Sex Differences in Stroke

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Disclosures

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• Speakers Panel for Genentech (tPA)
Types of Stroke

- Intracranial Hemorrhage
- Subarachnoid Hemorrhage
- Ischemic

Source: AHA Disease Statistics Circulation 2012;125 (e2-e220)
Sex Differences in Stroke

- Stroke Epidemiology
- Prevention
- Risk factors
- Acute presentation
- Acute management
- Recovery/Outcomes
- Estrogen
Epidemiology

- 780,000 people/year experience a new or recurrent stroke
- 50,000 more women than men suffer a stroke annually
- Women accounted for 63.0% of US stroke deaths in 2005
- Women have low rates of stroke until >20 years post-menopause then stroke incidence increases and surpasses men in the elderly population—Estrogen?
- Women have worse functional outcomes after a stroke (some of this is age-independent)
Guidelines for the Prevention of Stroke in Women: A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association
on behalf of the American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, Council on Epidemiology and Prevention, and Council for High Blood Pressure Research

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Table. Risk Factors for Stroke

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Sex-Specific Risk Factors</th>
<th>Risk Factors That Are Stronger or More Prevalent in Women</th>
<th>Risk Factors That Are Similar in Men and Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy, preeclampsia, or gestational diabetes</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>Oral contraceptive or postmenopausal hormone use</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>Migraine headache with aura</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Atrial fibrillation</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>Hypertension</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>Physical inactivity, obesity, or unhealthy</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Prior cardiovascular disease</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td>X</td>
<td></td>
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<tr>
<td>The metabolic syndrome</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Psychosocial stress</td>
<td></td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>
Age distribution by sex of 502,036 ischemic stroke admissions in the GWTG-Stroke program

Projected number of deaths from stroke among whites (USA, 2000–2050)

The most frequent sites of arterial and cardiac abnormalities causing ischemic stroke

- Intracranial Atherosclerosis
- Carotid Plaque with Arteriogenic Emboli
- Flow Reducing Carotid Stenosis
- Aortic Arch Plaque
- Atrial Fibrillation
- Cardiogenic Emboli
- Valve Disease
- Left Ventricular Thrombi
Lenticulostriate Arteries Supply the Basal Ganglia and Internal Capsule: Lacunar or “Mini-strokes” (yuck!)
Cumulative frequency of stroke etiology in women and men with AIS
Case

85 F with recent loss of her longtime husband presents with acute left sided weakness and neglect.

She was found by her daughter in the afternoon. Time of onset was unknown.
Psychosocial Factors

• Depression and psychosocial stress increase risk for incident stroke by 25% to 45% in women

• Higher serum inflammation

• Increases risk of recurrent stroke
Progressive Isolation

Figure 2.
Households by Type: 1990, 2000, and 2010
(Percent distribution. For information on confidentiality protection, nonsampling error, and definitions, see www.census.gov/prod/cen2010/doc/sf1.pdf)

Epidemic of Loneliness

- 52% of women live alone compared to 29% for men after age of 80.
- Many will have outlived not only spouses/partners but also their friends and children.
- Cardiovascular, nervous and immune targets.
Practical Issues?
The detrimental effects of isolation can be modeled in animals!
Infarct Size was equivalent at 30 and 90 days when SI was delayed 72 hours after stroke.
Mortality

![Survival analysis](image)

- Percent survival vs. Day
- Lines represent different groups:
  - Sham
  - Sl
  - PH-SP
  - PH-HP
- Statistical significance:
  - P < 0.01
  - P < 0.05
Hypertension

• Hypertension, the most modifiable risk factor for stroke, is more prevalent in women than men.

• More often poorly controlled in older women;

• Only 23% of women versus 38% of men older than 80 years have a blood pressure less than 140/90 mm Hg.

• No sex-specific guidelines for treatment- goal is excellent control!
Case

76 F with history of hypertension and hyperlipidemia presents to the ED with acute onset of aphasia and R hemiparesis

CTA shows proximal L MCA occlusion but no significant stenosis in the carotid.
Atrial Fibrillation

• Higher prevalence and a higher associated risk for thromboembolic events in women

• CHA2DS2-VASc score incorporates sex

• 30% of women with A. fib had stroke (RR 5.5), vs 17% of men with A. fib (RR 2.1)

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHF</td>
<td>1</td>
</tr>
<tr>
<td>HTN</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥75</td>
<td>2</td>
</tr>
<tr>
<td>Age 65-74</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1</td>
</tr>
<tr>
<td>Stroke/TIA/thromboembolism</td>
<td>2</td>
</tr>
<tr>
<td>Vascular disease</td>
<td>1</td>
</tr>
<tr>
<td>Female</td>
<td>1</td>
</tr>
</tbody>
</table>

• Screen older patients, especially women, for afib!
• Anticoagulate (warfarin or NOACs) for CHA2DS2-VASc ≥2
Prevention of Stroke

![Annual Thromboembolism Rate](chart)

- Women
- Men

**RR** = 1.6 [1.3-1.9] for Age ≤ 75

**RR** = 1.8 [1.4-2.3] for Age > 75

Migraine with Aura

- Women are 4 times more likely than men to have migraine headache.
- Absolute risk for stroke associated with migraine headache is low, age, smoking, complex neurological signs increase risk
- Association between migraine headache with aura and stroke strongest in women younger than 55 years.
Management of Migraineurs with aura

• Prophylaxis to reduce migraine frequency

• Cautious about use of oral contraceptives in migraineurs with aura...

• Avoid OCPs in migraineurs with aura who smoke (OR 7 for stroke) and aggressive management of their other risk factors
Hormonal Contraception

• The use of OC is a risk factor for stroke in young women, increasing the risk from 1.4- to 2.0-fold

• The absolute risk is low—approximately 2 events per 10,000 women per year with the use of the lowest-dose estrogen formulation

• The risk for stroke among women using OC increases with age
  • 3.4 per 100 000 women aged 15 to 19 years
  • 64.4 per 100 000 women aged 45 to 49 years

• Modify other risk factors- SMOKING!, HTN, diabetes, hyperlipidemia

• SCREEN for BP after starting and FAMILY HISTORY
Hormonal Replacement Therapy

- Epidemiology showing relative protection in women until after menopause
- Observational studies showing protection in HRT users from both stroke and MI/CAD
- Preclinical/Experimental evidence of robust neuroprotective effects in vivo and in vitro
Estrogen

Male

Female
Ischemic stroke risk - WHI hormone trial

Hendrix, S. L. et al. Circulation 2006;113:2425-2434
Timing matters!

(A) Chronic ERT | Acute ERT
Male
Female
Other presentations of stroke in women

39 F on oral contraceptives presents with 7 day history of headache and progressive left arm numbness and weakness.

Notes some worsening of headache in the morning as well as some blurred vision

Thoughts?
What is it?
Case

- MRV/MRI showed SSS and right cortical vein thrombosis.
Female sex is risk factor for CVT

- Likely due to oral contraception and pregnancy.
- CVT is sex-independent in very young and old.
Case

- 39 y/o female with a history of migraine c/o right facial and throat pain for the past week. Notes “unequal pupils” this am

- R pupil miotic

- ? Reported parasthesias along $V_1$-$V_2$ distribution
See anything?
Arterial dissections

• Migraine doubled the risk of cervical artery dissection (pooled odds ratio [OR]=2.06, 95% confidence interval [CI] 1.33-3.19)

• Risk may be increased post-partum period

• Treatment- aspirin versus anticoagulation

• tPA for acute presentations of stroke

Vasculopathies and peripartum stroke

- RPLS or RCV
- Postpartum angiopathy
- Preeclampsia, moderate/severe

- Ischemic stroke
- Reversible brain swelling, subarachnoid hemorrhage
- Intracerebral hemorrhage
Pregnancy

- Age at pregnancy >35 years doubles the risk of stroke, especially in African-American women

- Age >35 years multiplies 4-fold the risk of stroke associated with pregnancy

- As women are older when they are becoming pregnant, incidence of stroke is increasing

- Can contribute to up to 12% of maternal deaths
# Pregnancy-Related Stroke Incidence

<table>
<thead>
<tr>
<th>Race</th>
<th>Cases (n)</th>
<th>Rate (per 100,000)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>1078</td>
<td>31.7</td>
<td>(28.8, 34.6)</td>
</tr>
<tr>
<td>Black</td>
<td>435</td>
<td>52.5</td>
<td>(44.1, 60.9)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>356</td>
<td>26.1</td>
<td>(21.2, 31.0)</td>
</tr>
</tbody>
</table>

## Pregnancy-related Stroke Incidence

<table>
<thead>
<tr>
<th>Age</th>
<th>Cases (n)</th>
<th>Rate Per 100,000</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20 y</td>
<td>290</td>
<td>30.3</td>
<td>(25.0, 35.6)</td>
</tr>
<tr>
<td>20-24</td>
<td>535</td>
<td>26.3</td>
<td>(23.0, 29.6)</td>
</tr>
<tr>
<td>25-29</td>
<td>575</td>
<td>26.3</td>
<td>(23.3, 29.4)</td>
</tr>
<tr>
<td>30-34</td>
<td>697</td>
<td>35.3</td>
<td>(30.6, 40.0)</td>
</tr>
<tr>
<td>35-39</td>
<td>564</td>
<td>58.1</td>
<td>(51.4, 64.8)</td>
</tr>
<tr>
<td>40+</td>
<td>190</td>
<td>90.5</td>
<td>(71.9, 109.1)</td>
</tr>
</tbody>
</table>

Increased risk of thrombotic complications lasts 3 months, not 6 weeks.
**Hypertension and Preeclampsia**

• Women with chronic primary or secondary hypertension or previous pregnancy-related hypertension should take low-dose aspirin from the 12th week of gestation until delivery.

• Calcium supplementation (of ≥1 g/d, orally) should be considered for women with low dietary intake of calcium (<600 mg/d) to prevent preeclampsia.

• Severe hypertension in pregnancy should be treated with safe and effective antihypertensive medications (e.g. methyldopa, labetalol, or nifedipine).

• **RISK FOR LATER STROKE IS SIGNIFICANT!!!!**
Vasculopathy and eclampsia
Reversible cerebral vasoconstriction syndrome

- Presents with “thunderclap headache”

- Relatively rare pregnancy-related complication and it is seen more commonly in patients with pre-eclamptic toxemia or eclampsia

- Etiology is not understood angiographic finding of vessel constriction and dilation suggests an alteration in cerebral tone (source).
41 yo G5P4 presented with an acute onset of right hemiparesis and aphasia at 9am.

Last seen at 8:30 am, called husband “not feeling well”

On arrival she was mute, lying on the floor.

In ED she had a NIHSS of 22. Alert, awake, global aphasia, left gaze preference, visual field cut, normal pupils, right facial, 0/5 on right and moving spontaneously on left.

5 months pregnant-What next?

TPA?
Summary

- **Sex-specific risk factors that require special attention**
  - Pregnancy
  - Hormonal contraception and replacement therapy
  - Migraine with aura
  - Hypertension and atrial fibrillation

- **Acknowledgement of the burden of stroke on older women**
  - Poor social support
  - Outlived spouses, isolation
  - May contribute to poorer outcomes in this group
Translational Implications

• In 1993, the NIH Revitalization Act required the inclusion of women in NIH-funded clinical research.

• However, inclusion of women is **not required** at phases 1 and 2 of NIH-funded human subject trials when critical safety and dosage issues are addressed (Ambien).

• 80% of the drugs taken off the market between 1997 and 2000 “had disproportionately adverse effects on women”

• Call for Action for “Sex Balancing” in clinical and now pre-clinical studies

[www.gao.gov/new.items/d01286r.pdf](http://www.gao.gov/new.items/d01286r.pdf)
Policy: NIH to balance sex in cell and animal studies
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