Stroke in Women: Sex Differences in Adult Stroke

Connecticut Stroke Symposium

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Presenter Disclosure Information

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Stroke in Women

FINANCIAL DISCLOSURE: No Disclosures

UNLABELED/UNAPPROVED USES DISCLOSURE: None
Learning Objectives

- Discuss the unique epidemiology and risk factors for stroke in women
- Identify possible health disparities in aging women
- Understand the role of HRT in postmenopausal women
- Identify the role of anticoagulation in women
- Recognize differences in stroke outcome in men and women
- Recognize basic biological differences in men and women regarding inflammation and fibrinolysis
Sex Differences in Stroke

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

- 750,000 people/year experience a new or recurrent stroke
- About 46,000 more women than men suffer a stroke annually
- Women accounted for 63.0% of US stroke deaths in 2005
- The same holds for cardiovascular disease-more women than men will die within 1 year of having an MI (38% vs. 25%)
- Women have low rates of stroke until >10 years post-menopause then stroke incidence increases and surpasses men in the elderly population-Estrogen?
Stroke Prevalence by Sex

Reeves MJ et al., 2008
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)

Reeves MJ et al., 2008
Risk Factors

Figure 1. Prevalence of Hypertension* in US Women and Men Aged 45 and Older: 1999–2000.

<table>
<thead>
<tr>
<th>Age Groups</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>40-54</td>
<td>19.1</td>
<td>20.4</td>
</tr>
<tr>
<td>55-64</td>
<td>31.9</td>
<td>24.8</td>
</tr>
<tr>
<td>65-74</td>
<td>53.0</td>
<td>53.0</td>
</tr>
<tr>
<td>75 and Older</td>
<td>64.4</td>
<td>50.6</td>
</tr>
</tbody>
</table>

*Defined as systolic BP of ≥140 mm Hg or diastolic BP of ≥90 mm Hg.


Prevalence of High Blood Pressure in Adults Age 20 and Older by Age and Sex*

<table>
<thead>
<tr>
<th>Age Groups</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-34</td>
<td>12.2</td>
<td>6.6</td>
</tr>
<tr>
<td>35-44</td>
<td>24.4</td>
<td>18.2</td>
</tr>
<tr>
<td>45-54</td>
<td>38.6</td>
<td>38.4</td>
</tr>
<tr>
<td>55-64</td>
<td>53.2</td>
<td>54.1</td>
</tr>
<tr>
<td>65-74</td>
<td>70.8</td>
<td>70.8</td>
</tr>
<tr>
<td>75+</td>
<td>77.3</td>
<td>77.3</td>
</tr>
</tbody>
</table>

*Hypertension is defined as systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg, taking antihypertensive medication, or being told twice by a physician or other professional that one has hypertension.

Source: NCHS and NHBSL.
Diabetes/ Metabolic syndrome

- Formal recommendation in women is HbA1c <7%
- NHS: 116,316 women 30 through 55 yrs of age in 1976;
  - Diabetes was strongly associated with risk for stroke
- Metabolic syndrome (insulin resistance/ glucose intolerance, abdominal girth, HTN, dyslipidemia) dramatic increase in prevalence in American women (2.2% increase in men over past decade versus 23.5% in women!)
- Diabetes may be a stronger risk factor for stroke in women than in men
- May have more of an effect in middle aged women
Sex Differences in Carotid Disease

- Women are less likely to be operated on for carotid artery disease

- NASCET and ACAS trials showed that CEA reduced stroke and death at 5 years by only 17% in women, as compared to a 66% reduction in men

- Greater incidence of peri-operative complications in women (3.6%) than in men (1.7%)

- Women receiving CEA had a higher incidence of intra-operative stroke, and had only half of the long-term benefit as compared to men especially in those with asymptomatic disease.
The effect of CEA for asymptomatic carotid stenosis on the risk of any stroke and operative death by sex

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Events/Patients</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Surgical</td>
<td>Medical</td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>51 /1021</td>
<td>97 /1023</td>
<td>0.50</td>
</tr>
<tr>
<td></td>
<td>18 /544</td>
<td>38 /547</td>
<td>0.46</td>
</tr>
<tr>
<td></td>
<td>69 /1565</td>
<td>135 /1570</td>
<td>0.49</td>
</tr>
<tr>
<td>Females</td>
<td>31 /539</td>
<td>34 /537</td>
<td>0.90</td>
</tr>
<tr>
<td></td>
<td>15 /281</td>
<td>14 /287</td>
<td>1.10</td>
</tr>
<tr>
<td></td>
<td>46 /820</td>
<td>48 /824</td>
<td>0.96</td>
</tr>
</tbody>
</table>
Secondary Stroke Prevention: Cardioembolic Stroke

- Cardioembolic stroke is responsible for ~20% of ischemic strokes
- High risk of recurrence depending on CHADS score
- May be an additional risk for women?
- Could be related to age?
- Higher rates atrial fibrillation
- Likely contributes to poor functional outcomes in elderly women after stroke
Atrial fibrillation

- Conflicting data on differences in frequency of A. fib
- Stroke risk is higher in women with A. Fib than in men with A. fib:
  - 30% of women with A. fib had stroke (RR 5.5), vs
  - 17% of men with A. fib (RR 2.1)
  - This difference is more extreme in individuals *not* on anticoagulation
Atrial Fibrillation

- ATRIA study: women on warfarin had RR 0.4 for combined thromboembolic events, vs RR 0.6 in men; no hemorrhage differences
- Women tend to be undertreated for A. fib, with more reluctance to prescribe anticoagulation to elderly women who are often at highest risk (? Dabigatran)
Prevention of Stroke

Outcomes?
Cumulative frequency of stroke etiology in women and men with AIS

Men and women may respond differently to stroke prevention strategies.

2 different sex-specific cohorts.

In the Women’s Health Study, women 45 years or older at low risk for cardiovascular disease had a reduced risk of ischemic stroke with low-dose aspirin. There was no effect on CAD/MI risk.

An identical male-only cohort in the Physician’s Health Study showed no benefit from aspirin in ischemic stroke rates, but a reduction in MI.

No differences with statins.
Aspirin in the Primary Prevention of Myocardial Infarction and Stroke among Men and Women

Aspirin and estrogen

- Hormones may differentially affect platelet aggregation
- Estrogen and/or progesterone inhibit platelet aggregation
- Platelet reactivity may differ by gender:
  - Women had more platelet reactivity at baseline and retained more platelet reactivity after receiving 81 mg ASA for 14 days
- Aspirin leads to further inhibition of ADP- and collagen- induced platelet aggregation in men than in women
Estrogen and stroke

- Situations where changes in estrogen levels may increase risk for stroke:
  - Pregnancy: estrogen levels are higher throughout pregnancy and then drop before delivery (highest risk for cerebrovascular problems in peri- or postpartum period)
  - Menopause: When estradiol levels drop
  - Exogenous estrogen use: Oral contraceptives, Hormone replacement therapy
Earlier observational studies, epidemiologic data suggested that HRT was preventive for CVD and stroke. Most of this was probably due to the healthy user effect. Randomized Women’s Health Initiative trial: Estrogen + progestin vs placebo was associated with HR 1.33 for combined hemorrhagic/ischemic stroke. WEST study: Estrogen for secondary prevention vs placebo, higher risk of fatal stroke.
1. For women with ischemic stroke or TIA, postmenopausal hormone therapy (estrogen with or without a progestin) is **not recommended** (Class III, Evidence A).

2. Not recommended for primary prevention of CAD or CVD
Estrogen and the Vasculature

- The protective effects of estrogen predominate before vascular damage occurs.
- Once atherosclerosis is established, estrogen may be detrimental.
- Animal studies: In surgically postmenopausal monkeys fed atherogenic diets coronary atherosclerosis is delayed only if treatment is started immediately after ovariectomy.
- Suggest that estrogen's atheroprotective effects are lost with prolonged estrogen deficiency.
- Dosing in some of these studies was also high (WEST) and non-cyclical.
Women over 65 were randomized to one of three doses (0.25 mg/day, 0.5 mg/day, and 1 mg/day) of 17beta-estradiol (E2) or placebo.

After 12 weeks of treatment, CRP decreased 59% in the 0.25 mg/day E2 group and increased 65% in the 1 mg/day E2 group, compared with placebo.

The CRP level continued to be elevated (92%) in the 1 mg/day E2 group, even 12 weeks after treatment was discontinued.
CRP levels before and after oral estrogen (left), placebo (middle), and transdermal estrogen (right)

Vongpatanasin, W. et al. J Am Coll Cardiol 2003;41:1358-1363
Acute Management/Lytics

- PROACT and IV TPA pooled trials (NINDS, ECASS II, ATLANTIS, CASES): Women were more likely to benefit from lytics compared with men
- This may be due to poor outcomes in women after stroke
- Men are 3x as likely to have good functional outcomes
- The sex-difference in natural history may be nullified with thrombolysis
Outcomes

- Poor outcomes in women are not just related to stroke at older ages—still present after age adjustment—but social issues are hard to quantify ("frailty, social isolation")

- 31% of women are widowed compared to 7% of men at the time of stroke

- Women have greater pre- and post-stroke disability, a higher likelihood for admission to nursing facilities, and greater mental impairments than men (6.3x risk)

- Prevalence now 2.5M vs. 3.9 M

- In our cohort significantly lower functional outcomes at both 3 and 12 months

- Sex specific rehabilitation strategies (social isolation)
Probability of independent outcome adjusted for age and baseline NIHSS score
“Real World Data”

![Graph showing estimated marginal means for males and females over time points.](Image)
<table>
<thead>
<tr>
<th>#</th>
<th>Sex Differences in Clinical Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Incidence rate</td>
</tr>
<tr>
<td>2</td>
<td>Clinical presentation</td>
</tr>
<tr>
<td>3</td>
<td>Stroke Evaluation</td>
</tr>
<tr>
<td>4</td>
<td>Stroke treatment</td>
</tr>
<tr>
<td>5</td>
<td>Secondary stroke prevention</td>
</tr>
<tr>
<td>6</td>
<td>Post stroke disability</td>
</tr>
<tr>
<td>7</td>
<td>Five year rate of a recurrent stroke after the first stroke</td>
</tr>
<tr>
<td>8</td>
<td>Mortality rate</td>
</tr>
</tbody>
</table>
Pregnancy and Stroke

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May 20th, 2011

Catherine M. Hosley, MD
The Stroke Center at Hartford Hospital
Catherine M. Hosley
Stroke in Pregnancy
Disclosures

Financial: None

Unlabeled/Unapproved Uses: Pregnancy is a relative contraindication to the use of tPA given concerns of bleeding side effects.
Pregnancy and Stroke

~6 million pregnancies in US each year with over 4 million live births

<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 (28.8, 34.6)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>435</td>
<td>52.5 (44.1, 60.9)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>356</td>
<td>26.1 (21.2, 31.0)</td>
<td></td>
</tr>
</tbody>
</table>

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

### Pregnancy and Stroke

#### Stroke type

<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>Intracranial hemorrhage</td>
<td>8.5</td>
</tr>
<tr>
<td>Cerebral venous thrombosis</td>
<td>0.6</td>
</tr>
<tr>
<td>Pregnancy-related CVE</td>
<td>15.9</td>
</tr>
</tbody>
</table>

#### Incidence and Risk Factors for Stroke in Pregnancy and the Puerperium

- **Preeclampsia**
  - First Trimester
  - Second Trimester
  - Third Trimester
  - Post Partum

- **Primary CNS vasculopathy**
  - First Trimester
  - Second Trimester
  - Third Trimester
  - Post Partum

- **Carotid dissection**
  - First Trimester
  - Second Trimester
  - Third Trimester
  - Post Partum

- **TTP**
  - First Trimester
  - Second Trimester
  - Third Trimester
  - Post Partum

- **Cortical-vein thrombosis**
  - First Trimester
  - Second Trimester
  - Third Trimester
  - Post Partum

- **Postherpetic vasculitis**
  - First Trimester
  - Second Trimester
  - Third Trimester
  - Post Partum

- **Indeterminate cause**
  - First Trimester
  - Second Trimester
  - Third Trimester
  - Post Partum

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**Pregnancy and the Risk of Stroke.** Kittner, et al. NEJM 1996;335:768-774

Causes of Peripartum Stroke

- **Vasculopathies:**
  - Atherosclerosis
  - Cervical dissection
  - Moyamoya disease
  - Fibromuscular dysplasia
  - Takayasu’s arteritis
  - Reversible vasculopathy of pregnancy

- **Hematologic:**
  - Sickle hemoglobinopathies
  - APL syndrome
  - TTP
  - Homocysteinuria
  - Thrombophilias
  - DIC

- **Cardiogenic:**
  - Valvular disease
  - SBE
  - Marantic endocarditis
  - Atrial fibrillation
  - Peripartium cardiomyopathy
  - PFO / paradoxical embolism

- **Other embolism**
  - Fat
  - Amniotic fluid
  - Air

- **Miscellaneous**
  - Hypotension
  - Drug abuse
  - Cryptogenic
Risk Factors for Peripartum Stroke

- Pregnancy related:
  - Pre-eclampsia/eclampsia
  - Pre-pregnancy hypertension
  - Increasing maternal age
  - Fluid, electrolyte, acid-base disorders
  - Hyperemesis
  - Cesarean delivery

- “General” risk factors:
  - heart disease
  - Migraine
  - Lupus
  - Anemia
  - Diabetes
  - Alcohol, drug abuse, & smoking

Risk Factors for Peripartum Stroke

PRES

Preeclampsia, moderate/severe

Postpartum angiopathy

Ischemic stroke

Reversible brain swelling, subarachnoid hemorrhage

Intracerebral hemorrhage
Pre/Eclampsia

- Preeclampsia defined by gestational HTN and proteinuria after 20 weeks. Eclampsia is the addition of seizure or unexplained coma in this clinical setting.

- The incidence of gestational hypertension/preeclampsia has been estimated to be approximately 6% to 8% in the United States. The rate of preeclampsia is 2% to 7% in healthy nulliparous women; 14% in women with twin gestation; and 18% in women with prior preeclampsia.

- Only a small proportion of these women will go on to develop eclampsia but if they do morbidity and mortality are elevated, particularly in underdeveloped countries.

Pre/eclampsia

Clinical features may include:

- Headache
- Visual changes
- Generalized edema
- Metabolic abnormalities
- Reduced fetal growth
- Seizures / coma
- ICH
- HTN encephalopathy
- Pulmonary edema
- Renal failure

Table 2. Time of Onset of Eclampsia in Relation to Delivery

<table>
<thead>
<tr>
<th>Study</th>
<th>Antepartum</th>
<th>Intrapartum</th>
<th>Postpartum</th>
<th>AT 48 h</th>
<th>&gt; 48 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Douglas and Redman(^3) N = 383</td>
<td>38</td>
<td>18</td>
<td>44</td>
<td>39</td>
<td>5</td>
</tr>
<tr>
<td>Katz et al(^7) N = 53</td>
<td>53</td>
<td>36</td>
<td>11</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Mattar and Sibai(^6) N = 399</td>
<td>53</td>
<td>19</td>
<td>28</td>
<td>11</td>
<td>17</td>
</tr>
<tr>
<td>Chames et al(^8) N = 89</td>
<td>67*</td>
<td>...</td>
<td>33</td>
<td>7</td>
<td>26</td>
</tr>
</tbody>
</table>

Data are presented as percentage. * Includes antepartum and intrapartum cases.
PRES

- Posterior reversible encephalopathy syndrome involves a neurotoxic state most often characterized by headaches, confusion, seizures, and visual changes.

- In pregnancy PRES generally develops in the setting of pre-eclampsia / eclampsia.
  - Symptoms may develop days after delivery as part of a late-eclampsia syndrome.
  - Most patients do well if the seizures and hypertension are well controlled.
  - More severe cases can result in lasting neurological morbidity or mortality due to ischemic stroke or hemorrhage.

Characteristic imaging features associated with the syndrome include focal regions of symmetric edema in the posterior brain parenchyma.
The pathogenesis of PRES is unclear and controversial but it is hypothesized that there may be an underlying disorder of cerebral auto-regulation (HTN) and/or endothelial dysfunction which can be then be augmented by metabolic derangements and drug exposures.

In eclampsia, both of these hypotheses may be relevant given the baseline state of diffuse endothelial activation and presence of inflammatory markers in pregnancy as well as a common finding of relative hypertension in affected patients.

There is likely some shared pathophysiology between hypertensive encephalopathy, PRES, and eclampsia given the overlapping presentations and clinical findings. For example, hypomagnesemia may play a common pathophysiologic role as magnesium wasting is noted in pre-eclampsia and has been described in PRES.
• Reversible cerebral vasoconstriction syndrome (RCVS) is a descriptive term which encompasses a variety of syndromes including post-partum angiopathy and puerperal vasospasm.

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

RCVS clinical features
- Diffuse severe headache (often “thunderclap”) with or without focal neuro deficits and/or seizures
- No evidence of aneurysmal SAH
- Normal (or near normal) CSF
- Angiography showing segmental vasoconstriction
- Reversibility of vascular lesions within 3 months on repeat imaging
The prothrombotic state occurring during pregnancy is associated with an increased incidence of venothromboembolism.

Pregnancy-related ischemic strokes attributed to CVT have been reported in 10 to 20 per 100,000 deliveries in the Western world, with higher incidence in developing countries.

The majority of cases occur during the second or third week postpartum.

**Associated symptoms:**
- Most commonly the superior sagittal and transverse sinuses are affected.
  - headache,
  - seizures
  - papilledema if severe enough to cause increased intracranial pressures.
- The deep structures of the brain, including the basal ganglia and thalamus, may be involved with occlusion of the deep cerebral veins.
  - Hemiparesis
  - aphasia.

**References:**
Left transverse sinus venous thrombosis with involvement of the jugular and sagittal vein in a woman 4 weeks postdelivery with an uncomplicated pregnancy. The lower figures show cortical venous congestion and high signal in the superior sagittal sinus.
Anticoagulation

- Treatment of CVT in the non-pregnant population generally involves anticoagulation with warfarin for to prevent clot extension.

- The American Stroke Association recommendations identify warfarin as safe in the second and third trimester with the caveat that it must be discontinued late in the pregnancy in anticipation of delivery.

- Heparin or low-molecular-weight heparin (LMWH) are the preferred anticoagulants in pregnancy because they do not cross the placenta and, therefore, are not associated with teratogenicity or increased risk of fetal hemorrhage.

- Following delivery warfarin can be utilized for anticoagulation which is generally continued for a 3-6 month period with repeat imaging to establish the status of recanalization over time.

Stroke treatment: beyond the three-hour window and in the pregnant patient. Cronin CA, Weisman CJ, Llinas RH. Ann NY Acad Sci 2008;1142:159-78
Hemorrhagic Stroke in Pregnancy

- The incidence rate of intracerebral hemorrhage is 3.5 to 4.6 per 100,000 deliveries. The risk of bleeding from an aneurysm or AVM also increases during pregnancy. Subarachnoid hemorrhage has an incidence of 1 per 10,000 pregnancies.

- Mortality rates from SAH in pregnant women are reported to be 27% to 40%; arteriovenous malformations is reported as 28%. Prognosis is related to severity of neurologic grade at presentation of bleed.

- Labor and delivery does not appear to increase the risk of hemorrhage from arteriovenous malformations or smaller aneurysms, and the decision to perform caesarean section should be based on obstetric indications.

Hemorrhagic Stroke in Pregnancy

- Recognized causes:
  - Cerebral aneurysm
  - AVM
  - Hypertension or pre-eclampsia/eclampsia
  - Hemorrhagic transformation of CVT or IS
  - Choriocarcinoma
  - Septic embolism from bacterial endocarditis
  - Moyamoya disease
  - Cocaine or other drug abuse
  - Vasculitis or vasculopathy
  - Bleeding diastheses

ICH with surrounding edema
Hemorrhagic Stroke in Pregnancy

- Hemorrhage in the pregnant patient is primarily associated with pre-eclampsia / eclampsia, arteriovenous malformations, and cerebral aneurysms.

- The incidence is similar to ischemic stroke in but intracerebral hemorrhage has a high maternal mortality rate and is estimated to account for 5-12% of overall maternal mortality during pregnancy.

![Table 1. Stroke Risk Among Women in the Third Trimester, Peripartum, and Postpartum Periods Compared to Nonpregnant and Early Pregnant Women](image)

<table>
<thead>
<tr>
<th>Stroke Subtype</th>
<th>3rd Trimester</th>
<th>Around Delivery</th>
<th>Puerperium</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR</td>
<td>95% CI</td>
<td>RR</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>2.2</td>
<td>0.8-4.8</td>
<td>33.8</td>
</tr>
<tr>
<td>Intracerebral hemorrhage</td>
<td>.3</td>
<td>0.3-4.1</td>
<td>95.0</td>
</tr>
<tr>
<td>Subarachnoid hemorrhage</td>
<td>.8</td>
<td>0.2-2.5</td>
<td>46.9</td>
</tr>
</tbody>
</table>

Results of study by Salonen and colleagues (Salonen Ros et al 2001).
Aneurysm in Pregnancy

- **Unruptured aneurysms**
  - Increase in size as pregnancy advances
  - Strategies to reduce risk of rupture: shorten 2\textsuperscript{nd} stage of labor, epidural analgesia, and instrumental delivery (if necessary)
  - Not necessary to do c-section
- **Treat if:**
  - Symptomatic (acute headache and/or cranial nerve paresis) and lobulated
  - Associated with prior aneurysm rupture elsewhere
  - Greater than 10 mm
  - Any size, but has increased growth over time on serial scans

- **Ruptured aneurysms**
  - Normal delivery if successfully clipped or coiled post-rupture in 1\textsuperscript{st} or 2\textsuperscript{nd} trimester
  - If rupture after 34 weeks, then C-section

Stroke

• The physiologic and hemodynamic changes that occur in pregnancy promote a state of relative hypercoaguability, increased cardiac burden, and altered vascular tone in order to meet the physiologic demands of the growing fetus and reduce hemorrhage during delivery.

• The overall incidence of ischemic stroke during pregnancy is low, 3.5-5 per 100,000 pregnancies, with the majority of these events occurring late in pregnancy and particularly in the postpartum period.

• However, when considering stroke in the young as a broader group, it should be noted that strokes related to pregnancy accounted for 12-35% of events in this otherwise low risk population.

Stroke

- Pregnancy does not “cause” stroke and patients should undergo full evaluations.

- Most cardioembolic events are due to previously underlying heart disease, such as a prosthetic heart valve, or atrial fibrillation.

- The increased rate of venous thrombosis combined with changing intrathoracic pressures during pregnancy and delivery may increase the risk of paradoxical embolism through a patent foramen ovale.

- Peripartum cardiomyopathy is an uncommon idiopathic congestive cardiomyopathy specific to pregnancy and the puerperium. It occurs in approximately 1 in 1300 to 15,000 pregnancies in the US with high mortality rate: up to 18% in U.S. studies.


The primary treatment for ischemic stroke is administration of tissue plasminogen activator (tPA). However, pregnant patients were excluded from tPA clinical trials and there has been no systematic study of the treatment in this population.

Concerns regarding the risks of tPA on the pregnant patient and fetus (e.g. uterine hemorrhage, placental abruption, abortion, preterm delivery) have been raised but, with admittedly limited data, it appears that maternal mortality (1%), fetal loss (6%), and preterm delivery (6%) are all low.

Pregnancy is considered to be a relative contraindication for treatment with tPA.


Neuroimaging

- MRI generally preferred

- Gd should be avoided as it crosses the placenta. Clearance rates are unknown

- Some concerns based on animal studies regarding ocular deformities and growth retardation with early exposure to a strong magnetic field
Neuroimaging

- American College of Radiology guidelines note that for diagnostic radiologic procedures outside of the abdomen/pelvis the radiation dose is characteristically very low as the fetus is exposed only to scattered radiation.

- Single maternal NC CT head exposes the fetus to ~1% of the accepted threshold for cumulative fetal radiation.

- CTA/CTP is felt to be a somewhat different story although very limited data available.

- The dose of radiation in conventional cerebral angiography is usually small (< 1 mrad) if care is taken to limit fluoroscopy times.

- Use of iodinated contrast medium in pregnancy is also considered safe, with only a slight risk of treatable fetal hypothyroidism if contrast is used in the 3rd trimester.

Neuroimaging

Common Radiographic Studies

Radiation source

- Chest (two views): 0.00007 rad
- Upper or lower extremity: 0.001 rad
- CT of head: 0.05 rad
- Background radiation: 0.09 rad
- Ventilation-perfusion scan: 0.215 rad
- Abdomen (multiple views): 0.245 rad
- CT pelvimetry: 0.25 rad
- Lumbosacral spine: 0.359 rad
- Intravenous pyelogram: 1.398 rad
- CT of abdomen: 2.6 rad
- CT of lumbar spine: 3.5 rad
- Fluoroscopic barium enema: 3.986 rad

The accepted maximum cumulative fetal dose during pregnancy is 5 rad.

FIGURE 1. Graphic comparison of common radiographic studies with the accepted 5-rad cumulative fetal exposure limit. (CT=computed tomographic; Gy=gray)
Parting thoughts

• There are a number of significant and potentially catastrophic neurological complications that can be associated with pregnancy

• Prompt diagnosis and treatment facilitated by imaging is important

• Eclampsia remains a significant contributor to maternal morbidity and mortality. While the mechanisms haven’t been clearly worked out, there appears to be shared pathophysiology between “toxemia”, eclampsia, PRES, and potentially RCVS. Additionally, patients with eclampsia are at a higher risk of developing CVT and stroke/ICH. Treatment of seizures and hypertension likely reduces the risk of severe sequellae.

• tPA…remains on a (fortunately rare!) case by case basis

• Pregnancy is not a contraindication to aneurysm treatment
• Presence of an aneurysm does not need to dictate delivery mode