the effect of HRT on stroke risk in postmenopausal women. Five case control studies, which were examining the association of HRT and risk of all strokes or ischemic strokes, reported null effects, with relative risks ranging from 0.97 to 1.20[20–24].

Among four uncontrolled cohort studies, two found a 20–50% reduced risk (statistically significant) of stroke among estrogen users, while in two there was only a trend to reduction[25–28]. Among twelve of the 15 internally controlled cohort studies, four found a reduction of 30% or more in stroke risk among estrogen users, and in eight there was a trend to reduction[29–32]. According to these studies, the association of estrogen and stroke is not consistent. The relative risk for to-

tal stroke from all studies ranged from 0 to 3.2. Furthermore, surveys comparing current users with never or past users did not find any significant decrease in the risk of coronary events, but found an increase in transient ischemic attacks and strokes[23,33].

In 2001, Paganini-Hill summarized the literature on HRT and stroke and concluded that there was little, if any association[34].

Some data indicate that estrogen users have a moderately reduced risk of fatal stroke, but details about the optimal dose, duration and type of estrogen are insufficient[34]. Larger doses have shown association with increased stroke risk[26]. Recent data from the Nurses Health Study (NHS) (observational cohort study including 70,533 postmenopausal women) have shown that risk of ischemic stroke was significantly increased among those women receiving 1.25 mg conjugated estrogen daily (RR = 2.1) as well as in women taking 0.625 mg daily (RR = 1.4), but not in those receiving 0.3 mg daily (RR = 0.4)[35]. Increased stroke risk may be induced by the procoagulant effect of HRT when using higher doses.

No clear trend (decreasing/increasing risk) could be found in relation to duration of HRT in ischemic stroke but the risk for fatal stroke seems to be reduced in both long-term and short-term users[24,32]. The Leisure World Study found risk of occlusive stroke decreased with increasing recency of use (for trend, $p<0.05$); women who had used estrogen replacement therapy within one year of study enrollment had the lowest risk (RR = 0.7, $p<0.05$)[36]. However, three other studies found no effect of current use on stroke risk (RR= 1.0–1.2) and 1 study showed increased risk in current users (RR = 1.3) but not in past users (RR = 1.0)[21,23,24,35].

Evidence for effect of HRT on stroke is most consistent for fatal stroke; all but two of nine studies found at least 20% reduced risk in current users[32,35,37–43]. Both low (<0.625 mg) and high (>1.25 mg) doses of oral conjugated equine estrogens were associated with significantly reduced risk of fatal stroke (RR = 0.4)[32]. The only apparent difference in the findings of studies of fatal and non-fatal stroke suggests that estrogen may prevent the most lethal form of stroke or may improve survival.

Reports of effect of HRT on SAH are also differing. Two case control studies found a 35–50% reduced risk among ever users of estrogen (significant in one)[44,45]. One uncontrolled cohort study found that HRT was associated with a non-significant increased risk of SAH (RR = 1.2)[46]. In three studies hemorrhagic strokes were analyzed together. No effect of estrogen therapy was found in two and in one a significantly reduced risk in current users[20,24,36].

So far studies have not shown beneficial effect of HRT in a stroke subtype since most epidemiological studies have grouped together all stroke subtypes. We can speculate that HRT might affect risks of stroke subtypes in a different way, combining them would not show beneficial effect but mask a positive effect in a subgroup. This may be one of the reasons for observed scattered relative risks in epidemiological studies[21,23,24,28]. The preponderance of evidence in these studies suggests however that HRT does not increase the risk for stroke.

Several randomized, placebo controlled studies have recently been published: The Women's Health Initiative (WHI)[47], Heart and Estrogen-progestin Replacement Study (HERS)[48,49], The Estrogen Replacement and Atherosclerosis Trial (ERA)[50] and Women's Estrogen for Stroke Trial (WEST)[51]. We discuss these studies more thoroughly.

The Women's Health Initiative trial has been recognized as one of the most important (and one of the largest) prevention studies ever conducted. A total of 16,608 postmenopausal women aged 50–79 years with an intact uterus were randomly assigned to receive either CEE 0.625 mg and MPA 2.5 mg daily, or placebo. The third group of 10 739 hysterectomized women received 0.625 mg CEE (without progestin). After a mean of 5.2 years of follow-up the trial of estrogen plus progestin vs. placebo was stopped when the results met predetermined levels of harm for breast cancer. The excess risk of stroke in the estrogen plus progestin group was not present in the first year but appeared during the second year and persisted through the fifth year. No interaction with age, ethnicity, body mass index, prior hormone use, smoking status, blood pressure, diabetes, aspirin or statin use were found for the effect of estrogen plus progestin on CHD, stroke or VTE (venous thromboembolism). Therefore it appears that estrogen plus progestin increases the risk of stroke in apparently healthy women. The trial results indicate that risk reduction attributable to this HRT regimen is low and not beneficial overall; there is early harm for CHD, continuing harm for stroke and VTE, and increasing harm for breast cancer with increasing duration of treatment. All –cause mortality was not affected during the trial. The absolute excess risk events included in the global index was 19 per 10,000/person years-in another words – 1000 women would have to be treated during 1 year in order to cause two events. Beneficial effects were observed for colorectal cancer and hip fractures. This risk-benefit profile is not consistent with the requirements for a viable intervention for the primary prevention of chronic disease. The WHI report stresses that the results do not necessarily apply to lower dosages of those drugs, to other formulations of oral estrogen and progestin or other route of administration.

There was a high differential unbinding rate in the WHI study (40.5% in the HRT vs. 6.8% in the placebo group), mostly due to vaginal bleeding, but there was no information about which of the age groups had the bleeding. Thus this fixed regimen of HRT is obviously not suitable for all women, and does not reflect good clinical practice[47].

In HERS, a total of 2,763 postmenopausal women with established coronary disease was taking either 0.625 mg/d of CEE plus 2.5 mg/d of MPA or placebo and were followed-up for 4.1 years. The results showed no significant difference between groups in the primary outcome (occurrence of nonfatal myocardial infarction or CHD death (RR 0.99) or secondary outcome (stroke or TIA, coronary revascularization, unstable angina, congestive heart failure, and peripheral artery disease). The results showed a statistically significant time trend with more CHD events in HRT group in year 1 and fewer in years 4 and 5, thus the authors have not recommended starting this treatment for the purpose of secondary prevention of CHD. Given the favorable pattern of CHD events after several (4–5) years of therapy, the authors assume it could be appropriate for women already receiving the treatment to continue. However, in a re-analysis of the study (HERS II), follow-up during 6.8 years of HRT has shown that lower rates of CHD events among women in the hormone group in the final years of HERS did not persist during additional years of follow-up. Furthermore, more women in the hormone group than in the placebo group experienced venous thromboembolic events (RR 2.89) and gallbladder disease (RR 1.38)[48,49].

The Estrogen Replacement and Atherosclerosis Trial (ERA), was the first randomized angiographic end-point trial

to test the effect of ERT and HRT on the progression of atherosclerosis in postmenopausal women with documented coronary stenosis. The results showed no benefit of CEE (0.625 mg) + MPA (2.5 mg) on angiographic progression of the disease. An arm of the ERA trial tested a group of women taking only estrogen vs. placebo, the results showed no angiographic benefit of the hormone group as well[50].

In the Women's Estrogen for Stroke Trial of estradiol (without progestin) (WEST), the first double blind, placebo-controlled trial among postmenopausal in women with prior stroke, no effect of estrogen on recurrent stroke or death was found. Furthermore, women randomized to estrogen had a significant increase in the risk for fatal stroke and more severe neurological impairments after stroke[51].

The studies of HRT and stroke had a number of potential biases: most data were derived from observational studies not randomized trials; the number of cases included was often very small reaching low statistical power; confounding factors such as concurrent medications were often not considered; comparison between – ever/never users was usually made and not evaluating the duration of use/current use etc; often not specific (varying) definitions of stroke end-points were used as well as specific stroke types were not considered; HRT use patterns were different among studies – estrogen, progesterone, combination, doses, duration etc.

The problems of data interpretation from observational studies due to the diversity of studies are well recognized, however, the overall results and meta-analysis of these studies should be taken into consideration when giving final recommendations.

On the other hand, randomized, double blind, placebo-controlled trials such as WHI or HERS have failed to show benefit of HRT in primary/secondary prevention. Several explanation have been suggested for the overall null effect: relatively short time of follow up, adverse effects of MPA, bidirectional effects of estrogen (early risk and late benefit), a combination of hormones (CEE+MPA) that was not ideal for all women, a subgroup of women too old to benefit from such therapy. Randomized clinical trials have inclusion and exclusion criteria much more rigid than observational studies, hence results are valid only for those who meet those criteria.

Recommendations of the WHI writing group and HERS trial are given on general basis and focus on public rather than individual health. The data describe increased risk (stroke, VTE,) of general population of women (healthy in WHI or with CHD in HERS), but not the increased risk for individual woman. Although WHI, HERS and similar studies are important, they only failed to show clinical effectiveness of a specific hormone regimen in certain population groups. Nevertheless, a message sent from these studies is not to recommend HRT for the sole purpose of chronic disease prevention (primary or secondary).

It has been suggested that the results of secondary prevention trials may not be applicable to younger women because it is less common for the occurrence of cardiovascular events before the 6th decade of life. Furthermore, one can hypothesize that the development of CHD could be more easily preventable than to slow the progression once established if women were given HRT early enough after menopause. So far, no controlled trial addressed the timing of initiation of HRT on rates of CHD events.

Alzheimer's disease and HRT

During the past decade, a significant number of studies have been conducted to explore the possibility of a connection be-

tween sex hormones and dementia[52]. Alzheimer's disease (AD) is the most common dementing illness and is associated with significant morbidity and mortality among older adults[53]. Recent advances in understanding neurophysiology have led to the potential use of estrogen as an agent that can favorably alter the pathobiology of AD and may lead to improvement of cognitive decline associated with the disease.

Several biologic mechanisms by which estrogen could affect cognitive functioning and dementia have been postulated. Estrogen may affect the progression of Alzheimer's disease via its effects on the metabolism of amyloidal precursor protein (APP) by reducing plaque formation[54]. Promotion of cholinergic activity in the brain and stimulation of axonal sprouting have been observed[55,56]. Estrogens administered prior to a diagnosis of Alzheimer's disease showed some positive effects due to its anti-inflammatory properties. Although estrogen has antioxidant qualities, the hormone is thought to be unable to slow progression of the disease after onset. However, studies have shown that women with AD taking estrogen perform better on a variety of cognitive tasks than women with AD who are not taking estrogens[57,58].

Published trials of HRT for women diagnosed with Alzheimer's disease have produced conflicting evidence regarding the potential benefits of the hormones.

Up to date no firm data can be offered that HRT can be used as a treatment for Alzheimer's disease[59]. Recent randomized, double blind, placebo-controlled studies failed to show an enhancement of cognitive function by estrogen. The Alzheimer's Disease Cooperative Study, a randomized, double blind placebo controlled study included 120 women diagnosed with mild to moderate Alzheimer's disease who were taking two different dosages of estrogens (0.625 mg or 1.25 mg daily) or placebo for 12 months. A brief, short-lived benefit was seen on Mini Mental State Examination for women taking low dose estrogen but no significant cognitive or functional outcomes were noted at the end of the study[60]. Other two studies were also negative; both used conjugated equine estrogens for periods of 12 and 16 weeks in small groups of patients ($n = 42$; $n = 50$)[61,62].

These studies have been criticized for the small sample size, short duration of HRT, use of inappropriate cognitive assessment scales, presence of other risk factors, older age of the subjects and advanced stage of the disease[61,62].

However, there is more exciting data on whether estrogen can be used against longtime decline and development of the disease. Recent evidence from epidemiological studies indicates that estrogen replacement can significantly reduce the risk for development of AD for postmenopausal women[63,64].

Observational trials have shown that estrogen improves cognitive performance particularly in women without dementia, or when estrogen was started prior to the development of cognitive dysfunction. A recent longitudinal study reported that prolonged use of hormone replacement therapy decreases the risk and delays the onset of Alzheimer's disease by 5% annually [65]. In another study, risk for AD was less pronounced in women ever-users of estrogen than in never-users. In a population cohort ($n = 2,073$) of older (aged >65), non-demented women, lifetime HRT exposure was associated with improved global cognition and attenuated decline over a 3-year interval [66]. A study including 7,705 postmenopausal women with osteoporosis receiving 60 mg, 120 mg of raloxifene or placebo for 3 years showed no improvement in cognitive scores, although there was a trend toward less decline on tests of verbal memory and attention[67].

Several studies have attempted to explore the association between the blood level of estrogen and cognitive decline in postmenopausal women. Yaffe et al. reported that higher concentrations of endogenous estrogens prevent cognitive decline; after 6 years of follow up, women in highest tertile (according to free estradiol levels) were three times less likely to demonstrate cognitive decline than subjects in the lowest tertile[68]. In a placebo controlled trial, administration of higher dose of estrogen (0.10 mg/day) was found to enhance attention and memory for postmenopausal women with Alzheimer's disease; however, women were followed up for only 8 weeks[69]. Women who had ever taken estrogens were one-third less likely to develop Alzheimer's disease. Additionally, researchers noted that risk for the disease decreases, as estrogen dosages as well as duration of therapy were increased[70]. Although these studies provide further clinical evidence to support cognitive benefit of estrogen for women with AD, longer treatment durations as well as larger sample sizes and studies evaluating the effect of estradiol administration are further warranted.

It has been observed that Alzheimer's patients tend to be thinner than other older persons, so hypothetically, body weight might modify a woman's risk of Alzheimer's disease[71]. In the Leisure World study higher body weight at the time of initial cohort enrollment was associated with a reduced likelihood of a subsequent Alzheimer's disease diagnosis[72]. It is possible however, that estradiol levels were lowered as a result of women having AD because of decrease of amount of adipose tissue; a recent case-control study showed that estradiol levels may decline significantly in women with AD[73]. In either way, it seems like estrogen plays a role in cognitive functioning.

In general, women who received estrogen had a lower risk of developing AD, but results are inconsistent. The cognitive benefits of estrogen are confounded by the observations that women who take estrogen replacement therapy are often younger, have higher education levels and follow better nutritional and life-style practices than women who do not choose HRT. Only few studies establish the way in which estrogen is administered, i.e. by patch or by pill, and different presentations, i.e. estradiol or conjugated equine estrogen; both possibly impacts the efficacy and tolerance profiles for the treatment of Alzheimer's disease.

However, studies seem to provide evidence of modest cognitive improvements, although HRT regimens need to be standardized and replicated.

There may be a critical window in the early stages of the disease when estrogen therapy may prevent neuronal degeneration. Early initiation of HRT seems to be critical for cognitive benefits. Several observations support this view: accelerated development of AD in women with premature natural menopause or surgical bilateral ovariectomy, amelioration of Ab deposition and inflammatory reaction in ovariectomized animals by estrogen pretreatment, enhancement of cognitive function in preadolescent girls with Turner's syndrome by estrogen, observations that women who started HRT in their forties experienced significantly less cognitive decline over time[54,74–76]. Therefore, it has been suggested that estrogen therapy may be more effective in the initiation phase of neurodegeneration than in the advanced stage.

Risks of HRT

The WHI trial is the first randomized controlled trial to confirm that combined estrogen plus progestin does increase the risk of incident breast cancer (RR = 1,26); because of the relatively short follow-up time the WHI could not address the risk of death due to breast cancer. A cumula-

tive effect of years of exposure to hormones is suggested since hazard ratio was not higher in women with family history or other risk factors for breast cancer (RR = 1,06)[47]. This is consistent with estimates from pooled epidemiological data, which reported a 15% increase of breast cancer in estrogen plus progestin users for less than 5 years and a 53% increase for use over 5 years[77]. In HERS, non-significant increase (RR = 1,26) was found after 6.8 years of follow-up[78]. HERS also showed increased risk for VTE (RR = 2,89) and gallbladder disease (RR = 1,38)[78]. Risks for development of endometrial cancer increases with the length of estrogen therapy: less than 1 year RR = 1,4; 5–9 years RR = 5,9 and over 10 years RR = 9,5[79]. Estrogen dependent risk of endometrial cancer may be abolished by the addition of progestin[80]. This effect has been observed in WHI where the RR was 0.83[47].

Conclusions

There is no strong evidence that HRT increases stroke, on the contrary, there is some evidence that HRT may moderately reduce the risk of fatal stroke. Unfortunately, the majority of epidemiological studies of HRT and stroke are observational studies with certain limitations. Definite recommendations regarding optimal dose, duration and type of estrogen cannot yet be established. Randomized, placebo controlled trials are needed to demonstrate more clearly the potential benefits of estrogen and the cardiovascular/cerebrovascular system.

So far epidemiological, neuropsychological and biological studies support the hypothesis that estrogens have a role in the genesis and prevention of Alzheimer's disease. Results of some clinical trials of HRT in patients with AD are promising but need larger sample sizes, longer duration of follow-up and more standardized assessment scales. Since recent trials with Alzheimer's disease and HRT have been negative, it remains to be clarified whether HRT may be used only as a preventive measure.

Several questions need answers: the role of HRT as adjuvant therapy, should estrogen be combined with progesterone for positive cognitive effect, is transdermal versus oral HRT more beneficial, and dosing regimens-alternating or long-term steady exposure.

Advising postmenopausal women is definitely not easy, it assumes giving the best possible approach to preventive medicine. Prescribing HRT must depend always on a benefit/risk analysis, which means careful individual tailoring of the therapy. Not all postmenopausal women must necessarily be under HRT; the doctor must assess which therapy is best suitable for the individual woman- estrogen plus progestin, only estrogen, proper dosage, right timing for commencement of therapy, duration, risks.

HRT still has its primary indication for relief of climacteric symptoms. The stratification of individual risk should be based on classical risk factors and algorithms: »initiation and continuation of HRT should be based on established noncoronary benefits and risks, possible coronary benefits and risks, and patient preference» (American Heart Association statement)[81]. If HRT is not suitable, nonhormonal medications and alternative strategies should be promoted. These include lifestyle changes including smoking avoidance, proper nutrition (diet), regular exercise, drugs such as cholesterol lowering statins (stabilization of the plaque), blood pressure medications (particularly ACE inhibitors) and if necessary antiplatelet agents or anticoagulants[81,82].

Finally, the answer to our question is not easy and certainly not definite; however at this moment, having in mind results of given trials and the idea of good

clinical practice, we conclude: HRT should not be recommended on general basis for the primary or secondary prevention of cardiovascular/cerebrovascular diseases or for primary prevention of degenerative diseases such as Alzheimer's disease. Individual approach should be respected, initiation and continuation of HRT should be based on the benefit/risk ratio. Osteoporosis, cognitive decline and climacteric symptoms that are likely to impact on quality of life, speak in favor for recommendation of HRT use. On the other side, family history of breast carcinoma, mastopathy, thromboembolism, in certain cases gallbladder disease, will discourage the commencement of HRT.

Respecting the patient's preferences and having benefits and risks in mind as well as science advisory statements, individual counseling regarding HRT should be the leading concept in the healthcare of postmenopausal women.

REFERENCES

1. RINK, J. D., E. R. SIMPSON, J. J. BARNARD, S. E. BULUN, J. Clin. Endocrinol. Metab., 81 (1996) 2443. — 2. BAYARD, F., S. CLAMENS, F. MEGGETTO, N. BLAES, G. DELSOL, J. C. FAYE, Endocrinology, 136 (1995) 1523. — 3. JAKOB, F., H. SIGGELKOW, D. HOMANN, J. KOHRLE, J. ADAMSKKI, N SCHUTZE, J. Steroid. Biochem. Molec. Biol., 61 (1997) 167. — 4. MICHAELSON, K., J. A. BARON, B. Y. FARAHMAND, Br. Med. J., 316 (1998) 1858. — 5. DE LIGNIERES, B., Curr. Opin. Obstet. Gynecol., 5 (1993) 389. — 6. ESPLAND, M. A., W. APPLEGATE, C. D. FURBERG, Am. J. Epidemiol., 142 (1995) 1011. — 7. PENTZ-VIDOVIĆ, I., V. DEMARIN, G. GRUBIŠIĆ, K. KUNA, A. LOVRENČIĆ-HUZJAN, Croat. Med. J., 42 (2001) 54. — 8. HODIS, H. N., W. J. MACK, R. A. LOBO, D. SHOUPE, A. SEVANIAN, P. R. MAHRER, R. H. SEKLZER, C. R. LIU, C. H. LIU, S. P. AZEN, Ann. Intern. Med. 135 (2001) 939. — 9. ERSHLER, W. B., J. Am. Geriatr. Soc., 41 (1993) 176. — 10. MORADIAN, A. D., J. Steroid. Biochem. Mol. Biol., 45 (1993) 509. — 11. SIDNEY, S., D. B. PETITTI, C. P. QUENSBERRY, Ann. Intern. Med., 127 (1997) 501. — 12. LIMOUZIN-LAMOTHE, M. A., N. MAIRON, C. R. B. JOYCE, Am. J. Obstet. Gynecol., 170 (1994) 618. — 13. POLO-KANTOLA, P., R. PORTIN, H. HELENIUS, K. IRJALA, R. ERKKOLA, Obstet. Gynecol., 91 (1998) 459. — 14. CROATIAN DEMOGRAPHICS. In: Croatian Health Service yearbook 1999. (Croatian National Institute of Public Health, Zagreb, 2000) — 15. FUKUDA, K., Y. HIROSHI, S. IBAYASHI, T. NAKAHARA, H. UCHIMURA, M. FUJISHIMA, Stroke, 31 (2000) 155. — 16. LI, K., J. S. TOVAR, Stroke, 27 (1996) 498. — 17. DUBAL, D. B., M. L.KASHON, L. C PETTIGREW, J. Cerebral. Blood Flow Metab., 18 (1998) 1253. — 18. MCNEILL, A. M., C. ZHANG, Z. STANCZYK, S. P. DUCKLES, D. N. KRAUSE, Stroke, 33 (2002) 1685. — 19. GRODSTEIN, F., M. STAMPFER, Prog. Cardiovasc. Dis., 38 (1995) 199. — 20. PFEFFER, R. I., J. Chron. Dis., 31 (1978) 389. — 21. ROSENBERG, S. H., V. FAUSONE, R. CLARK, West J. Med., 133 (1980) 292. — 22. THOMPSON, S. G., T. W. MEADE, G. GREENBERG, J. Epidemiol. Community Health, 43 (1989) 173. — 23. PEDERSEN, A. T., O. LIDEGAARD, S. KREINER, B. OTTESEN, Lancet, 350 (1997) 1277. — 24. PETITTI, D. B., S. SIDNEY, C. P. QUIENSBERYY, A. BERNSTEIN, Stroke, 29 (1998) 23. — 25. BYRD, B. F., J. C. BURCH, W. K. VAUGHN, Ann. Surg., 185 (1977) 574. — 26. MACMAHON, B., In: OLIVER, M. F. (Ed.): coronary heart disease in young women. (Churchill Livingstone, New York, 1978). — 27. HUNT, K., M. VESSEY, K. MCPHERSON, Br. J. Obstet. Gynecol., 97 (1990) 1080. — 28. SCHAIRER, C., H. O. ADAMI, R. HOOVER, I. PERSON, Epidemiology, 8 (1997) 59. — 29. HAMMOND, C. B., F. R. JELOVSEK, K. L. LEE, Am. J. Obstet. Gynecol., 133 (1979) 525. — 30. FINUCANE, F. F., J. H. MADANS, T. L. BUSH, Arch. Intern. Med., 153 (1993) 73. — 31. LAFFERTY, F. E., M. E. FISKE, Am. J. Med., 97 (1994) 66. — 32. PAGANINI-HILL, A., In: LOBO, R. A., (Ed.): Treatment of the postmenopausal women: basic and clinical aspects. New York. (Raven Press, New York, 1994). — 33. GRODSTEIN, F., M. J. STAMPFER, J. E. MANSON, New Engl. J. Med., 335 (1996) 453. — 34. PAGANINI-HILL, A., Maturitas, 38 (2001) 243. — 35. GRODSTEIN, F., J. E. MANSON, G. A. COLIDITZ, W. C. WILLETT, F. E. SPEIZER, M. J. STAMPFER, Ann. Intern. Med., 133 (2000) 933. — 36. PAGANINI-HILL, A., M. PEREZ BARRETO, J. Gender-Specific Med., 4 (2001) 1. — 37. BUSH, T. L., E. L. D. BARRETT-CONNOR, M. H. COWAN, Circulation, 75 (1987) 1102. — 38. STURGEON, S. R., C. SCHAIRER, L. A. BRINTON, T. PEARSON, R. N. HOOVER, Epidemiology, 6 (1995) 227. — 39. FOLSOM, A. R., P. J. MINK, T. A. SELLERS, C. P. HONG, W. ZHENG, Am. J. Publ. Health, 85 (1995) 1128. — 40. CAULEY, J. A., D. G. SEELEY, W. S. BROWNER, K. ENSRUD, L. H. KULLER, Arch. Intern. Med., 157 (1997) 2181. — 41. SOURANDER, L., T. RAJALA, I. RAIHA, J. MAKINEN, R. ERKKOLA, H. HELENIUS, Lancet, 352 (1998) 1965. — 42. FUNG, M. M., E. BARRETT-CONNOR, R. R. BE-

TTENCOURT, J. Women's Health, 8 (1999) 359. — 43. RODRIGUEZ, C., E. E. CALLE, A. V. PATEL, E. J. JACOBS, M. J. THUN, Am. J. Epidemiol., 153 (2001) 145. — 44. ADAM, S., V. WILLIAMS, M. P. VESSEY, Br. Med. J., 282 (1981) 1277. — 45. LONGSTRETH, W. T., L. M. NELSON, T. D. KOEPSELL, G. VAN BELLE, Ann. Intern. Med., 121 (1994) 168. — 46. FALKEBORN, M., I. PERSSON, A. TERENT, H. O. ADAMI, Arch. Intern. Med., 153 (1993) 1201. — 47. WRITING GROUP FOR THE WOMEN'S HEALTH INITIATIVE INVESTIGATORS., J. Am. Med. Assoc. 288 (2002) 321. — 48. HULLEY S., D. GRADY, T. BUSH, C. FURBERG, D. HERRINGTON, B. RIGGS, E. VITTINGHOFF, J. Am. Med. Assoc., 280 (1998) 605. — 49. SIMON, J. A., J. HSIA, J. A. CAULEY, C. RICHARDS, F. HARRIS, J. FONG, E. BARRET-CONNOR, S. B. HULLEY, Circulation, 103 (2001) 638. — 50. HERRINGTON, D. M, D. M. REBOUSSIN, K. B. BROSNIHAN, N. Engl. J. Med., 343 (2000) 522. — 51. VISCOLI, C. M., L. M. BRASS, W. N. KERMAN, P. M. SARREL, S. SUISSA, R. I. HORWITZ., N. Engl. J. Med., 345 (2001) 1243. — 52. HENDERSON, V. W., (The Partenon Publishing Group, New York, 1999). — 53. DEMARIN, V., A. LOVRENČIĆ-HUZJAN, Acta Clinica Croatica, 37 (1998) 201. — 54. LI, R., L. B. SHEN, J. Neurochem., 75 (2000) 1447. — 55. TORAN-ALLERAND, C. D., R. C. MIRANDA, W. D. BENTHAM, Proc. Natl. Acad. Sci. USA, 89 (1992) 4668. — 56. MCEWEN, B. S., C. S. WOOLEY, Exp. Gerontol., 29 (1994) 431. — 57. HENDERSON, V. W., A. PAGANINI-HILL, C. K. EMANUEL, M. E. DUNN, J. G. BUCKWALTER, Arch. Neurol., 51 (1994) 896. — 58. HENDERSON, V. W., J. G. BUCKWALTER, Psychoneuroendocrinology, 21 (1996) 421. — 59. MARDER, K., Neurology, 54 (2000) 2035. — 60. MULNARD, R. A., JAMA, 283 (2000) 307. — 61. WANG, P. N., S. Q. LIAO, Neurology, 54 (2000) 2061. — 62. HENDERSON, V. W., A. PAGANINI-HILL, B. MILLER, Neurology, 54 (2000) 295. — 63. KAWAS, C., S. RESNICK, A. MORRISON, Neurology, 48 (1997) 1517. — 64. BALDERESCHI, M., A. DI-CARLO, V. LEPORE, Neurology, 50 (1998) 996. — 65. TANG, M., D. JACOBS, Y. STERN, Lancet, 348 (1996) 429. — 66. CARLSON, M. C., B. L. ZANDI, J. T. PLASSMAN, K. A. TSCHANZ, K. A. BOHMER-WELSH, Neurology, 57 (2001) 2210. — 67. YAFFE, K., K. KRUEGER, S. SARKAR, D. GRADY, E. BARRETT-CONNOR, D. COX, T. NICKELSEN, N. Engl. J. Med., 344 (2001) 1207. — 68. YAFFE, K., L. Y. LUI, D. GRADY, J. CAULEY, J. KRAMER, S. R. CUMMINGS, Lancet, 356 (2000) 708. — 69. ASTHANA S., L. D. BAKER, S. CRAFT, F. Z. STANCZYK, R. C. VEITH, M. A. RASKIND, S. R. PLYMATE, Neurology, 57 (2001) 605. — 70. PAGANINI-HILL, A., Am. J. Epidemiol., 140 (1994) 256. — 71. BERLINGER, W. G., J. F. POTTER, J. Am. Geriatr. Soc., (1991) 973. — 72. PAGANINI-HILL, A., V. W.HENDERSON, Arch. Intern. Med., 156 (1996) 2213. — 73. MANLY, J. J., C. A. MERCHANT, D. M. JACOBS, S. A. SMALL, K. BELL, M. FERIN, R. MAYEUX, Neurology, 54 (2000) 833. — 74. PETANCESKA, S. S., Y. NAGY, D. FRAIL, Neurology, 54 (2000) 2212. — 75. THOMAS, T., J. RHODIN, Ann. NY Acad. Sci., 903 (2000) 501. — 76. THOMAS, T., BRYANT, M., CLARK, L., Microvasc. Res., 61 (2001) 28. — 77. COLLABORATIVE GROUP ON HORMONAL FACTORS IN BRAEST CANCER, Lancet, 350 (1997) 1047. — 78. HULLEY, S., C. FURBERG, E. BARRET-CONOR, J. Am. Med. Assoc., 288 (2002) 58. — 79. GRADY, D., T. GEBRETSADIK, K. KERLIKOWSKE, Obstet. Gynecol., 85 (1995) 304. — 80. PIKE, M. C., R. K. PETERS, W. COZEN, J. Natl. Cancer Inst., 89 (1997) 1110. — 81. MOSCA, L., P. COLLINS, D. M. HERRINGTON, M. E. MENDELSOHN, R. C. PASTERNAK, R. M. ROBERTSON, K. SCHENCK-GUSTAFSSON, S. SMITH, K. A. TAUBERT, N. K. WENGER, Circulation, 104 (2001) 499. — 82. DEMARIN, V., A. LOVRENČIĆ HUZJAN, V. ŠERIĆ, V. VARGEK SOLTER, Z. TRKANJEC, V. VUKOVIĆ, V. UPRET, M. KALOUSEK, D. DESYO, D. KADOJIĆ, I. LUŠIĆ, M. DIKANOVIĆ, M. VITAS, Acta Clin. Croat., 40 (2001) 127.

V. Demarin

Department for Neurology, University Hospital »Sestre milosrdnice«, Vinogradska c. 29, 10000 Zagreb, Croatia

HORMONALNO NADOMJESNO LIJEČENJE I NJEGOVO MJESTO U NEUROLOGIJI

S A Ž E T A K

Usprkos trendu smanjivanja incidencije u posljednjim desetljećima, moždani udar je i dalje treći uzrok smrti u razvijenim zemljama. S obzirom da je moždani udar vodeći uzrok invaliditeta i drugi uzrok demencije, primarna prevencija bi trebala biti vodeći oblik borbe protiv bolesti, jer dostupna terapija danas nije dovoljno učinkovita. Zapaženo je da estrogen ima protektivna svojstva koja mogu smanjiti rizik od moždanog udara, studije su međutim pokazale oprečne rezultate. Nema čvrstih dokaza da hormonsko nadomjesno liječenje (HNL) povećava rizik od moždanog udara. U nekim studijama pokazalo se da HNL može smanjiti rizik od fatalnog moždanog udara. Oprečni rezultati su se također pokazali i kod Alzheimerove bolesti i korištenja HNL. U nekim studijama utvrđena je povezanost viših koncentracija serumskog estradiola i poboljšanja kognitivnih sposobnosti, što podržava hipotezu da koncentracija estrogena može imati značajnu ulogu u zaštiti moždanih funkcija. Imajući na umu rezultate randomiziranih studija, predloženo je da se HNL ne bi trebalo općenito preporučivati za primarnu ili sekundarnu prevenciju kardiovaskularnih/cerebrovaskularnih bolesti kao i degenerativnih bolesti kao što je Alzheimerova bolest. Osteoporoza, smanjenje kognitivnih sposobnosti i simptomi menopauze koji u većoj mjeri utječu na kvalitetu života žene, govore u prilog korištenja HNL. S druge strane, obiteljska anamneza karcinoma dojke, mastopatija, tromboembolizam, u nekim slučajevima kolelitijaza, vjerojatnije će obeshrabriti potencijalne korisnice HNL. Poštujući želje pacijentice i imajući na umu koristi i štete kao i savjete stručnih tijela, individualno savjetovanje u pogledu korištenja HNL trebalo bi biti vodeći koncept u zdravstvenom zbrinjavanju žena u menopauzi.