Is Estrogen Replacement safe for Women with Stroke Risk? Asked and not quite answered.

Stroke is the 4th leading cause of death in women in the United States[1] and is a major cause of disability. While the majority of stoke risk factors are common to both men and women, this article will provide an overview of some specific factors that are exclusively experienced by women in relation to changes in estrogen levels.

Many of the diverse biological effects of estrogen are mediated by ligand interactions with two classical nuclear estrogen receptors (ER), ER-alpha (ER) and ER-beta (ER). Estrogen receptors(ER) have been identified in a number of non-reproductive locations including the brain, specifically the amygdala, cerebral cortex, hippocampus, and basal forebrain.[2] ERs have also been identified in nearly all cell types found in the CNS, including neurons, astrocytes, microglia, oligodendrocytes, and vascular smooth muscle cells. Estrogens have been shown to impact distinct cell types, neuronal signaling cascades, and nervous system substrates associated with injury, cognitive aging, and disease.[3] Estrogen can be synthesized via aromatase in various brain regions, such as the hippocampus, and in neurons and astrocytes.[4]

Some specific estrogenic neuroprotective effects related to stroke risk include:

- Acting through both genomic and non-genomic mechanisms, 17E2 increases expression of endothelial nitric oxide synthase (eNOS) which promotes increased vasodilation through enhanced nitric oxide availability in cerebral tissues.[5] eNOS plays an important role in reducing clot adhesion, aggregation, and recruitment.
- Reducing blood brain barrier permeability, especially after injury.[6]
- Mediating leukocyte endothelial actions through maintaining the structure and integrity of the vascular endothelial membrane in capillaries.[7]
- With physiologic levels of estrogen, conferring an overall anti-inflammatory effect as indicated by a negative correlation with CRP protein.[8]

To explore these relationships further, the following links are provided:
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3426619/figure/F1/
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3426619/figure/F3/

Risk Factors

There is a potential risk between early menopause, with consequential lowering of estrogen, and increased stroke risk, although data is so far limited. However, the increase in cardio vascular disease (CVD) incidence following menopause suggests the protective effect of 17E2. Physiological levels of estradiol are associated with lower levels of hepatic lipase[9] so a drop in estrogen may adversely affect lipid levels, the ratio of high to low density lipoproteins, and subsequently risk for CVD.[10] Age at menarche appears to have a U-Shaped relationship with cerebrovascular disease[11] with increased risk below age 10 and after age 17 having increased risk.

Low dehydroepiandrosterone (DHEA) levels have been associated with increased risk of ischemic stroke with women in the lowest quartile having a relative risk of 1.41 for ischemic stroke after adjustment for other risk factors.[12] It would be interesting to see if breast cancer survivors on aromatase inhibitors showed elevations of DHEA and whether any such increased levels in DHEA conferred stroke protection in the absence of estrogen supplementation. No studies identified to date appear to explore this.

Oral contraceptives have historically been correlated with increased risk for CVD including stroke, even at the lower doses of second and third generation medications. With regards to post- menopausal hormone replacement and stroke risk, an extremely high proportion of studies have investigated the risk for stoke in relation to pharmaceutically produced hormone products. It is hard to find any significant study that looks at the relationship between supplementation with physiologic estradiol, estriol, and progesterone and stroke risk. Oral pharmaceutical hormones, whether estrogen or estrogen + progestin seem to consistently, and repeatedly, demonstrate an increased risk for stroke events.[13] There is some evidence that low dose pharmaceutical hormones applied vaginally are not associated with increased stroke risk.[14,15,16]

The insulin like growth factor (1IGF-1) and estradiol relationship is beginning to gain more attention in relation to understanding of stroke risk. Both IGF-1 and estrogen independently exert neuroprotective actions in neurologic diseases such as stroke but less is known of the combined impact. A thorough review of the microbiology of this topic by Farida Sohrabji[17] is worth a read.

It is clear that estrogen can play a significant role in stroke recovery and in prevention of ischemic stroke risk. The distribution of ERs throughout the brain as well as its role in reducing inflammation and CVD suggests strongly that supplementation with 17E2 is a clinical consideration. This expansive base of literature and research on 17E2 utility seems very positive. However, the situation is confused by the significant volume of research that connects use of pharmaceutically manufactured estrogens and progestins with increased risk of stroke. Among this body of research only low dose vaginal supplementation has been shown to not *increase* stroke risk, while not actually conferring protection. This continued confusing of pharmaceutically manufactured HRT with bioidentical HRT makes it challenging to know what to advise patients. What appears to be missing is robust research into the use of physiologic (bioidentical) estrogen and progesterone for use in reducing risk of stroke at menopause and beyond. Does this topic deserve further attention and research in regards to treatment modality?

References

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