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Ischemic stroke and cerebral venous sinus thrombosis in pregnancy

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Abstract

Maternal ischemic stroke and cerebral venous sinus thrombosis (CVST) are dreaded complications of pregnancy and major contributors to maternal disability and mortality. This chapter summarizes the incidence and risk factors for maternal arterial ischemic stroke (AIS) and CVST and discusses the pathophysiology of maternal AIS and CVST. The diagnosis, treatment, and secondary preventive strategies for maternal stroke are also reviewed. Special populations at high risk of maternal stroke, including women with moyamoya disease, sickle cell disease, HIV, thrombophilia, and genetic cerebrovascular disorders, are highlighted.

INTRODUCTION

Maternal stroke, defined as stroke occurring during pregnancy or the postpartum period, is increasingly recognized as a major cause of maternal morbidity and mortality. While differing definitions of “stroke” have hampered epidemiologic estimates of its incidence, most studies point to an increasing incidence of maternal strokes of all types (Kuklina et al., 2011; Liu et al., 2019a). Pregnancy-related physiologic changes raise the risk of thromboembolic events, including arterial ischemic stroke (AIS) and cerebral venous sinus thrombosis (CVST). Modern medicine has paved the way for women with increasingly complex medical issues to successfully become pregnant; however, pregnancy constitutes a stress test for the maternal cardio- and cerebrovascular system, and hypertension, underlying cardiac disease, or hematologic disorders in women have increased risk of complications, including AIS and CVST, during pregnancy and postpartum. In addition, the increasing incidence of pregnancy-induced hypertensive disorders contributes to maternal stroke risk.

Acute stroke treatment has made great strides over the last decade, and life- and function-preserving treatments are now available to additional patients (Albers et al., 2018; Nogueira et al., 2018; Thomalla et al., 2018; Ma et al., 2019). However, pregnant women have been excluded from randomized trials, and acute stroke treatment is generally off-label for this population. Nevertheless, pregnant and postpartum women may benefit enormously from

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acute stroke treatments and secondary prevention strategies used in other populations (Powers et al., 2018).

This chapter reviews the epidemiology, risk factors, and pathophysiology of maternal AIS and CVST, and discusses pregnancy in special populations who have baseline increased risk of stroke, including women with moyamoya disease, sickle cell disease (SCD), HIV, thrombophilia, and genetic cerebrovascular disorders. Lastly, we review current recommendations for diagnosis, treatment, and secondary prevention of AIS and CVST in pregnancy and postpartum.

EPIDEMIOLOGY OF MATERNAL ARTERIAL ISCHEMIC STROKE AND CEREBRAL VENOUS SINUS THROMBOSIS

Maternal stroke incidence

Stroke risk during pregnancy and the puerperium is an estimated threefold higher compared to nonpregnant women of childbearing age (Swartz et al., 2017). A recent meta-analysis found a crude incidence of stroke during pregnancy and the puerperium of 30 per 100,000 deliveries (95% confidence interval [95% CI] 18.8–49.4). Maternal strokes are approximately evenly divided between hemorrhagic, ischemic, and CVST (Swartz et al., 2017). The incidence of maternal stroke is variably reported from the low single digits (Wiebers and Whisnant, 1985) to greater than 60 per 100,000 deliveries (Jaigobin and Silver, 2000). The variability arises due to many reasons, including study era, patient demographics (i.e., community hospitals vs referral center, geographical area, socioeconomics), study definition of stroke, inclusion of various stroke subtypes, and defined length of postpartum period.

Impact

Despite the variability in reported rates, compelling data establish maternal stroke as a serious public health issue. Stroke is the most common cause of serious long-term disability following pregnancy (Treadwell et al., 2008; Sells and Feske, 2017) and is the seventh leading cause of death among pregnant women, accounting for 7.4% of pregnancy-related deaths, in the United States (Creanga et al., 2017). Mortality rates from maternal stroke ranges from 2.7% to 20.4% (Swartz et al., 2017). One United Kingdom study found a case fatality rate of 20% for ante-natal stroke and that 45% of stroke survivors remained significantly disabled (Scott et al., 2012). Epidemiologic studies in East Asia also show a high rate of maternal stroke, although hemorrhagic events are relatively more common (Jeng et al., 2004; Liang et al., 2006). Data on the global impact of maternal stroke are lacking, but the World Health Organization (WHO) found stroke was one of the 10 leading causes of death in women of reproductive age (15–44 years) in low-, middle-, and high-income countries (World Health Organization, 2008).

A significant proportion of strokes among women of childbearing age are pregnancy-related (Awada et al., 1995; Miller et al., 2016a), accounting for an estimated 12%–35% of strokes among women 15–45 years of age (Kittner et al., 1996). A French study of maternal strokes found most stroke-related deaths were unavoidable; however, diagnostic delay, diagnostic

error, and inadequate treatment contributed in some cases (Cohen and Rossignol, 2017). Another study at the University of Tennessee-Memphis documented frequent delays in diagnosis of stroke during pregnancy because of a presumption of eclampsia as the etiology of focal neurologic symptoms (Witlin et al., 1997).

Temporal trends

While evidence is mixed, available data suggest that the rate of maternal stroke is likely increasing. An early epidemiologic study in Rochester, Minnesota using 1955–1979 data reported just 3.5 strokes per 100,000 deliveries (but did not include the postpartum period) (Wiebers and Whisnant, 1985); whereas, later studies of maternal stroke in the United States consistently find much higher rates (Sharshar et al., 1995; Kittner et al., 1996; Jaigobin and Silver, 2000; Lanska and Kryscio, 2000; James et al., 2005; Ban et al., 2017; Yoshida et al., 2017; Liu et al., 2019a). A review of US hospital discharge data demonstrated increased rates of maternal stroke from 1994 to 2007, with a 47% increase in antepartum stroke and 83% increase in postpartum stroke and unchanged risk at time of delivery (Kuklina et al., 2011). A study by the Canadian Institute of Health similarly noted an increase in strokes from 2003 to 2016 (Liu et al., 2019a). However, another meta-analysis found the rate of maternal stroke unchanged from 1990 to 2017 (Swartz et al., 2017).

The possible reasons for increased incidence include both reporting and public health trends. Improved diagnostic testing, awareness of stroke, and surveillance systems may increase the number of reported cases with or without an actual increase in incidence. The increased rate of maternal stroke in the US hospital discharge data was almost entirely attributed to the increased prevalence of hypertensive disorders in pregnancy (Kuklina et al., 2011).

Timing of stroke during pregnancy and the puerperium

The risk of arterial and venous infarcts changes throughout the antepartum, peripartum, and postpartum period. While there is some variation between studies, in general, epidemiologic data show that the highest risk periods for stroke are the third trimester, time of delivery, and early postpartum periods. One study found that almost half (48%) of strokes occurred postpartum and most of the remainder (41%) occurred at the time of delivery (Rantanen and Tatlisumak, 2013), which was similar to the Nationwide Inpatient Sample, which found that 89% of strokes occurred at the time of delivery or postpartum (James et al., 2005). A review of maternal strokes at a stroke referral center in New York City found that over 70% occurred postpartum (Miller et al., 2016a). A systematic review found slightly more strokes occurred in the antepartum and delivery period, but given most studies included about 6 weeks of postpartum data vs 9 months of pregnancy, the per-day stroke risk was significantly higher in the postpartum period (Swartz et al., 2017).

Epidemiology of cerebral venous sinus thrombosis

CVST occurs when a clot forms in the cerebral venous system or dural sinuses, which may lead to venous congestion, cerebral edema, and ischemic and/or hemorrhagic stroke. Overall, 75% of CVST occur in women (Ferro et al., 2004). Known risk factors for CVST include oral contraceptives, hypercoagulability, infection, malignancy, and pregnancy (Ferro et al., 2004). Venous strokes account for a disproportionate amount of all strokes during

pregnancy (Jeng et al., 2004) with estimates ranging from 6% to 64% of all maternal strokes (Feske and Singhal, 2014). The risk of pregnancy-related CVST increases with the presence of hypertensive disorders, age, cesarean section, infections, and excessive vomiting (Lanska and Kryscio, 2000). Approximately three-quarters of pregnancy-related CVST occur in the postpartum period, with the greatest risk approximately 1–4 weeks after delivery (Jeng et al., 2004; Coutinho et al., 2009; Yoshida et al., 2017). While many epidemiologic studies of maternal stroke include only 6 weeks postpartum, the risk may be increased for 12 weeks (Kamel et al., 2014) or up to 1 year postpartum (Cheng et al., 2017).

RISK FACTORS FOR MATERNAL STROKE

Risk factors for maternal stroke include general risk factors for stroke in young adults, and unique risk factors specific to pregnancy, summarized in Table 1.1. This section reviews general risk factors first, followed by pregnancy-specific factors.

General risk factors that affect risk of maternal stroke

Age—Maternal stroke is more common in older pregnant women (Lanska and Kryscio, 2000; Katsuragi et al., 2018; Liu et al., 2019a). The absolute risk is lowest among women aged 20–34 and highest among women aged 40 and over (James et al., 2005). In a logistic regression model designed to distinguish stroke from stroke mimickers during pregnancy, age was a strong predictor of stroke (Meyer et al., 2018). Interestingly, a population-based analysis of New York State data suggested that while the absolute risk of maternal stroke increases with age, the incidence risk ratio (IRR) for pregnancy-related stroke compared to nonpregnancy-related stroke was higher in younger age groups: the IRR in women aged 18–24 was 2.2 (95% CI 1.9–2.6), and for ages 25–34 was 1.6 (95% CI 1.4–1.7), whereas in women aged 35–44 the IRR was 1.1 (95% CI 0.9–1.2). Of note, maternal strokes accounted for 18% of all strokes in women aged 18–35. However, the absolute risk of maternal stroke was more than three times higher in the oldest group (46.9 per 100,000 deliveries) compared to the youngest group (14 per 100,000 deliveries) (Miller et al., 2016b).

Race/ethnicity—Health disparities affect risk of maternal stroke. In the National Inpatient Sample from 2000 to 2001, Black women had nearly twice the risk of maternal stroke compared to Hispanic and white women (James et al., 2005). Recent data from the National Inpatient Sample showed a significant interaction between hypertensive status and race on the risk of maternal ischemic stroke: among women without hypertension, only Black women had increased risk of ischemic stroke compared to whites (adjusted RR 1.41, 95% CI 1.07–1.85). However, among women with pregnancy-induced hypertension, Black, Hispanic, and Asian/Pacific Islander women all had higher risk of ischemic stroke, with the highest risk seen in Black women (adjusted RR 2.44, 95% CI 2.00–2.97) (Zambrano et al., 2019).

Heart disease—Cardiac disease, including structural and rhythm abnormalities, is a well-known stroke risk factor. Many types of heart disease have been described as risk factors for maternal stroke. US inpatient data found an odds ratio of 13.2 (95% CI 10.2–17.0) for maternal stroke with heart disease, including congenital and acquired causes (James et al.,

2005). Congenital heart disease encompasses a diverse range of cardiac anomalies present from birth, which may predispose to stroke in children and adults. Canadian inpatient data found a greater than 35 times risk of maternal stroke in women with congenital heart disease (Liu et al., 2019a). Globally, acquired heart disease may account for a greater proportion of maternal stroke; a Taiwanese study found rheumatic heart disease present in almost half of patients with ischemic stroke and CVST in pregnancy and the puerperium (Jeng et al., 2004). Other intrinsic cardiac anomalies, including a reported case of cardiac papillary fibroelastoma, may lead to maternal stroke (Binhas et al., 2019).

Patent foramen ovale (PFO)—A PFO occurs when the fetal connection between the cardiac atria fails to fuse after birth. About a quarter of all adults have a PFO, according to autopsy studies (Hagen et al., 1984). When present, blood can shunt from the right atrium to the left atrium, particularly during Valsalva maneuvers, and may lead to ischemic stroke via paradoxical emboli. Pregnancy and the puerperium are associated with high risk of venous thromboembolism and therefore, unsurprisingly, maternal stroke may result from paradoxical emboli (Daehnert et al., 2001; Giberti et al., 2005; Miller et al., 2015; Chen et al., 2016). Additionally, straining during labor may predispose to paradoxical embolization. In a review of reported cases of PFO-related strokes during pregnancy, key factors included high-risk PFO morphology (atrial septal aneurysm), larger right-to-left shunt, multiple gestation, and concurrent hypercoagulability (Chen et al., 2016).

The risk of paradoxical embolism score can help clinicians assess whether cryptogenic strokes are likely to be the result of a PFO vs an alternative etiology by assessing the presence of traditional risk factors for stroke (hypertension, diabetes, smoking, prior transient ischemic attack (TIA)/strokes, and age) and imaging characteristics (Kent et al., 2013). One study comparing maternal stroke due to PFO vs alternative etiologies found that women with PFO-related strokes were statistically more likely to have hypercoagulable state, migraine with aura, and iliac vein compression syndrome (May–Thurners syndrome) (Chen et al., 2016). Clinical equipoise persists regarding PFO closure, but several randomized clinical trials guide recommendations (Furlan et al., 2012; Carroll et al., 2013; Mas et al., 2017; Søndergaard et al., 2017) and suggest that closure, in cases of large interatrial shunts or associated atrial septal aneurysms, may reduce risk of recurrent stroke vs antiplatelet therapy alone. Medical management (including antiplatelet and/or anticoagulation) and surgical closure for women with PFO-related maternal stroke requires consideration of her medical history and PFO characteristics. Whether women with a known PFO and no history of thromboembolic events should be treated prophylactically during pregnancy with antiplatelet or anticoagulation has not been studied.

Tobacco and other drug use—The WHO recommends all healthcare providers screen pregnant women for tobacco use. In the United States, more than 7% of women self-report smoking during pregnancy (Drake et al., 2018). Internationally, tobacco use during pregnancy varies from <1% to as high as 18% and secondhand smoking exposure is often much higher (Bloch et al., 2008). In a Swedish cohort, the relative risk for maternal stroke in smokers was 2.4 times (95% CI 1.9–3.0) that of nonsmokers (Ros et al., 2002). In a hospital database in the United States, pregnant smokers were also found to have much greater risk

of stroke, odds ratio 1.7 (95% CI 1.2–2.5) (Roelands et al., 2009). In addition to the association between tobacco use and maternal stroke, pregnancy may be a “teachable moment” to help women, and potentially their partners, quit smoking early in life to help reduce lifetime stroke risk.

The impact of illicit drugs on maternal stroke is not well studied. A review of hospital discharges for pregnant women in the United States from 2002 to 2014 found an alarming 300% increase in opioid use over the period, while amphetamine use remained stable and cocaine use declined, reflecting trends in the general population (Salihu et al., 2018). While the study did not examine strokes, acute cardiac events increased with opioid use. A case report documents the use of thrombolysis for a left posterior cerebral artery ischemic stroke in a 33-year-old pregnant woman with known tobacco, cocaine, cannabis, heroin, and amphetamine use (Khan et al., 2017).

Infection—Infections contribute to stroke risk, including during pregnancy. A case–control study of inpatient data in California, Florida, and New York found a statistically significant 1.74 times (95% CI 1.29–2.35) peripartum stroke risk for women with an infection at the time of admission for delivery compared to uninfected women. Stroke risk was highest in sepsis and with genitourinary infections, and the relationship persisted after controlling for vascular risk factors, including hypertensive disorders of pregnancy (Miller et al., 2018). Among women with preeclampsia, presence of an infection at the time of admission triples the risk of maternal stroke, according to inpatient data from the state of New York (Miller et al., 2017). A review of nationwide inpatient data similarly found postpartum infection increased maternal stroke risk (James et al., 2005). A more recent study using data from the US Nationwide Readmissions Database found that women with infections had higher risk of readmission for postpartum ischemic stroke (adjusted risk ratio [RR] 1.75, 95% CI 1.37–2.22) but not for postpartum hemorrhagic stroke (adjusted RR 0.96, 95% CI 0.75–1.23) (Miller et al., 2019a). Case reports also document instances of maternal stroke attributable to reactivation of varicella zoster virus (McNamara et al., 2016) and meningovascular syphilis (Bowring et al., 2008). CVST in pregnancy is also highly associated with infection (Lanska and Kryscio, 2000). Efforts for prevention, earlier/increased detection, and appropriate treatment of infections at the time of labor and delivery may potentially reduce maternal strokes.

Migraine—Migraines are highly prevalent in women of childbearing age (Lipton et al., 2007). While many women may have a decrease in migraine frequency and/or severity during pregnancy, a migraine history is a well-established risk factor for maternal stroke (James et al., 2005; Scott et al., 2012; Feske and Singhal, 2014). In a review of national US inpatient data, migraine had the highest association with maternal stroke with an odds ratio of 16.9 (95% CI 9.7–29.5) (James et al., 2005). However, the diagnosis of stroke is not standardized nationally, and the association may be confounded to some degree by complex migraines and migraine auras being misdiagnosed as TIA or stroke. Nonetheless, preconception counseling for female migraineurs should aim to minimize other stroke risk factors, particularly smoking and elevated blood pressure.

While a discussion of migraine management in pregnancy is reviewed elsewhere in this collection, clinicians should note that many preventive and abortive headache medications, particularly vasoactive agents, may have adverse fetal drug effects. Vasoconstrictive medications should be avoided in women with a history of cerebrovascular disease. In addition, new-onset headaches in pregnancy or postpartum should prompt consideration of a broad differential diagnosis, including preeclampsia, ischemic or hemorrhagic stroke, and CVST, in addition to migraine and other primary headache disorders.

Intimate partner violence—While literature review did not identify any reported cases during pregnancy, strangulation is a reported etiology of cervical artery dissection (Malek et al., 2000). Intimate partner violence is more prevalent during pregnancy, including physical abuse, and all women should be screened (Bailey and Daugherty, 2007).

Maternal stroke risk factors specific to pregnancy

Hypertensive disorders of pregnancy—Hypertensive disorders of pregnancy, including chronic hypertension, gestational hypertension, preeclampsia, and eclampsia, are well-established risk factors for maternal stroke (Sharshar et al., 1995; Scott et al., 2012; Liu et al., 2019a). The disorders are classified based on the degree of blood pressure elevation and the presence of systemic involvement. Gestational hypertension is the development of new-onset elevated blood pressure after 20 weeks of gestation in the absence of other systemic manifestations and is classified as severe if systolic blood pressure is persistently over 160 mmHg or diastolic over 110 mmHg, or both, according to the American College of Obstetricians and Gynecologists (American College of Obstetricians and Gynecologists and Task Force on Hypertension in Pregnancy, 2013). A study of inpatient data from 1994 to 2011 in the United States found that women with hypertensive disorders of pregnancy were 5.2 times more likely (95% CI 4.9–5.6) to have a stroke (hemorrhagic or ischemic) than those without (Leffert et al., 2015). Many other studies have also identified hypertension as a risk factor for maternal stroke (Cheng et al., 2017; Yoshida et al., 2017; Katsuragi et al., 2018; Lappin et al., 2018; Liu et al., 2019a). Chronic hypertension, too, has been shown to increase the risk of maternal stroke (Too et al., 2018) and augments stroke risk in women with preeclampsia, although the level of blood pressure used to define chronic hypertension cannot be determined from administrative data (Miller et al., 2017). Among women with preeclampsia, those who suffer a stroke are more likely to have severe preeclampsia or eclampsia and to have coexisting prothrombotic states, coagulopathies, infections, and/or chronic hypertension (Miller et al., 2017).

Hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome is a severe variant of preeclampsia. Neurologic complications in HELLP syndrome are common and may include posterior reversible encephalopathy syndrome, subarachnoid hemorrhage, and hemorrhagic and ischemic stroke (Paul et al., 2013). In a study of maternal death due to stroke in Japan, more than half of the cases of stroke related to hypertensive disorders of pregnancy were complicated by HELLP syndrome (Hasegawa et al., 2015).

Hypertensive disorders of pregnancy can begin in the postpartum period. A retrospective study of readmissions for stroke within 60 days of delivery discharge found women with

chronic hypertension and hypertensive diseases of pregnancy are at higher risk of postpartum stroke; most occur within 10 days of discharge (Too et al., 2018).

In addition, hypertensive disorders of pregnancy may predict future cardiovascular disease, including stroke. Gestational hypertension and preeclampsia are associated with increased incidence of future renal, cardiovascular, and cerebrovascular disease even after adjusting for common vascular risk factors, suggesting they are independent predictors of overall vascular health (Schokker et al., 2015; Wu et al., 2017). In the California Teachers Study, women with a history of hypertensive disorders of pregnancy were at 1.3 times greater risk (95% CI 1.2—1.4) of stroke later in life (Miller et al., 2019b).

Gestational diabetes—Limited data suggest gestational diabetes mellitus may be associated with increased maternal stroke risk: a case–control study found a more than 20-fold increase in stroke risk in women with gestational diabetes, but small numbers precluded precise estimates (Scott et al., 2012). Administrative data from Canada showed a crude odds ratio of 1.7 (95% CI 1.2–2.3) for maternal stroke in women with gestational diabetes, but the association was no longer significant after adjustment for other risk factors (Liu et al., 2019b). In addition, gestational diabetes mellitus is a risk factor for developing cardiovascular and cerebrovascular disease later in life after controlling for subsequent nongestational diabetes and other traditional vascular risk factors (Fadl et al., 2014).

Cesarean section—Higher rates of postpartum stroke may occur in women who deliver via cesarean section vs vaginal delivery (Lanska and Kryscio, 2000; Lin et al., 2008). One Taiwanese study found a 1.49 times risk (95% CI 1.27–1.76) of stroke within 12 months of delivery via cesarean section (Lin et al., 2008). However, delineating an increased stroke risk from the underlying indication for the cesarean section and an increased risk from the procedure is difficult. Notably, in the Taiwanese study, the elevated stroke risk did not persist when the cesarean was “maternally requested” and the association was largely driven by cesarean deliveries for preeclampsia/eclampsia. One hypothesis regarding the association between cesarean section and maternal stroke is that women who have cesarean sections may have a priori health conditions predisposing to stroke; however, the procedure itself may also predispose to arterial and venous stroke through greater blood loss and hypotension, inflammatory or infectious sequela of the procedure, and increased length of inactivity and venous stasis postoperatively.

Peripartum cardiomyopathy—Peripartum cardiomyopathy, left ventricular dysfunction in the last month of pregnancy or within 5 months postpartum in women without preexisting cardiac disease or alternative etiology, is another possible cause of maternal cardioembolic stroke, with a few documented cases in the literature (Dyken and Biller, 1994; Lappin et al., 2018). A review from the University of Iowa found cardiomyopathy occurred about once per 8000 deliveries and there was one known postpartum stroke among five postpartum cardiomyopathy cases (Dyken and Biller, 1994).

Assisted reproductive technology (ART)—ART is an umbrella term for reproductive techniques including in vitro fertilization (IVF), artificial insemination, surrogacy, and fertility medications. IVF involves medically stimulating the ovaries to release eggs that are

then extracted and fertilized in vitro prior to returning to the uterus. Thrombosis occurs in 0.2% of IVF cycles but when IVF is complicated by ovarian hyperstimulation syndrome (OHSS), the incidence of thrombosis rises to around 10% (Kasum et al., 2014). Of the thrombotic events, most are venous, including CVST; among the arterial events, most are ischemic strokes (Alatri et al., 2011). OHSS is an iatrogenic complication of fertility treatments where the hyperstimulation of ovaries leads to high levels of human chorionic gonadotropin (hCG), overexpression of vascular endothelial growth factor and activation of the renin–angiotensin–aldosterone system, leading to hemoconcentration and hypercoagulability. A meta-analysis comparing pregnancies via ovulation induction to controls found a trend toward increased risk of ischemic stroke and TIA (pooled hazard ratio of 1.25, 95% CI 0.96–1.63) (Dayan et al., 2017). One case of successful intraarterial thrombolysis for a right proximal middle cerebral artery stroke occurring due to OHSS has been reported (Elford et al., 2002). In addition to OHSS, pregnancies conceived with ART may be at higher risk for stroke due to maternal factors such as advanced age and multiple gestation.

In addition, infertility may result from an underlying risk of vascular disease. A prospective cohort study compared successful and unsuccessful ART and found women who failed ART, over 8 years follow-up were more likely to have an adverse cardiovascular event, including stroke, regardless of the number of IVF treatment cycles (Udell et al., 2017). The results suggest that infertility may reflect an underlying predisposition to vascular disease and pregnancy can unmask this predisposition in women undergoing IVF or other forms of ART.

PATHOPHYSIOLOGY OF MATERNAL THROMBOTIC STROKE

Pregnancy is associated with several physiologic changes that increase risk of thrombotic stroke including (1) coagulation factor changes (see Fig. 1.1); (2) connective tissue changes, increasing venous compliance; (3) cardiac and hemodynamic changes; and (4) immunological and inflammatory changes, modulating endothelial cell function. Pregnancy is also associated with several rare pathophysiologic stroke mechanisms, such as postpartum angiopathy, pituitary apoplexy due to Sheehan syndrome, and metastatic choriocarcinoma.

Changes in the maternal coagulation system

During pregnancy, concentrations of coagulation factors V, VII, VIII, IX, X, XII, and von Willebrand factor rise, accompanied by an increase in fibrinogen levels up to twofold compared to prepregnancy values (Stirling et al., 1984; Brenner, 2004). Von Willebrand factor and factor VIII increase in late gestation (Stirling et al., 1984; Brenner, 2004), promoting a prothrombotic state, particularly during the third trimester and postpartum (Pomp et al., 2008).

Intrinsic anticoagulation factors are also altered during pregnancy. Protein S acts as a cofactor of protein C to inactivate Factors Va and VIIIa, preventing thrombosis. Total protein S (both active and inactive), as well as the ratio of active to inactive protein S, decreases during pregnancy (Castoldi and Hackeng, 2008). There is also evidence that resistance against protein C develops during pregnancy (Cumming et al., 1995). Similarly, activated protein C (APC) resistance can be induced via oral contraceptive or hormone replacement

therapy (Fleischer et al., 2009). Decreased sensitivity to APC is associated with preeclampsia, as well as pregnancy loss and placental abruption (De Stefano et al., 2003; Fleischer et al., 2009).

Endogenous tissue plasminogen activator (tPA) activity, produced by endothelial cells, decreases during the first trimester of pregnancy but then increases during the third trimester (Coolman et al., 2006). At 35 weeks, plasminogen activator inhibitor-1 (PAI-1) values were fivefold higher than in the 12th week of pregnancy (Lecander and Åstedt, 1986). In addition, the placenta produces a unique antifibrinolytic, PAI-2, with variable levels depending on the amount of placental tissue (Lecander and Åstedt, 1986). PAI-2 plays an important part in the vascular remodeling necessary for successful placental implantation, replacing maternal endothelial cells with trophoblast cells that have reduced capacity to lyse fibrin (Sheppard and Bonnar, 1999).

Changes in vascular compliance

Total intravascular volume is significantly higher in pregnant than in nonpregnant women (Goulart et al., 2013). Elevated estrogen levels increase venous compliance and reduce systemic vascular resistance during pregnancy (Gherman et al., 1998, 1999). Progesterone and relaxin are both elevated during pregnancy and contribute to systemic vasodilation and increased venous capacitance (Sanghavi and Rutherford, 2014). In conjunction with the overall hypervolemic state, increased vascular compliance promotes venous stasis and predisposes to formation of venous thromboses, especially when coupled with mechanical compression of the iliac veins by the gravid uterus and delivery-associated endothelial damage, completing Virchow’s triad of stasis, hypercoagulability, and endothelial damage. In addition, sex hormones may contribute to aneurysm growth or rupture; see also Chapter 2 of this volume for a detailed discussion of this.

Hemodynamic changes during pregnancy

The growing fetus puts high demands on the maternal cardiovascular system. Beginning at approximately 6 weeks’ gestation, increasing levels of estrogen stimulate renin production in the kidneys, uterus, and liver (Hsueh et al., 1982; Shufelt and Bairey Merz, 2009). Increased levels of renin stimulate aldosterone production, resulting in an increase in total body water. Concurrently, progesterone, placental chorionic somatomammotropin, and prolactin lead to increased erythropoiesis (Jepson, 1968). On average, plasma volume increases 45% but red blood cell production increases only 30%, resulting in physiologic hemodilution of pregnancy and an overall decrease in hemoglobin concentration, as low as 11–12g/dL (Pritchard, 1965; Chesley, 1972). Oral iron supplementation can decrease severity of this anemia; however, its clinical utility is unknown (Milman, 2006). Other hormones, including deoxycorticosterone, prostaglandins, prolactin, placental lactogen, growth hormone, and adrenocorticotrophic hormone, also contribute to the hypervolemic state (Duvekot and Peeters, 1994).

Prior studies have linked anemia with AIS in the general population; the odds ratio of morbidity, hospitalization, and mortality in patients with anemia is similar to those of smoking, diabetes mellitus, hypertension, and hypercholesterolemia (Spence, 2010). A

larger population-based study found, after controlling for other stroke risk factors, the adjusted odds ratio of prior iron deficiency anemia for cases with ischemic stroke was 1.45 (95% CI 1.34–1.58) compared to controls (Chang et al., 2013). Anemia may also impair stroke recovery (Chan and Ganasekaran, 2015). The mechanism by which anemia confers additional stroke risk is undetermined. One potential mechanism is that increased erythropoietin levels lead to a reactive thrombocytosis as a result of similarities between erythropoietin and thrombopoietin (Stohlawetz et al., 2000). However, how physiologic anemia of pregnancy contributes to maternal stroke risk and recovery is unknown.

Blood pressure starts to decline around the 7th week of pregnancy, reaching its nadir near the 20th week of pregnancy, before gradually rising again to prepregnancy levels by term (MacGillivray et al., 1969; Morganti et al., 1980). The decline in blood pressure is driven primarily by a decrease in systemic vascular resistance (Capeless and Clapp, 1989). Excluding hypertensive disorders of pregnancy, systolic blood pressure returns to near prepregnancy levels (Morganti et al., 1980) or up to 10mmHg higher (MacGillivray et al., 1969) by term, depending on the study.

The heart undergoes temporary remodeling during pregnancy that may predispose to formation of an intracardiac thrombus. Mild four chamber dilatation, right atrium and ventricle more so than the left-sided chambers, is a normal transthoracic echocardiographic finding in pregnancy (Bredy et al., 2018). The dilatation is thought to occur due to hypervolemia and decreased systemic vascular resistance. The cardiac structural changes increase the risk of atrial arrhythmias and right-to-left shunting (Bredy et al., 2018), which in turn increase risk of AIS due to cardioembolism, including paradoxical embolism. Although development of atrial fibrillation is uncommon in pregnancy (Butt and Latif, 2018), it may contribute to increased stroke risk in patients with preexisting heart conditions.

Immunologic and inflammatory changes

Pregnancy-related changes in inflammatory cytokine levels may contribute to increased risk of stroke, although this has not been well studied. The first trimester is characterized by a high level of proinflammatory T helper (Th)-1 activity and subsequent elevation of interleukin-6 (IL-6), C-reactive protein (CRP) and tumor necrosis factor alpha (TNFα) (Mor et al., 2011). Several large epidemiologic studies have consistently found higher circulating levels of CRP (induced by IL-6) to be associated with an increased risk of stroke. IL-6, CRP, and TNFα act on endothelial cells and acutely can induce thrombus formation (Esenwa and Elkind, 2016).

Pathophysiologic mechanisms of maternal stroke

Common mechanisms for maternal ischemic stroke include cardioembolism and paradoxical embolism; atherosclerotic causes are uncommon in this age group (Table 1.2). In addition, the following uncommon pregnancy-related conditions may result in maternal ischemic stroke.

Postpartum cerebral angiopathy—Postpartum cerebral angiopathy, sometimes referred to as Call–Fleming syndrome, is a form of the reversible cerebral vasoconstriction syndrome

(RCVS) (Call et al., 1988). RCVS most often presents as a single or recurrent thunderclap headache, commonly occurring within 1 week of delivery, and may cause ischemic stroke via vasospasm (Konstantinopoulos et al., 2004; Gupta et al., 2016). Postpartum angiopathy is more common in women with preeclampsia and HELLP, although most cases occur in women with uncomplicated pregnancy and delivery (Fugate et al., 2012). Other arteriopathies, including Takayasu arteritis, can also cause maternal ischemic stroke (Zhang et al., 2017).

Sheehan syndrome—Sheehan syndrome is pituitary infarction secondary to severe postpartum hemorrhage and may present as persistent hypotension and tachycardia despite adequate volume resuscitation, as hypoglycemia, or in lactation failure (Sheehan, 1971).

Amniotic fluid embolism—Amniotic fluid embolism is a reported cause of maternal stroke via paradoxical cerebral embolism (Sharshar et al., 1995) and may present with respiratory failure, cardiogenic shock, and disseminated intravascular coagulation.

Metastatic choriocarcinoma—Metastatic choriocarcinoma has been reported to invade cerebral vessels, leading to local thrombosis and distal tumor embolization (Saad et al., 2006). hCG levels may be included as part of a postpartum stroke work-up, as markedly elevated levels may lead to additional work-up for choriocarcinoma.

SPECIAL POPULATIONS AT RISK FOR MATERNAL STROKE

Moyamoya disease and syndrome

Moyamoya disease is a progressive, stenoocclusive cerebrovascular disease affecting the proximal arteries, particularly the internal carotid arteries, which predisposes affected individuals to ischemic and hemorrhagic strokes. Primary moyamoya disease occurs for idiopathic reasons, likely genetic, and is most common in Asian populations (Burke et al., 2009). Secondary moyamoya syndromes may occur due to trisomy 21, SCD, brain radiation, and neurofibromatosis type 1, as well as severe intracranial atherosclerotic disease. Moyamoya disease is more common in women and often presents in early adulthood. A systematic review of 54 articles related to moyamoya and pregnancy found that over 95% of women diagnosed prior to pregnancy had good outcomes (Maragkos et al., 2018). In patients who were first diagnosed during pregnancy, most were diagnosed in the second half of pregnancy and more than two-thirds presented with intracerebral hemorrhage, with a high rate of maternal and fetal morbidity and mortality. In those diagnosed with moyamoya following a postpartum stroke, the vast majority occurred within 3 days of delivery and were predominately ischemic strokes (Maragkos et al., 2018). The review concluded that moyamoya disease is not a contraindication to pregnancy if hemodynamics are properly managed. They also found no compelling evidence to perform bypass surgery prior to pregnancy or to prefer cesarean section over vaginal delivery (Maragkos et al., 2018). With regard to the mode of delivery, a Japanese-based study of maternal and fetal outcomes comparing vaginal delivery with epidural analgesia and cesarean section found no significant difference between the two groups, but the number of patients was small (Sato et al., 2015). Another retrospective study of moyamoya during pregnancy and the puerperium

suggested that frequent prior TIAs or strokes, along with imaging showing severely reduced regional blood flow, predicted a higher risk of neurologic deterioration during pregnancy. The authors suggest that surgical revascularization prior to pregnancy may be beneficial for carefully selected patients (Park et al., 2018).

Sickle cell disease (SCD)

SCD is an inherited red blood cell disorder that causes erythrocytes to become deformed (sickle) in the deoxygenated state. Patients with SCD are hypercoagulable and at risk for many vascular and thrombotic complications, including AIS and CVST. Risk factors for SCD-related stroke include prior TIA, low hemoglobin, hypertension, and acute chest syndrome (Ohene-Frempong et al., 1998). Pregnancy in women with SCD confers a high rate of both maternal and fetal morbidity, including a higher risk of preeclampsia/eclampsia, vaso-occlusive crises, acute chest syndrome, and stroke (Boga and Ozdogu, 2016). Elevated cerebral blood flow velocity on transcranial Doppler (TCD) is the best known predictor of stroke risk in young patients with SCD (Adams et al., 1992). Prophylactic red blood cell transfusion is standard of practice for stroke prevention in children with elevated TCD velocities. The role of transfusion in pregnancy is uncertain but may be beneficial (Asma et al., 2015). Hydroxyurea, which may lower TCD velocities and provide primary and secondary stroke prevention in patients with SCD, is teratogenic and should not be used during pregnancy (Ware and Helms, 2012; Ware et al., 2016). Transfusions in pregnant women are recommended for those who develop stroke, preeclampsia/eclampsia, acute chest syndrome, or significant anemia and should be considered in women with severe SCD; for women on a long-term transfusion program, transfusions should be continued during pregnancy (Boga and Ozdogu, 2016). Notably, in acute stroke management, SCD is not a contraindication to intravenous thrombolysis (Powers et al., 2018).

Human immunodeficiency virus (HIV)

HIV is a retrovirus spread via sexual contact and blood products, which causes immunosuppression and can lead to the acquired immunodeficiency syndrome (AIDS), causing hosts to be susceptible to opportunistic infections, neoplasms, and many neurologic conditions. HIV/AIDS confers an increased risk of stroke after controlling for other traditional vascular risk factors (Gutierrez et al., 2017). The etiology for increased stroke rates in HIV is likely multifactorial and includes HIV-associated vasculopathy, opportunistic infections, antiretroviral (ART) therapy side effects, and metabolic syndromes (Gutierrez et al., 2017). In terms of ART therapy, the risk of stroke is highest in the first 6 months after starting medication, which is hypothesized to be due to an inflammatory process; however, in the long term, higher CD4 counts are associated with a reduced stroke risk, suggesting that ART therapy is overall beneficial for stroke prevention among patients with HIV.

According to the WHO, over 1.5 million pregnant women have HIV globally (World Health Organization, 2014). Research specifically examining maternal stroke among women with HIV is lacking. However, a Boston-based retrospective study found increased stroke rates among HIV-infected patients with a greater relative risk of ischemic stroke in women and young patients with HIV (Chow et al., 2012). After controlling for traditional vascular and sex-specific stroke risk factors, women living with HIV had a statistically significant hazard

ratio of 1.89 (95% CI 1.28–2.81) compared to women without HIV (Chow et al., 2018). A study using transthoracic echocardiography in women with HIV at term found reduced left and right ventricular systolic function and increased ventricular dilation compared to HIV-negative controls in South Africa (Dennis et al., 2015). These data suggest that pregnant women with HIV may have increased risk of stroke, but more research is needed.

Antiphospholipid syndrome (APLS) and other rheumatologic syndromes

As many autoimmune conditions commonly present in young women, considering the impact of them on maternal stroke risk is relevant. APLS is an autoimmune disorder associated with persistent antiphospholipid antibodies (APLA) and predisposes to arterial and venous thrombosis and pregnancy morbidity, including miscarriages. A systemic review suggested that among patients with maternal stroke, 13.5% of patients had APLA positivity (Andreoli et al., 2013).

Systemic lupus erythematous (SLE) is an autoimmune condition with protean multisystemic involvement, including neuropsychiatric symptoms. In a review of national US inpatient data, women with SLE had an odds ratio of 15.2 (95% CI 7.4–31.2) for maternal stroke compared to women without SLE (James et al., 2005). Another cohort study in Sweden found that women with SLE were more likely to have worse maternal and fetal outcomes, including higher rates of preeclampsia, infection, and maternal stroke (Arkema et al., 2016).

Thrombophilias

Thrombophilias are a group of inherited or acquired hematologic disorders that predispose to abnormal coagulation and thrombosis. Canadian epidemiologic data suggest that a known thrombophilia confers a 4.2 times (95% CI 1.5–12.1) greater risk of maternal stroke (Liu et al., 2019a). In US inpatient data, thrombophilia was associated with an odds ratio of 16.0 (95% CI 9.4–27.2) for maternal stroke (James et al., 2005). A single-center study of inherited thrombophilia in pregnant women found that thrombotic events (including deep vein thrombosis, pulmonary embolism, CVST, and ischemic stroke) were 2.66 times (95% CI 0.96–7.37) as common in women with a factor V Leiden (FVL) mutation (grouping heterozygotes and homozygotes), which occurred most often in the third trimester and postpartum (Coriu et al., 2014). Several studies have reported that patients with FVL mutations are at higher risk of developing CVST (Ginsberg et al., 1989; Rizk et al., 1990). A study of venous thromboembolism during pregnancy and the puerperium (not maternal stroke) found FVL mutation homozygotes were several-fold more likely to develop thromboses than women who were heterozygotes for the FVL mutation (Zotz et al., 2003).

A meta-analysis of risk of AIS in thrombophilia found the strongest relative risk in the young female demographic, though pregnancy status was not delineated in the pooled results (Kim and Becker, 2003). Women with a family history of thrombosis were also more than twice as likely to have a thrombosis during pregnancy. Instances of maternal stroke with other hereditary thrombophilia, including homozygous type-II HBS antithrombin deficiency, have also been reported (Kovac et al., 2016).

Hypercoagulable disorders such as FVL-related thrombophilia and APLS share similar mechanisms in favoring a prothrombotic state. In people with FVL mutation, amino acid

deletion renders the cleavage site of Factor V impervious to APC activity. Similarly, APLA-positive women with a history of thromboembolism and/or repeated fetal loss have a reduced response to APC when compared with APLA-negative women (Brenner, 2004).

Genetic stroke syndromes

While genetic cerebrovascular diseases are rare causes of stroke, these patients require highly specialized care during pregnancy.

Mitochondrial disease—Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) is a rare mitochondrial disorder and only a handful of case reports address MELAS during pregnancy. The available literature documents clinical deterioration in the form of new-onset status epilepticus, neuropathy, myopathy, diabetes, pulmonary edema, and obstetrical complications (Yanagawa et al., 1998; Kovilam et al., 1999; Sikdar et al., 2007; Bell et al., 2017). Although successful deliveries are reported and sample sizes are small, women with mitochondrial disorders are believed to be at high risk for pregnancy-related complications due to the high energy demands.

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)—CADASIL, a genetic disorder due to autosomal dominant inheritance of a NOTCH3 gene mutation, leads to migraine, mood disorders, recurrent lacunar strokes, and vascular dementia. A single-center review of CADASIL during pregnancy, including 50 patients and a total of 93 pregnancies, found no ischemic strokes occurred during pregnancy (Donnini et al., 2017). However, another retrospective review including 25 women with CADASIL and 43 pregnancies found high rates of neurologic symptoms, particularly postpartum, although some may have presented with migraine with aura (Roine et al., 2005).

Fibromuscular dysplasia (FMD)—FMD is an angiopathy of medium-sized vessels, which often occurs in women of childbearing age and commonly affects the cervical arteries. A case report of a woman with FMD and history of left middle cerebral artery stroke due to internal carotid artery dissection documents a spontaneous vaginal delivery at 34 weeks gestation without maternal complications; she was maintained on low-molecular weight heparin (LMWH) and aspirin during pregnancy (Cunningham et al., 2018).

DIAGNOSIS AND MANAGEMENT OF ARTERIAL ISCHEMIC STROKE IN PREGNANCY

AIS is defined as an episode of acute neurologic dysfunction attributable to focal infarction of the brain, spinal cord, or retina in a defined arterial distribution (Sacco et al., 2013). While AIS maybe confirmed via radiologic evidence, AIS can be diagnosed clinically if neurologic symptoms can be localized to an area of the central nervous system served by a single vascular territory.

Acute management of maternal AIS

Current guidelines regarding management of maternal strokes recommend treatment very similar to that of the general population (Table 1.3). The clinician must establish time of symptom onset (or “last known well”) and obtain a history focused on exclusion criteria for intravenous thrombolysis (Table 1.4) (Powers et al., 2018). Additional pertinent history for pregnant patients includes weeks of gestation and any pregnancy complications that may increase the risk of bleeding. Early collaboration between the stroke and obstetrics teams is of critical importance.

If a focal neurologic deficit is identified (Table 1.5), brain imaging should be obtained as with any nonpregnant patient. Current guidelines aim for noncontrast computed tomography (NCCT) of the brain within 20 min of arrival to the emergency department or symptom discovery (if stroke occurs in hospital) (Powers et al., 2018).

Imaging for acute stroke

When an acute stroke is suspected, the standard of care is to obtain brain imaging within minutes of arrival at the hospital, most often with computed tomography (CT) (Powers et al., 2018). A frequent concern is radiation exposure causing harm to the developing fetus (Ratnapalan et al., 2004). Based on currently available evidence, the ionizing radiation exposure from NCCT in pregnant patients does not expose the fetus to levels of radiation that are associated with increased risks of miscarriage, malformation, or other adverse pregnancy outcomes (Tremblay et al., 2012). The growing fetus is most vulnerable to teratogens between the 8th and 15th week of gestation (Brent, 2009), during which ionizing radiation in the 50–500 milliGray (mGy) range is associated with increased risk of intellectual disability and may increase the risk of major malformations and fetal growth restriction (International Commission on Radiological Protection, 2000). The dose of radiation to the fetus from a single NCCT is just 0.01–0.001 mGy (Jain, 2019). Currently, the American College of Radiology (ACR) states that doses below 50–100 mGy do not meet the necessary threshold to induce any developmental abnormalities (American College of Radiology, 2013) and similarly, the American College of Obstetricians and Gynecologist (ACOG) states that doses below 100 mGy represent minimal risk to the fetus (Jain, 2019).

Computed tomographic angiography (CTA) of the head and neck confers approximately 2–3 times more radiation but is still well below the accepted risk threshold. Studies have shown that small doses of iodinated contrast can cross the placenta and enter fetal circulation or pass directly into amniotic fluid (Puac et al., 2017). There are theoretical concerns for neonatal hypothyroidism from contrast, based on animal studies where contrast was introduced directly into the amniotic cavity (Kodzwa, 2017; Puac et al., 2017); however, intravenous iodinated contrast has not been shown to affect neonatal thyroid activity (Bona et al., 1992). ACR and ACOG state that the risk of intravascular iodinated contrast during pregnancy is unknown (Chen et al., 2008). Despite the uncertainty, CTA head and neck with intravenous contrast is recommended for pregnant patients with suspected stroke who may be candidates for acute intervention, as the potential benefit outweighs the risk (Grear and Bushnell, 2013; Powers et al., 2018). Regarding iodinated contrast and breastfeeding, human studies found very low doses in breast milk, less than 1% of the dose given to the mother

(Kodzwa, 2017), and studies have shown no adverse effects from these doses. Current guidelines from ACOG do not recommend interrupting breastfeeding due to the administration of intravenous iodinated contrast (Jain, 2019).

In some clinical centers, magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) are obtained in lieu of CTA for evaluation of thrombectomy candidacy. MRI and MRA have the advantage of no ionizing radiation and are regarded as very safe for pregnancy (Jain, 2019). Though gadolinium is rarely needed during acute stroke management, the effects of gadolinium on human pregnancies are poorly characterized; a 2016 retrospective study of gadolinium exposure during the first trimester found an increased rate of stillbirths (Ray et al., 2016). Current guidelines from ACR and ACOG recommend against the routine use of gadolinium in pregnant patients. Thus, if perfusion-based imaging is desired for identification of potential extended-window thrombolysis or thrombectomy candidates, CTA with perfusion would be preferable to MRI/MRA with perfusion, which requires gadolinium.

In cases of suspected angiopathy or in cases of AIS due to large vessel occlusion, cerebral angiography (threading a catheter into the large vessels, injecting iodinated contrast, and using X-ray to image the cerebral vessels) may be used for diagnostic or therapeutic purposes. When maternal stroke is due to large vessel occlusion, mechanical thrombectomy (using angiography to deploy suction and/or stent retriever to remove the clot) may be an option for acute treatment. While the quantity of fetal radiation exposure from cerebral angiography is difficult to estimate, the neuro-interventionist can help limit radiation exposure to the fetus through proper positioning, abdominal shielding, and limiting fluoroscopy in proximity to the uterus (Meyers et al., 2000). While potential fetal risks from iodinated contrast, radiation, arterial puncture, and anesthesia are present, the significant potential benefit to the mother and fetus from treatment of a large vessel occlusion is felt to outweigh the theoretical exposure risk to the fetus (Ladhani et al., 2018). The risk-benefit of performing diagnostic cerebral angiography in the setting of suspected arteriopathy should be decided on a case-by-case basis. In pregnant and postpartum patients with a clinical history and imaging consistent with RCVS, cerebral angiography to exclude primary central nervous system vasculitis is not necessary (Singhal et al., 2016).

Intravenous tissue plasminogen activator (tPA)

Pregnant women were excluded from all trials of tPA use for ischemic stroke, so studies evaluating the use of tPA in the pregnant population have been limited to case reports and series. Though data are limited, the percentage of good outcomes and of complications is commensurate with those reported in the nonpregnant population, despite the fact that pregnant women given tPA had more severe strokes (Sousa Gomes et al., 2019). As of 2019, more than two dozen cases of maternal stroke treated with thrombolysis are published; cases are summarized in Table 1.6. Currently, tPA is recommended for acute stroke management in pregnant patients with disabling deficits when the benefits are felt to outweigh the risks (Tversky et al., 2016; Powers et al., 2018; Pacheco et al., 2019). Contraindications to tPA are identical to those in the nonpregnant population (Powers et al., 2018). The tPA dose is unchanged in pregnant patients (0.9 mg/kg IV, with maximum dose of 90mg, 10% as a bolus

and the remainder as a drip over 60min); however, whether prepregnancy or actual body weight is preferred is unknown (Peksa et al., 2019). Tenecteplase is a newer alternative thrombolytic for ischemic stroke with longer half-life, greater fibrin specificity, and easier administration than tPA (Burgos and Saver, 2019); no reported cases of its use in maternal stroke or other thromboses are known (Sousa Gomes et al., 2019).

Major obstetric concerns regarding use of thrombolytics are whether their use increases the risk for premature labor, placental abruption, miscarriage, peripartum uterine bleeding, postpartum hemorrhage, and fetal demise (Wiese et al., 2006; Landais et al., 2018). A review of thrombolytic use in pregnancy for thromboembolic diseases including ischemic stroke, pulmonary embolism, deep venous thrombosis, and mechanical valve thrombosis (Sousa Gomes et al., 2019) identified 141 cases and found the following rates of adverse events: 2.8% maternal mortality, 8.5% major bleeding, 9.2% mild/moderate bleeding, 6.4% miscarriage, 9.9% preterm delivery, 1.4% fetal death, and 0.7% neonatal death. tPA for acute stroke treatment in pregnant women is off-label and the risks and benefits must be thoroughly discussed with the patient and her family, with close involvement of the obstetrical team.

The safety of thrombolysis in the early postpartum period (<2 weeks following delivery) is not well established (Powers et al., 2018). One successful case of IV tPA and mechanical thrombectomy without complications at 2 weeks postpartum has been reported (Bereczki Jr et al., 2016). However, a small retrospective review of 13 cases of postpartum thrombolytic administration within 48 h of delivery (predominately for acute pulmonary embolism but one AIS included) found that bleeding complications were the norm: 92% required blood transfusion and 38% required laparotomy to control bleeding. In the review, all five cases requiring laparotomy followed cesarean deliveries. However, no maternal deaths occurred (Akazawa and Nishida, 2017).

Mechanical thrombectomy

Similar to thrombolysis, all randomized trials establishing efficacy of early endovascular intervention for large vessel arterial occlusion excluded pregnant women, so data regarding efficacy in the pregnant population is currently limited to case reports (Campbell et al., 2014; Berkhemer et al., 2015; Goyal et al., 2015, 2016; Molina et al., 2015; Saver et al., 2015). To date, 10 case reports have been published regarding use of thrombectomy in pregnant patients (Aaron et al., 2016; Bereczki Jr et al., 2016; Boyko et al., 2016; Bhogal et al., 2017; Shah et al., 2018; Zhu et al., 2018; Blythe et al., 2019; Kristiansen et al., 2019; Watanabe et al., 2019). In this small group, there was only one case of asymptomatic hemorrhage, no cases of symptomatic hemorrhage, and no reports of dissection or vasospasm. Given that the majority of pregnant patients are young, healthy, and fully functional at baseline, pregnancy is not a reason to delay or forgo mechanical thrombectomy (Ladhani et al., 2018). Obstetric anesthesiologists should be involved in guiding appropriate anesthetic use, hemodynamic monitoring, and fetal monitoring during the procedure.

There are no specific contraindications to mechanical thrombectomy in the postpartum period.

Blood pressure management

The involvement of experts in obstetrics, particularly maternal-fetal medicine, is recommended for ongoing assessment in determining blood pressure goals for the maternal-placental-fetal unit. Blood pressure goals that optimize maternal cerebral perfusion while minimizing risk of placental abruption are undetermined, and blood pressure targets must be determined on a case-by-case basis. Canadian guidelines recommend acute management of severe hypertension (SBP > 160mmHg or DBP > 110mmHg) for all pregnant women presenting with focal neurologic deficits (Ladhani et al., 2018) but neurologic exam, fetal monitoring, and other maternal comorbidities should be assessed when adjusting blood pressure parameters.

DIAGNOSIS AND MANAGEMENT OF CEREBRAL VENOUS SINUS THROMBOSIS IN PREGNANCY AND POSTPARTUM

Presentation

The most common presenting symptom of CVST is headache (90%–97% of CVST presentations in the general population and 73% in the pregnant population). During pregnancy and the puerperium, CVST can also present with obtundation (40%), motor weakness (35%), seizures (48%), and visual disturbance (27%) (de Bruijn et al., 2001; Kashkoush et al., 2017). Presentation with headache only was associated with a favorable prognosis (Kashkoush et al., 2017). Onset is often gradual; a systematic review of CSVT in pregnant patients found mean duration of symptom onset to diagnosis to be 5.9 days (95% CI 4.2–7.6) (Kashkoush et al., 2017). The diagnosis is frequently delayed because symptoms may be erroneously attributed to preeclampsia or postdural puncture headaches. Approximately 28% of cases present with a syndrome resembling benign intracranial hypertension with headache, papilledema, and visual disturbances (Villringer et al., 1994). The headache of CVST is most commonly described as diffuse and often progresses in severity over days to weeks. Case reports have described thunderclap headache as a presentation, though this is uncommon (de Bruijn et al., 1996). Most pregnancy-related CVST occurs in the third trimester or puerperium. Seven of eight cases of CVST among the 50,700 admissions for delivery in Canada occurred postpartum (Jaigobin and Silver, 2000).

Imaging and diagnostic studies

Diagnosis can be confirmed with either CT venography or MR venography (Stam, 2005). Clot involvement of the superior sagittal sinus was seen in 67% of cases involving pregnant patients, transverse/sigmoid in 64% and deep venous system in 15% of cases (Kashkoush et al., 2017). Lumbar puncture is not typically helpful in cases with focal neurologic abnormalities and radiographic confirmation of the diagnosis of CVST (Furie et al., 2011). Elevated opening pressure may help diagnose CVST in patients who present to the emergency department with headaches, and cerebrospinal fluid abnormalities can also be seen, elevated cell count (~50%) and elevated protein (~35%) (Ferro et al., 2004). Fibrin split products (D-dimer) may support the diagnosis, but if there is a strong clinical suspicion of CVST, a normal D-dimer level should not preclude further evaluation.

Management of CVST

One prospective study of CVST outcomes enrolled 624 patients, of which 77 were pregnant (Ferro et al., 2004). Subgroup analysis of pregnant patients were not included but following CVST, 79% of the total cohort had a modified Rankin Score (mRS 0–1); 10% had amRS 2–3; and 2% had a mRS 4–5. A 2017 systematic review of all published cases of CVST in pregnancy found that 91% were treated with anticoagulation, while a minority of patients were treated with thrombolysis and/or thrombectomy. Intracranial hemorrhage occurred in 4 of the 66 patients; all of them had received both anticoagulation and thrombolysis (Kashkoush et al., 2017). Importantly, CVST with associated intracranial hemorrhage should still be treated with anticoagulation (Masuhr and Einhaupl, 2008).

Unfractionated heparin is associated with teratogenicity and increased fetal bleeding (Saposnik et al., 2011). LMWH is the recommended anticoagulant during pregnancy and the puerperium (Ferro et al., 2017). European guidelines also recommend prophylactic LMWH during pregnancy for women with prior history of CVST (Ferro et al., 2017).

POSTSTROKE MANAGEMENT OF THE PREGNANT OR POSTPARTUM PATIENT

The goal of poststroke management is (1) to prevent poststroke complications and (2) to determine the etiology of stroke to guide secondary prevention. In pregnant and postpartum women, special considerations apply.

Prevention of immediate poststroke complications

Pregnant patients are at risk for the same poststroke complications as the general population, including dysphagia-related aspiration, infections, and thromboembolic events. General stroke guidelines should be followed to prevent these complications, including mechanical venous thromboembolismprophylaxis, early mobilization if there are no contraindications, dysphagia screening and evaluation, oral hygienic care, and limiting use of urinary catheters and other lines as able (Powers et al., 2018). In addition, obstetric management must also be considered poststroke. Increased fetal surveillance may be warranted depending on maternal and fetal health (Ladhani et al., 2018). We believe maternal stroke patients should be managed on a specialized stroke unit to allow close neurologic checks with close involvement of the obstetrical and/or maternal-fetal medicine team.

American Stroke Association guidelines recommend initiating an enteral diet within 7 days of admission for acute stroke in the general population and consideration of nutritional supplements for those at risk of malnourishment (Powers et al., 2018). However, as pregnant and postpartum patients have additional caloric and nutrient requirements, early involvement of a nutritionist, particularly for patients with significant dysphagia, should be considered. A lactation specialist should be consulted and should collaborate with occupational therapists, to aid with initiation of breastfeeding.

As in the general stroke population, rehabilitation should be started early, as tolerated, in the acute care hospital (Powers et al., 2018).

Diagnostic evaluation after maternal stroke

Poststroke diagnostic evaluation aims to establish the stroke mechanism to guide secondary prevention. Evaluation may include additional brain parenchyma imaging, cervical and cerebral vessel imaging, blood or cerebrospinal fluid testing, and cardiac evaluation. Of note, the serum lipid profile may be difficult to interpret during pregnancy due to physiologic elevations in both cholesterol and triglycerides (Wiznitzer et al., 2009). Cardiac evaluation may include transthoracic and/or transesophageal echocardiogram to assess for intracardiac thrombi/vegetation, valvular disease, shunting, or other structural abnormalities. Prolonged heart rhythm monitoring to assess for occult arrhythmia may be pursued for suspected cardioembolic strokes. If a PFO is identified by cardiac imaging, sources of venous thromboembolism should be investigated with Doppler ultrasound of the extremities and magnetic resonance venography of the pelvis. If no mechanism is readily identified, additional testing for an underlying hypercoagulable, autoimmune, or genetic condition should be pursued, as these conditions are associated with higher rates of maternal stroke (James et al., 2005; Andreoli et al., 2013; Liu et al., 2019a). However, testing for hypercoagulable conditions, particularly protein S, may be unreliable in the setting of pregnancy and a hematologic consultation should be considered (Faught et al., 1995).

Secondary stroke prevention after maternal ischemic stroke

Secondary prevention strategies differ depending on the mechanism of the stroke. After maternal ischemic stroke, additional considerations apply, as some medications used in nonpregnant patients have poor or unknown safety profiles in pregnancy.

Aspirin—The majority of systematic reviews of randomized controlled trials have found no increase in hemorrhagic complications associated with low-dose aspirin during pregnancy (Askie et al., 2007; LeFevre, 2014; Duley et al., 2019). ACOG guidelines currently state that low-dose aspirin (81 mg/day) use in pregnancy is considered safe and is associated with low likelihood of serious maternal or fetal complications (American College of Obstetricians and Gynecologists, 2018). In fact, prophylactic low-dose aspirin use in women at high risk for preeclampsia protects against preeclampsia and other adverse health effects (Henderson et al., 2014). During the postpartum period, while there is a theoretical risk of Reye's syndrome from breastfeeding, no confirmed reports associated with maternal low-dose aspirin use are known (Swartz et al., 2018).

Other antiplatelet agents—The safety of clopidogrel during pregnancy, with regard to both teratogenicity and bleeding risk, is unknown and data are limited to case reports (De Santis et al., 2011; Myers et al., 2011). Similarly, the teratogenicity of other adenosine diphosphate receptor inhibitors and glycoprotein IIb/IIIa inhibitors is unknown (Ismail et al., 2017).

Anticoagulation—When anticoagulation is indicated for secondary stroke prophylaxis, LMWH is generally the preferred agent during pregnancy (Swartz et al., 2018). Warfarin is potentially teratogenic and should typically be avoided, particularly during the first trimester; however, when a strong indication for warfarin exists (such as a mechanical heart valve), its use may be considered after consultation with vascular neurology, obstetrics, and

cardiology and appropriate patient counseling. The American Heart Association valvular heart disease guidelines support the use of warfarin at doses less than or equal to 5mg/day throughout pregnancy for women with mechanical heart valves and recommend substitution with LMWH during the first trimester if therapeutic levels are not reached with that dose; however, a clear multidisciplinary management plan should be in place for pregnant women with mechanical heart valves (Alshawabkeh et al., 2016). The safety of direct oral anticoagulants is unknown (Swartz et al., 2018).

Statins—Statins, a mainstay of secondary stroke prevention therapy, are generally contraindicated in pregnancy because of concern for higher rates of birth defects (Bateman et al., 2015). However, a recent systematic review found no evidence to support an association between statin use and teratogenicity, although the authors recommend avoiding statin use in the first trimester (Karalis et al., 2016). Interestingly, a small randomized phase 2 pilot study found that pravastatin use starting in the second trimester appeared safe and may reduce the risk of preeclampsia (Costantine et al., 2016). A larger phase 3 study is currently planned (Costantine et al., 2016).

STROKE RECOVERY: SPECIAL CONSIDERATIONS

Delivery considerations after stroke

Maternal stroke is not an absolute contraindication to vaginal delivery. As summarized in the Canadian Stroke guidelines, an interdisciplinary team involving vascular neurology, obstetrics, maternal-fetal medicine, obstetric anesthesiology, and neonatology, together with the patient and her family, should make decisions regarding method and timing of delivery based on maternal and fetal condition (Ladhani et al., 2018). If cesarean delivery is planned, obstetric anesthesiology guidance regarding regional vs general anesthesia and blood pressure management are required. Cesarean delivery should be considered in women with elevated intracranial pressure and at high risk of hemorrhagic conversion. If delivering vaginally, neuraxial anesthesia may be beneficial to reduce Valsalva efforts (active pushing during the second stage of labor) and sympathetic response; however, mass effect, increased intracranial pressure, or active anticoagulation may present contraindications to neuraxial anesthesia. A history of stroke makes continuous fetal monitoring during labor appropriate (Ladhani et al., 2018).

In women using antiplatelet and/or anticoagulation for secondary prevention following maternal stroke, the decision and timing for holding or adjusting agents prior to delivery, given the bleeding risk, should be decided by a multidisciplinary team that considers delivery mode, stroke mechanism and recurrence risk, obstetrical history, medical conditions, and patient preference.

Breastfeeding considerations after stroke

Decisions regarding breastfeeding after stroke should consider maternal condition and comorbidities, medicationuse, and patient preferences. While low-dose aspirin, LMWH, and warfarin are considered safe during breastfeeding, the safety of direct oral anticoagulants and other antiplatelet agents is unknown (Swartz et al., 2018). Accommodations should be

made to facilitate breastfeeding including availability of a lactation consultant and nutritionist. Depending on the disability from the stroke, she may need additional assistance from physical and occupational therapy or rehabilitation medicine for pumping breast milk and breastfeeding the infant.

Poststroke depression in the setting of pregnancy/postpartum

Depression in the months following stroke is common and is associated with increased mortality. The rate of poststroke depression increases with stroke severity, prior depression, and female gender (Jørgensen et al., 2016). Similarly, postpartum depression is a significant public health issue. One review found women with a history of neurologic disorders were at increased risk of peripartum mental illness (adjusted pooled OR 1.45, 95% CI 1.19–1.77) compared to peripartum women without chronic medical conditions (Brown et al., 2018). Therefore, patients with maternal stroke are at high risk for depression and should all be screened (Ladhani et al., 2018). Early referral to psychiatry (with specialized perinatal mental health services as available) should be expedited when indicated.

RISK OF RECURRENT ARTERIAL ISCHEMIC STROKE OR VENOUS SINUS THROMBOSIS IN FUTURE PREGNANCIES

For physicians treating women of childbearing age with a stroke history, preconception counseling may include the risk of recurrent stroke during potential future pregnancies. The risk varies considerably based on the etiology of the initial stroke, and data in the area are limited, but a few studies have addressed this question. A French observational study following 373 women with a history of AIS found that over the next 5 years, 13 women had recurrent strokes, of which two were pregnancy-related (Lamy et al., 2000). The FUTURE study of stroke in the young found that women with a prior stroke had higher rates of pregnancy loss and pregnancy-related complications, such as gestational hypertension, but no recurrent strokes during pregnancy were identified (van Alebeek et al., 2018). In another observational study of 26 pregnancies following a diagnosis of TIA, AIS, or CVST, no recurrent strokes occurred during pregnancy or the postpartum period (Cruz-Herranz et al., 2015). Another study on the risk of CVST recurrence in future pregnancies calculated an overall rate of 2.2% per subsequent pregnancy (Aguiar de Sousa et al., 2017). In women with a history of stroke, guidelines recommend secondary prevention based on stroke mechanism and aggressive management of additional stroke risk factors, such as hypertensive disorders of pregnancy (Swartz et al., 2018).

CONCLUSION

Maternal stroke constitutes a major public health concern and is a leading cause of maternal disability. Understanding of the heightened risk of stroke that pregnancy confers and education of patients with known risk factors about stroke signs and symptoms have the potential to reduce maternal stroke morbidity. In addition, current acute stroke treatment options can dramatically reduce disability after stroke, especially in young patients. Stroke diagnostic and therapeutic procedures should be offered to pregnant and postpartum patients, with a candid discussion of the risks and unknowns. Optimal treatment of maternal stroke

requires close collaboration with a multidisciplinary team that includes vascular neurologists, maternal–fetal medicine specialists, obstetric anesthesiologists, neurointerventionists, and rehabilitation medicine specialists.

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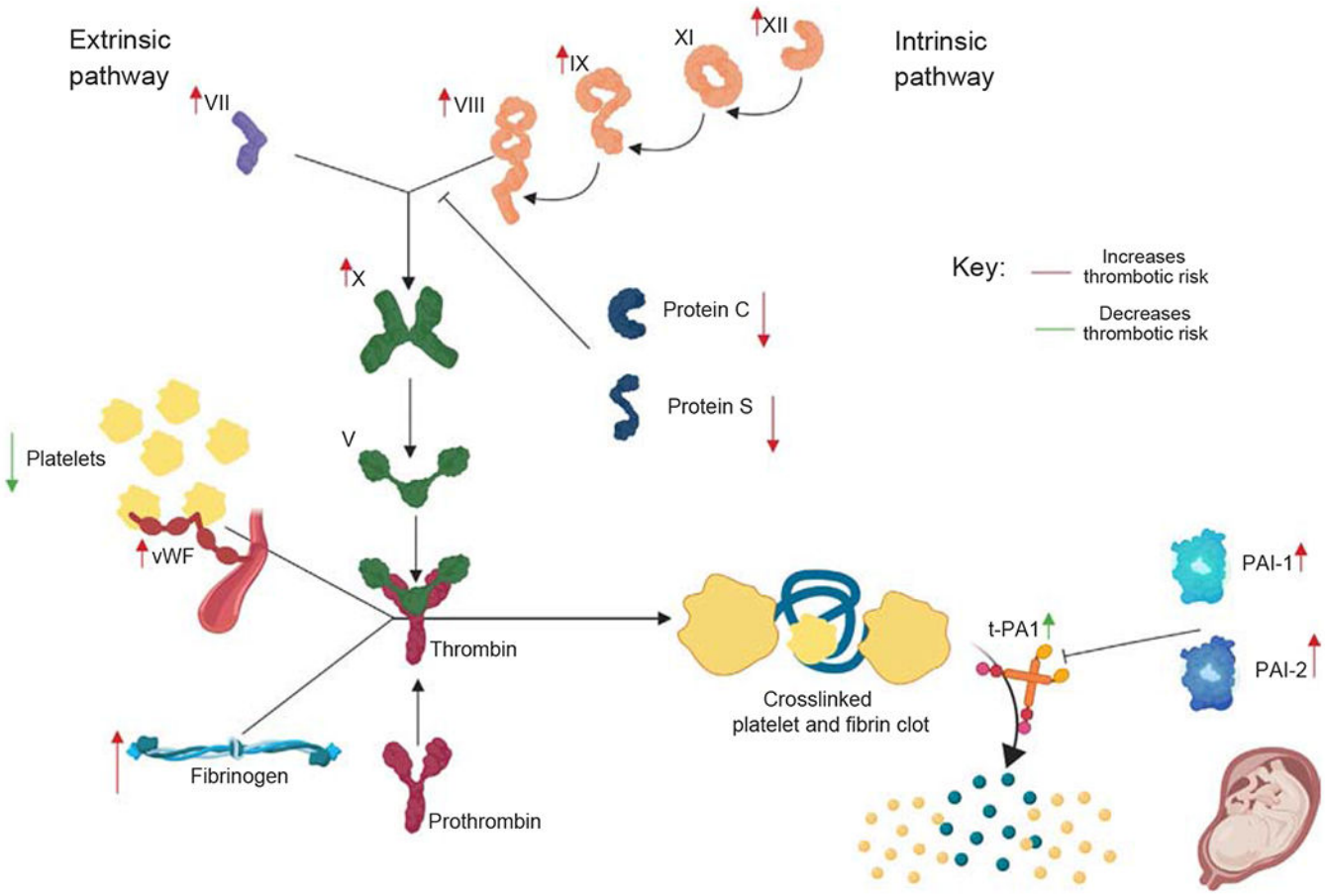

Fig 1.1.

Many changes occur in the coagulation system during pregnancy. The *red arrows* represent changes that predispose toward a prothrombotic state, including increases in intrinsic and extrinsic clotting factors (factors VII, VIII, IX, X, XI and XII), decreases in intrinsic anticoagulation factors (protein C and protein S), and increases in PAI-1 and PAI-2, including placental production of PAI-2. Increases in von Willebrand factor and fibrinogen also increase clotting risk during pregnancy. However, other changes, indicated by *green arrows*, including pregnancy-related thrombocytopenia and increases in t-PA1 later in pregnancy also occur.

Table 1.1

Risk factors for maternal stroke

Nonpregnancy-specific		Pregnancy-specific
Modifiable	Nonmodifiable	
•Smoking and other drug use	• Age	• Hypertensive disorders of pregnancy (gestational hypertension, preeclampsia/eclampsia, HELLP)
• Diabetes	• Race	• Assisted reproductive technology (ovarian hyperstimulation syndrome)
• Hypertension	• Socioeconomic status	• Cesarean section
• Cardiac disease (structural, arrhythmias)	• Genetic stroke and hypercoagulable syndromes	• Postpartum cerebral angiopathy
• Arterial disease		• Peripartum cardiomyopathy
• Patent foramen ovale		• Amniotic fluid embolism
• Migraine		• Sheehan syndrome
• Infection		• Metastatic choriocarcinoma
• Malignancy		• Age
		• Race/socioeconomic status
		• Genetic stroke and hypercoagulable syndromes

Table 1.2

Mechanisms of arterial ischemic stroke in pregnancy

Mechanism	Presentation	Risk factors
Cardiogenic embolism	Acute onset focal deficit determined by vessel distribution, more likely to have cortical signs (e.g., aphasia, neglect) More frequently associated with altered mental status given involvement of cortical structures	Cardiac arrhythmia (e.g., atrial fibrillation) Mechanical heart valves Reduced ejection fraction Cardiac thrombus or vegetation Congenital heart disease
Paradoxical embolism	Similar to cardiogenic embolism	Patent foramen ovale Pulmonary shunt (may be associated with hereditary hemorrhagic telangiectasia syndrome)
Artery-to-artery embolism	Acute onset focal deficit determined by vessel distribution, more likely to have cortical signs (e.g., aphasia, neglect) Limited to single artery territory	Hypertension Hyperlipidemia Diabetes Tobacco use Prior head and neck radiation (radiation vasculopathy)
Cerebral small vessel disease	Acute onset Less frequently associated with altered mental status	Hypertension Hyperlipidemia Diabetes Tobacco use
Cervical artery dissection (carotid or vertebral)	Similar to artery-to-artery embolism Often associated with neck pain or headache	Atherosclerosis Hypercholesterolemia Prior head and neck radiation (radiation vasculopathy) Connective tissue abnormalities: Ehlers-Danlos syndrome IV (EDS IV) Marfan syndrome Osteogenesis imperfecta type I Fibromuscular dysplasia Head or neck trauma – Victim of domestic violence – Chiropractic manipulation – Motor vehicle accident
Reversible cerebral vasoconstriction syndrome (RCVS)	Recurrent, sudden onset, severe thunderclap headache Transient acute onset focal deficits that may resolve within minutes or hours Persistent acute onset focal deficits if infarction occurs Seizure may be initial symptom	Migraines Hypertension Exposure to serotonergic and adrenergic drugs Postpartum state

Table 1.3

Principles of acute ischemic stroke management in pregnancy

Management step	General population	Additional considerations due to pregnancy status
Initial history	• Last known well • Brief history focusing on tPA exclusion criteria	•Determine gestational age •Early involvement of obstetrics team
Initial studies	• Blood glucose by fingerstick • Complete blood count, basic metabolic panel, and coagulation studies • EKG and troponin Note: *only* blood glucose by fingerstick is needed prior to tPA unless there is suspicion for thrombocytopenia or coagulopathy	• Urine or serum beta-HCG test (for all women of childbearing age) • Fetal monitoring when >24 weeks gestation (particularly when abnormal maternal blood pressure)
Other considerations		• Magnesium sulfate administration in cases of severe preeclampsia
tPA candidates	• Clinical diagnosis of stroke with disabling deficits • Defined onset and able to start treatment within 4.5h of onset • Brain imaging without evidence of hemorrhage, most commonly by noncontrast head CT • No contraindications to tPA by history and labs	• No additional inclusion or exclusion criteria • CT head without contrast acceptable with counseling on imaging-associated risks • MRI also acceptable, but imaging modality should be determined by whichever modality most readily available
Thrombectomy	• Vessel imaging, most commonly by CT angiography, showing a large vessel occlusion • Defined onset and able to start treatment within 6h of onset • If onset within 6–24 h, perfusion imaging showing a large area of salvageable brain tissue relative to the core infarct (with additional criteria per DEFUSE-3 and DAWN studies)	• CT angiography (head and neck) acceptable vessel imaging • MRA also acceptable, but imaging modality should be determined by whichever imaging modality most readily available • If perfusion imaging required for extended-window thrombectomy eligibility, CT perfusion should be used rather than MR perfusion to avoid use of gadolinium contrast

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Table 1.4

Main contraindications for intravenous thrombolysis

	Unclear time of onset Unwitnessed symptom onset
Time of onset	Last known normal >4.5 h[a]
CT	Intracranial hemorrhage identified by CT Hypodensity >1/3 cerebral hemisphere
Vitals	Uncontrolled hypertension above 185/110 mmHg, despite use of antihypertensive agents
Anticoagulation	Therapeutic enoxaparin in the previous 24h (prophylactic dosing is not a contraindication) Current use of direct thrombin or factor Xa inhibitors (within 48 h)
History	Prior ischemic stroke within 3 months Severe head trauma within 3 months Intracranial/intraspinal surgery within 3 months Major surgery within past 14 days (including cesarean delivery) GI bleeding within 21 days Arterial puncture at noncompressible site within 7 days Note: lumbar puncture is NOT an absolute contraindication
Labs	Platelet <100,000/μL INR >1.7 PT > 15s aPTT >40s
Comorbidities	Infective endocarditis Intraaxial neoplasm Aortic arch dissection Structural GI malignancy

[a]The recently published EXTEND trial (Ma et al., 2019) and a subsequent meta-analysis (Campbell et al., 2014) suggest a benefit for thrombolysis in selected patients beyond the 4.5 h window, based on identification of patients with perfusion mismatch on imaging. However, this is not yet guideline-based standard of care.

Table 1.5

Common arterial ischemic stroke syndromes

Artery	Presentation
Left internal carotid artery	Right face/arm/leg weakness; left gaze deviation; aphasia (typically global)
Right internal carotid artery	Left face/arm/leg weakness; right gaze deviation; neglect of left side
Left middle cerebral artery	Aphasia; right face, arm > leg weakness; right sensory loss; left gaze deviation
Right middle cerebral artery	Neglect of left side; left face, arm > leg weakness; right gaze deviation; anosognosia; agitation
Anterior cerebral artery	Contralateral leg weakness; abulia; occasionally can present with bilateral leg weakness
Posterior cerebral artery	Contralateral homonymous hemianopsia; contralateral sensory loss
Posterior inferior cerebellar artery	Vertigo, nausea, hiccups, headache, direction-changing nystagmus Dysarthria, ipsilateral deviation of tongue “Crossed” motor deficits: ipsilateral facial and contralateral limb/trunk numbness Horner syndrome (ptosis, miosis, anhidrosis)
Anterior inferior cerebellar artery	Ataxia; contralateral weakness/numbness; acute hearing loss
Superior cerebellar artery	Ataxic gait; vertigo; nystagmus, dysarthria
Basilar artery and basilar perforators	Locked-in syndrome: quadriplegia with preserved consciousness, preserved vertical eye movements and blinking

Table 1.6

Reported cases of thrombolysis and thrombectomy in pregnancy

Author (year)	Maternal age (year)	Gestational age	Signs/ symptoms	Risk factors/ comorbidities	Imaging	Thrombolysis and/or thrombectomy (time after symptom onset)	Potential complications	Secondary prevention	Mode of delivery	Maternal outcome	Fetal outcome
Rodrigues et al. (2019)	29	27 weeks	R-sided weakness/ numbness, hemianopsia, and aphasia	NA	Stroke code CTH/CTA: unremarkable Follow-up CTH: L MCA/ACA stroke	IV tPA	NA	Aspirin and LMW heparin	C-section	Persistent expressive aphasia and R-sided weakness	Healthy
Blythe et al. (2019)	29	39 weeks	L-sided weakness and neglect	Factor XI deficiency, gestational thrombocytopenia	CTA with R M1/2 occlusion	Thrombectomy (no tPA due to low platelets)	NA	Not reported	C-section	Asymptomatic	Healthy
Peksa et al. (2019)	35	9 weeks	L-sided weakness and L visual field deficit and neglect	Prior history of preeclampsia, GDM	CTH with hyperdense R MCA, CTA with M1 occlusion	IV tPA	NA	Aspirin and LMW heparin	Vaginal	Mild residual symptoms (NIHSS 0, mRS 0)	Healthy
Watanabe et al. (2019)	36	21 weeks	R-sided weakness, dysarthria, headache	NA	MRA: L ICA occlusion	IV tPA+ thrombectomy	NA	Not reported	Not reported	Mild residual weakness	Healthy
Landais et al. (2018)	32	13 weeks	Aphasia and R-hand numbness	NA	MRI DWI restriction in L MCA territory and chronic R MCA stroke	IV tPA	NA	Aspirin, transitioned to warfarin postpartum	Vaginal	Residual aphasia	Healthy
Zhu et al. (2018)	28	9 weeks	R-sided weakness and numbness and dysarthria	Previous miscarriage	CTH: early L MCA infarct signs and hyperdense MCA CTA: L MCA occlusion	IV tPA+ thrombectomy	NA	LMW heparin	Vaginal	Asymptomatic at 1 year follow-up	Healthy
Shah et al. (2018)	37	9 weeks	Recurrent L-sided weakness and R gaze preference 2 days apart	Hypertension, hyperlipidemia, and dilated cardiomyopathy	(1) CTH: early loss of gay-white differentiation in R MCA territory and hyperdense R MCA CTA:	(1) Initial occurrence tPA with improvement (2) Thrombectomy after	NA	LMW heparin	Published prior to delivery	Mild residual weakness	Fetus healthy at follow-up

Author (year)	Maternal age (year)	Gestational age	Signs/ symptoms	Risk factors/ comorbidities	Imaging	Thrombolysis and/or thrombectomy (time after symptom onset)	Potential complications	Secondary prevention	Mode of delivery	Maternal outcome	Fetal outcome
					inferior M2 cutoff (2) CTH/CTA: R proximal M1 cutoff	recurrence 2 days later					
Jiang and Hu (2018)	26	31 weeks	R-sided weakness and dysarthria	History of rheumatic fever with mitral regurgitation and prolapse	CTH: unremarkable MRI: multiple bilateral acute infarcts (R caudate, L BG, L CR)	IV tPA	Small L cerebellar and R temporal hemorrhage	LMW heparin, then long-term warfarin	Vaginal	Asymptomatic	Healthy
Bhogal et al. (2017)(A)	38	24 weeks	R-sided weakness/ numbness, L gaze deviation, and aphasia	Drug abuse, PFO	CTH: hyperdense L MCA MRI: L lentiform nucleus and insular diffusion restriction Angio: terminal L ICA occlusion	Thrombectomy (outside tPA window once transferred to referral center)	NA	Clopidogrel + aspirin for 3 month and then aspirin indefinitely	Vaginal	Mild residual weakness	Healthy
Bhogal et al. (2017) (B)	36	25 weeks	Headache, nausea and vomiting, progressing to stupor	Prior type A aortic dissection	CTH: dense basilar CTA: distal basilar occlusion	IV tPA + thrombectomy	NA	Ticagrelor +aspirin, then switched to prasugrel +aspirin	Published prior to delivery	Internuclear ophthalmoplegia only	Fetus healthy at follow-up
Khan et al. (2017)	33	9 weeks	R-sided weakness/ numbness and visual field cut	Prior miscarriages (11), tobacco and substance use disorder	CTH: unremarkable Repeat CTH: PCA infarct	IV tPA	Fetal hemorrhage/ demise	Aspirin, then long-term clopidogrel	D&C	Residual visual symptoms and weakness	First trimester loss
Reining-Festa et al. (2017)	37	5 weeks	L-sided weakness	HTN, obesity, history of rheumatic fever, prior second semester miscarriage	MRI: R MCA diffusion restriction	IV tPA	NA	Aspirin, then LMW heparin	C-section	Residual sensory symptoms	Healthy
Tversky et al. (2016)	31	5 weeks	R-sided weakness and dysarthria	Protein C and S deficiencies, DVT, PFO (presumed	CTH unremarkable, MRI with L thalmocapsular	IV tPA	NA	LMW heparin	NA (published prior to delivery)	Asymptomatic at discharge	No evidence of abnormalities in second trimester

Author (year)	Maternal age (year)	Gestational age	Signs/ symptoms	Risk factors/ comorbidities	Imaging	Thrombolysis and/or thrombectomy (time after symptom onset)	Potential complications	Secondary prevention	Mode of delivery	Maternal outcome	Fetal outcome
				paradoxical embolism)	DWI restriction						
Bereczki Jr et al. (2016)	40	2 weeks postpartum	R-sided weakness and aphasia	Cervical artery dissection, migraine, childhood epilepsy	CTH: R MCA hyperdensity CTA: RM1 occlusion, b/l ICA dissections	IV tPA + thrombectomy (and stended R ICA)	NA	LMW heparin and clopidogrel	Vaginal	Asymptomatic at 6 weeks	Healthy
Boyko et al. (2016)	32	37 weeks	R-sided weakness/ numbness and aphasia	Hypothyroidism, obesity, and obstructive sleep apnea	CTH: hyperdense L MCA with early loss of gray-white differentiation CTA: L M1 occlusion	IV tPA + thrombectomy	Asymptomatic hemorrhage	Aspirin	C-section	Residual facial droop	Healthy
Aaron et al. (2016) (A)	24	Third trimester	L-sided weakness	Rheumatic fever, mitral valve replacement (on LMWH)	MRI/A: diffusion restriction involving lateral lenticulostriate territory; R M1 occlusion	Thrombectomy	NA	Oral anticoagulation	Vaginal	Mild residual weakness	Healthy
Aaron et al. (2016) (B)	28	37 weeks	L-sided weakness	Rheumatic fever, mitral valve replacement (on LMWH), severe IUGR	MRI/A: diffusion restriction in R putamen and R M1 occlusion	Thrombectomy	NA	LMW heparin, then oral anticoagulants postpartum	C-section	Residual weakness	Healthy
Pongracz et al. (2015)	21	21 weeks	L-sided weakness	Tobacco use	CTH: unremarkable CTA: R M1 cutoff	IA tPA	NA	LMW heparin	C-section	Mild residual weakness	Healthy
Ritchie et al. (2015)	28	39 weeks	L-sided weakness/ numbness	NA	MRI: small R MCA stroke	IV tPA	NA	Aspirin until delivery, clopidogrel and tinzaparin postpartum	Vaginal (forceps-assisted)	Full recovery at 8 months	Healthy
Ritter et al. (2014)	32	36 weeks	R-sided weakness/ numbness, dysarthria, neglect	Migraine with aura	CTA: L lower M2 occlusion	IV tPA	NA	Aspirin until delivery, clopidogrel postpartum	C-section	Residual weakness	Healthy

Author (year)	Maternal age (year)	Gestational age	Signs/ symptoms	Risk factors/ comorbidities	Imaging	Thrombolysis and/or thrombectomy (time after symptom onset)	Potential complications	Secondary prevention	Mode of delivery	Maternal outcome	Fetal outcome
Tassi et al. (2013)	28	16 weeks	R-sided weakness/ numbness and aphasia	PFO, factor V Leiden	MRI/A: L MCA territory ischemic stroke	IV tPA	NA	Aspirin	Vaginal	Mild residual deficits	Healthy
Hori et al. (2013)	35	13 weeks	L-sided weakness and visual field cut	Protein S deficiency	R PCA occlusion	IV tPA	NA	IV heparin—> warfarin at 15 weeks	C-section (w/general anesthesia)	Residual visual deficits	Healthy
Li et al. (2012)	24	11 and 13 weeks	R-sided weakness and dysarthria at 11 weeks and facial numbness at 13 weeks	PFO, pulmonary AVM	L MCA ischemic stroke at 11 weeks and vertebrobasilar territory at 13 weeks	IA tPA	NA	Aspirin and enoxaparin	Vaginal	Residual weakness	Healthy
Yamaguchi et al. (2010)	36	18 weeks	R-sided weakness/ numbness and aphasia	Hashimoto disease	MRI/A: L MCA occlusion and high intensity areas	IV tPA	NA	Aspirin and heparin	Vaginal	Asymptomatic	Healthy
Méndez et al. (2008)	37	15h after delivery	L-sided weakness/ numbness, dysarthria and visual field cut	migraine	CTH: unremarkable Angiogram distal R M1 occlusion	IA urokinase	NA	LMW heparin	C-section	Asymptomatic	Healthy
Wiese et al. (2006)	33	13 weeks	R-sided weakness, aphasia	Prosthetic mitral valve thrombois, prior GDM	CTH: L BG/IC hypodensity	IV tPA	NA	LMW heparin	C-section	Residual weakness	Healthy
Murugappan et al. (2006) (A)	37	12 weeks	NIHSS = 19	Mitral valve replacement	R MCA occlusion	IV tPA	Intrauterine hematoma	NA	NA	Healthy	Medical termination of pregnancy
Murugappan et al. (2006) (B)	31	4 weeks	Not reported	Protein S deficiency	L MCA occlusion	IV tPA	NA	NA	NA	Healthy	Medical termination of pregnancy
Murugappan et al. (2006) (C)	29	6 weeks	NIHSS = 13	Aortic valve replacement	R MCA occlusion	IV tPA	Arterial dissection during angioplasty	NA	NA	Death	Death
Murugappan et al. (2006) (D)	43	37 weeks	NIHSS = 25	Antithrombin 3, protein C and S deficiencies	L MCA occlusion	IA tPA	NA	NA	Not reported	Healthy	Healthy

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Author (year)	Maternal age (year)	Gestational age	Signs/ symptoms	Risk factors/ comorbidities	Imaging	Thrombolysis and/or thrombectomy (time after symptom onset)	Potential complications	Secondary prevention	Mode of delivery	Maternal outcome	Fetal outcome
Murugappan et al. (2006) (E)	28	6 weeks	Not reported	Protein C and S deficiency, PFO	Basilar occlusion	IA urokinase	Buttock hematoma	NA	Not reported	Healthy	Healthy
Murugappan et al. (2006) (F)	40	6 weeks	Not reported	PCV, essential thrombolysis	Superior sagittal sinus thrombosis	Local urokinase	Partial recanalization	NA	NA	Healthy	Fetal demise, chromosomal abnormality
Murugappan et al. (2006) (G)	21	8 weeks	Not reported	+dRVVT, antiphospholipid antibodies	Cerebral venous thrombosis	Local urokinase	Enlargement of IVC-related hemorrhage	NA	NA	Healthy	Medical termination of pregnancy
Murugappan et al. (2006) (H)	25	First trimester	Not reported	Bacterial endocarditis	L MCA occlusion	Local urokinase	NA	NA	NA	Healthy	Spontaneous abortion
Leonhardt et al. (2006)	26	23 weeks	R-sided weakness	Antiphospholipid syndrome	MRI: L BG diffusion restriction and L M1 occlusion	IV tPA	NA	LMW heparin	Vaginal	Residual weakness	Healthy premature
Johnson et al. (2005)	39	37 weeks	L-sided weakness, dysarthria, field cut, and neglect	Chronic hypertension	CTH: unremarkable Angiogram: R M1 occlusion	IA tPA	NA	Not reported	Vaginal (forceps-assisted)	Asymptomatic	Healthy
Weatherby et al. (2003)	29	9 weeks	L-sided weakness and papilledema bilaterally	NA	CTH: increased attenuation of superior sagittal sinus with associated edema MRI/ MRV: absence of flow in SSS	Direct thrombolysis	NA	Dalteparin	Vaginal	Asymptomatic	Healthy
Elford et al. (2002)	28	3–4 weeks (7 days embryo transfer of IVF)	L-sided weakness, dysarthria	Ovarian hyperstimulation syndrome	CTH: early R perisylvian/ frontal/parietal changes CTA: R M1 occlusion	IA tPA	Small R BG hemorrhage	Dalteparin	Vaginal	Mild residual symptoms	Healthy
Dapprich and Boessenecker (2002)	31	12 weeks	R-sided weakness and aphasia	Protein S deficiency	CTH: early L BG hypodensity; TCD w/L M1 occlusion MRI: L BG	IV tPA	Small L BG hemorrhage	Aspirin 100mg and LMW heparin	Not reported	Mild residual symptoms	Healthy

Author (year)	Maternal age (year)	Gestational age	Signs/ symptoms	Risk factors/ comorbidities	Imaging	Thrombolysis and/or thrombectomy (time after symptom onset)	Potential complications	Secondary prevention	Mode of delivery	Maternal outcome	Fetal outcome
					hemorrhagic transformation						