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Stroke Risk Factors Unique to Women

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I. INTRODUCTION

Stroke is the third leading cause of death in women in the United States and is a leading cause of disability. Each year 55,000 more women than men have a stroke, a discrepancy largely driven by longer life expectancy in women (www.stroke.org). While the majority of stroke incidence can be attributed to traditional vascular risk factors that occur in both men and women, including hypertension, hyperlipidemia, diabetes, smoking and atrial fibrillation, there are a number of stroke risk factors that are specific to women. Specifically, differences in sex hormones, exogenous estrogens and pregnancy exposures are factors exclusively experienced by women. In this review we will summarize the current state of the literature with regards to women specific factors such as endogenous hormone levels, exogenous hormone therapy, pregnancy, parity, timing of age at menarche and menopause in relation to stroke risk.

II. METHODS

The following terms were searched with "women and stroke" in PubMed and Google Scholar, mainly for original articles and meta-analysis/systematic reviews, "estrogens," "estradiol," "testosterone," "DHEAS," "menarche," "menopause," "oophorectomy," "postmenopausal hormone therapy," "oral contraception," transgender," "transmen," transwomen," "pregnancy," "peripartum," "postpartum" and "parity." The following search was also performed: "therapy" OR "treatment" OR "secondary prevention" AND

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"pregnancy" AND "stroke". The resultant literature was reviewed by the authors and the data covering the topics outlined below were reviewed in this manuscript.

III. ENDOGENOUS ESTROGEN STATE

IIIa. Endogenous hormone levels

Data on the relationship of endogenous sex hormones and risk of stroke in women are relatively limited. Estrogen levels fluctuate dramatically in women with the menstrual cycle, and then drop dramatically in the menopausal transition and in post-menopause. In data from the Copenhagen City Study, neither high nor low estradiol levels were associated with increased risk of ischemic stroke.[1] In premenopausal women, those in the lowest 10th percentile of estradiol had a more than 2-fold increased risk of ischemic stroke, but this was based on very small case numbers. There was no relationship observed for postmenopausal estradiol levels and risk of ischemic stroke. Similarly, the authors of a study of French women over the age of 65 found no association between estradiol levels and risk of ischemic stroke.[2] In the Study of Osteoporotic Fractures, women in the highest category of free estrogen index had a higher age-adjusted risk of ischemic stroke, but this was not independent of standard stroke risk factors including hypertension, diabetes and adiposity.[3] Subsequently a meta-analysis of the 3 available studies found no association, further supporting the lack of a relationship between estradiol levels and risk of ischemic stroke.[1]

Testosterone levels are more stable than estrogen levels across the lifespan in women, with relatively constant levels from ages 30 to 70 years.[1] While low testosterone levels have been associated with increased stroke risk in men, no clear relationship has been seen for testosterone levels and risk of stroke in women.[1] The investigators of the aforementioned study of French women over the age of 65 found no association between high or low testosterone levels and risk of stroke.[2]

Dehydroepiandrosterone (DHEAS), an adrenal hormone which can also be used for the synthesis of estrogen and testosterone, has also been investigated. Low DHEAS levels have been associated with increased risk of ischemic stroke, with women in the lowest quartile having a RR of 1.41 (95% CI: 1.03-1.92) for ischemic stroke after adjustment for other risk factors.[4] DHEAS levels at presentation of acute stroke were also inversely associated with stroke severity in a hospital-based study of stroke in postmenopausal women.[5] Another study of women undergoing coronary angiography provided evidence that lower DHEAS levels were associated with increased cardiovascular mortality, including death from stroke.[6]

Additional prospective studies of endogenous sex hormones and risk of stroke in women are needed, particularly with more sensitive measures of hormones, and in high-risk groups including African American and Hispanic women.

IIIb. Age at menarche

Earlier age at menarche has been associated with greater cardiovascular disease (CVD) morbidity and mortality in some[7–9], but not all studies,[10–12] and data specific for stroke are limited. In the Million Women Study from the UK, a U-shaped relation between age at menarche and cerebrovascular disease was observed.[9] Women who experienced menarche at

age 10 years or younger were at higher risk of developing stroke in later life compared to those with age at menarche at 13 years (RR 1.16 [95% CI 1.09-1.23]); on the other hand, women who experienced menarche at age 17 years or older were also at higher risk of developing stroke compared to those with age at menarche at 13 years (RR 1.13 [95% CI 1.03-1.24]).[9] Women with extremely early age at menarche may experience hormonal disturbances such as higher exposure to estradiol, potentially mediated through childhood obesity.[13] The timing of menarche is associated with type 2 diabetes risk[14, 15], an association which may be influenced by childhood adiposity and endocrinopathies.[13, 16] Although the Million Women Study attempted to control for potential confounding factors such as body mass index (BMI) through statistical adjustment[9], obesity may have been present before the onset of menarche, complicating inferences about cause and effect.

IIIc. Age at natural menopause and surgical menopause

Women of reproductive age are at a lower risk of CVD compared with men of similar age and lifestyle, but women who experience early menopause have increased cardiovascular risk.[17] In a recent meta-analysis, investigators reported that early age at natural menopause (menopause onset before 45 years) was associated with a slightly higher risk of total CVD mortality (RR 1.12 [95% CI 1.03-1.21]) than onset at age 45 years or later; however, this association was not observed for stroke mortality risk independently.[18] Surgical menopause, bilateral oophorectomy with or without hysterectomy has also been associated with higher risk of CVD.[19, 20] In the Nurses' Health Study, bilateral oophorectomy before age 50 years was associated with increased CVD mortality in women, and especially in women who did not use hormone therapy.[21] When a sensitivity analysis of stroke mortality was conducted, the confidence interval of this association widened potentially due to low numbers, although the risk estimate remained elevated (RR 1.15 [95% CI 0.85-1.56]).[21] Therefore, further investigations are warranted to examine these potential associations for early menopause and stroke.

Specific mechanisms responsible for the association between the timing of age at menopause and CVD are unclear. However, CVD incidence rising sharply after menopause suggest protective benefits of ovarian hormones.[22] Estrogen inhibits hepatic lipase,[23] thus decline in endogenous estrogens in the menopausal transition may adversely affect lipid levels and subsequently cardiovascular risk.[24] The menopausal transition is associated with declines in HDL cholesterol and increases in LDL cholesterol,[24] as well as changes in HDL composition, with higher number of small HDL particles, which confer less cardiovascular protection than large HDL particles.[25] Hence, decreased estrogen concentrations over the menopause transition and effects on lipoprotein profiles may subsequently contribute to atherosclerosis. In a cross-sectional, population-based study, longer duration of reproductive lifespan, years from menarche to menopause, was associated with a lower 10-year CVD risk assessed by the Framingham Risk Score in postmenopausal women.[26] In the prospective cohort Nurses' Health Study, a shorter duration of reproductive lifespan was associated with a higher risk of stroke, as well as CVD, which was likely driven by earlier age at menopause (either naturally or surgically).[27]

IV. EXOGENOUS ESTROGENS AND STROKE RISK

IVa. Hormone-containing birth control and stroke

Hormonal contraceptives, including oral, transdermal and vaginal formulations, are very effective and are used world-wide by over 100 million women (WHO 2014). There are various formulations containing either combined estrogen and progestogen or progestogen alone, administered as pills, patches and rings. Combined oral contraceptives (COC), comprised of both estrogen and progestogen, are thrombogenic[28] and, historically, have been associated with increased risk of cardiovascular disease.[29, 30]. Oral estrogens have a dose-response association with risk, and doses have declined since their introduction in the 1960's. Most COCs now contain <50 mcg and some contain as low as 15 mcg of estrogen. Authors who evaluated the risk of second and third generation estrogen-containing oral contraceptives, continued to find a 60 – 80% increased odds [95% CI 1.2 – 2.8] of the combined endpoint of myocardial infarction and/or ischemic stroke among COC users compared with nonusers[30–33]. In a separate study, second generation COCs were associated with an OR = 2.54 [95% CI 1.96 – 3.28] and third generation OCs with an OR = 2.03 [95% CI 1.15 – 3.57] of stroke.[34] Progestogen-only hormonal contraceptives have not been associated with increased risk of ischemic stroke, although data are limited[30, 35]. Non-oral methods of delivering combined hormonal contraceptives, including the vaginal ring and contraceptive patches, appear to have the same risk as oral contraceptives.[36]

Risk of stroke with COC use rises in the presence of other cardiovascular risk factors (ie smoking, age (> 35 years) and history of migraine with aura. Migraine with aura is a common condition in younger women and the risk of stroke in patients with migraine with aura is increased approximately two-fold.[37] Women with migraine who also use COCs have a further increased risk of ischemic stroke (7.02 [95% CI 1.51 – 32.68]) where women with migraine with aura, COC use and who are active smokers have a dramatically elevated risk for stroke (RR: 10; [95% CI: 1.4 – 73.7]).[37] Guidelines from the International Headache Society Task Force on COC prescribing recommendations have been published previously.[38] Women who have migraine with aura should be advised to control all modifiable risk factors, including tobacco use and hypertension, and birth control methods other than COCs should be considered[31].

Hormonal contraceptives are used by millions of women, and for most low-risk women the risk of stroke associated with COC is lower than the risk of stroke during pregnancy. However, there is a clear association between hormone-containing birth control methods and ischemic stroke. This is magnified by stroke risk factors. While a COC pill containing 30 mcg of estrogen is considered safe and effective hormonal contraception,[30] careful attention to stroke risk should be made prior to prescribing. Non-hormonal and progestogen-only methods of contraception should also be considered in high-risk patients. Further research to evaluate the risk of progestogen-only methods (depot injection, pills, implants and intrauterine devices) is needed.

IVb. Postmenopausal hormone therapy and stroke risk

Prospective observational studies and randomized trials consistently demonstrate an increased risk of stroke, particularly ischemic stroke, with oral postmenopausal hormone therapy.

In prospective cohort studies, data suggest that postmenopausal users of oral estrogens with or without progestin have a 27-39% increased risk of stroke compared with nonusers.[39] In the Women's Health Initiative (WHI), women randomized to combined estrogen plus progestin had a HR of 1.31 (95% CI: 1.02-1.68) for total stroke and 1.44 (95% CI, 1.09-1.90) for ischemic stroke.[40] In the WHI trial of unopposed estrogen, women randomized to active therapy had a HR of 1.37 (95%CI: 1.09 - 1.73) for total stroke and 1.55 (95% CI: 1.19 - 2.01) for ischemic stroke.[41]

While some data suggest an association between timing of hormone therapy and coronary heart disease, time since menopause is not associated with differences in stroke incidence in either observational studies[39] or clinical trials.[42] The incidence of stroke is relatively low in younger women (age 50–59 years), with approximately 2 additional cases of stroke per 10,000 women per year taking postmenopausal hormones.[42] Additionally, there is a dose-response relationship between dose of oral conjugated estrogen and stroke, with RRs of 0.93 for a dose of 0.3 mg, 1.54 at 0.625 mg, and 1.62 at 1.25 mg (p for trend, <.001).[39]

Similar results have been found in secondary cardiovascular prevention. Both the Heart and Estrogen/Progestin Replacement Study (HERS) in women with prior coronary heart disease, [43] and the Women's Estrogen for Stroke Trial (WEST) in women with recent mild ischemic stroke or transient ischemic attack[44] found no significant effect of treatment with oral estrogen or combined oral estrogen and progestin on risk of stroke, with a trend towards harm.

Limited data are available for transdermal estrogens, which have been associated with lower risk of venous thromboembolism. In a population-based nested case-control study, current use of transdermal hormone therapy was not associated with an increased risk of stroke (HR 0.95 [0.75-1.20]).[45] However, when the dose was examined, low-dose transdermal estrogen (≤50 μg/d estradiol) was not associated with risk, while high-dose transdermal estrogen (>50 μg/d) was associated with increased stroke risk.[45]

IVc. Transgender Medicine

Transgender individuals are people whose gender identity differs from their sex assigned at birth. The prevalence of self-identified transgender adults in the United States is estimated to be about 0.5% of the population.[46] Some transgender people pursue hormonal therapy and/or gender-affirming surgery to assume secondary sex characteristics consistent with their gender identity. The use of certain hormonal therapies has implications for the incidence of cerebrovascular disease in these individuals.

Transwomen are people with an assigned male sex and a female gender identity. Transwomen may undergo medical treatment with estrogens, anti-androgens, or a

combination of both.[47] Those who have undergone orchiectomy may pursue only estrogen therapy.

Anti androgen therapies do not appear to increase stroke risk in transwomen. Spironolactone is the anti-androgen most commonly prescribed to transwomen in the United States.[47] Spironolactone, a potassium-sparing diuretic, may lower blood pressure but does not increase thrombotic risk. Similarly, finasteride, a less commonly used anti-androgen, does not appear to increase thrombotic risk.

Direct data on the effect of exogenous estrogens in transwomen is scant. Much of our knowledge about the effects of exogenous estrogen is derived from studies of the increased risk of thrombotic complications including stroke among post-menopausal women using postmenopausal hormone therapy.[48, 49] Prospective trials of thrombotic risk in transwomen receiving estrogen therapy are lacking.[50] A 1997 Dutch single-center retrospective descriptive study of 816 transwomen treated for a mean 9.5 patient-years with ethinyl estradiol and the anti-androgen cyproterone acetate found that 45 (5.5%) developed deep vein thrombosis (DVT) or pulmonary embolism (PE), 5 (0.6%) experienced a transient ischemic attack (TIA) and none experienced ischemic stroke.[51] A 2013 Belgian single-center case-control study evaluated 214 transwomen who were maintained on estrogen therapy for a median of 6 years.[52] Eleven of the 214 transwomen (5.1%) developed DVT and/or PE during hormonal treatment. Five of the 214 transwomen (2.3%) were diagnosed with TIA or “cerebrovascular disease” during treatment, a higher prevalence than in the age-matched control men. In a 2011 Dutch retrospective single-clinic cohort mortality study of 966 transwomen on estrogen with or without anti-androgen therapy with a mean follow-up of 19.4 years, no difference was found in the incidence of fatal stroke in transwomen compared to the incidence in the general population.[53]

As we await prospective studies of estrogen therapy in transwomen, we recommend that medical providers maintain a high index of suspicion for DVT/PE and cerebral venous thrombosis (CVT) in transwomen receiving estrogen therapy. Cardiovascular risk should be evaluated and transwomen who smoke should be encouraged to quit smoking and provided with appropriate pharmacologic and psychosocial support.

Transmen are individuals with an assigned female sex and male gender identity. Transmen may undergo treatment with testosterone to promote development of male secondary sex characteristics. Testosterone is available via transdermal and intramuscular routes. Unlike estrogen, testosterone does not appear to be associated with an increased risk of thromboembolic complications. The majority of existing studies of transmen do not suggest an increased risk of cardiovascular morbidity with exogenous testosterone therapy.[51–54]

In general, providers should be aware that transgender people may be less likely to seek medical attention than their cisgender peers due to previous negative interactions with the medical community, poor psychosocial wellbeing, and/or fear of stigma.[55, 56] This has direct implications for delay of appropriate stroke care. Health systems and medical providers can improve the medical care of transgender people by asking about gender identity and preferred pronouns on intake forms[57]; promoting an explicitly supportive and inclusive

clinic or unit culture for transgender patients and their families; and pursuing research into the unique health needs of transmen and transwomen.

V. ISSUES OF PREGNANCY, PARITY AND STROKE

Pregnancy and the peripartum are associated with increased risk of stroke. The peripartum period from 2 days before to 1 day after delivery and, to a lesser extent, up to 6 weeks postpartum, is associated with an increased risk of ischemic stroke and intracerebral hemorrhage (ICH).[58–60] In a very large population-based study of women in England (age 15–49 years), authors found that the baseline incidence of stroke was 25.0/100 000 person-years in women when they were not pregnant. The incidence rate dropped during early pregnancy, but was 9-fold higher in the peripartum period (161.1/100 000 person-years and 3-fold higher in the early postpartum period (47.1/ 100 000 person-years, 95% CI 31.3-70.9).[61] For subarachnoid hemorrhage (SAH), only the peripartum period confers increased risk[60, 61]; non-aneurysmal SAH is likely a major contributor to this risk. The risk of any thrombotic event that includes ischemic stroke remains increased to a lesser extent until 12 weeks postpartum[62] but it is not established that the risk of stroke remains increased beyond 6 weeks post-partum.[61] Eclampsia and pre-eclampsia are the strongest risk factors for both ischemic stroke and ICH accounting for 24-48% of all pregnancy-associated strokes[58, 59]; this risk is potentiated by pre-existing genitourinary tract infection, chronic hypertension, prothrombotic states, and coagulopathies.[63]

Complications of pregnancy, specifically pregnancy-inducted hypertension, gestational diabetes, and preeclampsia are also associated with long-term risk of stroke.[64] There is evidence that women with pregnancy outcomes of preterm birth and small for gestational age infants have higher rates of cerebrovascular events even after adjusting for other pregnancy complications.[65]

For women with prior stroke, the risk of recurrent stroke is increased in the peripartum and postpartum periods. Limited data from case series[66–68] suggest an absolute risk of recurrent arterial ischemic stroke associated with pregnancy of 0.7%, similar to the <1% yearly risk of recurrent stroke among young adults who have no vascular risk factors;[69] however, the 95% confidence interval is very wide, 0.04%–4.4%, indicating the need for further study. In addition, the absolute risk depends on clinical circumstances, with the presence of vascular risk factors or a definite cause of stroke, including thrombophilic disorders, conferring an increased risk. Similarly, there is a paucity of information on the excess risk of pregnancy complications to mother and child among women with prior ischemic stroke.[70]

The role of pregnancy on risk of intracranial hemorrhage from pre-existing AVMs is uncertain. The 2 largest case-crossover studies of AVMs, single-center studies from China[71] and Baltimore[72] yielded conflicting results. The preponderance of available evidence suggests that pregnancy and delivery does not increase the risk of aneurysm rupture.[73, 74]

VI. CONCLUSION

It is important to be aware of stroke risk factors specific to women. Table 1 summarizes the associations for stroke risk factors unique to women. Specific considerations that include

endogenous hormone levels, exogenous hormone therapy, pregnancy and the peripartum period, and pregnancy-related complications change the risk of stroke for women as well as the optimal stroke prevention strategies. Special attention and further research is also needed in the area of transgender individuals. Further research to determine whether risk prediction models should include risk factors specific to women, including hormonal and reproductive exposures, is needed.

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Table 1

Summary of female-specific stroke risk factors

Exposure	Risk association	Further research needed
Endogenous hormones		
Early age at menarche (<10)	↑	
Early age at menopause/BSO * (<45 years)	↑	
Reproductive lifespan	?	Yes
Low DHEAS **	↑	
Estradiol	?	Yes
Testosterone	→	
Exogenous hormones		
PMH ***: Oral estrogens	↑	
PMH ***: Transdermal estrogens	?	Yes
Combined oral contraceptives	↑	
Progestogen only contraceptives	→	Yes
Transgender exogenous estrogens	↑	Yes
Transgender exogenous testosterones	→	Yes
Pregnancy related exposures		
Pregnancy/ Peripartuition	↑	
Gestational diabetes	↑	
Hypertension in pregnancy/ pre-eclampsia	↑	Yes

* BSO = bilateral salpingo-oophorectomy

** DHEAS = dehydroepiandrosterone

*** PMH = Postmenopausal hormones