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Pregnancy and Cardiovascular Disease (N Scott, Section Editor)

Management of Maternal Stroke and Mitigating Risk

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Abstract

Purpose of review Pregnancy places women at a higher risk for hemorrhagic and ischemic strokes. This review discusses the pathophysiological mechanisms underlying this increased risk, management considerations for pregnant patients, and ways to decrease the risk of stroke in this patient population.
Recent findings Rates of ischemic and hemorrhagic pregnancy-associated stroke have increased over the past 20 years, particularly events associated with hypertensive disorders of pregnancy. There is a growing body of evidence supporting the use of acute reperfusion therapies in ischemic pregnancy-associated stroke including tissue plasminogen activator (tPA) and endovascular thrombectomy.
Summary While the unique physiology of pregnancy places women at a higher risk of stroke, acute ischemic stroke management in pregnant patients should closely mirror the management of non-pregnant patients. Secondary stroke prevention agents should be selected with consideration of the pregnancy.

Introduction

Stroke is a major contributor to morbidity and mortality in pregnancy. Pregnant and early postpartum women are at a higher risk of both ischemic and hemorrhagic stroke than non-pregnant women of the same age. A recent meta-analysis reported rates of pregnancy-associated stroke as high as 30/100,000 pregnancies, approximately three times the rate of non-pregnancy-associated stroke in women of child-bearing age (~ 18–44 years old) [1••]. In addition to hemorrhagic and ischemic stroke, pregnant women are at a higher risk for other cerebrovascular disorders including cerebral venous sinus thrombosis (CVST), reversible cerebral vasoconstriction syndrome (RCVS), and posterior reversible encephalopathy syndrome (PRES).

Women are at highest risk of pregnancy-associated strokes within the peripartum period and early postpartum period, with many studies demonstrating the highest rates of stroke within the puerperium, defined as the first 6 weeks postpartum [2, 3••, 4–6], potentially extending up to 12 weeks for some patients [7]. Recent work has suggested the first 10 days postpartum are a particularly higher risk period [8].

Many factors account for this increased risk including hypertensive disorders of pregnancy, hypercoagulability, vascular and connective tissue changes, and hemodynamic changes. Hypertensive disorders of pregnancy, particularly preeclampsia, are likely the most important contributors to both hemorrhagic and ischemic pregnancy-associated stroke [9] and are discussed in detail below. Briefly, preeclampsia is a systemic endotheliopathy which is associated with endothelial dysfunction in the brain and blood-brain barrier breakdown, predisposing women not only to stroke but also to reversible cerebral vasoconstriction syndrome (RCVS) and posterior reversible encephalopathy syndrome (PRES). RCVS and PRES both cause neurological symptoms and can lead to ischemic or hemorrhagic stroke.

Pregnancy and the early postpartum period are a time of hypercoagulability, with a four- to ten-fold increased risk of thrombosis [10], thought to be an adaptive mechanism to assist with postpartum hemostasis. Pregnant women have increased levels of many procoagulant factors including factors V, VII, IX, X, XII, and XIII as well as the von Willebrand factor. Plasminogen activator inhibitors 1 and 2 also increase, leading to the downregulation of fibrinolysis. Lastly, within the third trimester and early postpartum period, protein C resistance occurs and levels of protein S and antithrombin III decrease, effectively decreasing intrinsic anticoagulation [10].

Notably, the time period women are at highest risk of hypertensive disorders of pregnancy and are most hypercoagulable (third trimester into early postpartum period) corresponds to the time at which women are at the highest risk of pregnancy-associated stroke.

Pregnant women experience large systemic hemodynamic changes in order to support pregnancy. These changes include an increase in plasma volume, mild hemodilutional anemia, and increases in heart rate and cardiac output [11]. These changes serve to make pregnancy a high-volume, low-resistance state and can result in venous stasis and pooling. These are risk factors for venous thrombosis and can lead to thromboembolic stroke and cerebral venous sinus thrombosis. These changes can also promote peripartum cardiomyopathy [12, 13], placing patients at risk for cardioembolic ischemic stroke.

In order to accommodate large increases in plasma volume associated with pregnancy, blood vessels become more distensible throughout the body with decreased vascular tone and increased vascular compliance [14]. These changes lead to substantial increases in blood flow into many organs including a 10-fold increase in uterine blood flow. It remains unknown whether baseline cerebral perfusion pressure and blood flow increase during pregnancy and to what degree, with many conflicting studies in both humans and animals [15–19]. One mechanism by which cerebral parenchymal arterioles may adapt to increases in cerebral perfusion is outward hypotrophic remodeling with thinning of the vessel wall and increases in luminal diameter [20], potentially making vessels more prone to rupture and hemorrhagic stroke.

This review will address the major cerebrovascular disorders which occur in pregnancy. Risk factors as well as preventative and management strategies for each of these types of vascular events are discussed further below.

Hypertensive disorders of pregnancy

Hypertensive disorders of pregnancy (HDP) place patients at higher of risk pregnancy-associated stroke: pregnant women with HDP are 5.2 times more likely to have a pregnancy-associated stroke than those without HDP [9]. Rates of HDP are increasing in the USA, with data suggesting that this is leading to increasing rates of pregnancy-associated stroke. A recent cross-sectional study examining 81,983,216 pregnancy hospitalizations in the USA reported that rates of pregnancy-associated

stroke increased by 61.5% between 1994 and 1995 and 2010–2011 with a disproportionate increase in strokes related to HDP [9]. Kuklina et al. additionally found an increased rate of pregnancy-associated stroke between 1994 and 1995 and 2006 and 2007, with increases in the prevalence of HDP and heart disease (including heart failure, coronary atherosclerosis, valvular disease, conduction disorders, and other disorders) nearly fully accounting for these increased rates [21].

HDP includes all instances of hypertension in pregnancy and can be classified as either hypertension present prior to the pregnancy or in the first 20 weeks of gestation vs. hypertension which develops after 20 weeks of gestation ("de novo hypertension"). De novo hypertension includes gestational hypertension (either sustained or transient) and preeclampsia (with or without the presence of chronic hypertension). In addition to being related to higher rates of pregnancy-associated stroke, HDP also places patients at higher risk for stroke and other cardiovascular diseases later in life, with up to an 80% risk of future stroke in women with a history of preeclampsia [22, 23]. HDP leads to the loss of premenopausal cardiovascular advantage, with cardiovascular disease occurring approximately a decade earlier than the average for patients who did not suffer from HDP.

Preeclampsia

Approximately 20% of patients with gestational hypertension will develop preeclampsia [24]. Preeclampsia is a multiorgan system disorder of endothelial function, which can lead to both systemic and central nervous system damage. Preeclampsia is defined by the presence of hypertension (blood pressure > 140/90 mmHg) and evidence of end-organ damage including proteinuria, renal insufficiency, impaired liver function, pulmonary edema, thrombocytopenia, or neurological or visual changes [25]. Preeclampsia with seizures is termed eclampsia.

Preeclampsia is a significant risk factor for stroke and is present in 21–47% of pregnancy-associated strokes [26], with a particularly strong association with hemorrhagic stroke [27]. A recent study demonstrated that patients with preeclampsia who are at highest risk of stroke include those with chronic hypertension, peripartum infections, coagulopathies, and pre-existent prothrombotic conditions [28].

While the mechanisms of preeclampsia are still not fully understood, preeclampsia is thought to result from incomplete remodeling of the uterine spiral arteries leading to shallow placentation and placental ischemia [29]. This placental dysfunction leads to the release of "placental factors" into the maternal circulation which include antiangiogenic and inflammatory factors [30, 31]. One of the major elements of cerebral endothelial dysfunction in preeclampsia is blood-brain barrier breakdown, contributing to the pathogenesis of both cerebral edema and hemorrhage [15, 19, 20, 32, 33]. Additionally, cerebral autoregulation may be impaired in preeclamptic patients [17, 18], predisposing women to both cerebral ischemia and hemorrhage with blood pressure fluctuations; however, this remains controversial [19, 34].

Management strategies to mitigate risk of stroke in HDP

The United States Preventive Services Task Force (USPTSTF) currently recommends the use of low-dose aspirin (81 mg/d) after 12 weeks gestation in women at high risk of preeclampsia to help prevent progression to

preeclampsia [35••]. This guideline is supported by a recent double-blinded study of 1776 women at high risk of preeclampsia which demonstrated that daily aspirin 150 mg from gestational weeks 11 to 14 until 36 weeks decreased rates of preeclampsia at delivery [36]. This study selected women at high risk for preeclampsia using an algorithm considering maternal demographic characteristics including medical and obstetric history, mean arterial blood pressure, uterine-artery pulsatility index, and maternal serum pregnancy-associated plasma protein A and placental growth factor [36].

Patients with blood pressures > 160/110 mmHg should be closely monitored and treated urgently with intravenous blood pressure medications (e.g., labetalol and hydralazine). However, tighter BP control during pregnancy may be associated with intrauterine growth restriction [37], and in women with mild chronic hypertension, there is no persuasive evidence to date that treatment improves pregnancy outcomes [38]. The exception is in patients with diabetes and renal disease, in whom blood pressure should be maintained at 120–160/80–105 mmHg throughout the pregnancy.

Hemorrhagic stroke

The relative risk of hemorrhagic stroke in pregnant women is 2.5 times than that of non-pregnant women and reaches up to 28.5 times than that of non-pregnant women in the early postpartum period [39]. HDP, as discussed above, are the major risk factors for pregnancy-associated intracerebral hemorrhage. In addition to HDP, patients with preexisting cerebral aneurysms and arteriovenous malformations (AVM) are at higher risk of intracerebral hemorrhage during pregnancy. Most aneurysmal ruptures tend to occur in the 3rd trimester or in the puerperium, with risk peaking at 30–34 weeks gestation [26]. AVMs may be at higher hemorrhage risk during pregnancy, particularly at the time of delivery [40, 41].

Management considerations

In cases of intracerebral hemorrhage in pregnancy, decreasing systolic blood pressures to at least < 160 mmHg in the acute setting may help to limit hematoma expansion; however, particular care should be taken in pregnancy to avoid hypotension which can lead to placental hypoperfusion and fetal hypoxia [42].

In cases of preexisting or incidentally discovered intracerebral aneurysms, women with stable and asymptomatic aneurysms should not be treated unless otherwise indicated. However, aneurysms at significant risk of rupture should be treated prior to the pregnancy if possible. In cases of aneurysmal rupture during pregnancy, priority should be placed on securing the aneurysm either by endovascular coiling or clipping.

Known AVMs should be operated on prior to pregnancy if possible in order to decrease risk of hemorrhage. If an AVM is incidentally found during pregnancy (with no hemorrhage), it can be managed conservatively throughout the pregnancy with a plan for definitive treatment after delivery. However, if an AVM is found to have bled during pregnancy, it is at significantly higher risk for rebleeding and immediate

management should be considered. As for other patient populations, low-grade AVMs can be treated immediately, but higher-grade lesions may need to be treated in a delayed fashion [41].

Ischemic stroke

Pregnancy is also associated with an increased risk of ischemic stroke. Presenting symptoms of pregnancy-associated stroke echo those of non-pregnancy-associated ischemic stroke with acute onset focal neurological deficits including aphasia, dysarthria, numbness, weakness, and changes in vision. Recent data suggest that management of acute ischemic strokes in pregnancy should not differ from non-pregnant patients and include both thrombolysis and endovascular thrombectomy, as appropriate.

Acute ischemic stroke management

i. Imaging considerations

When a patient presents with focal neurological symptoms concerning for an acute stroke, the first step in management is a non-contrast CT scan of the head to assess for potential intracerebral hemorrhage. This imaging modality should also be used with pregnant women, with shielding of the fetus. If there is concern for a large vessel occlusion, CT angiograms can also be performed safely in pregnant women, with shielding of the fetus and intravenous hydration to help with clearance of contrast. While iodinated contrast agents (CT contrast agents) do cross the placenta, they are thought to be safer than gadolinium-based contrast agents (MR contrast agents) as gadolinium can accumulate in the amniotic fluid and deposit in fetal tissue. MR contrast agents should be avoided in pregnancy; however, non-contrast enhanced MRI is a safe imaging modality in pregnancy. Note: if pregnant women present outside of the acute stroke window, MRI is the preferred imaging modality and MR time-of-flight imaging, which does not require contrast, can be used for vessel imaging.

ii. Treatment

The mainstay of acute ischemic stroke management is the administration of tissue plasminogen activator (tPA). While tPA is approved for use in pregnancy and does not cross the placenta, many providers have been cautious with its use in pregnancy given concerns for maternal and fetal hemorrhage. A recent study utilizing US Stroke Registry-Get With The Guidelines data examined tPA use in pregnancy-associated stroke and demonstrated that outcomes and complications were not significantly different between pregnancy-associated stroke and non-pregnancy-associated stroke, although there was a trend toward increased rates of hemorrhagic transformation in pregnancy-associated stroke [3••]. Additionally, numerous recent case reports and reviews have supported the use of tPA in pregnancy [43–48].

While endovascular thrombectomy has recently revolutionized acute stroke management for patients with large vessel occlusions with dramatic improvements in outcomes [49–53], pregnant women were not included in any of the initial trials of endovascular thrombectomy, limiting evidence for its use in pregnancy. While further studies are needed, recent case reports have

demonstrated successful use of endovascular thrombectomy in pregnant women [54–57], and it should be considered in this patient population. Similar to CT imaging, care should be taken to shield the fetus and intravenous hydration should be used to help with contrast clearance.

Secondary ischemic stroke prevention

If anticoagulation is indicated for secondary stroke prevention (i.e., atrial fibrillation or hypercoagulability disorder is thought to be the etiology of a patient's prior stroke), heparins are the preferred agent in pregnant women, including both low-molecular-weight heparin (LMWH) and unfractionated heparin, as heparin does not cross the placenta. Warfarin should be avoided in pregnancy, as it is a known teratogen. There has not yet been a safety study for the use of direct-acting oral anticoagulants in pregnancy.

For non-thromboembolic stroke secondary prevention, antiplatelet agents are the standard of care. Aspirin is the only agent which has been extensively studied in pregnancy. Aspirin has been shown through numerous studies to be safe in the 2nd and 3rd trimesters; however, its potential teratogenicity in the 1st trimester remains controversial. A recent meta-analysis demonstrated a possible 2-fold increased risk of gastroschisis when given during the 1st trimester [58]. Therefore, in women with a strong indication for antiplatelet secondary stroke prevention, heparins can be considered in the first trimester as an alternative to aspirin [59].

While statins are typically used for secondary stroke prevention, they are currently FDA category X in pregnancy and are contraindicated in pregnancy. A recent review examined current evidence for teratogenicity of statins and determined that there is insufficient data at this time to assess the safety profile of statins in pregnancy [60].

PRES and RCVS

PRES and RCVS occur at increased rates during pregnancy and the pathophysiology of each is likely closely related to endothelial dysfunction, such as that observed in preeclampsia. These are associated conditions that frequently coexist but have distinct clinical and imaging presentations. Both of these disorders can lead to ischemic and hemorrhagic strokes.

PRES (posterior reversible encephalopathy syndrome) is defined by the presence of cerebral edema and encephalopathy, often associated with hypertension. Patients typically present with headache, confusion, visual changes (as edema most commonly occurs in the occipital lobes), and/or seizures. There is significant overlap between PRES and preeclampsia/eclampsia with recent studies demonstrating that 92–98% of patients with eclampsia have cerebral edema on imaging consistent with a diagnosis of PRES [61, 62], suggesting significant overlap in the pathophysiological mechanisms underlying seizures in PRES and eclampsia.

RCVS (reversible cerebral vasoconstriction syndrome) is characterized by diffuse, segmental cerebral vasoconstriction that can be complicated by both subarachnoid hemorrhage and ischemia. When associated with pregnancy, RCVS is often referred to as postpartum cerebral angiopathy and may have a

poorer prognosis than non-pregnancy associated RCVS [63, 64]. It typically presents with a "thunderclap" headache, described as acute onset, "worst headache of life", and sometimes focal neurological deficits.

Management

PRES is managed primarily with blood pressure control, with recommendations to decrease blood pressures by 25% every 24 h with an eventual goal of achieving normotension. If present, seizures should be treated with antiepileptics.

RCVS should be managed symptomatically with headache treatment, and avoidance of known triggers, including Valsalva maneuvers, in the acute period.

Cerebral venous sinus thrombosis

As discussed above, pregnancy is a state of both venous stasis and hypercoagulability, predisposing women to venous thrombosis throughout the body including deep vein thrombosis, pulmonary embolus, and cerebral venous sinus thrombosis (CVST). In fact, up to 20% of CVST in women occurs in pregnancy and the early postpartum period [65]. The main presenting symptoms of CVST are headache, seizure, and focal neurological signs, symptoms which overlap with many other pregnancy-associated pathologies including preeclampsia/eclampsia and post-epidural low-pressure headaches, which can lead to delays in diagnosis [66]. CVST can be diagnosed by CT venogram or susceptibility-weighted MRI images. MR venograms can also be used to diagnose CVST; however, they require gadolinium contrast so they cannot be performed in pregnancy but can be used in the early postpartum period.

Treatment

CVST should be treated with therapeutic anticoagulation; heparins are the preferred agent during pregnancy as discussed above. Patients should be anticoagulated throughout the pregnancy and for at least 6 weeks postpartum, with a minimal total duration of anticoagulation of 3 months. After delivery, women may be transitioned from heparins to warfarin (safe in breastfeeding), but direct-acting oral anticoagulants should be avoided in breastfeeding women as their safety profile has not yet been studied.

Cardiovascular disorders which predispose patients to pregnancy-associated stroke

Peripartum cardiomyopathy

Peripartum cardiomyopathy is defined by left ventricular systolic dysfunction which occurs either during pregnancy or in the early postpartum period. Affected patients have a reduced left ventricular ejection fraction (EF) (typically < 45%) and cardiac remodeling can lead to dilatation of the heart chambers, in some cases leading to atrial fibrillation. Both low ejection fraction and atrial fibrillation place patients at risk for cardioembolic stroke; women with an EF < 30% or atrial fibrillation should be placed on anticoagulation during pregnancy

and in the postpartum period [12]. In some patients peripartum cardiomyopathy is associated with significant morbidity and mortality; in other patients, peripartum cardiomyopathy resolves within 6 months postpartum [13], which may allow for cessation of anticoagulation.

Patent foramen ovale

Patent foramen ovale (PFO) place patients at risk for ischemic stroke secondary to "paradoxical embolus," i.e., venous clots entering the arterial circulation leading to stroke. Given the higher rates of venous thrombosis in pregnancy, PFOs may add to the risk of ischemic stroke in this population. A recent review article reported that PFO-associated strokes primarily occur in the first and second trimesters of pregnancy [67], differing from other pregnancy-associated strokes. In pregnant women who have an ischemic pregnancy-associated stroke and are found to have a PFO, anticoagulation is recommended for the duration of the pregnancy and into the postpartum period. Further studies are needed to determine whether these women should undergo PFO closure and, if so, the ideal timing of this closure. Additional research is also necessary to establish management strategies for women with known PFOs planning a pregnancy. The current recommended practice is to risk-stratify patients with known PFOs for likelihood of hypercoagulability and then have a multidisciplinary discussion regarding risks and benefits of anticoagulation.

Congenital heart disease

Patients with congenital heart disease are at higher risk of stroke and pregnancy compounds this risk. In particular, patients who have undergone the Fontan procedure are at a high risk of thromboembolic events at baseline, and it remains unclear whether these patients should be placed on therapeutic anticoagulation for the duration of pregnancy and the postpartum period. One recent retrospective study examined rates of thromboembolism and hemorrhagic complications in pregnant women with a history of a Fontan procedure on either prophylactic or therapeutic heparin, observing increased rates of thromboembolic events in patients without anticoagulation but also both maternal and fetal complications in patients receiving anticoagulation. The authors concluded that patients with low thromboembolic risk should be on prophylactic heparin, while patients with higher thromboembolic risk should be on therapeutic heparin both antepartum and in the early postpartum period [68].

Cervical artery dissection

One of the most common etiologies of stroke in younger patients is cervical artery dissection. Up to 6% of cervical artery dissections in women < 50 years old occur in the postpartum period, possibly related to either the stress of vaginal delivery and/or peripartum angiopathies as discussed above [69]. A recent observational study examined whether women with prior cervical artery dissection (without known connective tissue disease) were at risk for recurrence in the setting of pregnancy (and vaginal delivery): the authors found no increased risk in women > 1 year from their dissections [70]. Cervical artery dissections should be

treated for at least 3 months with antiplatelet therapy, with repeat imaging in approximately 3 months to ensure resolution of the dissection. While the use of anticoagulation vs antiplatelet agents in the immediate post-dissection period has been controversial, recent data suggests no benefit of anticoagulation over antiplatelet therapy [71]. This study was performed in non-pregnant patients, and further work is needed to determine if anticoagulation may be more beneficial than antiplatelet therapy in pregnant or early postpartum women with cervical artery dissection.

Delivery considerations

In women who experience a pregnancy-associated stroke, timing of delivery should be determined on a case-by-case basis depending on both maternal and fetal stability. If both are stable, current recommendations are to plan delivery at ~ 39 weeks gestation and there is no contraindication to vaginal delivery [72].

In general, caesarian sections should be avoided in this patient population as it remains a question of whether caesarian delivery is an independent risk factor for stroke [73]. Caesarian section is recommended for patients with incompletely treated AVMs or unsecured ruptured cerebral aneurysms, and those who have undergone neurosurgery within the 7 days prior to delivery.

Conclusions

Pregnant and early postpartum women are at an increased risk of both hemorrhagic and ischemic stroke, with hypertensive disorders of pregnancy being a particularly important contributing factor. Cerebrovascular conditions such as RCVS and PRES are also more prevalent in this patient population, likely secondary to endothelial dysfunction as is observed in preeclampsia.

Management strategies for these conditions are similar between pregnant and non-pregnant patients with a few caveats as discussed above. Importantly, recent data supports the use of reperfusion therapies including tPA and endovascular thrombectomy for acute ischemic stroke management in pregnant patients.

Compliance with Ethical Standards

Conflict of Interest
The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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