



Women and Stroke

A Lecture Summary

In April, the Heart and Stroke Foundation of Ontario hosted a morning in clinical neuroscience. As part of the event, Dr. Robin Brey of the University of Texas at San Antonio addressed the issues surrounding stroke in women.



Stroke afflicts 450,000 people in the United States each year, 200,000 of whom are women. In spite of this, stroke is often viewed as a man's disease. This misconception is being corrected as new research focusing on both stroke in women and on gender differences in stroke comes to light.

Dr. Robin Brey, professor of neurology, department of medicine at the University of Texas Health Science Center at San Antonio, presented some of these new data at the Heart and Stroke Foundation of Ontario's annual H.J.M Barnett Stroke Lectureship and Visiting Fellowship. The lecture was held in Hamilton, Ont., on April 20, 2001.

Dr. Brey's lecture focused on several key areas. She looked first at stroke risk factors that are specific to women, such as pregnancy, hormonal contraception and hormone replacement therapy. She then examined the risk factors that affect both men and women and discussed the different ways in which each gender is affected. Finally, she focused on cerebrovascular disease prevention. The following is a summary of her presentation.

Stroke and Pregnancy

It has long been known that both pregnancy and the post-partum state are risky times for female patients, in terms of their susceptibility to a variety of conditions. Several

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studies have examined the risk of stroke during pregnancy and found it to be elevated. A recent case-controlled study by Kittner *et al*,¹ from the University of Maryland, went a step further and examined the risk of stroke in both the pregnant and post partum states as compared to the risk of stroke in non-pregnant women. They found that the risk of ischemic infarctions during pregnancy was no different for pregnant women than for non-pregnant women. There was an elevated risk of hemorrhagic stroke, however, the confidence intervals respecting the risk of hemorrhagic stroke were quite wide.

The post partum state, however, was different. The risk of stroke was increased nearly ninefold in the first six weeks after delivery. This indicated that changes post-partum convey a huge risk of both hemorrhagic and ischemic stroke that translates

into eight excess strokes in the post-partum state for every 100,000 pregnancies.

There are several changes that can be result in the increased risk of stroke in the pregnant and post-partum states. During pregnancy, eclampsia and pre-eclampsia are among the most important of these conditions.

In addition, changes occur in the woman's coagulation system that can lead to a more prothrombotic state. Glucose levels rise and the lipid profile becomes more atherogenic. These changes are usually thought of as chronic risk factors, however, they could certainly contribute to the development of stroke during pregnancy in certain women.

Hemorrhagic infarction is a particularly interesting case due to differences in the natural history between pregnant patients and non-pregnant patients. Only one third

of hemorrhagic strokes in pregnant patients are due to eclampsia, while fully half are the result of either aneurysm or ruptured arteriovenous malformations (AVMs).

The risk of aneurysmal rupture is not much different in the pregnant patient than the non-pregnant patient, with older patients at higher risk than younger patients. The risk does, however, increase as the pregnancy progresses. The risk of aneurysmal hemorrhage during the actual delivery process is quite low and, in contrast to ischemic strokes, the risk of post-partum aneurysmal rupture is lower than during the pregnant state.

The risks associated with AVM rupture contrast with those associated with aneurysmal hemorrhage. Delivery, for example, is a very high risk time for AVM, the frequency of bleeding is equal throughout the pregnancy and bleeding is more common in younger women than older women. There is also a difference in the presentation of AVM rupture between pregnant and non-pregnant women. Hemorrhage is the most common presentation of AVM in the pregnant state, while in non-pregnant women, seizures are the most common presentation.

This information leads to the conclusion that, while extreme concern for the fetus is a must, pregnant women need to be evaluated for their risk of stroke just as aggressively as non-pregnant patients. This can be safely accomplished through computed tomography (CT) scans with abdominal shielding, angiography with abdominal shielding and magnetic resonance imaging (MRI). MRI is probably the best initial step in pregnant patients.



Hormonal Contraception

Hormonal contraception remains a rather controversial area in terms of stroke risk. Many studies currently suggest that the higher the doses of estrogen, the higher the risk of stroke. With use of hormonal contraception, coagulation factors increase, platelets are activated and hypertension will occur in 4% to 6% of women and be exacerbated in 10% to 15% of women. These issues need to be carefully considered when choosing hormonal contraception.

On the other hand, research has shown that there is a potential decrease in risk because of beneficial effects on arterial walls, and the lipid profile. More recent work, however, indicates an excess risk for those with any other stroke risk factors, such as smoking, hypertension, migraine or

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diabetes. It is extremely important to counsel patients and carefully consider the excess risk when deciding what type of contraceptive to use. As a general rule, anybody with a known hypercoagulative state or who smokes cigarettes should avoid hormonal contraception.

Hormone Replacement Therapy

Hormone replacement therapy is commonly used for its beneficial effects on bone mass and for the relief of the symptoms of menopause. Retrospective and case-controlled studies also have found a positive effect on the risk of coronary artery disease.

It is becoming apparent, however, that hormone replacement therapy may not be effective in decreasing the risk of stroke. In the Nurse's Health Study,² which looked at 50,000 to 60,000 women, the risk of stroke and deep vein thrombosis was actually increased, indicating that hormone replacement therapy has a different effect on brain and venous circulation than in the coronary arteries.

A variety of other studies have had some very interesting findings. The HERS trial,³ which was published several years ago, came as a shock to the scientific community. It found, as expected, that when women were randomized to hormone replacement (estrogen plus progesterone) plasma lipid levels were lowered by about 11% compared to the control group. There was, however, no difference in clinical outcomes. Both groups had 33 non-fatal

myocardial infarctions (MIs) per 1,000 women.

The reason behind this finding lies in the fact that risk of MI was highest early in the treatment period. For the first year after treatment was initiated, the MI rate in the treatment group was very high. In the longer term, the risk decreased to a level below that of the placebo group. The WEST trial,⁴ which looked at stroke instead of MI, found essentially the same things. The trial, which is currently only available in abstract form, looked at 652 postmenopausal women who had had either a transient ischemic attack (TIA) or non-disabling stroke that was found to have occurred within 90 days of entering the trial. The women were randomized to unopposed estrogen therapy or placebo. After three years, the death rate was essentially the same in both groups. Again, study investigators found that the risk was highest in the first year after initiation of therapy and lower in the following years.

In both cases, this may be explained by the fact that, in the first year, negative changes in platelet adhesiveness and abnormalities in coagulation may actually outweigh the improved lipid profile. Those who survive the risky period may go on to see long-term benefits, perhaps due to the changes in the lipid profile. Unfortunately, there is no way to determine who may be most at risk in the first year.

Other Risk Factors

Hypertension. Hypertension is probably the most important risk factor for stroke. Some older literature suggests that the treatment of women with hypertension may not be as effective in preventing

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stroke and MI as it is in men. More recent literature and meta-analysis of the data, however, dispute these findings, suggesting that good blood pressure control is extremely important in both genders. A recent study in Pennsylvania⁵ found in eightfold increase in the risk of stroke in hypertensives with poor blood pressure control, compared to a twofold increase in those with good blood pressure control.

Diabetes. In general, young women have a very low stroke risk. Young women with diabetes however, have the exact same stroke risk as men with diabetes—a huge increase, given their age range. Some data even suggest that, under certain conditions, young women with diabetes may even have a higher risk than their male counterparts. This indicates a need for extremely aggressive risk reduction in this patient group.

Smoking. Almost every smoking study published is showing that increasing numbers of young women are starting to smoke, are smoking longer and are consuming more cigarettes than men. The Nurse's Health Study⁶ found that cigarettes increased the risk of all stroke types about fourfold and of hemorrhagic stroke almost 10 fold. This makes smoking an important modifiable risk factor in women for both primary and secondary stroke prevention.

Non-Valvular Atrial Fibrillation. Data from the Framingham study⁷ indicate that, in older women non-valvular atrial fibrillation (AFib) is an important risk factor. The attributable risk for stroke presented by non-valvular AFib increases with age, in both men and women. It ranges from 1.5% in



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those aged 50 to 59 up to 23.5% in those aged 80 to 89. In men with non-valvular AFib there is a twofold increase in stroke risk, whereas women see a fivefold increase.

In addition, men with non-valvular AFib tend to have atherosclerotic strokes. Women, on the other hand, were more susceptible to other stroke etiologies. This means that women do not benefit from treatment with acetylsalicylic acid (ASA), as do older men, but instead benefit from treatment with warfarin.

Mitral Valve Prolapse. This is a relatively common condition in young women. There is, however, little solid evidence that indicates mitral valve prolapse is responsible for any increased stroke risk. It is not necessary to be overly aggressive in the treatment of what seems to be a benign problem.

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Migraine. Although migraine is a relatively common condition in young women, its association with stroke is low. Three recent studies, however, have found a striking association between oral contraceptive use, migraine and stroke.^{8,9}

Alcohol. The issue of the effects of alcohol on stroke risk is something that has seen a fair deal of discussion in recent years. There have been many studies done in male populations and, in the last year, two studies involving female subjects. One of these studies found that moderate alcohol intake actually decreased the risk of stroke in younger women.¹⁰ In the second study, older women enjoyed similar results.

Collagen Vascular Disease. Women with collagen vascular disease, particularly lupus, have a much greater risk of heart attack or stroke than those without these conditions. It is important to recognize that these conditions are much more common in women than men. There is no evidence to suggest that these women should be treated any differently than those with collagen vascular disease. Nevertheless, it may be worthwhile to be much more vigorous in reducing risk, counselling and educating these patients.

Lipids. There is not yet much data on the effects of lipid levels on stroke risk. One ongoing sub-study of the Women's Health Study has found that 50% of women in the study population who had suffered an MI or stroke had normal lipid levels.¹¹ The study investigators examined other markers to see if they could predict those at highest risk of stroke or MI. As is the case in previous studies involving men, investi-

gators found that testing for C-reactive protein was very effective for this purpose.

Conclusion

Stroke is clearly easier to prevent than it is to treat. This means that risk reduction through education and risk management is extremely important. Unfortunately, stroke is often still considered a disease more important in men than in women. This may lead to inadequate time spent counselling women on the importance of risk-reduction strategies. Physicians must not only keep in mind that women too are susceptible to stroke, but they must also consider the different ways in which risk factors manifest themselves in women. **Dx**

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