Factors Affecting Research and the Treatment of Stroke in Women

Written by Muriel Cunningham

Stroke is now the third-leading cause of death in women in the United States, killing twice as many women as breast cancer. Available evidence also suggests that women have worse outcomes after suffering a stroke. A panel of experts gathered to discuss various aspects of women and stroke. Dawn Kleindorfer, MD, University of Cincinnati, Cincinnati, Ohio, USA, led off with an overview of the epidemiology of stroke in women.

Women survive longer than men, and stroke incidence goes up significantly with age; therefore, age-specific incidence rates of stroke are lower in women, but stroke prevalence is higher. Women are also twice as likely as men to have a subarachnoid hemorrhage (SAH). Women who have an SAH are more likely to have a family history of it and have multiple aneurysms.

There are many variables that may explain sex differences in stroke. These include differences in genetics, immune system, and coagulation pathways; the role of sex hormones; life events such as pregnancy and menopause; and differences in social, cultural, and treatment arenas. Certain risk factors are specific to women—such as pregnancy, preeclampsia, gestational diabetes, oral contraceptive use, postmenopausal hormone use, and changes in hormonal status—while risk factors such as migraine with aura, atrial fibrillation, diabetes mellitus, and hypertension are not sex specific but are stronger or more prevalent in women [Bushnell C et al. *Stroke*. 2014].

Cheryl Bushnell, MD, Wake Forest Baptist Medical Center, Winston-Salem, North Carolina, USA, discussed stroke in pregnancy. Women are at increased risk of stroke during pregnancy, with the elevated risk continuing up to 6 to 12 weeks after delivery. The rate of pregnancy-related stroke appears to be increasing and is likely due to a rise in hypertension and heart disease. Stroke occurs in approximately 34 of 100 000 deliveries vs 21 of 100 000 in women who are not pregnant. The escalated stroke risk primarily occurs within the postpartum period. Risk factors may be for peripartum or postpartum stroke or both (Table 1).

Severe preeclampsia is defined as blood pressure > 160/110 mm Hg (2 measurements 4 hours apart), thrombocytopenia (platelet count < 100 000/μL), liver function impairment, and/or severe persistent right upper quadrant or epigastric pain that does not respond to analgesia, progressive renal insufficiency (creatinine > 1.1 mg/dL or doubling), pulmonary edema, and new onset cerebral or visual symptoms. There are 2 types of vasculopathies associated with preeclampsia/eclampsia: reversible cerebral vasoconstriction syndrome (RCVS) and posterior reversible encephalopathy syndrome (PRES). A thunderclap headache is the primary sign of RCVS. Cerebral vessels have diffuse or multifocal segmental narrowing and typically reverse 6 to 12 weeks after onset. PRES has endothelial leakage and vasogenic edema because sudden blood pressure increases exceed the capacity of the cerebrovascular autoregulatory system. This is reversible with blood pressure lowering.

Treatment strategies for pregnant women with acute ischemic stroke and aneurysms have not been optimized, because these patients are traditionally excluded from clinical trials.

Paola De Rango, MD, PhD, Hospital S. M. Misericordia, Perugia, Italy, presented an overview of sex-based differences in stroke care. A multitude of factors influence the care of men and women who have strokes—both physiologic differences and the types of comorbidities. For example, women are likely to be older, have more frequent atrial fibrillation, and are less likely to have coronary disease, have diabetes, or smoke. Nevertheless, different behaviors, access to care, and social and economic status also contribute to sex gaps in treatment and suboptimal stroke outcome in women.

Previously published studies reported that women with strokes experienced delays not only in diagnosis or workup but also in treatment with thrombolytics and that fewer women receive recommended treatments. Some improvements were noted in more recent publications: one study

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Table 1. Peripartum and Postpartum Stroke Risk Factors

	Stroke Risk	
Risk Factor	**Peripartum**	**Postpartum**
Older age	×	×
African American race	×	×
Hypertension	×	
Heart disease	×	
Primary thrombocytopenia	×	
Preeclampsia	×	×
Thrombophilia	×	
Sickle cell disease	×	
System lupus erythematosus	×	
Valve disorders	×	
Congenital heart disease	×	
Congenital coagulation defects	×	
Migraine	×	
Eclampsia		×
Chronic kidney disease		×
Pregnancy-related hematologic disorders		×
Congestive heart failure		×
Peripartum infection		×
Diabetes mellitus		×

Sources: James A et al. *Obstet Gynecol.* 2005. Leffert AR et al. *Obstet Gynecol.* 2015. Hovsepian DA et al. *Stroke.* 2014.

on revascularization interventions after acute ischemic stroke in the Nationwide Inpatient Sample from 1997 to 2006 saw no differences between men and women receiving intravenous tissue plasminogen activator by the end of the review period [Towfighi A et al. *J Stroke Cerebrovasc Dis.* 2013]; in another, women appeared to derive more benefit from thrombolytic therapy [Nathanson D et al. *Stroke Res Treat.* 2014]. In another recent registry analysis study, there were no sex-related differences in acute stroke care, including onset-to-door and door-to-needle times, the times to and rates of imaging, and thrombolytic treatment [Gattringer T et al. *Stroke.* 2014]. Removing barriers to care, increasing medication adherence, and making additional improvements to in-hospital care should continue to be targeted to narrow the sex treatment gap.

Women have historically been underrepresented in clinical research across multiple therapeutic areas. Seemant Chaturvedi, MD, University of Miami, Miami, Florida, USA, reviewed the evidence for this discrepancy and proposed potential solutions.

Interpretation of study results is problematic when few women are enrolled in a clinical trial. Subgroup analyses become more difficult; the potential for type II errors grows; and it is unclear how generalizable the study results are to larger populations of women. The percentages of women participating in key antiplatelet, acute stroke, and carotid stenosis trials have typically been between 30% and 40%. Dr Chaturvedi noted that trials must not discriminate against including elderly patients, as that leads to fewer women being enrolled due to the epidemiology of the condition. In a positive example, the mean age of participants in the Third International Stroke Trial [IST-3 Collaborative Group. *Lancet.* 2012] was 83 years, and 52% of the enrolled patients were women.

Dr Chaturvedi proposed several ways to address the problem of underrepresentation. Sex-specific trials could be conducted, or clinical trial protocols could implement a minimum percentage of women. Data safety monitoring boards could monitor trial enrollment more closely for the inclusion of women, or enrollment of men could be stopped once a particular threshold was reached. Developing recruitment plans specifically for women, removing exclusion criteria that may prevent women from enrolling, and including more elderly patients in stroke trials would also help address underrepresentation. Dr Chaturvedi and his colleagues hope to conduct a study comparing optimal medical therapy alone with optimal medical therapy plus carotid revascularization in women with recent stroke or transient ischemic attack to determine the best approach for women.