Stroke Risk Factors and Outcomes Unique to Women

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Overview

- Pregnancy
- Other risk factors unique to women
- Conventional risk factors
- Sex differences in evaluation and treatment
- Sex differences in outcomes

Case 1

34 year old obese female G1P0 at 31 weeks gestation who acutely developed left-sided weakness and neglect at 10:40 PM. She arrived and was seen in the ED at 1 hour from symptom onset.

No medications

BP 149/76. NIHSS 12

Glucose 102

Labs notable for Hb 10.7 and platelets 110,000

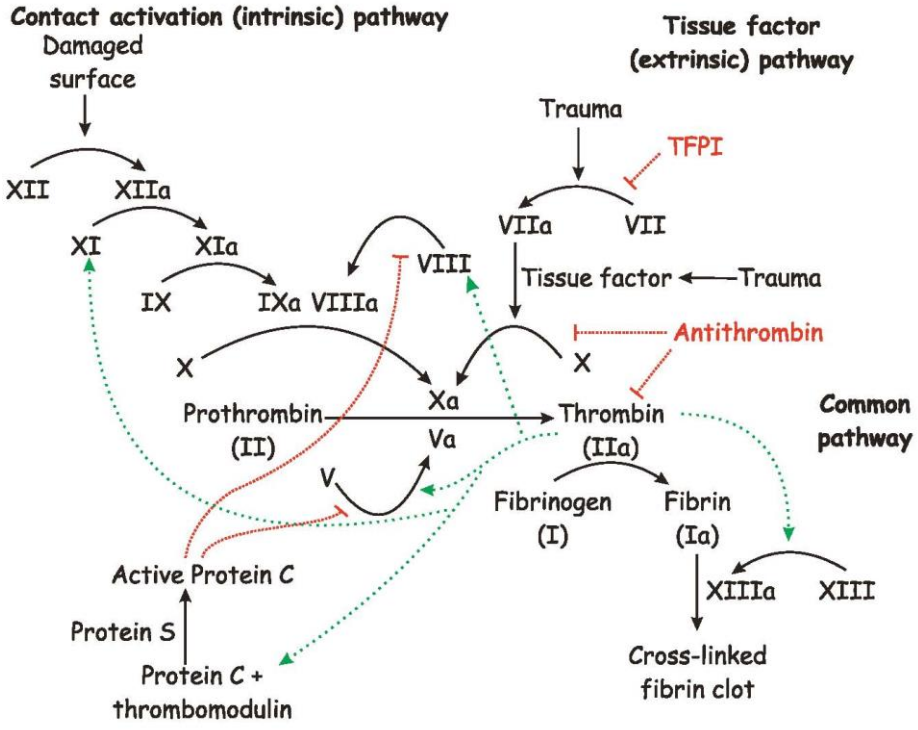
CTH within normal limits

Case 1 - Differential diagnosis

- Ischemic stroke (vs hemorrhagic stroke)
  - Underlying hypercoagulable state
  - Venous sinus thrombosis
- Preeclampsia +/- posterior reversible encephalopathy syndrome
- Subarachnoid hemorrhage
- Migraine with aura

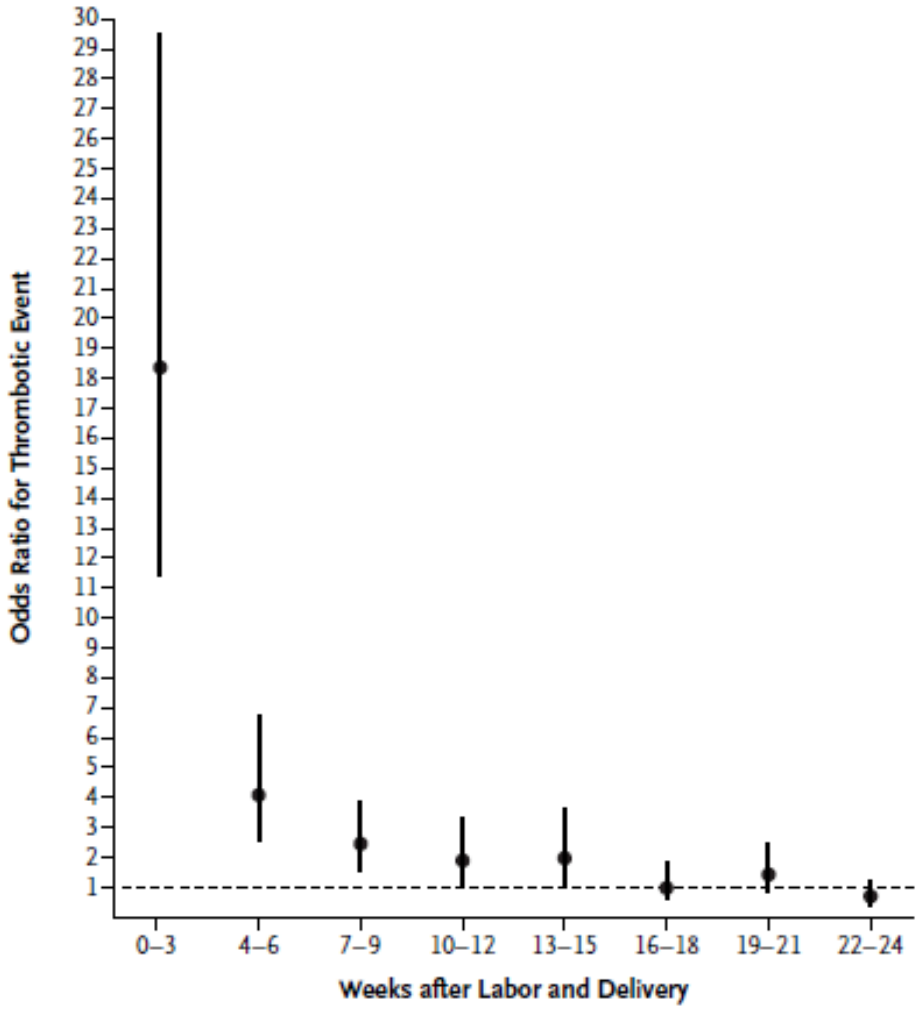
Pregnancy

- Prothrombotic state with an increase in procoagulant factors as pregnancy progresses
  - Fibrinogen increases
  - Protein S decreases
  - Functional protein C resistance
  - Prothrombin fragments increase
- Hormonal changes



https://en.wikipedia.org/wiki/File:Coagulation_full.svg

Risk of thrombosis after delivery



Kamel et al. NEJM 2014

Pregnancy associated strokes

- Ban et al. found that 2511 out of 2,046,048 women had an acute stroke during pregnancy or the postpartum period
- Kittner et al. found small increase in all strokes during pregnancy driven by hemorrhagic strokes
- Kittner et al. found significant increased risk of all strokes in the early postpartum period (up to 6 weeks)
  - Ischemic strokes (8.7 fold)
  - Hemorrhagic strokes (28.5 fold)

Hypertensive disorders of pregnancy

- Chronic HTN
- Gestational HTN
  - New onset HTN presenting at >20 weeks
- Preeclampsia and eclampsia
  - New onset HTN and proteinuria, can be associated with multisystem organ dysfunction and seizures
  - Significant overlap with PRES → associated ischemia or hemorrhage

Other risk factors/mechanisms of stroke

- Cardiac embolism – dilated peripartum cardiomyopathy
- Other embolism – amniotic fluid
- Cervical artery dissection – hyperemesis gravidarum

Back to Case 1

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No medications.

BP 149/76. NIHSS 12.

Glucose 102

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CTH within normal limits

Diagnostic considerations during pregnancy

- Radiation exposure
  - Highest risk is in the first trimester
  - In emergency setting, CTH (with abdominal shield if possible) is OK
- MR imaging is safe during pregnancy
- Avoid contrast whenever possible

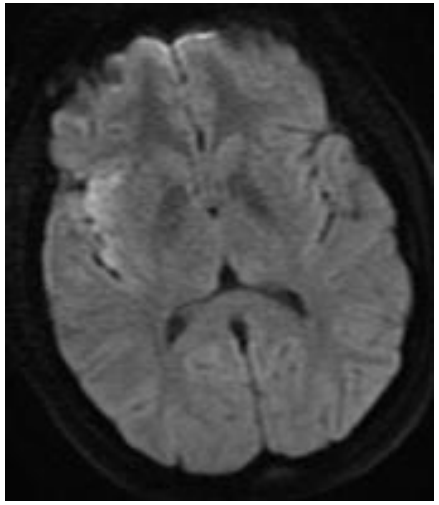
Treatment considerations during pregnancy

- Should we give tPA?
  - Large molecule that does not cross the placenta
  - Pregnancy category C
  - May have increased risk of sICH but there are case reports with good outcomes

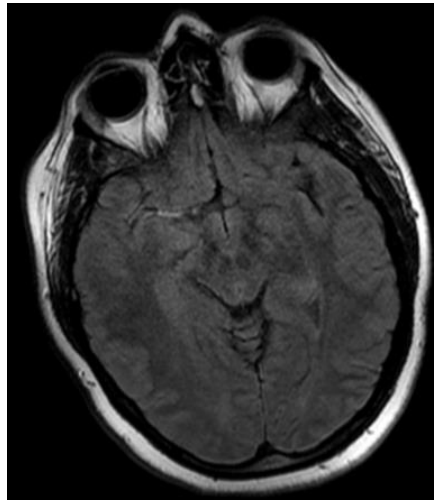
- 2018 AHA/ASA Guidelines
  - IV alteplase administration may be considered in pregnancy when the anticipated benefits of treating moderate or severe stroke outweighs the anticipated increased risks of uterine bleeding

Case 1 continued

- tPA was not given and MRI/MRA was obtained



DWI



T2 FLAIR

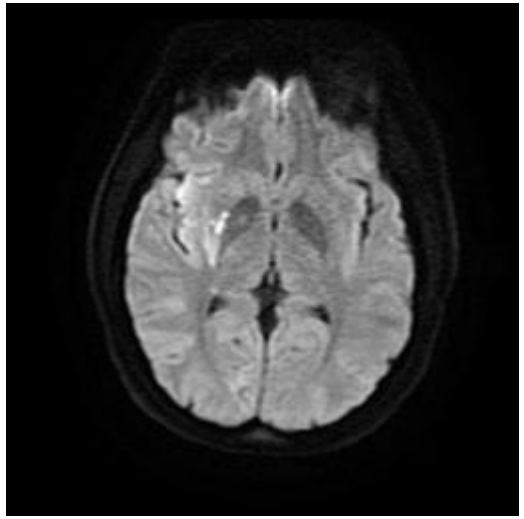
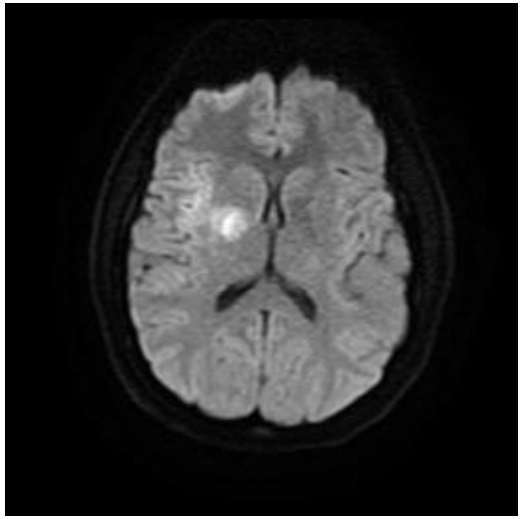
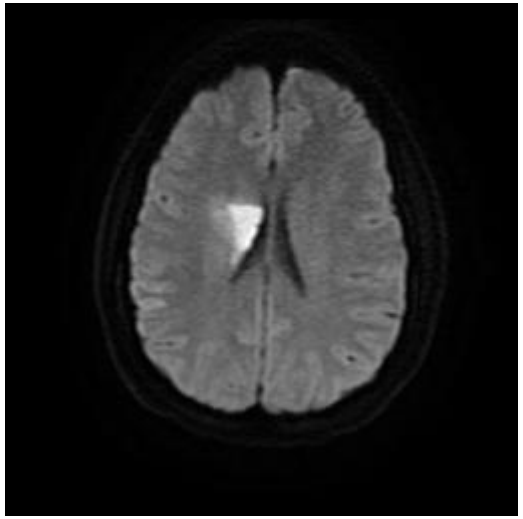
MRA-TOF

Treatment considerations during pregnancy

- Is endovascular therapy an option?
  - Case reports with good outcomes

Case 1 continued

- Cerebral angiography demonstrated R ICA terminus occlusion requiring extensive thrombectomy and intracranial stenting
- NIHSS 12 → 1

Stroke and pregnancy

- Stroke in pregnancy is rare
- Stroke characteristics rather than obstetrical concerns should guide treatment
- Gestational HTN, gestational DM, and preeclampsia increase long-term risk of stroke

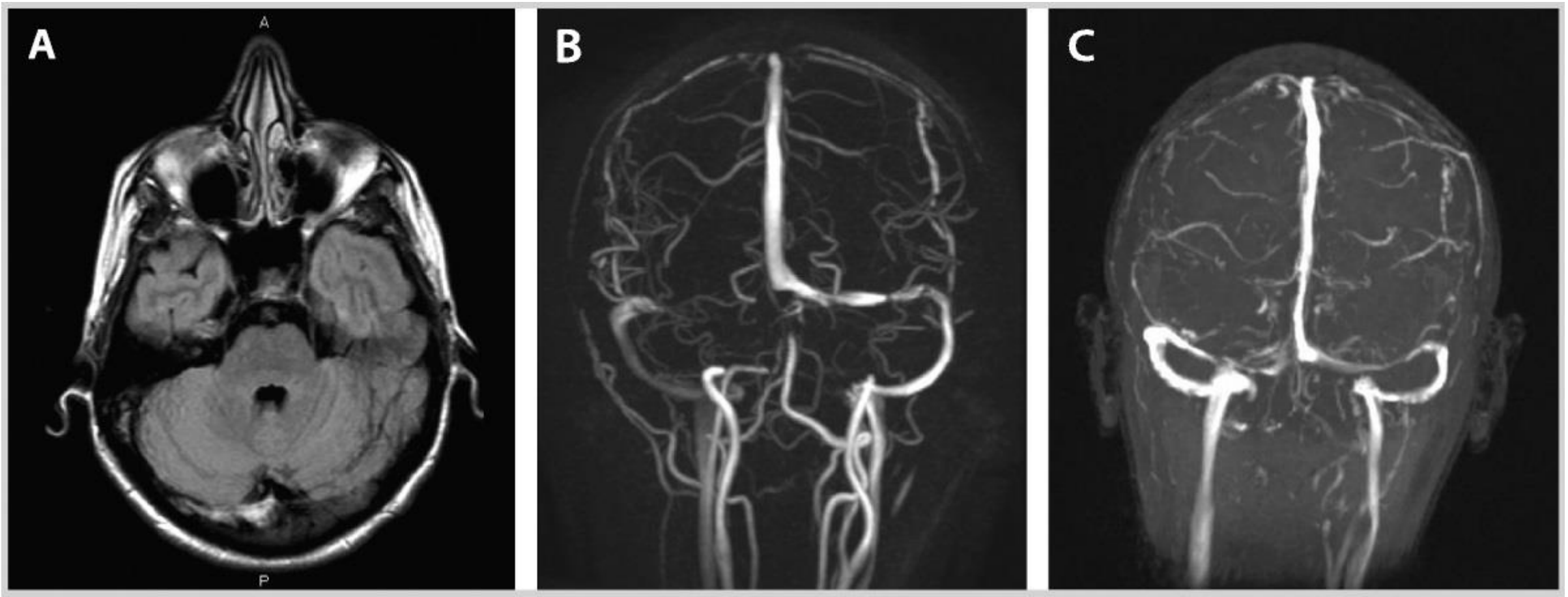
Case 2

19 year old woman on OCPs with history of migraines presents with 48 hours of a new type of headache – diffuse, severe, unrelenting pain.

BP 112/70 without focal deficits on exam.

Differential: Primary headache vs secondary headache

What would you do next?



T2 FLAIR **MRV** **MRV post-treatment**

Feske and Singhal. Continuum Feb 2014

Exogenous estrogens

- Combined OCPs associated with 7 fold increase in risk of VST
- Combined OCPs associated with 1.6 fold increase in risk of MI or ischemic stroke
  - Other combined hormonal contraceptives (patches and vaginal ring) have similar risk!
- Progestin-only hormonal contraceptives have not been associated with increased risk of stroke

Postmenopausal hormone therapy

- Women's Health Initiative

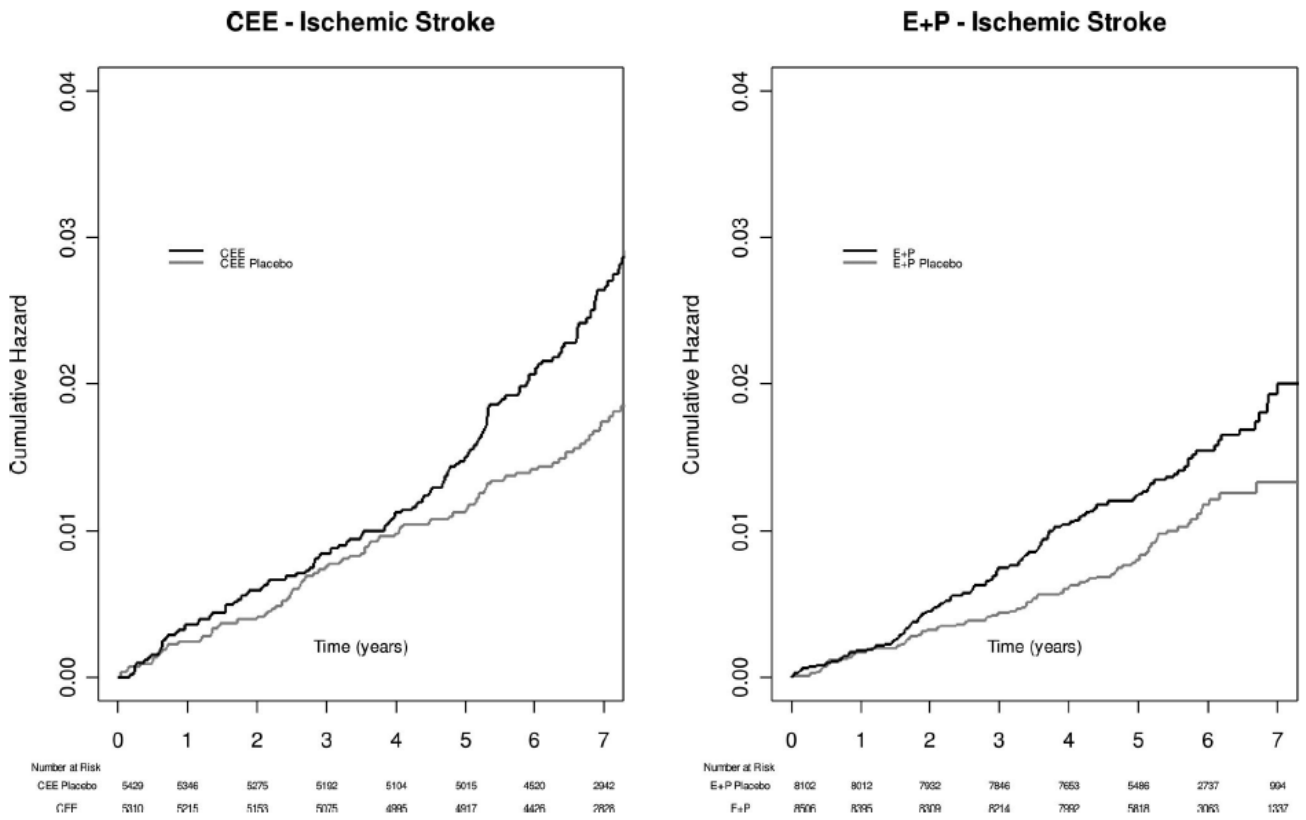


Figure 2. Ischemic stroke risk by WHI hormone trial.

Hendrix et al. Circulation 2006

Endogenous hormones

- No relationship between estradiol levels and ischemic stroke risk
- No relationship between testosterone levels and ischemic stroke risk
- Low dehydroepiandrosterone associated with increased ischemic stroke risk
- Cardiovascular risk rises dramatically after menopause

Case 3

Mary is a 74 year old female with history of DM, HTN and newly diagnosed atrial fibrillation

Tom is a 74 year old male with history of DM, HTN and newly diagnosed atrial fibrillation

Do Mary and Tom have the same risk of stroke?

Conventional risk factors

- HTN
  - Most prevalent modifiable risk factor for both sexes
  - Lower prevalence in women up until the 6th decade, then higher prevalence
- Dyslipidemia
  - No clear sex difference in associated stroke risk
  - Woman may be less likely to be treated appropriately with statins
- DM
  - Equal rates for both sexes
  - Women with DM have higher risk of stroke and higher risk of fatal stroke

Conventional risk factors

- Atrial fibrillation
  - AF in women associated with higher risk of all cause mortality as well as higher risk of stroke
  - Women with AF have higher risk of dependency after stroke
  - Women less likely to undergo cardiac ablation
  - Women less likely to receive oral anticoagulation

Back to Case 3

Mary is a 74 year old female with history of DM, HTN and newly diagnosed atrial fibrillation

Tom is a 74 year old male with history of DM, HTN and newly diagnosed atrial fibrillation

Do Mary and Tom have the same risk of stroke?

Mary likely has a higher risk of stroke

Evaluation and treatment

- Age is a major confounder because women tend to be older and have more severe strokes
- Limited studies designed to evaluate sex differences in evaluation and treatment

Sex differences in stroke symptoms

- In hypothetical situations:
  - Women were more likely to recognize traditional stroke signs
  - Women were less likely to call an ambulance or go immediately to the hospital
- 4 separate studies from 2009-2011 demonstrated increased prevalence of non-traditional stroke symptoms and signs in women

Bushnell et al. Lancet Neurol 2018

Sex differences in diagnosis

- Stroke mimics are more common in women
- Women may have longer door-to-imaging times

Sex differences in treatment

- Eligibility for tPA appears to be similar
- Several studies from 2009-2016 demonstrated small or no sex differences in use of tPA
- Data for sex differences with door to needle times are limited
  - GWTC stroke registry analysis (FL and Puerto Rico) indicated slight treatment delays among women relative to men

Bushnell et al. Lancet Neurol 2018

Outcome after tPA

- Four post-hoc analyses from randomized clinical trials failed to show sex difference in outcomes after treatment with tPA

Bushnell et al. Lancet Neurol 2018

Outcome after mechanical thrombectomy

- Madsen et al examined 90 day outcomes after thrombectomy
  - 279 patients
  - 53% female (older with higher baseline NIHSS)
  - Similar pre-stroke functional status (mRS)
  - Males and females had similar likelihood of independence at discharge
  - Females were less likely to be independent at 90 days

Summary

- Pregnancy and hypertensive disorders of pregnancy are important stroke risk factors in the young female population
- Pregnancy is NOT a contraindication to imaging, tPA administration, mechanical thrombectomy
- Exogenous hormones (combined contraceptives and hormone replacement therapy) increase the risk of thrombosis and stroke
- Conventional risk factors affect men and women differently in terms of stroke risk
- More research is needed to examine sex differences in stroke diagnosis, treatment, and outcomes

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