

## **Written Case: Stroke in Pregnancy**

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*A 30 year-old woman, currently pregnant at 33 weeks gestation and with a past medical history of migraine with aura, presents to the office complaining of right arm weakness and clumsiness, and unsteadiness on her feet for one week. Over the past five weeks, she has had more migraines than usual, characterized by throbbing pain at the temples, with light and sound sensitivity. During her prior pregnancy, she was diagnosed with gestational diabetes and suffered from migraine with aura. Initial examination is notable for mild right arm weakness.*

### **Which investigation, if any, would be appropriate?**

A history of focal neurological symptoms and an abnormal clinical exam require further neurological workup, and most importantly, neuroimaging. It is important to realize that underlying masses and vascular malformations can produce similar clinical features to migraine with aura, and that migraine should be a diagnosis of exclusion in the presence of focal neurological deficits. Furthermore, migraine with aura is a minor stroke risk factor. When a patient presents with over 24 hours of symptoms, MRI (up to 3 Tesla magnet field strength) is the test of choice. It has no adverse effects on the fetus and is most sensitive test to evaluate the brain parenchyma. Additional imaging of the arteries and veins of the head (MRA, MRV) can also be performed without the need for gadolinium, the MRI contrast agent. Gadolinium should be avoided if possible in pregnant women unless absolutely necessary.

### **Would it make a difference if this patient showed up with one hour, rather than one week, of symptoms?**

Within several hours of onset of acute stroke-like symptoms, or in a patient with a “first or worst” headache who is in the emergency room, computed tomography imaging should be utilized instead of MRI, given the speed of testing. Fetal radiation exposure in computed tomography is below the threshold thought to cause fetal harm<sup>[1]</sup> and can be used when necessary in an emergency. Such is the case for pregnant women with pulmonary embolus, who may require a rapid CT scan and even intravenous contrast for evaluation.<sup>[2]</sup> When considering which radiologic tests to perform, it is worth noting that the potential risk of birth defects due to radiation (CT, for example) are highest in the first few weeks of pregnancy within the first trimester, during which embryogenesis occurs. Risk is lower in the second and third trimesters. However, it is often the case that a pregnancy may not be discovered in those early weeks.

*An MRI brain without gadolinium was completed and revealed T2 hyperintense lesion in mid pons consistent with subacute stroke, likely related to basilar artery vasospasm in setting of acute migraine. This patient was not a tPA candidate because the symptoms had been ongoing for weeks. She was admitted to the inpatient stroke service.*

**If she had presented immediately after the onset of right arm weakness, would she be a candidate for IV-tpa (tissue plasminogen activator)?**

With 4.5 hours of symptom onset, IV-tPA (recombinant tissue plasminogen activator) administration is considered the standard of care in acute stroke management. However, there are no clinical trials to evaluate the use of recombinant tissue plasminogen activator in pregnant women with acute stroke, and data is limited to case reports and series. Pregnancy is considered a relative contraindication for administration, and pregnant women have been excluded from seminal studies.[\[3\]](#) Based on animal studies, there is no evidence of teratogenicity related to the use of IV-tPA, which is considered a category C drug. Tissue plasminogen activator is a large molecule does not cross the placenta and has not thus far shown to negative effects on the child.[\[4\]](#) Complications related to tPA use in pregnant patients with acute stroke show similar complication rates as non-pregnant patients.[\[5\]](#) Tissue plasminogen activator is a large molecule that does not cross the placenta and has not thus far shown to negative effects on the child. On the other hand, from a physiologic standpoint, blood volume and blood flow to the uterus increase in pregnancy, conferring a theoretical risk of uterine hemorrhage, in addition to “usual” IV tPA risks of intracranial and other types of hemorrhage. Because stroke in pregnancy treated with IV tPA exist as case reports in the medical literature, there have been few known cases of symptomatic hemorrhage, including uterine hemorrhage, reported to date.

Additionally, there has been a recent paradigm shift in the treatment of acute ischemic stroke since the publication of five major studies in 2015, concluding that endovascular treatment (including mechanical thrombectomy) for strokes due to large vessel occlusion is superior to IV tPA alone, and therefore mechanical thrombectomy should be considered in the acute stroke treatment algorithm.[\[6\]](#) Endovascular procedures are typically performed with angiography, and therefore the impact of intravenous contrast should be weighed in pregnancy. While endovascular treatments offer a potential way to avoid complications of systemic thrombolysis in candidate pregnant women, mechanical thrombectomy is often performed in conjunction with IV tPA, and therefore pregnancy stroke registries are in their earliest stages and therefore both neurologists and emergency medicine specialists agree that reperfusion therapy for acute ischemic stroke in pregnancy should be assessed on a case by case basis.[\[7\]](#) [\[8\]](#) [\[9\]](#)

Though, the overall rate of stroke in pregnancy is fairly uncommon, at 34 cases per 100,000 deliveries,[\[10\]](#) it does carry significant morbidity and mortality, accounting for for 12% of maternal deaths and contributing to significant fetal morbidity and mortality in pregnancy-related stroke.[\[11\]](#) Disability from stroke can include weakness, dysphagia, aphasia, sensory and visual loss, and should therefore be recognized and treated urgently in pregnant women.

### **What are stroke risk factors in pregnancy?**

Retrospective studies suggest a 3-fold increased risk of stroke in pregnancy compared to the nonpregnant state.[\[12\]](#) Physiologic changes in pregnancy impart an increased stroke risk, although the relationship is complex and not well understood. Underpinning the elevated stroke risk in pregnancy are hormonal factors that confer hypercoagulability, including activated protein C resistance, lower levels of protein S and increased fibrinogen, along with venous stasis and edema. These changes peak around full term and the immediate post-partum period, presumably to prepare the pregnant women for delivery.

The leading cause of both hemorrhagic and ischemic stroke in pregnancy and post-partum is hypertension,<sup>[13]</sup> especially in the context of pre-eclampsia. Additional medical conditions that pose risks factors for stroke in pregnancy include preeclampsia/eclampsia, cesarean section, pregnancy-related hematologic disorders, migraine, gestational diabetes, primary hypercoagulable states, and smoking history.<sup>[14]</sup> Meta-analyses show that migraine with aura imparts a 2-2.5 times greater risk of ischemic stroke.<sup>[15] [16]</sup> A recent systematic meta-analysis<sup>[17]</sup> found a stronger association between migraine and risk of ischemic stroke in pregnancy (OR range 7.9 to 30.7), particularly with active migraine. In nonpregnant patients, contraceptives containing estrogen add further risk of stroke for women with migraine with aura - and consequently, the American College of Obstetrics and Gynecology recommends against using estrogen-containing contraception in this population.

### **What are the mechanisms of stroke in pregnancy?**

The mechanisms of stroke in pregnancy appear to be similar to stroke in the non-pregnant, including arterial occlusions from artery-to-artery thromboembolism, cardiac embolism, and intracranial or extracranial atherothrombosis along with carotid and vertebral dissection. Preeclampsia/eclampsia is a mechanism unique to pregnancy and the postpartum period. In one retrospective study comparing pregnancy-associated stroke with stroke in non-pregnant women, pregnant women with stroke were less likely to have vascular risk factors such as hyperlipidemia and history of thromboembolism but more likely to have cerebral venous thromboses (21% vs 7%,  $p = 0.02$ ).<sup>[18]</sup> Reversible cerebral vasoconstriction syndrome (RCVS) is a stroke mechanism that more commonly occurs in pregnancy, particularly among migraineurs and pathophysiology may have some overlap with eclampsia.

*Lab studies while inpatient included lipid panel, a1c, TSH and hypercoagulable panel, which were all found to be normal. Echocardiogram was normal, with no evidence for a right to left shunt on bubble study. She underwent MRA/V of the brain and MRA of the neck, and cardiac telemetry, all of which were normal. The patient was started on aspirin 81mg/day, and she continued this medication throughout the remainder of her pregnancy, delivering a healthy baby girl.*

### **What medications are appropriate for secondary stroke prevention in pregnancy? What are the risks of antiplatelet and anticoagulation therapy in pregnancy and delivery?**

Treatment following a stroke is undertaken to prevent recurrent stroke. Hence, an understanding of the stroke etiology is important to guide treatment. Though there are no randomized controlled trials to guide stroke prevention in pregnancy, a recent American Heart Association/American Stroke Association have issued recommendations for pregnant women with stroke.<sup>[19]</sup> These include unfractionated heparin (UFH) or low molecular weight heparin (LMWH) for pregnant women needing anticoagulation due to cardioembolic source of stroke, or mechanical heart valves – with warfarin reserved for the second trimester through the middle of the third trimester (Class IIb; Level of Evidence C); and use of low dose aspirin after the first trimester of pregnancy for those without a high-risk thromboembolic condition. (Class IIb; Level of Evidence C).” In practice, UFH or LMWH is often utilized and warfarin avoided as it does cross the placenta and can have several potential deleterious fetal effects including birth defects

when used in the first trimester, increased risk of pregnancy loss, fetal hemorrhagic complications. There is not enough data on novel oral anticoagulants to recommend their use in pregnancy. Regarding antiplatelet therapy, it is known that full-dose aspirin (325mg/day) is contraindicated in pregnancy due to risk of closure of the patent ductus arteriosus, oligohydramnios, and bleeding risk.[20] However, several meta-analyses have demonstrated that low-dose aspirin (60–80 mg/day) in fact can be used safely in select populations of pregnant women. Low-dose aspirin (81mg/day) is beneficial in preventing preeclampsia, gestational hypertension, and preterm birth when started earlier than 16 weeks' gestation.[21] To date, the stroke literature confers no advantage of full-dose aspirin over low-dose aspirin, and therefore aspirin 81mg/day is sufficient for secondary stroke prevention in most cases of stroke in pregnancy. Of note, there is limited evidence on the use of clopidogrel during pregnancy and the post-partum period, and there are no formal guideline recommendations.

Whether to treat pregnant women who have had strokes with anticoagulation or antiplatelet depends primarily on the etiology of the stroke. Those with arterial stroke who do not have a history of venous thrombosis could benefit from either antiplatelet or anticoagulation, whereas those with cerebral venous sinus thrombosis and associated infarct are typically prescribed anticoagulation (both Class IIa recommendations, Category C).[22] Specific coagulopathies warrant anticoagulation – both in pregnant and nonpregnant patients. The presence of an antiphospholipid antibody suggests that antiplatelet therapy would be reasonable, whereas a diagnosis of the antiphospholipid *syndrome* typically necessitates anticoagulation. Women with inherited thrombophilic conditions who develop stroke in pregnancy should be assessed for deep vein thrombosis (DVT) to determine the need for anticoagulation.

### **Is it safe to breastfeed while on antiplatelets and anticoagulants?**

Data is limited on the use of anticoagulants in breastfeeding women, however, based on guidelines from the American College of Chest Physicians, breastfeeding may continue during treatment with unfractionated heparin, LMWH, warfarin, or aspirin.[23] Aspirin is excreted in breastmilk, and therefore, low-dose aspirin is preferable to full dose aspirin. Women taking full-dose aspirin are advised to wait two hours after taking the medicine to breastfeed, if possible.

### **What are the implications of stroke and the use of blood thinners for labor and delivery? *Can she push?***

There are no specific considerations to either vaginal delivery or caesarian section related to the stroke itself. Labor and delivery considerations following a stroke are related to the choice of the secondary stroke treatment and concern for maternal and fetal bleeding-related complications due to the combination of delivery-associated trauma and anticoagulant effects. Per the Chest guidelines,[24] “For pregnant women receiving adjusted dose LMWH therapy and where delivery is planned, we recommend discontinuation of LMWH at least 24 h prior to induction of labor or cesarean section (or expected time of neuraxial anesthesia) rather than continuing LMWH up until the time of delivery (Grade 1B).” In general, bleeding risk is higher with caesarian section versus a vaginal delivery. However, surgery can be performed if necessary in those taking antiplatelet therapy. The bigger risk to the patient relates to spinal or epidural anaesthesia. Though there is no contraindication to these procedures with aspirin, avoidance of

anticoagulation at least 12-24 hours – and in practice, up to 48 hours following therapeutic dosing of anticoagulation – prior to spinal anaesthesia is recommended to reduce the risk of spinal epidural hematoma – a guideline that also pertains to lumbar puncture.[\[25\]](#)

**Labor and delivery are successful, and the patient has a healthy baby girl. Three years later, she is pregnant again.**

**What medical precautions are recommended in a pregnant patient who has had a prior stroke?**

She should take aspirin 81mg/day throughout the pregnancy; blood pressure should be controlled. If there is a history of migraines, then migraines should also be controlled in order to reduce stroke risk factors. There is no specific anticipatory neuroimaging that needs to be done. She should be educated about stroke warning signs – specifically, if neurological symptoms occur (facial or limb weakness, dysarthria, problems with coordination or balance, visual or speech/language symptoms, for example), she should go to the emergency room immediately for acute stroke assessment and possible therapy.

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