



Stroke and pregnancy

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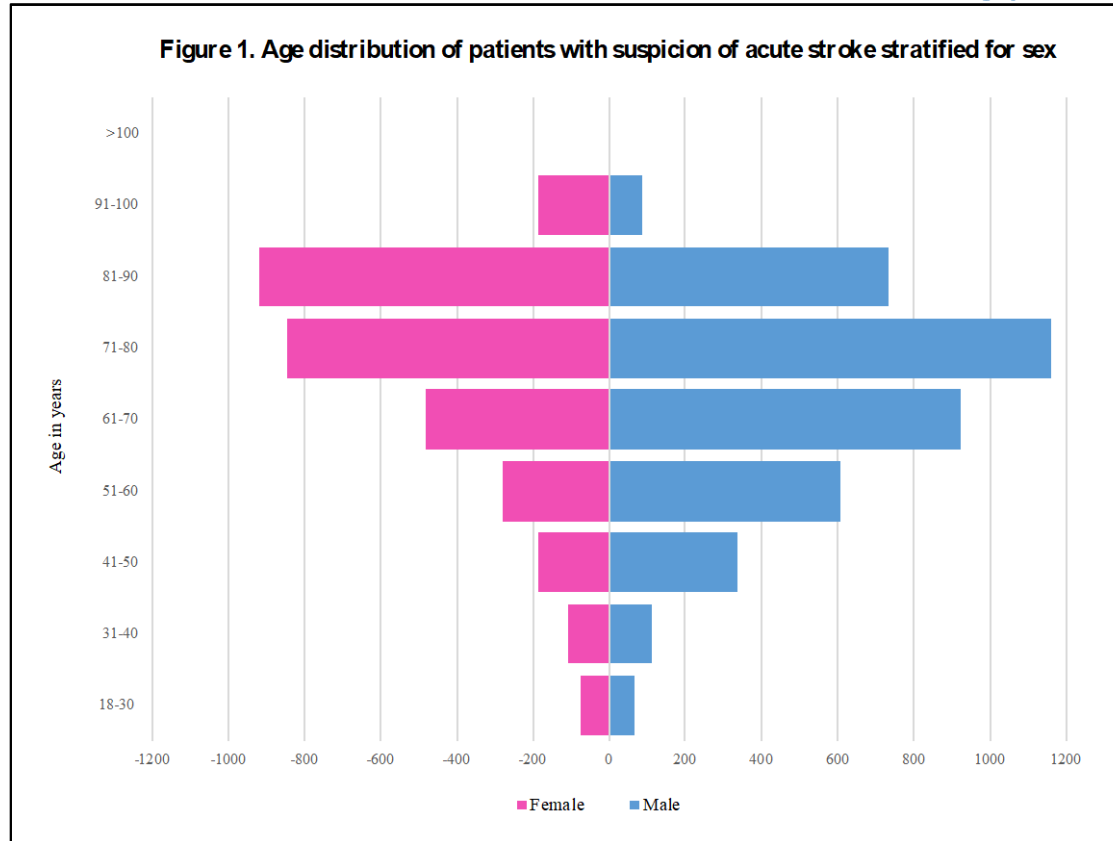
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1.1. Stroke and sex: epidemiology

- Age-dependent higher incidence of stroke in women due to higher life expectancy and occurrence in highest age groups, worse outcome regarding disability, quality of life and mortality¹
- Demographic changes with increasing age in particular of the female population → increasing prevalence of ischemic stroke in women²
- <65 yrs: stroke-related mortality significantly higher in men (high risk in middle age groups of 45-74 yrs) ^{1, 3}
- >75 yrs: trend reversal with increasing stroke-related disability and mortality in women worldwide exceeding that of men, 60% of stroke-related deaths >75 yrs of age¹



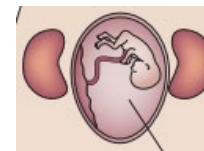
1.1. Stroke and sex: epidemiology



1.2. Stroke and sex: pathophysiology

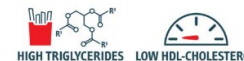
Distribution of vascular risk factors

- Atrial fibrillation occurs more often in women
 - Associated with ...
 - Twice the risk of stroke in women compared to men²
 - Higher stroke severity³
- Hypertensive disorders in women during pregnancy and after menopause
- Diabetes and smoking with higher prevalence in men
 - BUT: stroke risk due to diabetes, visceral adipositas and metabolic syndrome is higher in women compared to men



METABOLIC SYNDROME

Cluster of health conditions



1.2. Stroke and sex: pathophysiology

Hormonal factors

- **Fertile age:**
 - **Orale contraceptives**²
 - Combined estrogen/progesterone formulations → 1.7 - 2.5 ↑ risk
 - Gestagene mono → no elevated risk
 - Incidence of stroke associated with hormonal-based contraceptives is very low (21 per 100.000 person years)³
 - **Pregnancy**
 - Incidence of stroke is variable: 25-34 cases/100.000 deliveries
 - Stroke risk 9x increased in peripartal period
 - 3x increased 3 month postpartum for ischemic and hemorrhagic stroke⁶
 - **Migraine**
- **Menopause:**
 - ↓ estrogen → ↓ vasoprotective effects
 - Long term effects of hormonal replacement therapy are unclear to date
- **Age > 80 years:**
 - High proportion of women within the whole population of stroke patients, ↑ stroke severity, ↓ functional outcome
 - Limited access of women to specialized stroke centers
 - Secondary prevention: ↓ probability of adequate BP control, antiplatelet therapy and oral anticoagulation in women^{4,5}



- 1 Xu et al. 2015. *Thromb. Res*
- 2 Roach et al. 2015. *Cochrane Database Syst. Rev*
- 3 Lidegaard et al. 2012. *NEJM*
- 4 Glader et al. 2003. *Stroke*
- 5 Perrier et al. 2023. *Therapie*
- 6 Cordonnier et al. 2017. *Nature Rev Neurol*

2.1. Stroke and pregnancy: epidemiology

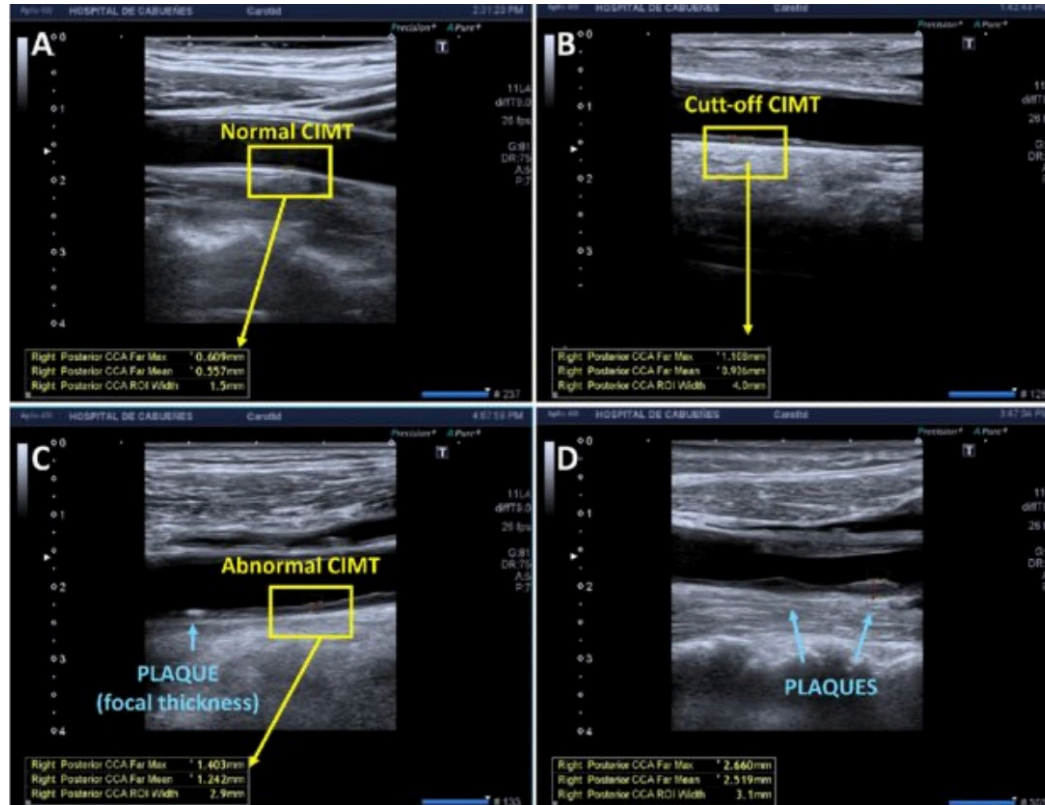
- 12-35% of cerebrovascular disease in those aged 15 to 45 years involved either pregnancy or recent delivery^{1, 2}
- Pregnancy and postpartum period are associated with an ↑ risk of ischemic and hemorrhagic stroke with reported incidences of 13 to 29 per 100.000 deliveries¹⁻³
- Arterial ischemic strokes are equally or more prevalent than venous infarcts
- Frequency of both ischemic and hemorrhagic events ↑ in third trimester, in particular closer to delivery, during delivery and postpartum



2.2. Stroke and pregnancy: risk factors

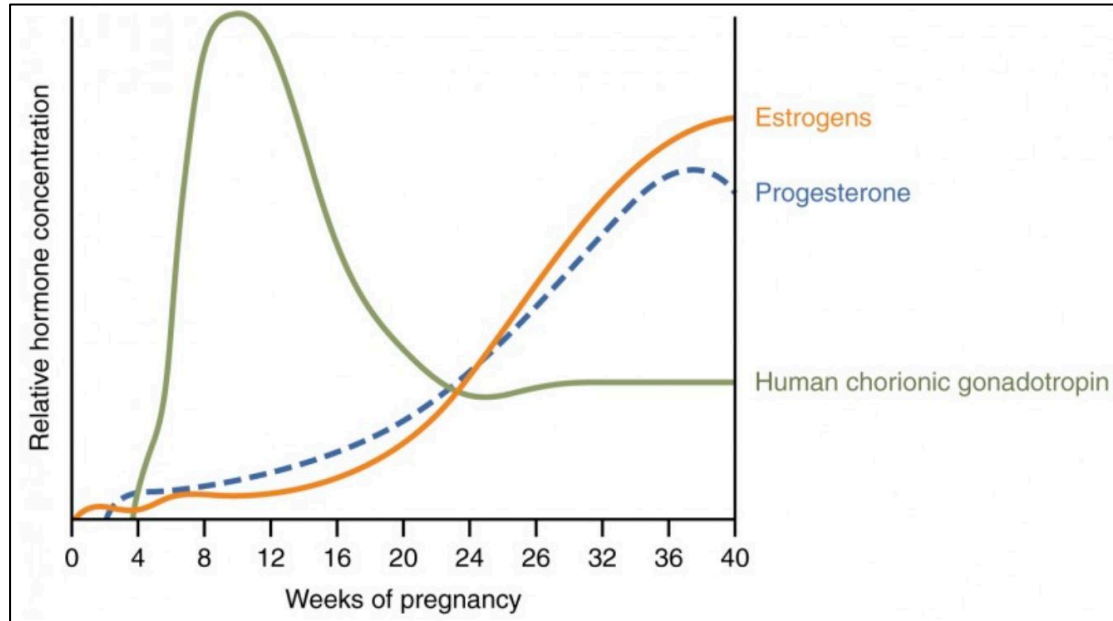
- Pregnant women can have **risk factors typically associated with stroke in the general population** (hypertension, diabetes, valvular heart disease, hypercoagulatory disorders)
 - → important with respect to **obesity at younger age and increasing maternal age** at pregnancy¹
- **Childbearing** can have a rapid **influence on progression of atherosclerosis**: study on 1005 women and 781 men with 6 yr-FU²:
 - women with childbirth during FU was associated with:
 - ↓ in HDL
 - ↓ apolipoprotein A-I/B
 - redistribution of adipositas to abdominal deposits
 - ↑ carotid IMT (not modified by adjustment for changes in cv risk factors)

2.2. Stroke and pregnancy: risk factors - atherosclerosis



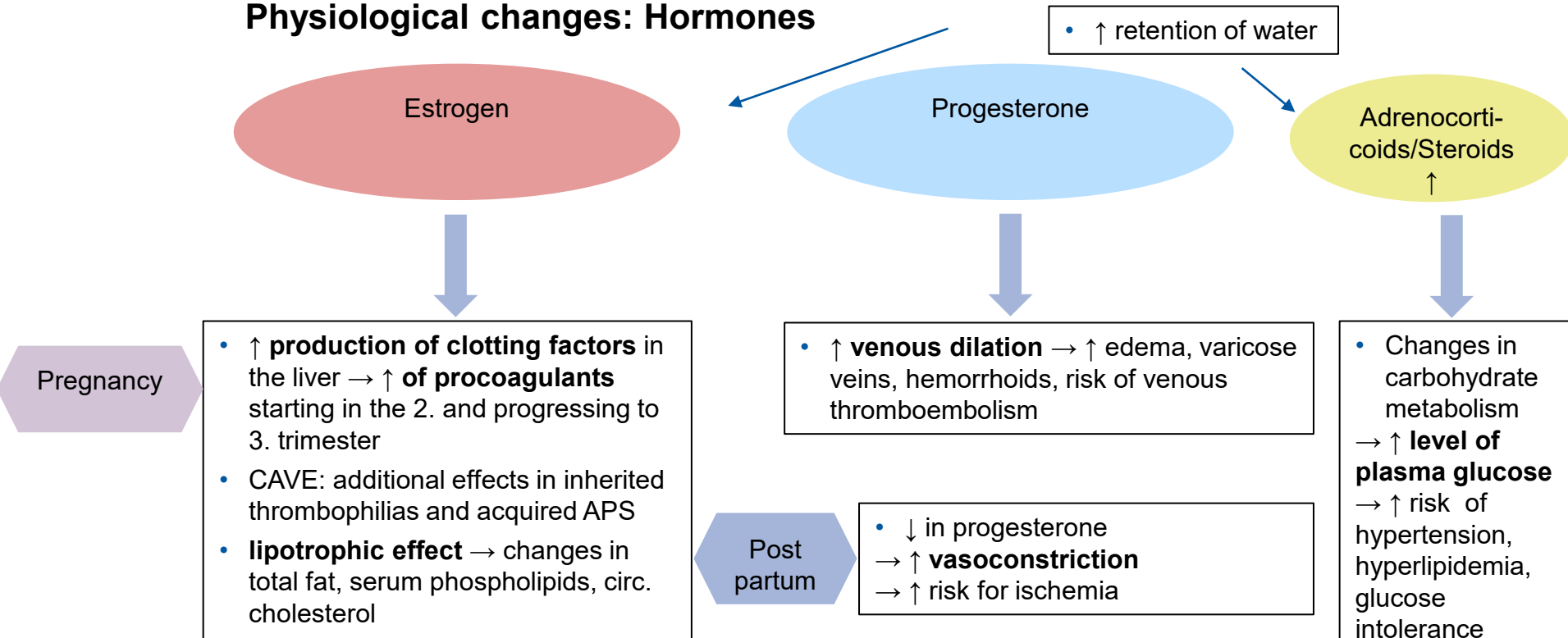
2.2. Stroke and pregnancy: (patho-)physiology

Physiological changes: Hormones



2.2. Stroke and pregnancy: (patho-)physiology

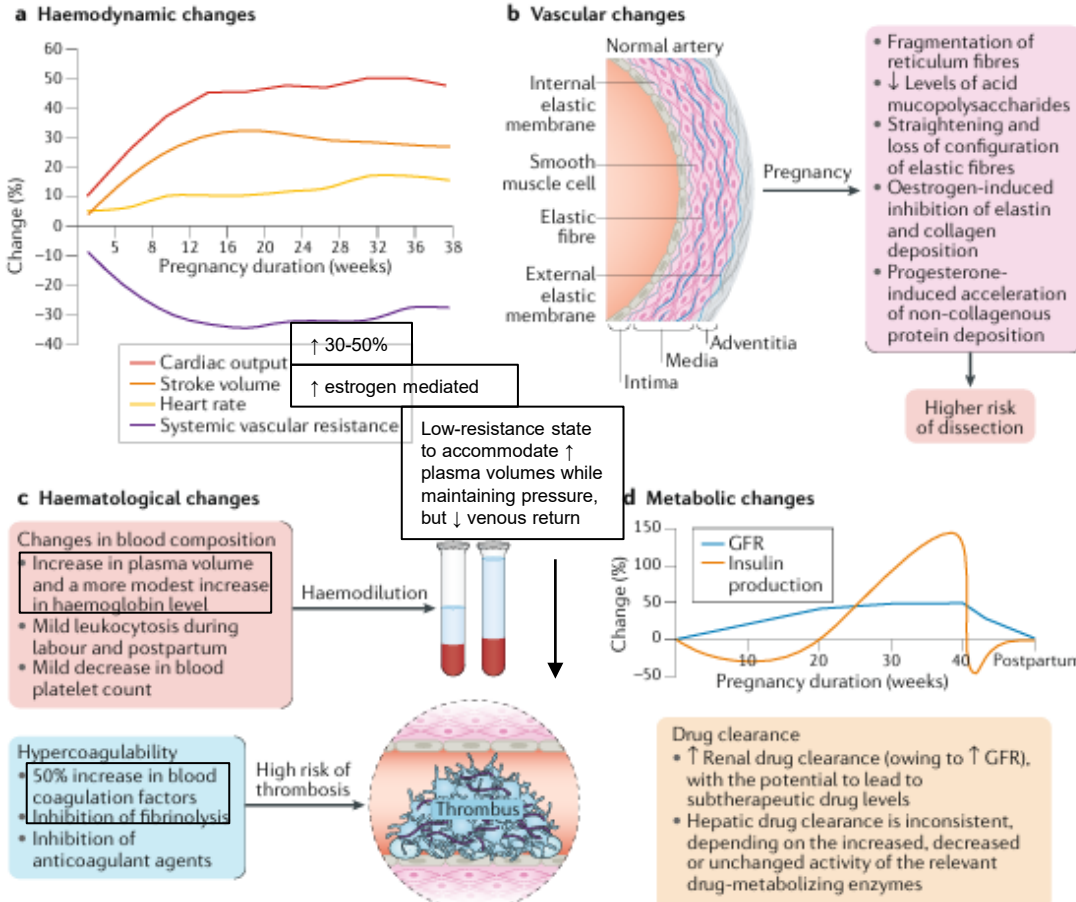
Physiological changes: Hormones



2.2. Stroke and pregnancy: risk factors/physiological changes

Physiological changes:

Circulatory, Vascular, Hematologic, Metabolic



Karishma et al. 2020. *Nature Reviews*

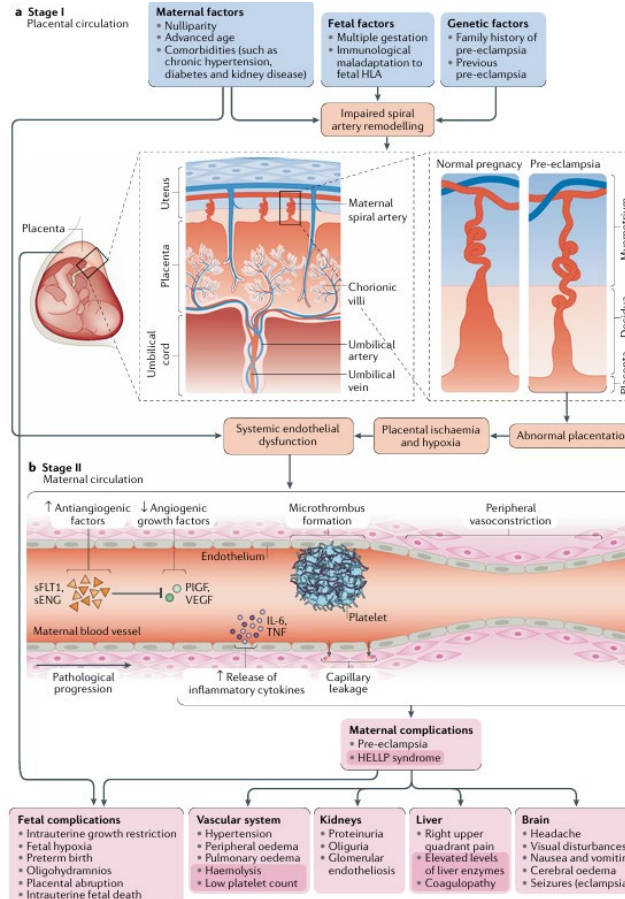
2.3. Stroke and pregnancy: pregnancy-specific causes of stroke

a.) Preeclampsia

- Usually develops in the **third trimester or within 48 hrs after delivery**, rarely up to 4 weeks post partum
- **Clinical symptoms:**
 - **New onset hypertension >140/90 mmHg**
 - **Proteinuria after 20 weeks of gestation**
 - **Eclampsia: additional generalized seizures**
- **Epidemiology:**
 - in the USA **5-8% of all pregnant women**, third leading cause of maternal mortality
 - More common in African American and Hispanic women, age >35 yrs, history of hypertension, diabetes, connective tissue disorder, multiple pregnancies, BMI>35, positive family history

2.3. Stroke and pregnancy: pregnancy-specific causes of stroke

a.) Preeclampsia



- Vascular mediators are released → injuries of vasc. endothelia and provoke vasoconstriction
- ↑ of sFMS-like tyrosine kinase by hypoxic trophoblasts, which bind placental and vascular growth factors
- → ↓ of these factors contributes to endothelial injury
- → cerebral infarction or hemorrhage

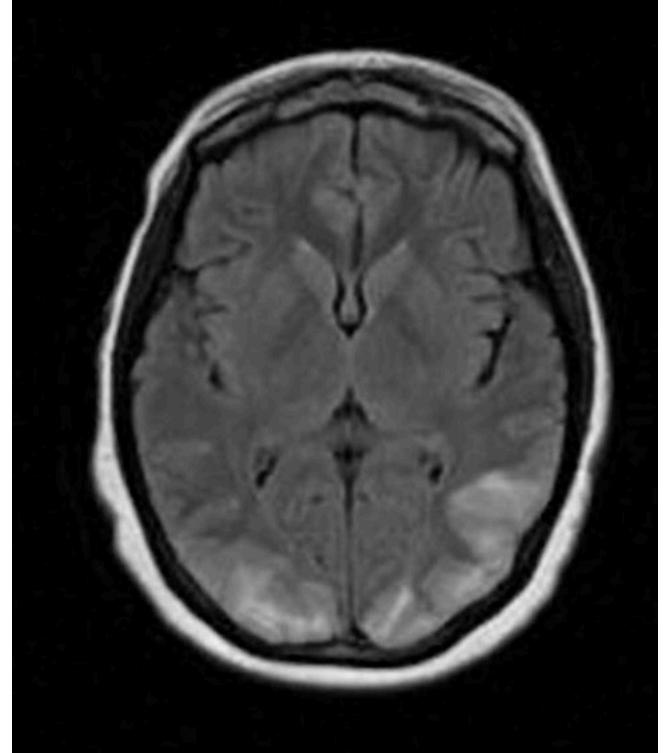
Karishma et al. 2020. *Nature Reviews*

2.3. Stroke and pregnancy: pregnancy-specific causes of stroke

a.) Preeclampsia

Complication: PRES (Posterior Reversible Encephalopathy Syndrome)

- Clinical findings:
 - Agitation and restlessness
 - Confusion
 - Seizures
 - Visual dysfunction including visual hallucinations and cortical blindness →
- Neuroimaging:
 - White matter hyperintensities max. in occipital and posterior temporal white matter sparing the paramedian occipital striate regions
- Pathophysiology:
 - ↑ BP → loss of self-regulation → hyperperfusion with endothelial damage and vasogenic edema



1 Sidorov et al. 2011. *Expert Rev Cardiovasc*
2 *Radiopaedia.org*

2.3. Stroke and pregnancy:

a.) Preeclampsia/PRES

Treatment:

- Strict lowering of blood pressure
- Decreasing brain edema
- Treatment of seizures
- Delivery of the baby
- Low-dose aspirin may reduce the occurrence of preeclampsia and its associated complications

2.3. Stroke and pregnancy:

b.) Reversible Cerebral Vasoconstriction Syndrome (RCVS)

- **Pathophysiology:**

- Rapid ↓ of progesterone postpartum (vasodilator)
- prolonged, but reversible changes in medium and large-sized arteries
- Triggered by SSRI, cocaine, amphetamines, triptans, alpha-agonists, cannabis
- Women with history of migraine are more susceptible

- **Clinical symptoms:**

- **Acute onset of severe recurrent headaches** (often abrupt begin as thunderclap headache)

- **Diagnostic:**

- **Angiographic evidence of segmental narrowing or beading on intracranial arteries** (vasoconstriction), may persist for days or weeks and **can progress to brain infarctions and hemorrhages**
- MRI has low sensitivity for RCVS, 1/3 of cases have normal brain images
- DSA and CTA – CAVE: radiation; angiographic findings are not specific – DD vasculitis
- TCD to measure non-invasively and without radiation mean flow velocities (to detect risk of critical vasospasms even before focal neurologic deficits occur)



2.3. Stroke and pregnancy:

b.) RCVS Secondary Complications:

- **Convexity subarachnoid hemorrhage (33%)**
 - Small and self-limited
 - Located near the vertex of the head
 - Risk of thrombosis in nearby cortical veins
- **Watershed ischemic strokes (15%)**
 - Most often in cortical and subcortical regions
 - Symmetric distribution along watersheds of ant./post. circ.
 - If seen within the ant./post circ. → search for cervical artery dissection
- **Intraparenchymal hemorrhages (10%)**
 - small and lobar
 - Probably due to reperfusion of brain ischemic lesions and acute hypertension
- **Seizures (5%)**

2.3. Stroke and pregnancy:

b.) RCVS

32 year old woman with a history of rheumatoid arthritis presenting postpartum with headache, right upper quadrant pain, and mild right hemiparesis:

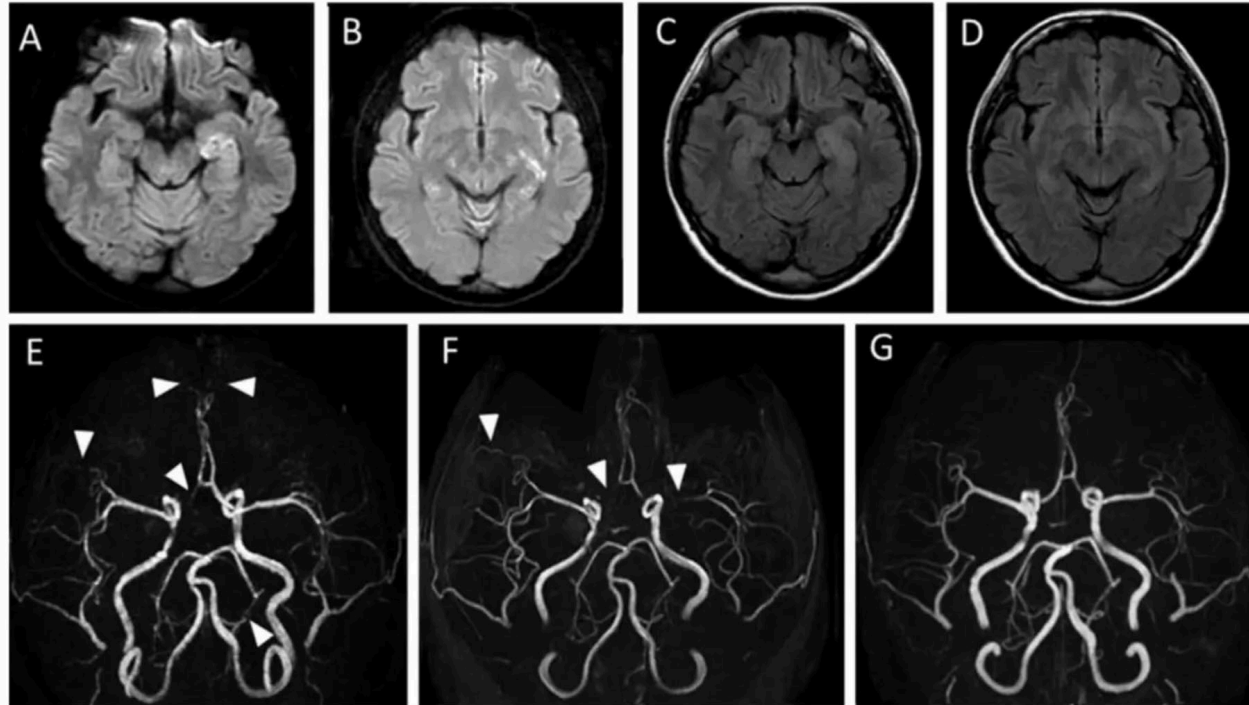


Figure 1. (A-D) MRI of the head (diffusion-weighted images: A, B; FLAIR images: C, D) on admission reveals cerebral infarction in the left hippocampus. (E-H) Magnetic resonance angiography (MRA) reveals reversible multiple vasoconstriction (white arrowhead) (E: day 1, F: day 2, G: day 17 from day of admission). Abbreviation: MRI, magnetic resonance imaging.

Hara D et al. PMID 30630756

Emcrit.org

2.3. Stroke and pregnancy:

b.) RCVS

Therapy:

- >90% will improve spontaneously
- Symptomatic management:
 - **Treatment of hypertension** to normal values
 - Nimodipine or other calcium channel blockers as long-acting Verapamil in doses of 180-360 mg daily
 - *CAVE: hypotension could worsen brain perfusion*
 - **Analgesia:**
 - opioid analgetics may be required, paracetamol may be beneficial; *CAVE: NSAIDs have been implicated in causing RCVS*
 - **Vasodilators:**
 - Magnesium sulfate i.v. 2-4g in acute setting

2.3. Stroke and pregnancy:

c.) Cerebral venous thrombosis (CVT)

- Incidence in pregnancy and puerperium in US studies was 11.6 per 100.000 deliveries
 - Higher incidence in developing countries up to 4.5 per 1.000 obstetric cases
 - **Pathophysiology:**
 - Hypercoagulability towards the end of the pregnancy
 - Cesarean section associated with higher rate of CVST
 - Other risk factors: infection in puerperium, lower blood volume due to peripartal hemorrhages
 - **Clinical symptoms:**
 - Headache
 - Seizures
 - **Diagnostic:**
 - MRI and venogram
- Therapy:**
heparin followed by warfarin 3-6 months
- Complications:**
venous brain infarcts or hemorrhages

2.3. Stroke and pregnancy:

c.) Cerebral venous thrombosis (CVT)

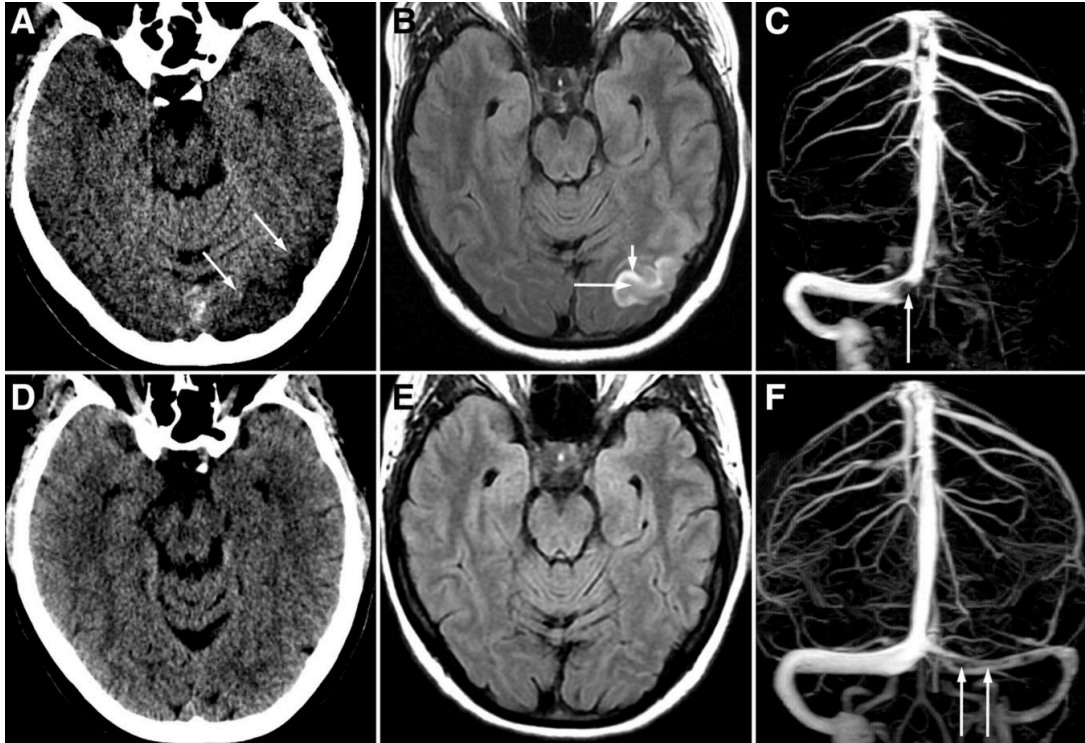


Figure 2. Illustrative case. A 31-year-old woman presented with 3 d of worsening headache and photophobia. Brain computed tomography (CT; **A**) shows hypodensity in the left occipital lobe (arrows) involving both cortex and white matter. T2-weighted FLAIR magnetic resonance imaging (MRI; **B**) shows corresponding hyperintensity in the cortex (long arrow) and white matter (short arrow). Diffusion-weighted MRI (not shown) has corresponding mild hyperintensity with isointensity on the apparent diffusion coefficient map. Contrast-enhanced magnetic resonance venogram (**C**), 3D rendering shows thrombus in the torcula (arrow) and complete occlusion of the left transverse and sigmoid sinuses. The patient was treated with intravenous then oral anticoagulation therapy, and with seizure prophylaxis. Follow-up CT (**D**) and MRI (**E**) after 3 mo shows complete resolution of the parenchymal abnormality with no infarction. Repeat magnetic resonance venogram shows that the venous sinus is mainly recanalized, with a small amount of residual, nonocclusive string-like material in the transverse sinus, which is likely fibrotic.

2.3. Stroke and pregnancy: d.) Other causes of stroke

- **Choriocarcinoma**
 - Malignant neoplasm from placental trophoblastic tissue usually following a molar pregnancy (incidence 1 per 30), but also term delivery (incidence 1 per 50.000)
- **Peripartum Cardiomyopathy**
 - Rare dilating CMP in last gestational month or until 5M pp
 - Ischemic stroke in 5% of patients
- **Amniotic Fluid Embolism**
 - Rare complication of disrupted barrier between amniotic fluid and maternal circulation potentially leading to stroke
 - Incidence 1 in 13.000-56.000 deliveries
 - Risk factors: maternal age >35 yrs, Cesarean section, vacuum-assisted delivery, placenta praevia
- **Paradoxical Embolism**
 - ↑ Risk of deep venous thrombosis in legs and pelvis during pregnancy and pp
 - Unknown whether paradoxical emboli through patent foramen ovale also occur more frequently, but high clinical suspicion and diagnostic is recommend

2.3. Stroke and pregnancy:

e.) Other causes of stroke in young women

- **Cervical artery dissection** – more common during delivery due to hyperextension of the neck during general anesthesia and ↑ in BP
- **Cardiac arrhythmias**
- **Heart valve disease**
- **Cerebral vasculitis**
- **Arteriovenous malformation**
- **Migraine**
- **Moya Moya disease**
- **Sickle Cell anemia**

2.4. Stroke and pregnancy: Treatment options

Antiplatelet therapy:

- Aspirin is reported to be beneficial in preventing preeclampsia when started earlier than 16 weeks of gestation, also ↓ in gestational hypertension and preterm birth
- AHA: low-dose aspirin (75-100 mg) once daily is considered safe in the 2. and 3. trimester, but the risk for its use during the 1. trimester is unknown

Anticoagulation:

- AHA: prevention options for pregnant women with ischemic stroke and high-risk thromboembolic conditions or mechanical heart valves:
 - UFH throughout pregnancy
 - LMWH throughout pregnancy
 - UFH/LMWH until week 13, followed by warfarin until the middle of the 3. trimester, the UFH/LMWH up to time of delivery

2.4. Stroke and pregnancy: Treatment options

Thrombolytic therapy:

- i.v. rtPA or mechanical thrombectomy are effective for acute ischemic arterial stroke applied with the treatment time window
- No direct evidence for safety of rtPA in pregnancy because pregnant women were excluded from large randomized clinical trials
- Several case reports show successful application of iv rtPA during pregnancy; 1 review of 172 pregnant patients reported maternal hemorrhage in a many as 8%

ACTILYSE Trockensub 20 mg c Solv ^{QA3}
Boehringer Ingelheim (Schweiz) GmbH

Fragen zum Produkt?

Drucken

DE ▾

Zusammensetzung

Darreichungsform und Wirkstoffmenge pro Einheit

Indikationen/Anwendungsmöglichkeiten

Dosierung/Anwendung

Kontraindikationen

Warnhinweise und Vorsichtsmassnahmen

Interaktionen

Schwangerschaft/Stillzeit

Schwangerschaft/Stillzeit

Schwangerschaft

Die Erfahrungen mit der Anwendung von Actilyse bei schwangeren Frauen ist begrenzt. Tierexperimentelle Untersuchungen mit höheren als beim Menschen verabreichten Dosen haben neben den bekannten pharmakologischen Wirkungen, **fötale Unreife und/oder Embryotoxizität gezeigt**. Im Falle einer akuten lebensbedrohenden Erkrankung ist der Nutzen gegen das potentielle Risiko abzuwägen.

Stillzeit

Es ist nicht bekannt, ob Alteplase in die Muttermilch übergeht.

Vorsicht ist geboten, wenn Actilyse einer stillenden Frau verabreicht wird, und es muss entschieden werden, ob das Stillen in den ersten 24 Stunden nach der Verabreichung von Actilyse unterbrochen werden sollte.

Fertilität

Klinische Daten zur Fertilität mit Alteplase liegen nicht vor. Tierstudien mit Alteplase haben keine negativen Auswirkungen auf die Fertilität gezeigt (siehe «Präklinische Daten»).

2.4. Stroke and pregnancy: Treatment options

Table 1 | Commonly used cardiovascular drug classes and their safety during pregnancy and lactation

Drug class	Indication	Frequently used drugs	Former FDA risk class	Safety during pregnancy	Safety during lactation
Angiotensin II receptor blockers	Hypertension, heart failure	Losartan, valsartan	D	Contraindicated owing to teratogenicity and fetal death	Incompatible
Angiotensin-converting enzyme inhibitors	Hypertension, heart failure, ischaemic heart disease	Enalapril, lisinopril, perindopril	D	Contraindicated owing to teratogenicity and fetal death	Enalapril and captopril are compatible, but potential risk of neonatal hypotension
Antiarrhythmic drugs	Arrhythmias	Adenosine, amiodarone, flecainide, lidocaine, sotalol	C	Adenosine, lidocaine and sotalol are probably safe, but potential risk of fetal bradycardia; amiodarone and flecainide are fetotoxic (fetal thyroid insufficiency; teratogenic effects in animals)	Adenosine and lidocaine are preferable; amiodarone is incompatible
Antiplatelet drugs	Ischaemic heart disease, pre-eclampsia prevention	Aspirin, clopidogrel	B	Aspirin is considered safe; clopidogrel is probably safe (on the basis of animal studies) but duration should be limited	Aspirin is compatible; clopidogrel transfers to breast milk, safety unknown
β -blockers	Hypertension, arrhythmias, ischaemic heart disease	Atenolol, bisoprolol, labetalol, metoprolol, propranolol	C	Probably safe, but potential risk of fetal intrauterine growth restriction and bradycardia; atenolol is contraindicated owing to teratogenicity	Compatible; propranolol and metoprolol are preferable
Calcium-channel blockers	Hypertension, angina, arrhythmias, tocolysis	Diltiazem, nifedipine, verapamil	C	Probably safe, but potential risk of maternal hypotension and fetal hypoxia, especially in sublingual or intravenous administration; diltiazem is associated with teratogenicity	Compatible
Cardiac glycosides	Arrhythmias, heart failure	Digoxin	C	Considered safe, digoxin is the preferred drug for arrhythmias, but beware of increased dosage requirements and monitor serum levels of the drug	Compatible
Central α -adrenergic receptor agonist	Hypertension	Methyldopa	B	Preferred drug for hypertension in pregnancy	Compatible
Diuretics	Hypertension, heart failure	Furosemide, hydrochlorothiazide	B (thiazide) and C (loop diuretics)	Probably safe, but potential risk of hypovolaemia and oligohydramnios; start at low doses	Compatible
Heparins	Anticoagulation	Low-molecular-weight heparin, unfractionated heparin	B	Considered safe, but potential risk of bleeding; carefully consider dose timing, in particular around delivery and analgesia or anaesthesia	Compatible
Nitrates	Angina, heart failure	Glyceryl trinitrate	C	Risk of maternal hypotension and fetal hypoxia	Safety unknown
Non-vitamin K antagonist oral anticoagulants	Anticoagulation	Apixaban, dabigatran, rivaroxaban	-	Contraindicated owing to teratogenicity in animal studies and risk of bleeding	Incompatible
Statins	Lipid lowering, cardiovascular disease prevention	Atorvastatin, simvastatin	X	Currently contraindicated owing to fetal teratogenicity; however, evidence for this risk is insufficient	Safety unknown
Vitamin K antagonists	Anticoagulation	Acenocoumarol, phenprocoumon, warfarin	D	Associated with embryopathy and risk of bleeding (in particular around delivery and analgesia or anaesthesia)	Compatible

Karishma et al. 2020. *Nature Reviews*

Thank you for
your attention!