Look Who’s Talking: Stroke and Stroke Prevention in Pregnancy

Pregnancy Care ECHO
Guests:
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Disclosures

• Lee Chung: none
• Peter Hannon: none
Objectives

• Discuss a case of acute stroke in pregnancy
• Review current acute stroke treatment guidelines
• Discuss current recommendations and data related to stroke in pregnancy
• Discuss stroke prevention in pregnancy
• Cerebral Venous Thrombosis*
A case…

• A 34 year old G2P1 woman at 26 weeks EGA presents to the ED with sudden onset language difficulties and right sided hemiparesis

• In the ED her BP is noted to be 176/95 and HR is 110. She is protecting her airway. OB and Neurology have been emergently paged.
A case

• On exam she is alert, crying and distraught. She is trying to communicate but is saying “my bate”…”my natey”…

• She appears that she is looking persistently to her left, and seems to have trouble trying to look to her right. Her right arm is plegic, though she does move her right foot slightly when instructed. She is able to move her left arm and leg without difficulty.

• An NIHSS stroke scale is performed, and she is scored as 19
NIHSS

- LOC: 0
- Month/Age: 2
- Open/close eyes/hands: 1
- Best gaze: 2
- Visual fields: 0
- Facial Palsy: 2
- Motor L: arm 0 leg 0
- Motor R: arm 4 leg 3
- Limb ataxia: 0
- Sensory: 2
- Best language: 2
- Dysarthria: 1
- Extinction/Inattention: 0

Total: 19
CT imaging
What do we do?
Stroke in the US

• Every 40 seconds someone in America has a stroke
  – Every 4 minutes someone dies of stroke

• In one second 32,000 brain cells die, in 59 seconds you will have killed 1.9 million brain cells.

• Nearly 800,000 Americans will have a new or recurrent stroke this year and over 130,000 of them will die
  – 5th leading cause of death in the US
  – #1 cause of preventable disability in the US

• Fewer than one in five Americans can identify even one stroke symptom.

• The economic impact of stroke is estimated to cost $40-$70 billion per year.
Types of stroke:

Ischemic stroke
A clot blocks blood flow to an area of the brain

Hemorrhagic stroke
Bleeding occurs inside or around brain tissue

Stroke Symptoms

- Face drooping
- Arm weakness
- Speech difficulty
- Time to call 911
Stroke in Women

- Most strokes in the US (53.5%) occur in women
  - Highest among blacks & Hispanics

- Most stroke deaths in the US (60%) occur in women

- Women have a higher lifetime risk of stroke than men (Framingham)

Stroke Risk Factors in Women

Stronger/More Common in Women in Men

- Migraine with aura
- Atrial fibrillation
- Diabetes
- Hypertension
- Depression

Unique to Women

- Pregnancy
- Preeclampsia
- Gestational diabetes
- Oral contraceptives
- Post-menopausal hormones

Stroke presentation in women

- 28-52% of women with stroke/TIA report at least 1 nontraditional symptom

- Non-traditional stroke symptoms more common in women include mental status change and pain

- Time from stroke symptom onset to hospital arrival was significantly greater among women (5 vs. 4 hours; p=0.05)

- Delayed hospital arrival is the single greatest barrier to stroke reversal (reperfusion) therapy
Stroke and Pregnancy

• Stroke is uncommon in pregnancy (34 in 100,000 deliveries)
  – 62% higher risk than non-pregnant women

• Risk is highest in the third trimester and post-partum

Pathophysiology of Stroke in Pregnancy

• Venous stasis

• Hypercoagulability
  – Activated protein C resistance
  – Lower levels of protein S
  – Increased fibrinogen

Hypertensive Disorders of Pregnancy

**Eclampsia/Preeclampsia**
- Pre-eclampsia: progressively worsening high BP with proteinuria (≥300 mg protein in a 24h urine specimen)
- Eclampsia:
  - Associated with HELLP, disseminated intravascular coagulation, acute renal failure, myocardial infarction, pulmonary edema, stroke

**Pregnancy-induced hypertension**
- Usually near term
- Without the other signs and symptoms of preeclampsia
- usually resolves by 12 weeks post-partum
Pregnancy-induced hypertension cutoffs

- **Mild:** systolic BP 140–149 mmHg, or diastolic BP 90–99 mmHg
- **Moderate:** 150–159 / 100–109
- **Severe:** ≥160 / ≥110
Stroke: Acute treatment

• IV tPA (Alteplase): up to 4.5 hours
  • 0.9mgs/kg
  • 10% bolus (1-2min), 90% infusion over an hour

• Endovascular treatment
  • FDA approved up to 6 hours in combination with tPA
Acute treatment of stroke in pregnancy

• 2013 AHA guidelines
  • Pregnancy is a relative contraindication for tPA
  • suggest that under some circumstances, with careful consideration and weighting of risk to benefit, pregnant patients may receive thrombolytic therapy

• FDA update: “the risks of alteplase therapy may be increased in pregnancy and should be weighed against the anticipated benefits.”
  • Listed as category C
  • Animal studies of alteplase at 1mg/kg did not show fetal toxicity or teratogenicity
Acute treatment of stroke in pregnancy

• 2015 AHA/ASA Scientific Rationale for the Inclusion and Exclusion Criteria for Intravenous Alteplase in Acute Ischemic Stroke

  • Intravenous alteplase administration for ischemic stroke may be considered in pregnancy when the anticipated benefits of treating moderate to severe stroke outweigh the anticipated increased risks of uterine bleeding (Class IIb; Level of Evidence C)

  • The safety and efficacy of intravenous alteplase in the early postpartum period (<14 days after delivery) have not been well established (Class IIb; Level of Evidence C)

  • Urgent consultation with an OB/GYN and potentially a perinatologist to assist with management of the mother and fetus is recommended (Class I; Level of Evidence C)
Acute treatment of stroke in pregnancy: Data

- AHA/ASA Review
- 12 reported cases of pregnant women with arterial stroke who were treated with IV tPA or endovascular therapy
  - 8 in first trimester
  - 2 in second trimester
  - 2 in 3rd trimester
- Most cases had proximal arterial occlusions in M1 or M2 MCA branches
Acute treatment of stroke in pregnancy: Data

• 6 treated with IV tPA
• 6 treated with IA tPA
• No cases reported clot aspiration or retrieval
• Outcomes
  • 2 sICH
    • 1 mild sICH with good neurologic outcome
    • 1 fatal sICH resulting from arterial dissection during angioplasty
• 2 systemic bleeding complications (IV tPA cases)
  • 1 case of a buttock hematoma managed conservatively, delivery of healthy infant
  • 1 case of intra-uterine hematoma requiring surgical drainage and associated with medical termination of the pregnancy
Acute treatment of stroke in pregnancy: Data

• Fetal Outcomes (12 cases)
  
  • 2 fetal demise (16.7%)
    • 1 in patient with fatal sICH
    • 1 as a result of spontaneous abortion
  
  • 2 medical terminations of pregnancy (16.7%)

• 8 healthy infants (67%)
IV thrombolysis in pregnancy

- 18 non-stroke cases identified (PE, cardiac valve thrombosis, MI)
  - Among 18 cases, 1 additional serious systemic bleeding complication in a mother with abruption utero and fetal demise

- 2 cases of acute stroke reperfusion therapy in early post-partum period
  - 1 IA alteplase 6d post partum
  - 1 IA urokinase 15hrs s/p C sections

- Neither case complicated by vaginal/uterine hemorrhage
Get With The Guidelines Database

- 338 pregnant or postpartum women with stroke (vs 24,000 nonpregnant women 18-44y with stroke)

- IV tPA monotherapy was less frequent in pregnant or postpartum women compared with nonpregnant women (4.4 versus 7.9 %)

- Higher rate of sICH in pregnant or postpartum women (7.5%) compared with nonpregnant women (2.6%); not significant

- No difference in rates of in-hospital death (2.1 versus 2.7 percent), discharge to home (75 versus 73 percent), or independent ambulation at home (74 versus 71 percent)

Endovascular treatment in pregnancy

• IV iodinated contrast is a class B agent
  • “Very little contrast crosses the placenta and entersthe fetal circulation”
    • No teratogenic effects have been reported to date

• Radiation
  • The National Council on Radiation Protection and Measurements states that radiation exposure less than 50 mGy to the fetus is considered negligible in comparison with baseline risks for all developmental abnormalities, but this risk increases significantly when exposure exceeds 150 mGy
    • CT Head: 2 mGy
    • CTA Head: 4.2 mGy
    • Conventional Angiogram: 3.6 mGy, though fluoroscopically guided procedures in the pelvis may deliver doses above 100 mGy—‘fetal dose’ of 2.8 mGy
Back to our patient

• A 34 year old G2P1 woman at 26 weeks EGA presents to the ED with sudden onset language difficulties and right sided hemiparesis

• OB is present and notes normal fetal heart tones

• Husband and parents are present at the bedside

• CT scan did not show ICH, and there are no other contraindications to tPA therapy other than her pregnancy…
Stroke workup

- Brain imaging
- Cerebrovascular imaging
- Cardiac imaging
- EKG, CBC, CMP, HIV, drug screen, ANA
- Hypercoagulable testing
Hypercoagulable workup

- 12 previously healthy pregnant women with first ischemic event during pregnancy (compared with 24 healthy controls)

- Inherited thrombophilias detected in 10/12 (83%) of cases:
  - 5 factor V Leiden mutation
  - 4 prothrombin gene mutation
  - 2 protein S deficiency
  - 1 antithrombin III mutation

Prevention
Hypertension treatment in pregnancy

- First-line: methyldopa, labetalol, nifedipine
- α-Blockers, β-blockers, CCBs, hydralazine, and thiazide diuretics all cross the placenta
- Contraindicated: ACEI, ARB, and direct renin inhibitors (teratogenic)
ACOG guidelines (2014)

• Treat severe hypertension with labetalol, nifedipine, or methyldopa

• Magnesium: Reduces risk of stroke in eclampsia

• Atenolol, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers
AHA guidelines:

• Severe hypertension in pregnancy should be treated with safe and effective antihypertensive medications (Class I; Level of Evidence A)

  – Consideration may be given to treatment of moderate hypertension in pregnancy with safe and effective antihypertensive medications (Class IIa; Level of Evidence B)
  
  – Increased stroke risk above systolic and diastolic BP cutoffs
  
  – Treatment decreases risk for the development of severe hypertension with treatment

• Atenolol, angiotensin receptor blockers, and direct renin inhibitors are contraindicated in pregnancy and should not be used (Class III; Level of Evidence C).

  – After giving birth, women with chronic hypertension should be continued on their antihypertensive regimen (Class IIa; Level of Evidence C)
  
  – With dosage adjustments
  
  – Care monitoring for postpartum preeclampsia

Prevention of preeclampsia

**AHA guidelines (2014)**
- 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 (Class I; Level of Evidence A)

**ACOG guidelines (2014)**
- Women with history of early-onset pre-eclampsia and preterm delivery (<34w), or prior recurrent preeclampsia, daily low-dose (60-80mg) aspirin beginning in the late first trimester

Long term risks of CVD

• Women with a history of preeclampsia: markedly increased risk for renal disease, 2-10x risk for chronic hypertension (the major risk factor for stroke)

• 50% of women with gestational diabetes will develop type 2 diabetes mellitus within 5-10 years

AHA guidelines

• Because of the increased risk of future hypertension and stroke 1-30 years after delivery in women with a history of preeclampsia (*Level of Evidence B*), it is reasonable to:
  - Consider evaluating all women starting 6 months to 1 year post partum, as well as those who are past childbearing age, for a history of pre-eclampsia/eclampsia and document it as a risk factor
  - Evaluate and treat for cardiovascular risk factors including hypertension, obesity, smoking, and dyslipidemia
  - *Class IIa; Level of Evidence C*

Cerebral Venous Thrombosis (CVT)

Age and sex distribution of CVT

Dr Jose Ferro, International Study on Cerebral Venous and Dural Sinuses Thrombosis
### Presenting Symptoms & Findings

<table>
<thead>
<tr>
<th>Increased ICP</th>
<th>Venous infarct/hemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Headache (90%), usually subacute</td>
<td>• Weakness (40%)</td>
</tr>
<tr>
<td>• Vision/papilledema</td>
<td>• Seizures (30-40%)</td>
</tr>
<tr>
<td></td>
<td>• Aphasia</td>
</tr>
<tr>
<td></td>
<td>• Mental status changes</td>
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</table>
### Risk Factors for Cerebral Venous Thrombosis

<table>
<thead>
<tr>
<th>Factor</th>
<th>No. of cases</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>None identified</td>
<td>78</td>
<td>12.5</td>
</tr>
<tr>
<td>Thrombophilia</td>
<td>213</td>
<td>34.1</td>
</tr>
<tr>
<td>Genetic</td>
<td>140</td>
<td>22.4</td>
</tr>
<tr>
<td>Acquired</td>
<td>98</td>
<td>15.7</td>
</tr>
<tr>
<td>Antiphospholipid antibody</td>
<td>40</td>
<td>5.9</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td>4</td>
<td>0.6</td>
</tr>
<tr>
<td>Hyperhomocysteinemia</td>
<td>28</td>
<td>4.5</td>
</tr>
<tr>
<td>Malignancy</td>
<td>46</td>
<td>7.4</td>
</tr>
<tr>
<td>CNS</td>
<td>14</td>
<td>2.2</td>
</tr>
<tr>
<td>Solid tumor outside CNS</td>
<td>20</td>
<td>3.2</td>
</tr>
<tr>
<td>Hematological</td>
<td>18</td>
<td>2.9</td>
</tr>
<tr>
<td>CNS disorders</td>
<td>12</td>
<td>1.9</td>
</tr>
<tr>
<td>Dural fistulae</td>
<td>10</td>
<td>1.6</td>
</tr>
<tr>
<td>Venous anomaly</td>
<td>1</td>
<td>0.2</td>
</tr>
<tr>
<td>Arteriovenous malformation</td>
<td>1</td>
<td>0.2</td>
</tr>
<tr>
<td>Hematological condition</td>
<td>75</td>
<td>12</td>
</tr>
<tr>
<td>Polycythemia, thrombocythemia</td>
<td>18</td>
<td>2.8</td>
</tr>
<tr>
<td>Anemia</td>
<td>58</td>
<td>9.2</td>
</tr>
</tbody>
</table>
## Risk Factors for Cerebral Venous Thrombosis

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vasculitis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>7</td>
<td>1.0</td>
</tr>
<tr>
<td>Behçet disease</td>
<td>6</td>
<td>0.9</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>1</td>
<td>0.2</td>
</tr>
<tr>
<td>Thromboangiitis obliterans</td>
<td>1</td>
<td>0.2</td>
</tr>
<tr>
<td>Nonspecified</td>
<td>4</td>
<td>0.6</td>
</tr>
<tr>
<td><strong>Other inflammatory systemic disorders</strong></td>
<td>11</td>
<td>1.8</td>
</tr>
<tr>
<td>Intestinal inflammatory disease</td>
<td>10</td>
<td>1.6</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>1</td>
<td>0.2</td>
</tr>
<tr>
<td><strong>Other systemic disorders</strong></td>
<td>15</td>
<td>2.4</td>
</tr>
<tr>
<td>Thyroid disease</td>
<td>11</td>
<td>1.7</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>4</td>
<td>0.6</td>
</tr>
</tbody>
</table>

| **Pregnancy**                                    | 24    | 6.3        |
| **Puerperium**                                   | 53    | 13.8       |

| **Infection**                                    | 77    | 12.3       |
| Central nervous system                           | 13    | 2.1        |
| Ear, sinus, mouth, face, and neck                | 51    | 8.2        |
| Other                                            | 27    | 4.3        |

| **Mechanical precipitants**                      | 28    | 4.5        |
| Lumbar puncture                                  | 12    | 1.9        |
| Cranial trauma                                   | 7     | 1.1        |
| Jugular catheter occlusion                       | 5     | 0.8        |
| Neurosurgery                                     | 4     | 0.6        |

| **Drugs**                                        | 47    | 7.5        |
| Oral contraceptives                              | 207   | 54.3       |
| Hormone replacement therapy                      | 27    | 4.3        |
| Steroid                                          | 10    | 1.6        |
| Cytotoxic                                        | 5     | 0.8        |
| Other                                            | 5     | 0.8        |

| **Surgery**                                       | 17    | 2.7        |
| Dehydration                                      | 12    | 1.9        |

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CVT in Pregnancy and Puerperium

- Mexico: ≈50% of CVT occurred during pregnancy or puerperium, usually third trimester or puerperium

- Canada: 7/8 of peripartum CVTs occurred post-partum

- Possible causes:
  - Persistent post-partum prothrombotic changes
  - Volume depletion, trauma, increased risk with instrumentation/infection

CVT around Pregnancy

- Greatest risk period for CVT: 3rd trimester - 4 weeks postpartum (73% of CVT)
- ACCP: LMWH until 6 weeks post-partum, at least 6 months total, for VTE
- Increased risk of thrombotic events in future pregnancies
- 88% of the recurrent pregnancies to women with past CVT resulted in normal birth
  - 1% recurrent CVT, but high rate of spontaneous abortion
CVT: Diagnostic pitfalls

Idiopathic intracranial hypertension
- Clinical IIH
- Headache with atypical features

Unusual ICH or stroke distribution
- Lobar ICH of otherwise unclear origin
- Cerebral infarction that crosses typical arterial boundaries
CVT Treatment: UH vs LMWH

- ISCVT: nonrandomized prospective cohort study
- 302 with UH (72%) vs. 119 with LMWH (28%)
- Functional independence @ 6 months better with LMWH (OR 2.1; CI, 1.0 to 4.2)
  - aOR 2.4 (CI, 1.0 to 5.7).
- Adverse events: LMWH with less new ICH (aOR 0.29; CI, 0.07 to 1.3)
  - Especially in patients with intracerebral lesions at baseline (aOR 0.19; CI, 0.04 to 0.99)

CVT Treatment: AHA/ASA guidelines

• Admission to a stroke unit is reasonable for treatment and for prevention of clinical complications of patients with CVT (C IIa; LOE C)

• For patients with CVT, initial anticoagulation with adjusted-dose UFH or weight-based LMWH in full anticoagulant doses is reasonable, followed by vitamin K antagonists, regardless of the presence of ICH (C IIa; LOE B)
Prognosis

- 23% with neurological worsening
- 15% die or become dependent after CVT
- 79% with complete recovery
- Recanalization rates:
  - 84% at 3 months
  - 85% at 1 year

Variables Associated With Poor Prognosis in Cohort Studies

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Clinical</th>
<th>Neuroimaging</th>
<th>Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;37 y$^{10}$</td>
<td>Coma$^{10,117,277}$</td>
<td>Intracerebral hemorrhage$^{10,277}$</td>
<td>Cancer$^{10,177}$</td>
</tr>
<tr>
<td>Male sex$^{10}$</td>
<td>Neurological deficit and severity (NIHSS)$^{177,179}$</td>
<td>Involvement of the straight sinus$^{277}$</td>
<td>CNS infection$^{10}$</td>
</tr>
<tr>
<td>Decreased level of consciousness$^{10}$</td>
<td>Encephalopathy$^{117}$</td>
<td>Thrombosis of the deep venous system$^{10}$</td>
<td>Underlying coagulopathy hereditary thrombophilia$^{66}$</td>
</tr>
<tr>
<td>Hemiparesis$^{10}$</td>
<td></td>
<td>Venous infarction$^{66,179}$</td>
<td></td>
</tr>
<tr>
<td>Seizures$^{10,179}$</td>
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</table>

Thank you!