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Estrogen and Neurovascular Disease: Friend or Foe?

Dr. Terri DeNeui, DNP, APRN, ACNP-BC

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This white paper will provide an in-depth review of the literature regarding estrogen hormone therapy and its relationship to neurovascular disease and stroke. After reviewing this paper and the literature presented, it will become apparent that not only does 17ß estradiol protect the neurovascular and neurological systems, but there is also no correlation between the use of non-oral 17ß estradiol preparations and stroke risk. Further, recent studies have pointed to the role 17ß estradiol may play in the treatment of ischemic stroke.

The intention of this paper is to disseminate current literature and expert opinions regarding this topic, thereby paving the way for an updated and more accurate collegial dialogue amongst clinicians and their governing boards. It is time we begin to look at factual data regarding stroke and stroke risk and stop relying on misguided “hormone therapy induced stroke theory” as a root cause or risk factor of ischemic stroke in post-menopausal women on estrogen therapy.

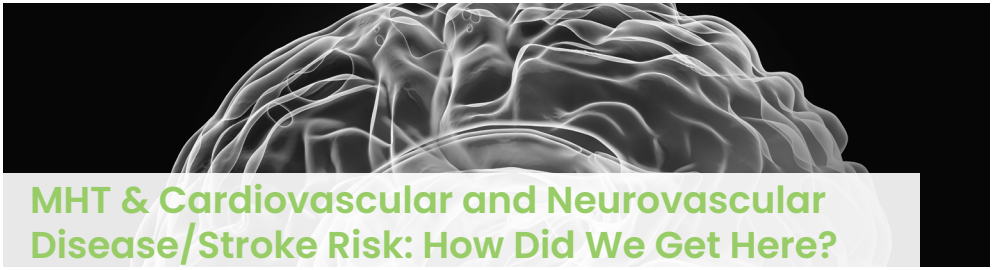
Menopausal Hormone Therapy

Menopausal Hormone Therapy (MHT) refers to the hormones used in the management of postmenopausal hormone decline. MHT may include the use of estrogen alone or in combination with micronized progesterone or progestin. Estrogens may be bioidentical or synthetic; progesterone is considered bioidentical and progestins are synthetic. The term "bioidentical" means the hormones in the product are plant sourced and are chemically identical to those the human body produces. Synthetic hormones are derived from man-made chemical compounds and are not chemically identical to those the human body produces.

MHT Options

Bioidentical	Route of Administration	Formulation
17ß - Estradiol	Oral	Tablet
	Non-Oral	
	TransdermalP	Patch, gel, film, spray
	Vaginal	Cream, ring, tablets
	Subcutaneous	Pellet
Estradiol	Vaginal, intramuscular	Tablet, ring, injection
Micronized Progesterone	Oral, vaginal	Capsules, cream, ovules
Non-Bioidentical/Synthetic	**Route of Administration**	**Formulation**
Conjugated Estrogens (CEE)	Oral, vaginal, intramuscular	Tablet, vaginal cream, injection
Progestins (MPA)	Oral	Tablet

(DeNeui, et.al.,2019)



MHT & Cardiovascular and Neurovascular Disease/Stroke Risk: How Did We Get Here?

The Women's Health Initiative Trial (WHI) was a large, randomized clinical trial funded by the National Institutes of Health to determine if MHT prevented heart disease, breast and colorectal cancer, and osteoporotic fractures in postmenopausal women. The WHI launched at a time when observational studies suggested a protective effect of estrogen on the heart and bones of postmenopausal women. The initiative purpose was to determine if postmenopausal hormone therapy should be prescribed for cardio- and osteoporosis protection for all women. The study, which began in 1991 and was to end in 2005, included the MHT clinical trials, an observational study, and two extension studies from 2005-2010 and 2010-2015 (Women's Health Initiative, 2017).

Research goals for the WHI were to: 1) determine the efficacy of MHT on non-fatal myocardial infarction and death; 2) determine the safety or risk of MHT for invasive breast cancer; and 3) determine secondary outcomes on osteoporosis, stroke, pulmonary embolism, venous thromboembolism, colorectal cancer, endometrial cancer, and mortality[6].

Women with previous hysterectomy (N=10,739) were randomized to conjugated equine estrogen, CEE (commonly known as Premarin) or placebo. For this group, the intervention lasted 7.2 years. Post-intervention follow-up was 6.6 years and cumulative follow-up was 13 years. Women with an intact uterus (N=16,608) were randomized to CEE + medroxyprogesterone acetate, MPA, (commonly known as Prempro) or to placebo. The intervention phase was 5.6 years, post-intervention follow-up was 8.2 years and cumulative follow-up was 13.2 years[6].

As it relates to the topic of this paper, preliminary results of the trial showed that compared to placebo, women in the CEE treatment group had an increased risk of stroke and blood clots. These results propagated the grave misinformation that all forms of menopausal hormones (estrogens) have a single class effect and therefore "all forms of estrogen must have an increased risk of blood clots and stroke". This misinformation, although refuted in the literature in dozens of clinical studies, continues to promulgate in mainstream and medical communities to this day.

The cost of estrogen avoidance data post WHI is astounding. Estrogen has rapid beneficial vascular effects in the cardio and neurovascular systems, and withdrawal of estrogen may result in clinically significant changes in arterial function, resulting an acute myocardial infarction and/or stroke[48]. In the Venetkoski, et.al., study of over 400,000 women on post-menopausal estrogen therapy, women younger than 60 years at discontinuation of HT showed a significantly increased risk of stroke death during the first year after treatment as compared with age matched female background population[48]. Data collected from Mikkola, et.al., 2-million-woman follow-up years of over 330,000 women, showed that discontinuing hormone therapy is harmful. The study further revealed women less than 60 years old had a two to threefold increased risk of cardiac and stroke mortality compared with the age-standardized background population death rate of the entire country after stopping MHT with estrogen[13].

Current Guidelines for MHT:

North American Menopause Society (NAMS) Position (2017):

- Individualized approach
- No longer "lowest dose for shortest period of time"
- Use evidence-based information to determine the appropriate type, dose, formulation, route, and duration.
- Should be based on the unique health risks of the woman and the goals of therapy.

American College of Obstetrics and Gynecology (ACOG):

- ACOG guidelines suggest alternative forms of estrogen and progesterone to those investigated in WHI (CEE/ CEE+MPA) for vasomotor symptom relief as alternative forms may be associated with different risk and stroke/clotting profile than CEE and CEE+MPA.

Estrogens for MHT: Is There a Risk?

Evidence from systematic reviews and guidelines support estrogen as effective in treating moderate to severe vasomotor symptoms, symptomatic vaginal atrophy, and in preventing postmenopausal osteoporosis in women transitioning through menopause; estrogen therapy remains the gold standard for relief of menopausal symptoms[6]. Estrogens are available in many formulations and routes of administration, which have similar efficacy for symptom relief, although their metabolic effects, and side effect profiles differ greatly.

Although typically associated with female reproductive function, estrogens mediate physiological processes in nearly every body tissue. 17 Beta estradiol (17ß-E2) is the most prominent and potent estrogen in circulation and during the menopause transition and post menopause, the ovaries cease to produce 17ß-E2. Estrogens are lipophilic in nature and therefore cross the blood brain barrier easily and diffusely. Estrogen is a pleiotropic hormone that exerts protective actions on multiple

tissues, including the brain, and the protective effects of estrogen carry tremendous implications for the promotion of health and the prevention of disease in postmenopausal women[8].

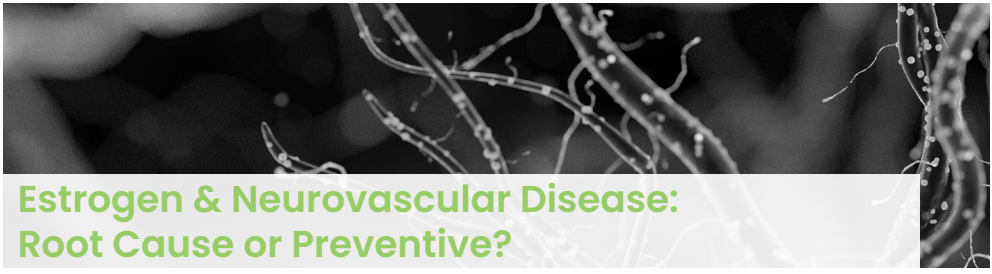
Oral estrogen preparations metabolize via the 'first pass' mechanism through the liver, thereby reducing the systemic bioavailability of the hormone to 2-10%. The major differences between administrations of oral versus non-oral preparations lie in the metabolic changes produced by the first pass effect and are expressed most notably in the cardiovascular and neurovascular systems. The first pass metabolism of oral estrogen has favorable effects on lipid parameters, insulin resistance and inflammatory markers, but less favorable effects on triglycerides and clotting factors[6].

Some oral estrogen formulations have been implicated in increasing the risk of clotting and concerns of the thrombotic potential of estrogen arose from early observations that oral contraceptives appeared to increase the risk of venous thrombosis, pulmonary embolism, and stroke[8]. We now know that the dose and the route of estrogen delivery are key components in determining clotting potential. At higher doses, oral estrogen, which is metabolized via a first pass through the liver, can stimulate the production of thrombogenic factors primarily through its actions in the liver; alternatively, non-oral delivery of estrogen bypasses this "first pass metabolism" through the liver and prevents estrogen induced thrombogenic factors in the liver[8].

In a review of thrombotic risk and estrogen use by Canonico, it was shown non-oral estrogens, such as patches and subcutaneous pellets, are not associated with an increased clotting risk and biological data support this difference between oral and non-oral preparations (2015). Additionally, significant differences in clotting risk between estrogen hormone preparations relate to the simultaneous use of a synthetic progestin. Studies have consistently shown that clotting risk is higher among users of combined estrogens plus progestins than among users of estrogens alone or estrogens with oral micronized (bioidentical) progesterone[4]. A clinical study by Rovinski, et.al., mirrored these results, concluding that blood clotting risk was increased in postmenopausal women with no previous thromboembolic events using oral estrogen

preparations, however non-oral preparations did not significantly affect this risk (2018).

Generally, non-oral, 17ß estradiol delivery has more physiologic systemic effect and a decreased risk of deep vein thrombosis, stroke, and myocardial infarction, secondary to the decreased clotting risks compared to oral administration. Studies comparing oral 17ß estradiol to CEE showed greater risk of venous thromboembolism (VTE) and myocardial events in the CEE group, suggesting not only the route, but the type of estrogen administration may be important to consider[6].



Estrogen & Neurovascular Disease: Root Cause or Preventive?

When discussing root cause and treatment options, risks, and benefits of certain therapies as it relates to stroke, it is important to understand what constitutes a stroke. Ischemic stroke is characterized by an abrupt deprivation of blood flow, oxygen, and vital nutrients to the brain that quickly leads to cell death, known as apoptosis[49]. The ischemic cascade also involves an inflammatory response triggered by damage-associated molecular patterns (DAMPs) released from the dying cells which trigger activation and recruitment of immune cells[30]. This environment of immune cells secretes pro-inflammatory cytokines that not only act locally in the brain but also may enter the systemic blood circulation to trigger a systemic immune response[29, 30]. Understanding the downstream effects of ischemic stroke induced inflammatory immune response may help explain why estradiol, as a potent immunomodulator, may not only prevent ischemic stroke, but also play a role in treatment.

Estrogen is the most extensively studied of the sex hormones in both laboratory and clinical settings and is considered increasingly to be an endogenous neuroprotective agent; further, many studies have shown that exogenous estrogen use reduces ischemia in both sexes[14,3]. Estrogen has immunomodulating and anti-inflammatory effects in numerous body systems, most notably the neurovascular system, and several studies have shown that estrogen, specifically 17ß-E2, protects the brain from ischemic injury following stroke [29, 44, 46].

Brown, et.al., reported 17ß-estradiol "powerfully protects the brain using multiple molecular mechanisms that promote decreased cell death, increased neurogenesis, enhanced neurotrophic support, and the suppression of pro-inflammatory pathways" (2009). The evidence that estradiol stimulates neurogenesis (new nerve tissue) in the adult ischemic brain suggest that **estradiol therapy may facilitate the brain to undergo repair and remodeling after stroke**[3].

Estrogen elicits effects through the estrogen receptor (ER) and the brain is rich with estrogen receptors, owing to the impact estradiol has in neurological and neurovascular function. ER alpha is critical in estradiol-mediated protection of the brain after stroke injury[49] and treatment with estradiol promotes rapid upregulation of the ER alpha[46].

Because the immune response following a stroke dictates recovery and the degree of brain damage, estrogen may be dually protective by also mediating the immune response. There are multiple mechanisms of 17ß-E2's neuroprotection, including activation of several neuroprotective pathways in the brain, but 17ß-E2 also mediates the local and systemic immune response to ischemic stroke through the estrogen receptor. Estrogen is a powerful antioxidant; however, analogs of estradiol (synthetic estrogens) do not appear to exert the same antioxidant effect as 17ß-E2. One theory is because synthetic analogs do not activate the estrogen receptor pathways, which are responsible for inducing the protective effects of estradiol[30].

Another mechanism by which estrogen may reduce stroke risk is through modifying risk factors that underlie both stroke and

coronary heart disease (CHD) such as the beneficial effects on diabetes and serum lipid profiles[8]. Further, CHD doubles the risk for stroke and estrogen therapy greatly reduces the risk for CHD up to 40%, thus it follows that estrogen
may decrease the risk for stroke in parallel with its protective actions on CHD[8]. Of grave concern is the impact of prolonged estrogen deprivation in postmenopausal women untreated with MHT and is now considered a critical health matter as we realize that these women are at increased risk for chronic and acute disease processes such as stroke and myocardial infarction[8].

Conclusion

Clinicians must take a closer look at root causes of stroke, such as lifestyle factors that cause systemic inflammation as well as epigenetic influences, prior to generalizing opinions regarding MHT and stroke risk. Systemic inflammation is associated with an increased risk of ischemic stroke[30], the primary causes of systemic inflammation being lifestyle factors such as smoking, stress and diet.

Although some studies have shown a slight increased risk of thrombotic events in postmenopausal women taking certain oral estrogen preparations, timing since menopause, co-morbidities and lifestyle factors such as smoking, and weight were all variables to consider. Of note, oral 17beta estradiol has been extensively studied and has been found to pose the least, only slightly statistically significant, risk of clotting and thrombotic events, compared to other preparations; all due to first pass metabolism through the liver. Synthetic estrogen preparations and estrogen preparations combined with progestins posed the highest risk. Most importantly, non-oral preparations, such as patches, subcutaneous pellets and others, have not been shown in any clinical study to increase thrombotic or ischemic stroke risk.

It is imperative clinicians understand the physiologic sequalae in ischemic stroke and the positive role estrogen plays in both sexes. Estradiol is a potent immunomodulator and powerful anti-inflammatory agent, both functions of which are vital for stroke prevention and post stroke recovery. Clinical studies have shown estrogen replacement in postmenopausal women to ameliorate cognitive dysfunction, decrease the risk and delay the onset of degenerative conditions such as Alzheimer's disease and stroke[8]. Estradiol has also been shown to favorably alter lipid parameters, prevent osteoporosis and cardiovascular disease, decrease, or eliminate depression, and improve overall quality of life.

Considering the chronic and acute disease risk posed to post-menopausal women avoiding MHT, it is vitally important clinicians give their patients seeking relief from menopausal hormone decline individualized, accurate information regarding disease prevention and risk, and the differences between the modalities of MHT from which to make the life altering decision of whether to initiate hormone therapy or not. It is equally important for the governing boards of clinicians to be up to date regarding the literature in this arena, enabling an adequate and accurate evaluation of any clinical cases involving MHT presented for review.

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