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

Pregnancy Care ECHO
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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…

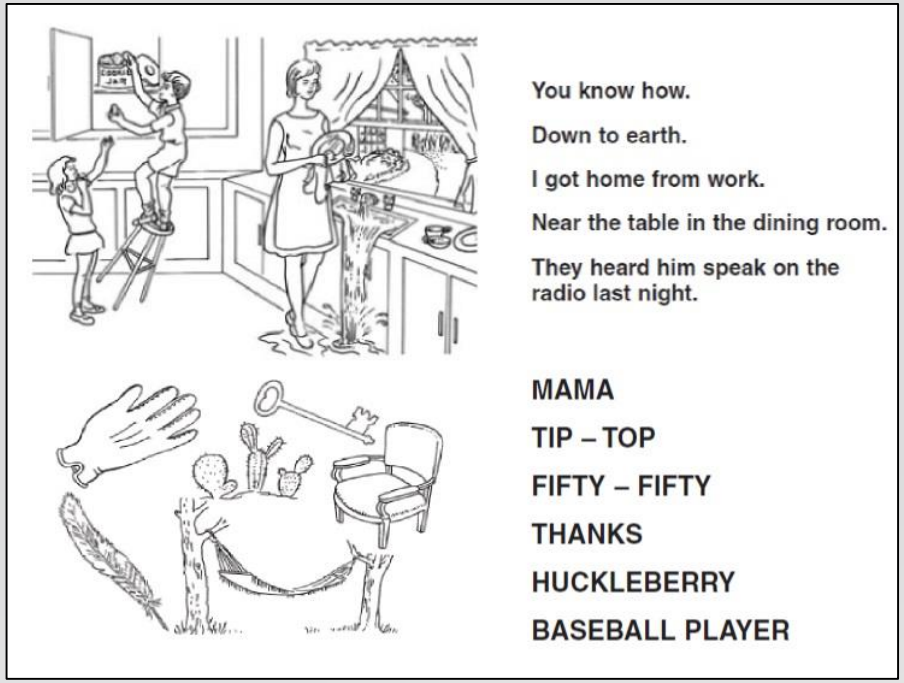
- A 34 year old G2P1 woman at 26 weeks EGA presents to the ED with sudden onset language difficulties and right sided hemiparesis

- 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/Innatention: 0

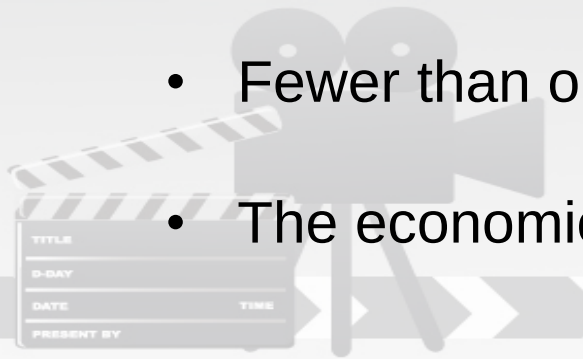
Total: **19**

CT imaging

What do we do?

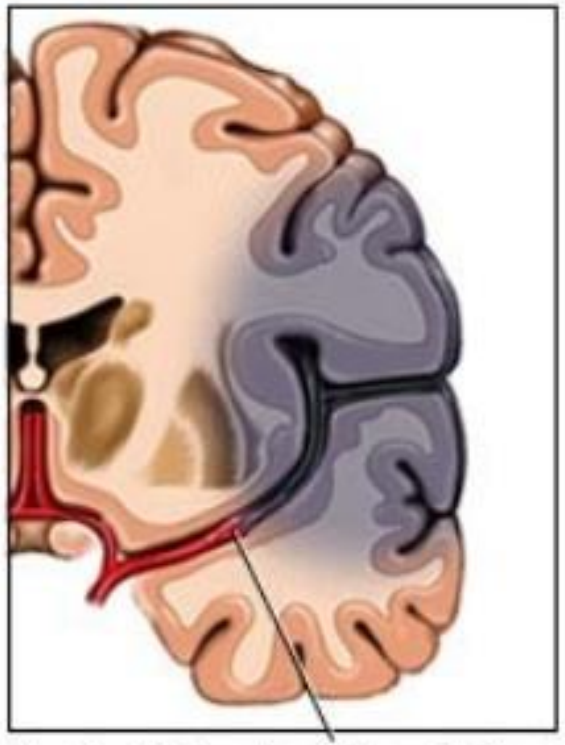
Stroke in the US

- 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.



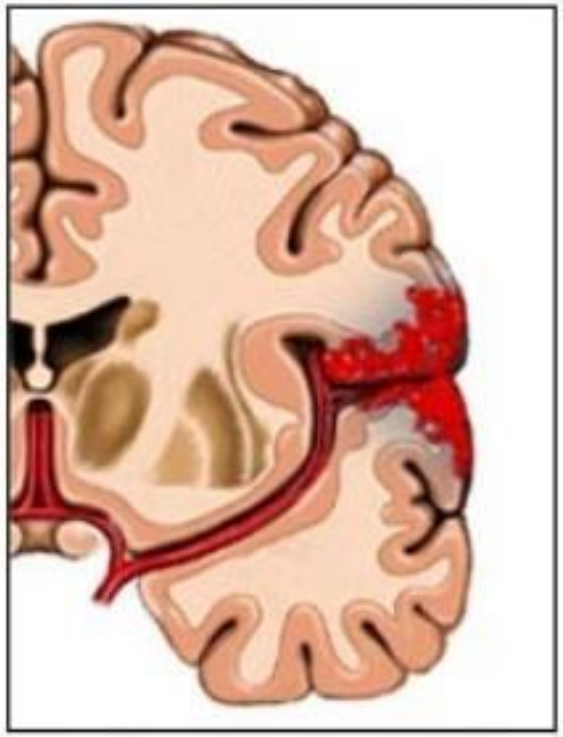
Types of stroke:

Ischemic stroke



A clot blocks blood flow to an area of the brain

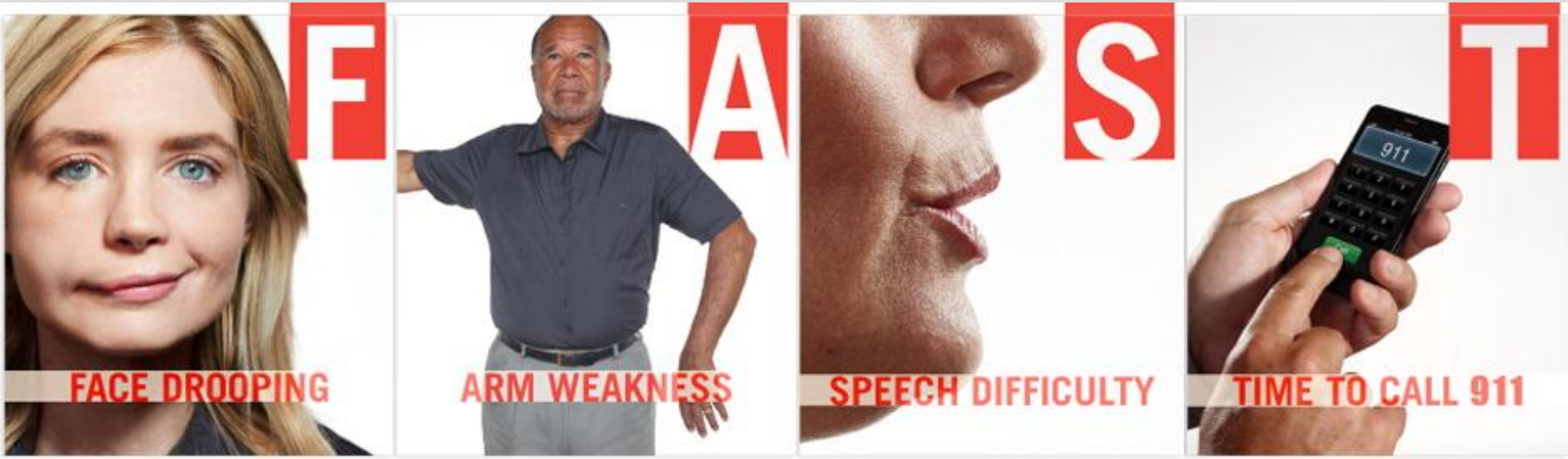
Hemorrhagic stroke



Bleeding occurs inside or around brain tissue

http://www.memorialhermann.org/library/healthguide/en-us/images/media/medical/hw/h5551195.jpg

Stroke Symptoms



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)

Bushnell, C. et al. Guidelines for the Prevention of Stroke in Women. Stroke 45, 1545–1588 (2014).

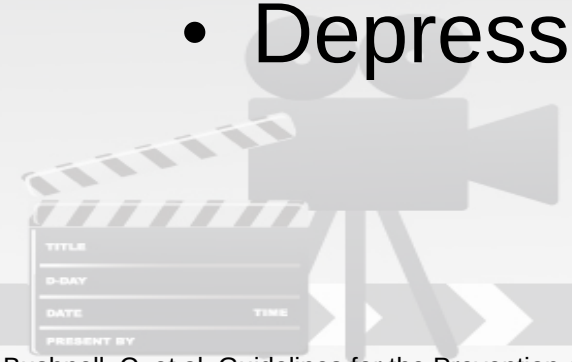
Stroke Risk Factors in Women

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



Bushnell, C. et al. Guidelines for the Prevention of Stroke in Women. Stroke 45, 1545–1588 (2014).

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

Lisabeth, L. D., Brown, D. L., Hughes, R., Majersik, J. J. & Morgenstern, L. B. Acute Stroke Symptoms. Stroke 40, 2031–2036 (2009)
Labiche, L. A., Chan, W., Saldin, K. R. & Morgenstern, L. B. Sex and acute stroke presentation. Annals of Emergency Medicine 40, 453–460 (2002)

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

Bushnell, C. et al. Guidelines for the Prevention of Stroke in Women. Stroke 45, 1545–1588 (2014).

Pathophysiology of Stroke in Pregnancy

- Venous stasis

- Hypercoagulability
  - Activated protein C resistance
  - Lower levels of protein S
  - Increased fibrinogen

Bushnell, C. et al. Guidelines for the Prevention of Stroke in Women. Stroke 45, 1545–1588 (2014).

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

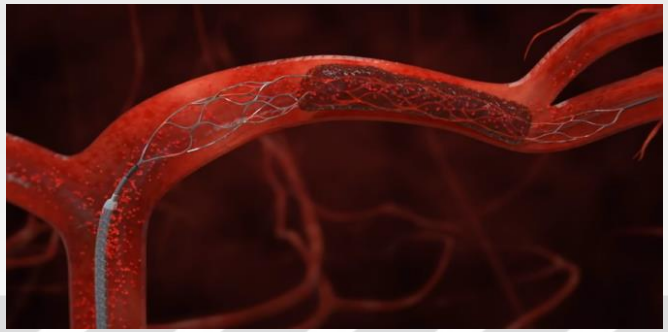
Pregnancy-induced hypertension cutoffs

- 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

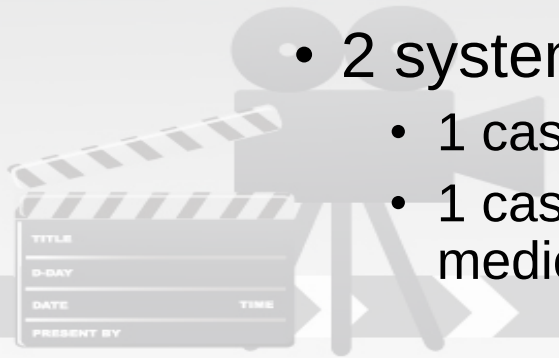
- AHA/ASA Review
- 12 reported cases of pregnant women with arterial stroke who were treated with IV tPA or endovascular therapy

- 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)

Leffert LR, et al. Treatment patterns and short-term outcomes in ischemic stroke in pregnancy or postpartum period. Am J Obstet Gynecol. 2016Jun;214(6):723.e1-723.e11.

Endovascular treatment in pregnancy

- IV iodinated contrast is a class B agent
  - “Very little contrast crosses the placenta and enters the 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 maydeliver doses above 100 mGy—’fetal dose’ of 2.8mGy

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

Kupferminc MJ, et al. Transient focal neurological deficits during pregnancy in carriers of inherited thrombophilia. Stroke. 2000 Apr;31(4):892-5.

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

Bushnell, C. et al. Guidelines for the Prevention of Stroke in Women. Stroke 45, 1545–1588 (2014).

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

Bushnell, C. et al. Guidelines for the Prevention of Stroke in Women. Stroke 45, 1545–1588 (2014).

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

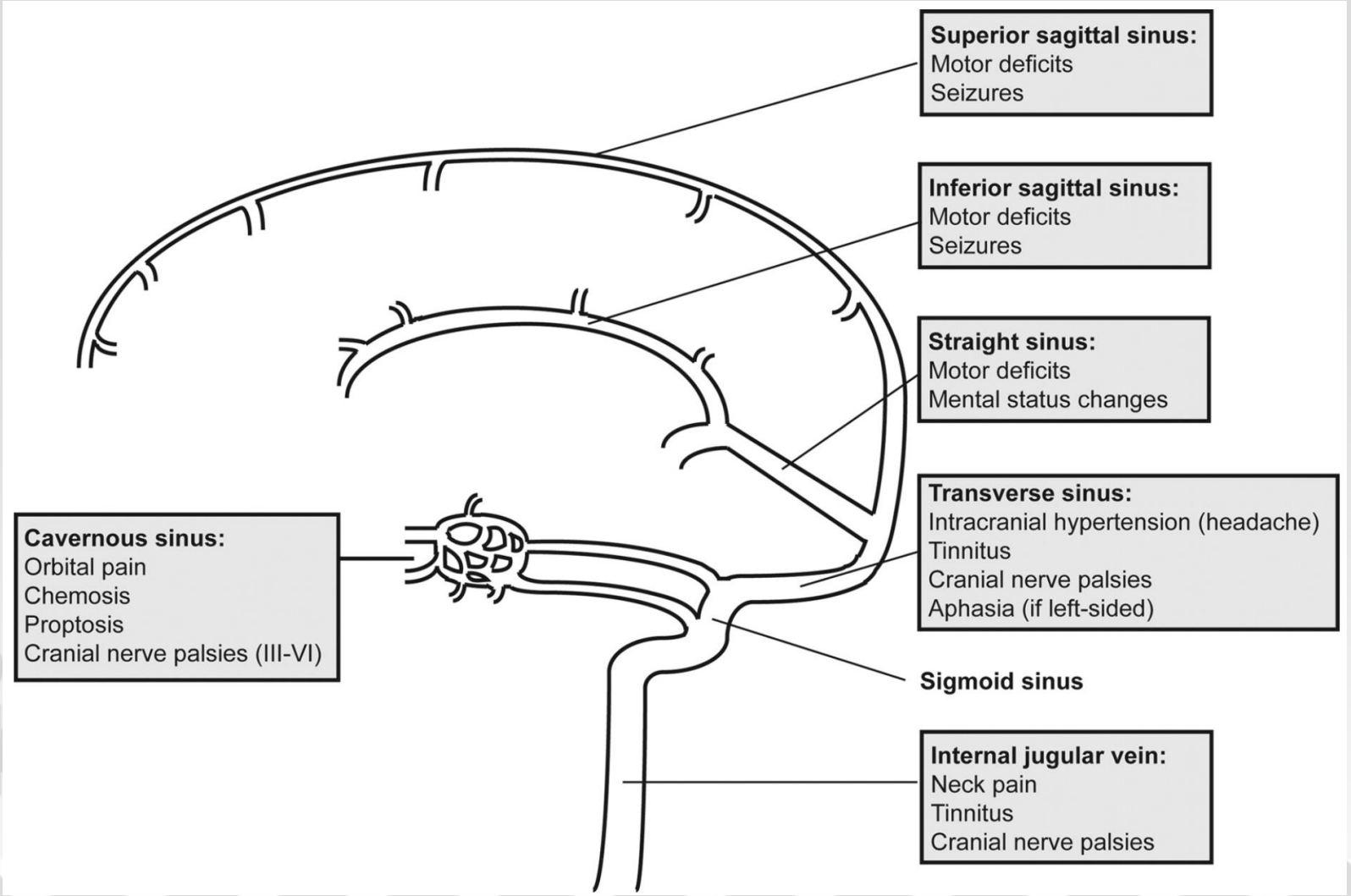
Bushnell, C. et al. Guidelines for the Prevention of Stroke in Women. Stroke 45, 1545–1588 (2014).

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*

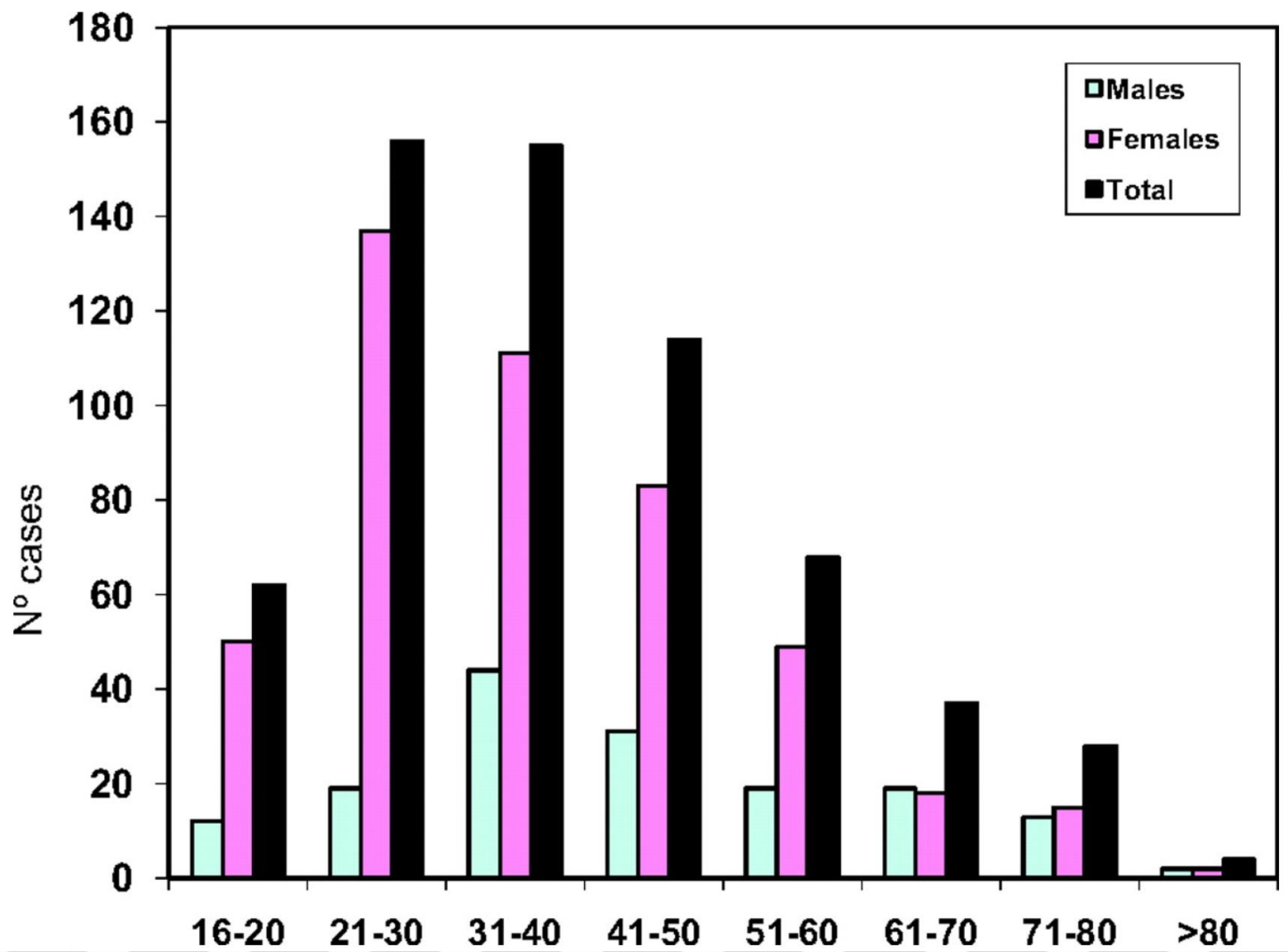
Bushnell, C. et al. Guidelines for the Prevention of Stroke in Women. Stroke 45, 1545–1588 (2014).

Cerebral Venous Thrombosis (CVT)



Piazza G. Cerebral venous thrombosis. Circulation. 2012 Apr 3;125(13):1704-9.

Age and sex distribution of CVT



Dr Jose Ferro, International Study on Cerebral Venous and Dural Sinuses Thrombosis

Presenting Symptoms & Findings

Increased ICP

- Headache (90%), usually subacute
- Vision/papilledema

Venous infarct/hemorrhage

- Weakness (40%)
- Seizures (30-40%)
- Aphasia
- Mental status changes

Risk Factors for Cerebral Venous Thrombosis

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

Ferro JM, Canhao P, Stam J, Bousser MG, Barinagarrementeria F. Prognosis of cerebral vein and dural sinus thrombosis: results of the International Study on Cerebral Vein and Dural Sinus Thrombosis

Risk Factors for Cerebral Venous Thrombosis

Vasculitis	19	3
Systemic lupus erythematosus	7	1
Behçet disease	6	1
Rheumatoid arthritis	1	0.2
Thromboangiitis obliterans	1	0.2
Nonspecified	4	0.6
Other inflammatory systemic disorders	11	1.8
Intestinal inflammatory disease	10	1.6
Sarcoidosis	1	0.2
Other systemic disorders	15	2.4
Thyroid disease	11	1.7
Other	4	0.6

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

Ferro JM, Canhao P, Stam J, Bousser MG, Barinagarrementeria F. Prognosis of cerebral vein and dural sinus thrombosis: results of the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT). Stroke. 2004;35:664-670.

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

Cantú C, Barinagarrementeria F. Cerebral venous thrombosis associate
Jaigobin C, Silver FL. Stroke and pregnancy. Stroke. 2000;31:2948–2951.d with pregnancy and puerperium: review of 67 cases. Stroke. 1993;24:1880–1884.

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)

Coutinho, J. M. et al. Unfractionated or Low–Molecular Weight Heparin for the Treatment of Cerebral Venous Thrombosis. Stroke 41, 2575–2580 (2010).

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

Demographic	Clinical	Neuroimaging	Risk Factors
Age >37 y[10]	Coma[10,117,277]	Intracerebral hemorrhage[10,277]	Cancer[10,177]
Male sex[10]	Neurological deficit and severity (NIHSS)[177,179]	Involvement of the straight sinus[277]	CNS infection[10]
	Encephalopathy[117]	Thrombosis of the deep venous system[10]	Underlying coagulopathy hereditary thrombophilia[66]
	Decreased level of consciousness[10]		
	Hemiparesis[10]	Venous infarction[66,179]	
	Seizures[10,179]		

Saposnik, G. et al. Diagnosis and Management of Cerebral Venous Thrombosis. Stroke 42, 1158–1192 (2011).
Ferro JM, Canhão P, Stam J, Bousser MG, Barinagarrementeria F; ISCVT Investigators. Prognosis of cerebral vein and dural sinus thrombosis: results of the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT). Stroke. 2004;35:664–670.

Thank you!