

Stroke in Women

Recognizing Opportunities for Prevention and Treatment

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Women have long been underrepresented in cardiovascular disease research. In 1970, women comprised 9% of participants within cardiovascular trials.¹ It has now been 3 decades since the landmark 1985 Task Force on Women's Health Issues,² first calling for expanded consideration of women in health, yet only one third of trial participants informing current cardiovascular guidelines are women.¹ Progress continues, however, with both women-exclusive randomized control trials³ and observational prospective studies currently being conducted.⁴ The information generated from this research has increased our understanding of the determinants of and medical therapies to prevent stroke in women, yet some questions remain, and ongoing surveillance of stroke incidence and outcomes after stroke is required.

In high-income countries, like the United States, women have a greater lifetime risk of stroke than men. Further, stroke rates differ by ethnoracial origin with a higher stroke rate occurring in Black and Hispanic women living in the United States. The major risk factors for stroke and the strength of association of the risk factors are similar in women and men, with preeclampsia, pregnancy, and use of exogenous hormones as the few exceptions. However, the frequency of each risk factor, and therefore the population attributable risk, differs between the sexes. As shown in the international INTERSTROKE case-control study,⁵ hypertension, abdominal obesity, and adverse lipid profile are the most impactful causes of stroke in women worldwide, with smoking, cardiac causes, and lifestyle factors (ie, diet quality, exercise, alcohol use) remaining as important, but not as frequent, risk factors. It is through screening and treatment of these common risk factors where the greatest gains in stroke prevention can occur. After a stroke occurs, ensuring equal access to health care and evidence-based stroke management will equalize stroke outcomes by sex. Although progress has been made, with the first guideline specifically targeted to stroke in women recently published,⁶ implementation of the optimal screening and treatment for women at risk for stroke is urgently needed.

In today's edition of *Stroke*, a series of 4 articles present aspects of stroke physiology and epidemiology unique to women: the vascular biology of preeclampsia and its

relationship to stroke; hormonal risk factors for stroke in women; an update on classical stroke risk factors in women; and sex/gender differences in stroke outcomes. Underscoring all of these sex- and gender-specific differences is a call for more intensive risk factor modification throughout the entirety of a woman's life course.

Pregnancy is often the first major stroke risk factor experienced by young women. As McDermott et al⁷ attest, stroke affects ≈30 women for every 100 000 pregnancies. Although hormonal factors, peripartum illness, and hemodynamic factors play a role, the majority of events are mediated through the spectrum of hypertensive disorders in pregnancy, particularly preeclampsia/toxemia. A systemic, multiorgan endotheliopathy, preeclampsia both predisposes to the malignant edema in posterior reversible encephalopathy syndromes and confers a 40-fold risk increase for true ischemic stroke. The most important prevention strategy is early detection, which should be emphasized with frequent antenatal blood pressure measurements and screening for signs and symptoms of toxemia in the latter half of pregnancy. Although aggressive blood pressure management was traditionally avoided for fear of affecting fetal growth, the CHIPS trial (Control of Hypertension in Pregnancy) has demonstrated the safety of tight blood pressure control in pregnancy⁸ and supports aggressive utilization of antihypertensives for the prevention of malignant hypertension. In addition, aspirin treatment^{9,10} and repletion of low calcium¹¹ have shown substantial risk reductions in preventing preeclampsia in those deemed high risk.

What is often not recognized in the treatment of pregnancy-induced hypertension and likewise gestational diabetes mellitus are the long-term ramifications of these conditions. This may occur because the physicians' treating women with hypertension in pregnancy or gestational diabetes mellitus are often not the ones managing their primary care thereafter. Although blood pressure often normalizes after delivery, vascular risk does not return to baseline. The same pattern is observed for gestational diabetes mellitus.¹² Although it remains unclear whether preeclampsia serves as a marker for future stroke or is within the causal pathway of arterial dysfunction, an 80% increased risk of stroke among those with

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a history of preeclampsia persists later in life. Despite these accepted associations, it may be decades before women with a history of preeclampsia or gestational diabetes mellitus have formal cardiovascular risk factor screening and treatment, thereby accumulating atherosclerotic burden all the while.

Outside of pregnancy, both endogenous and exogenous hormones largely influence women's stroke risk in young adulthood. Demel et al¹³ found no convincing evidence that endogenous estrogen or testosterone levels predict stroke risk, whereas the endogenous adrenal hormone DHEAS (dehydroepiandrosterone sulfate) is inversely related to both stroke incidence and severity. This is in contrast to exogenous estrogen in oral contraception, which demonstrates a dose-dependent association with the risk of major adverse cardiovascular events and stroke. Although it is important to recognize the hazards of prescription oral contraceptives, it is equally important to acknowledge that absolute risks are low, and in fact lower than the risk of stroke in pregnancy. However, the incidence of stroke significantly increases when oral contraceptives are prescribed to those with additional risk factors (ie, obesity, elevated cholesterol, or smoking).¹⁴ This is most pronounced when estrogen-containing oral contraception is used in current smokers, where the combination confers >4× the stroke risk when compared with oral contraception alone.¹⁵ Progestin-only contraceptives have not been associated with increased stroke and may be an option for those with coexisting stroke risk factors, although further research is required to precisely quantify risks.

The Women's Health Initiative is the largest investigation of the risk of hormone replacement therapy, and was a multicenter randomized double-blind trial in which women aged 50 to 79 years received combined estrogen and progesterone or estrogen alone, and compared with placebo.^{15,16} Postmenopausal hormonal therapy significantly increased stroke, with a 31% (confidence interval, 2%–68%) increase for estrogen with progesterone¹⁵ and a 37% increase for estrogen alone¹⁶ (confidence interval, 9%–73%). Although subgroup analyses have highlighted the varying risk of stroke depending on a woman's age, hormone replacement therapy is not recommended for stroke or other chronic disease prevention.

In the review by Madsen et al,¹⁷ the authors demonstrate that traditional stroke risk factors may be potentiated in women. Abdominal adiposity, metabolic syndrome, and diabetes mellitus all seem to interact with biological sex and confer an increased risk in women. Atrial fibrillation remains a leading cause of large stroke resulting in poor prognosis, with women experiencing greater proportional incidence of stroke and death as a result. Atrial fibrillation, however, is unique in incorporating female sex as an important risk factor in stroke clinical prediction rules, apparent in the CHA₂DS₂-VASc risk assessment.¹⁸

Perhaps most concerning, women may be systematically underscreened and undertreated in modifying these widely recognizable stroke risk factors. Women are less likely to be on an oral anticoagulant for atrial fibrillation at all levels of risk and have lower chances of being prescribed statin therapy or reaching cholesterol targets. This is well documented in multiple vascular disease states, from cerebrovascular to coronary disease,

where women are treated less aggressively than their male counterparts.^{19,20} As potentially modifiable risk factors account for 90% of the population attributable risk for stroke,⁵ it is in risk factor screening and treatment intensification where clinicians can best ameliorate the gender gap in stroke outcomes.

When prevention fails, and a stroke occurs, sex-specific discrepancies remain in functional outcomes and long-term prognosis. Gall et al²¹ show that women have poorer outcomes, including worse health-related quality of life with more activity limitations, as well as more poststroke depression. However, many of these associations are attenuated with adjustment for age at presentation, stroke severity, and comorbid conditions. Women are often older, with poorer health, at the time of stroke, and by that time are at least twice as likely as men to live alone. Many of these factors may not be modifiable, but remain important considerations when formulating treatment plans for rehabilitation including medication adherence and social support.

Sex-specific risk factors for stroke exist at all ages and stages of the life course. Whether mediated by the unique physiological stress of pregnancy, endogenous or exogenous hormones, or the ubiquitous nature of traditional stroke risk factors, understanding the epidemiology of stroke in women is integral to prevention and treatment. Underpinning all associations between biological sex and stroke is the need for risk factor identification and management. Aggressive treatment of obesity (even before pregnancy), hypertension, hyperlipidemia, diabetes mellitus, smoking, and atrial fibrillation in women should be emphasized.

In this edition of *Stroke*, the papers by McDermott et al,⁷ Demel et al,¹³ Madsen et al,¹⁷ and Gall et al²¹ argue for further recognition of the factors causing stroke in women and for systematic intensification of treatments. Sex differences in stroke burden are most influenced by differences in cardiovascular risk factor burden; thus, the greatest gains in stroke prevention will come from increased screening and treatment of these primary risk factors in women early in life, especially in the obese, during pregnancy, and those from high-risk ethnorracial groups.

Disclosures

None.

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