Women and Stroke

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Objectives

To review sex-related differences:

- Stroke Incidence
- Stroke risk factors
  - Conventional risk factors
  - Vascular and inflammatory disorders predisposing to stroke
  - Risks exclusive to women: OC, HRT, and Pregnancy
Stroke Incidence

Ischemic Stroke
Myocardial Infarction

Wolf PA. Stroke: Pathophysiology, Diagnosis, & Management. 1998
Stroke in Women

Conventional CV Risk Factors

Other Stroke Risk Factors

Exclusive to women:
- Exogenous hormones
- Pregnancy

Vascular Disorders
Inflammatory Disorder
Migraine
Conventional Stroke Risk Factors
Hypertension

- Most important modifiable risk factor
- Affects 50% of all women >50 yo, and more common than in men
- 4-8 fold increase in stroke risk, but stronger predictor of stroke in women
- Responsible for 66% of strokes in women

Keller KB, Lemberg L. Am J crit Care 2000;9:2017-9
Hypertension Prevalence

Percentage of Population

Age Groups

Wilson PW. Clin Cardiol 1999
Diabetes

- After age 45 yo, twice as many women develop DM c/t men
- DM overall doubles risk of stroke, but risk may be higher in women
- DM: higher risk of MI in women (RR 4.4) compared to men (RR 2.5)

Wenger NK. NEJM 1993;329:247-56
Obesity

- 51% of women are overweight or obese (BMI > 25 kg/m²)
- Obese women have twice the stroke risk c/t lean women
- Risk of CVD increases
  - 5.7% for every kg a woman gains vs 3.1% for every kg a man gains

Pradhan AD. J Cardiovasc Risk 2002
Rexrode KM. JAMA 1997
Anderson JW. Obes Res 2001
Cholesterol

- Increased in 40% of women >55 yo
- After age 50 yo, a higher percentage of women have cholesterol >200 mg/dL
- Statins are effective in both men and women

Atrial fibrillation

- Women have 5-fold increased risk of stroke with atrial fibrillation compared to men (HR 7.8 vs 1.7)
  Friberg J. Am J Cardiol 2004

- Lower use of ACG for atrial fibrillation
  Glader EL et al. Stroke 2003;34:1970-75
Other stroke risk factors
Vascular conditions more common in women

- Reversible cerebral vasoconstriction syndrome
- Giant cerebral aneurysm
- Atrial myxoma
- Fibromuscular dysplasia
Fibromuscular dysplasia

- Strong female predominance
- 0.25 to 0.5% of carotid angiograms
- Nonatherosclerotic cause of artery stenosis
  - Frequent association with vertebral (7-19%) and renal arteries (25-50%) disease
Vasculitides and inflammatory conditions more common in women

- Takayasu arteritis
- Primary CNS angiitis
- Moyamoya disease
- Sarcoidosis
- TTP
- Systemic lupus erythematosus
Systemic Lupus Erythematosus

- Female:Male ratio 9:1 (between ages 5 and 50 year old)
- Stroke occurs in 20% of patients with SLE
  - This risk is double that of a general age-matched population
- In SLE the highest risk of first stroke is during the first 5 years of the disease,
  - Highest stroke rate is during the first year
  - High risk of recurrence

Mechanisms of Stroke in SLE

- Vasospasm
- Microvascular disease, both small vessel occlusion and microbleeds
- Thrombosis (arterial or venous)
  - Antiphospholipid antibodies in 30% w. SLE
- Cardioembolism (Libman-Sacks endocarditis occurs in 16-57%)
- Lupus vasculitis is rare

Antiphospholipid Antibodies as a stroke risk factor in women

- Stroke Prevention in Young (15-44) Women Study:
  2-fold increase with LA and aCL.

- RATIO Study (women less than 50 yrs)
  - ACL not associated with stroke
  - β2-GP I antibodies: increased risk of ischemic stroke (OR 2.3)
  - LA: OR 43, LA + OCP: OR 200, LA + smoking: OR 87
  - Prevalence of LA is low, incidence of ischemic stroke among young women is low (3 per 10,000 person-years), the population attributable risk is 20%
    - LA is responsible for a large proportion of ischemic strokes in young women

Migraine and Stroke Meta-analyses

BMJ 2009;339:b3914
Studies: 7 case-control, 4 cohort (Meta-analysis)

The American Journal of Medicine 2010: 123, 612-624
Studies: 12 case-control, 8 cohort, 622,381 participants
Meta-analyses Results

- Stroke risk is double in women and likely NOT elevated in men
  - Women: RR, 95% CI \(2.08\) (1.13-3.84)
  - Men: RR, 95% CI \(1.37\) (0.89-2.11)

- Stroke risk is elevated in persons < 45 years old, especially women
  - Age <45: RR, 95% CI \(2.65\) (1.41-4.97)
  - Age < 45, Women RR, 95% CI \(3.65\) (2.21-6.04)
Absolute Risk of migraine-related stroke

- **Women <45 yo** the stroke incidence rate was:
  - No migraine: 6 ischemic strokes per 100,000 women per year
  - Migraine: 19 per 100,000 women per year
  - **Absolute risk of 13 additional cases of ischemic stroke per 100,000 women per year due to migraine.**


- **Women >=45 yo** the stroke incidence rate was:
  - No migraine: 88 ischemic strokes per 100,000 women per year
  - Migraine: 131 per 100,000 women per year
  - **Absolute risk of 40 additional cases of ischemic stroke per 100,000 women per year due to migraine.**

  Ref: Kurth et al. JAMA 2006;296:283-291 Women’s Health Study
## Meta-analysis Summary

<table>
<thead>
<tr>
<th>Factor</th>
<th>Ischemic Stroke Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Migraine Aura</strong></td>
<td>++</td>
</tr>
<tr>
<td><strong>In migraine with aura</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Migraine Frequency, Duration</strong></td>
<td>+</td>
</tr>
<tr>
<td><strong>Younger age (&lt;45 yo)</strong></td>
<td>+++</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td>++</td>
</tr>
<tr>
<td><strong>Smoking, OC, and combined</strong></td>
<td>+++</td>
</tr>
<tr>
<td><strong>Low CV Risk profile</strong></td>
<td>++</td>
</tr>
</tbody>
</table>

+ up to a 2-fold elevated risk
++ 2 to 4-fold elevated risk
+++ >4-fold elevated risk
Migraine and CV Risk factors in persons with stroke

The Italian Project on Stroke in Young Adults
981 subjects, <45 y (mean 36 y), 51% women

Migraine with aura was associated with:
- low cardiovascular disease risk profile
- Underlying pro-coagulant state
- Cardiac right-to-left shunt (PFO)

Stroke risk factors exclusive to women
Stroke risk in Women throughout the life span

- Age at menarche
  - extremes associated with increased stroke risk
- Age at menopause
  - before age 42 years associated with increased stroke risk
Oral Contraceptives

- Stroke risk doubles
- Venous thrombosis risk increases 4 to 6 fold
- Risk increases with dose
- Estrogen has higher risk than progesterone

<table>
<thead>
<tr>
<th>RATIO study</th>
<th>Adjusted OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any current use</td>
<td>2.1 (1.5-3.1)</td>
</tr>
<tr>
<td>1st generation OC use</td>
<td>1.8 (0.7-4.7)</td>
</tr>
<tr>
<td>2nd generation OC use</td>
<td>2.1 (1.3-3.3)</td>
</tr>
<tr>
<td>3rd generation OC use</td>
<td>2.3 (1.3-4.2)</td>
</tr>
</tbody>
</table>

Kemmeren et al. Stroke 2002;33:1202
Oral Contraceptive—factors that increase risk

Conventional risk factors
- Hypertension
- Hyperlipidaemia
- Obesity
- Age (>35)
- Smoking

Other risks:
- Migraine with aura
- Antiphospholipid antibodies

Genetic conditions:
- Factor V Leiden
- Prothrombin G20210A
- MTHFR C677T
- F13A1 Tyr204Phe

Genetic testing if there is a family or personal history of thrombosis.
HRT as a stroke risk factor

- Stroke risk is increased in primary prevention studies with HRT.
- There is no difference in risk in secondary prevention studies.
- The relationship of stroke and HRT is not affected by the timing of HRT use after menopause.

No indication for the use of HRT in stroke prevention.
Pregnancy

Peripartum stroke incidence

- Non-pregnant women: 3 to 10/100,000
- Pregnant women: 34/100,000

James Obstet Gyn 2005;106:509
### Pregnancy-related stroke incidence

<table>
<thead>
<tr>
<th>Stroke Type</th>
<th>Rate/100,000 deliveries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic stroke</td>
<td>9.2</td>
</tr>
<tr>
<td>Intracerebral bleed</td>
<td>8.5</td>
</tr>
<tr>
<td>Cerebral venous thrombosis</td>
<td>0.6</td>
</tr>
<tr>
<td>Pregnancy-related cerebrovascular event</td>
<td>15.9</td>
</tr>
</tbody>
</table>

James, Obstet Gyn 2005;106:509
Risk factors for peripartum stroke

- Hypertension OR 6.4
- Heart disease OR 13.2
- Sickle Cell disease OR 9.1
- SLE OR 15.2
- Migraine OR 16.9
- Pre-eclampsia OR 4.4
- Thrombosis OR 16.0

## Stroke-related pregnancy incidence by age

<table>
<thead>
<tr>
<th>Age</th>
<th>Cases (n)</th>
<th>Rate</th>
<th>95% CI</th>
</tr>
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<tbody>
<tr>
<td>&lt;20 y</td>
<td>290</td>
<td>30.3</td>
<td>(25.0, 35.6)</td>
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<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>

Rate=per 100,000 births

Timing and causes of stroke during pregnancy

<table>
<thead>
<tr>
<th>Cause</th>
<th>First Trimester</th>
<th>Second Trimester</th>
<th>Third Trimester</th>
<th>Post Partum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preeclampsia-eclampsia (n=4)</td>
<td></td>
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<tr>
<td>Primary CNS vasculopathy (n=2)</td>
<td></td>
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<tr>
<td>Carotid dissection (n=1)</td>
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<tr>
<td>TTP (n=1)</td>
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<tr>
<td>Cortical-vein thrombosis (n=1)</td>
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<tr>
<td>Postherpetic vasculitis (n=1)</td>
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</tr>
<tr>
<td>Indeterminate cause (n=6)</td>
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</tbody>
</table>

Kittner, et al. NEJM 1996;335:768-774
Postpartum Stroke


- Hospitalizations for pregnancy-related strokes and TIAs have increased by 54%
- Strokes have increased over time especially during the postpartum period
- Increase mostly related to changes in prevalence of hypertension and heart disease. Also advanced age.
- Rates of increase highest in the South
Summary

- Increase in conventional stroke risk factors (HTN, DM, Cholesterol, and obesity) and strength of the risk factors in women
- Increase of vascular/inflammatory disorder associated with stroke in women
- Risk of stroke associated with migraine is in those with aura, women < 45 yo, using OCs, and with low CV profiles
Summary

- Exogenous hormones (OCs, HRT) increase stroke risk in women.
- Pregnancy increases risk of stroke:
  - Age is a risk factor.
  - Ischemic > ICH >>>>> CVT.
  - Most occur in third trimester and early postpartum period.