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Maternal stroke: A call for action

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Abstract

Maternal mortality rates have been steadily increasing in the United States; and cardiovascular mortality is the leading cause of death among pregnant and post-partum women. Maternal stroke accounts for a significant burden of cardiovascular mortality. Data suggest that rates of maternal stroke have been increasing in recent years. Advancing maternal age at the time of birth and increasing prevalence of traditional cardiovascular risk factors as well as other risk factors such as hypertensive disorders of pregnancy, migraine, and infections may contribute to increased rates of maternal stroke. In this document, we provide an overview of the epidemiology of maternal stroke, explore mechanisms that may explain increasing rates of stroke among pregnant women, and identify key knowledge gaps for future investigation in this area.

Keywords

hemorrhagic stroke; intracerebral hemorrhage; ischemic stroke; pregnancy; preeclampsia; post-partum; subarachnoid hemorrhage

Introduction:

Maternal mortality remains a global health care concern (1). While low- and middle-income countries account for more than 90% of maternal mortality globally, rates in the United States (US) are on the rise and are considered the highest among developed countries (1,2). Cardiovascular disease is the most prevalent preventable cause of maternal mortality in developed countries, and also contributes substantially to the high maternal mortality rates in

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low-and middle-income countries (3). In the US, one-third of pregnancy-related deaths are attributed to cardiovascular conditions, and approximately 60% of these deaths are deemed preventable (4).

Stroke is the second leading cause of death worldwide, the fourth leading cause in US women (5), and is recognized as the leading etiology of long-term physical and cognitive disability in adults (6). Maternal stroke is an infrequent but debilitating complication of pregnancy and is the most frequent cause of serious long-term disability after pregnancy (5). It accounts for at least 7.7% of pregnancy-related deaths in the US (7), and results in residual neurological deficits in approximately half of maternal stroke survivors (8), potentially affecting their ability to care for a newborn.

Specific pregnancy-related conditions often trigger maternal stroke, many of which are potentially preventable (9). In this review, we provide an overview of the epidemiology, risk factors, mechanisms, and therapies for maternal stroke, as well as focus on potential preventive strategies. However, many important knowledge gaps remain regarding maternal stroke, so another focus of this review is to highlight these areas and provide some directions for future research.

Epidemiology of maternal stroke:

The risk of stroke among pregnant and post-partum women is ~3 times increased compared with non-pregnant women of similar age (10). In a meta-analysis of 11 studies including >85 million pregnant and post-partum women, from high-income countries, the incidence of maternal stroke was ~30 per 100,000 pregnancies; most occurred during the post-partum period (up to 6 weeks) (10). Although there is a paucity of robust large-scale studies, small studies from some countries indicate an alarmingly higher incidence of maternal stroke in low- and middle-income countries. In one study > 5,500 deliveries in Tanzania from 2009 to 2010, the incidence of maternal stroke was 89 per 100,000 deliveries (11). Another study of > 39,000 deliveries in India from 2006 to 2008 revealed that the incidence of cerebrovascular complications was 66 per 100,000 deliveries (12).

Maternal stroke is a frequent cause of strokes among younger women (i.e., maternal stroke accounts for 18% of strokes in women aged 12–35 years compared with 1.4% of strokes in women aged 35–55 years) (13). This difference is partially explained by distinct stroke mechanisms across the age spectrum. Strokes in older age groups are typically related to cardio-embolic events, large artery atherosclerosis, or cerebral small vessel disease, while strokes in younger women may result from rarer mechanisms such as cervical artery dissection (14), venous infarction or hemorrhage due to cerebral venous thrombosis, primary hypercoagulable states, and reversible cerebral vasoconstriction syndrome (13). In addition, unlike strokes in the general population which are 87% ischemic (6), half of maternal strokes are hemorrhagic (due to intracerebral hemorrhage [ICH] or subarachnoid hemorrhage [SAH]) (10).

Overall, the incidence of stroke in the US population has declined in recent years, which could partly be attributed to the improved control of some traditional cardiovascular risk

factors (15). However, an opposite trend has been observed with maternal stroke. In an analysis of the National Inpatient Sample (NIS) of >37 million hospitalizations for pregnancy and post-partum conditions from 2007 to 2015, the rates of acute stroke or transient ischemic attack (TIA) did not change over time (42.8 per 100,000 hospitalizations in 2007 versus with 42.2 per 100,000 hospitalizations in 2015). In a secondary analysis excluding TIA and specific codes for stroke during pregnancy, there was a small but significant increase in the rates of maternal stroke (29.8 per 100,000 hospitalizations in 2007 versus 33.0 per 100,000 hospitalizations in 2015), suggesting that the rates of maternal stroke might be on the rise (16). This suggestion is supported by a Canadian cohort of >3.9 million pregnant and post-partum women from 2003–2016, where there was also a temporal increase in the age-adjusted incidence of maternal stroke (10.8 per 100,000 deliveries in 2003, to 16.6 per 100,000 deliveries in 2016) (17).

The rates of maternal stroke appear higher in the US compared with other developed nations (Table 1) (8,12,16–21). In addition to increasing maternal age and rising trends in the prevalence of cardiovascular risk factors among young women, significant health disparities by race and ethnicity may contribute to the increased rate of maternal stroke in the US. Black women have been shown to have higher risk of maternal stroke and higher maternal stroke -associated in-hospital mortality (16). In another analysis of the NIS of > 65 million pregnant and post-partum women, among those with hypertensive disorders of pregnancy (HDP), Blacks and Hispanics had double the risk of maternal stroke during delivery admissions compared with non-Hispanic White women (Blacks: adjusted risk ratio [aRR], 2.07; 95% confidence interval [CI], 1.86–2.30; Hispanics: aRR, 2.19; 95% CI, 1.98–2.43). Among those with chronic hypertension, all minority women had a higher stroke risk (Blacks: aRR, 1.71; 95% CI, 1.30–2.26; Hispanics: aRR, 1.75; 95% CI, 2.32–5.63; Asian/Pacific Islanders: aRR, 3.62; 95% CI, 2.32–5.63). Among normotensive women, Black women, but not women in other minority groups, had a 17% excess risk of maternal stroke versus White women (18). Studies consistently indicate that Black women suffer disproportionately high risk of adverse maternal outcomes compared to other groups. While genetic and environmental factors may also be contributing factors, systemic racism must be confronted to address these troublesome trends (22).

Timing and risk factors for maternal stroke

Timing of maternal stroke: The majority of maternal strokes occur in the post-partum period (defined variously as up to 12 weeks after delivery), often after women have left the hospital (10). In a study using administrative data from the US Healthcare Cost and Utilization Project's Nationwide Readmissions Database from 2013–2014, the median time to readmission for stroke after delivery was 8 days (23). The risk of thromboembolic events in the 6 weeks postpartum has been estimated to be 15–35 times higher in the first week postpartum, compared with non-pregnant women, and the risk remains elevated up to 12 weeks postpartum (24). Hemorrhagic strokes, too, occur most frequently post-partum; a case-crossover study using administrative data from New York, California, and Florida found a 9-fold increased rate of ICH in the 12 weeks post-partum (rate ratio, 9.15; 95% CI, 5.16–16.23), compared with the non-pregnant state (25).

Maternal stroke risk factors: Risk factors for maternal stroke may be broadly classified as traditional cardiovascular or other risk factors. Traditional risk factors include older age, obesity, smoking, chronic hypertension, hyperlipidemia, and heart disease. Other risk factors include HDP, migraine, infections, and hypercoagulable states (Figure 1).

1. Traditional modifiable cardiovascular risk factors: While the rising trend in the incidence of maternal stroke might be partly attributed to advancing maternal age (26), recently there has also been a notable increase in the prevalence of traditional modifiable cardiovascular risk factors in younger patients (27). Of these, hypertension remains the most prevalent modifiable risk factor for stroke among the general population as well as pregnant and post-partum women (6). The prevalence of most other traditional cardiovascular risk factors including obesity, smoking, and hyperlipidemia is also increasing among women with maternal stroke (16). Nevertheless, these risk factors remain less prevalent among pregnant women with stroke compared with non-pregnant women with stroke, suggesting that underlying pathophysiological mechanisms for maternal stroke involve unique pregnancy-related mechanisms (28).

2. Hypertensive disorders of pregnancy (HDP): HDP, defined as gestational hypertension, preeclampsia/eclampsia, and chronic hypertension with or without superimposed preeclampsia, are associated with a higher risk for all stroke types during pregnancy and the post-partum period. Preeclampsia and stroke are known to share common risk factors such as obesity, metabolic syndrome, heightened inflammatory responses, hypercoagulable states, and endothelial dysfunction (29). In addition, mechanisms specific to HDP may contribute to maternal stroke risk (see *Mechanisms*, below). HDP confer a higher attributable risk to maternal stroke compared with traditional cardiovascular risk factors. In an analysis of ~82 million pregnancy-related hospitalizations from the NIS, women with HDP were ~5 times more likely to have an ischemic or hemorrhagic stroke (30). In a meta-analysis of 22 studies, comprising of >6.4 million women including ~250,000 women with pre-eclampsia, pre-eclampsia was independently associated with a 2-fold increased risk of maternal stroke after adjusting for other potential confounders including traditional cardiovascular risk factors (31).

3. Migraine: The association between migraine and both ischemic and hemorrhagic stroke in the general population has been demonstrated in multiple studies (32–33). This association appears to hold true among pregnant and post-partum women with migraine. In an analysis of the NIS including ~18 million pregnancy hospitalizations, migraine was strongly associated with maternal stroke after adjusting for other risk factors (odds ratio [OR] 15.05, 95% CI 8.26–27.4) (34). Notably, migraine might not be easily distinguished from pre-eclampsia in administrative datasets, which could potentially introduce misclassification bias (35). Like HDP, migraine predisposes to endothelial dysfunction and increased platelet activation and aggregation (36). In fact, HDP has been suggested to mediate the association between migraine and stroke. In an analysis of an administrative database from California including >3 million pregnant and postpartum women including ~26,000 with migraine, migraine was independently associated with HDP (aRR 1.6; 95% CI 1.6–1.7), as well as stroke during pregnancy or delivery (aRR 6.8; 95% CI 4.7–9.8) and

stroke during the post-partum period (aRR 2.1, 95% CI 1.2–3.7) (37). Importantly, HDP, especially pre-eclampsia, mediated one-fourth of the excess risk of maternal stroke associated with migraine, which indicates the role of pregnancy-related hemodynamic and circulatory changes in the pathogenesis of stroke among women with migraine (37).

4. Infection: Infections are now recognized as a trigger for strokes in people of all ages (38,39), but this association may be even stronger among younger patients, including children (40,41) and young adults (42). This association has also been observed among pregnant and post-partum women. Infections have been recognized as a risk factor for maternal stroke even among women with pre-eclampsia (43). The risk appears to be higher with genitourinary infections and sepsis (44). An analysis of the National Readmission Database including 17.2 million pregnant and post-partum women showed that infections were associated with higher rates of ischemic stroke but not hemorrhagic stroke at 30-days. This effect was mainly observed among women without HDP (45).

Proposed pathophysiological pathways for the association between infections and maternal stroke include activation of the inflammatory cascade, causing a surge in inflammatory cytokines leading to platelet activation and aggregation; increased oxidative stress; and impaired endothelial function, all of which are linked with maternal stroke (45).

5. Hypercoagulable states: Hypercoagulable states predispose pregnant and postpartum women to arterial and venous thrombosis as well as hemorrhagic stroke (43). An analysis of the New York State Department of Health inpatient database, comprising of >88,000 women with preeclampsia, showed that prothrombotic states including systemic lupus erythematosus and sickle cell disease were associated with higher risk of maternal stroke (OR 3.5; 95% CI 1.3–9.2) (43). Pregnancy with antiphospholipid syndrome (APS) increases the risk of recurrent ischemic stroke, preeclampsia and preterm delivery (46). A prospective analysis of 33 pregnant women with APS showed that strongest predictive factors for thrombotic event in pregnancy were the presence of lupus anticoagulant and a past thrombotic event (47).

Mechanisms of maternal stroke

Pregnancy is associated with a broad range of stroke subtypes (Figure 2). Arterial ischemic strokes may be caused by arterial occlusions due to cardio-embolism (48), paradoxical emboli in the setting of patent foramen ovale (49,50), cervical artery dissections (51), or severe vasospasm (28). Large artery atherosclerosis is rarely seen in this population due to their young age, but other causes of intracranial arterial stenosis such as moyamoya disease have been described in association with maternal stroke (52). Hemorrhagic strokes account for ~60% of maternal stroke (53), a dramatic difference compared with the general population where 87% of strokes are ischemic (6). Hemorrhagic stroke mechanisms include ICH and SAH, which have distinct etiologies. ICH can occur either as a result of ruptured small blood vessels, often in the setting of uncontrolled hypertension, or in the presence of underlying vascular abnormalities such as arteriovenous malformations, cerebral cavernous malformations, or fragile moyamoya collaterals. Similarly, SAH may occur due either to rupture of vascular lesions such as intracranial aneurysms or dural arteriovenous fistulae

(54,55), as a result of the reversible cerebral vasoconstriction syndrome, or from venous hemorrhages. Interestingly, the majority of pregnancy-associated ICH and SAH do not appear to be associated with underlying vascular lesions (25,56). Cerebral venous sinus thrombosis (thrombosis of the cerebral veins and/or dural sinuses) may also lead to maternal stroke due to cerebral venous congestion which can result in venous infarction, with or without hemorrhagic conversion (57).

Immunomodulatory and vascular changes in pregnancy may contribute to the mechanisms of both ischemic and hemorrhagic maternal strokes. Pregnancy is associated with changes in both innate immunity and T-cell-mediated immunity. Increased expression of Th17, a highly inflammatory subtype of regulatory T cells, is also seen, especially in the presence of infection (58,59). Similar inflammatory mechanisms have been shown to contribute to the pathogenesis of ischemic stroke outside of pregnancy (60). Furthermore, the cerebral vasculature may be more susceptible to ischemic or hemorrhagic stroke during pregnancy and postpartum. Animal studies have shown pregnancy-related physiological changes, including arteriolar dilatation and remodeling, decreased cerebrovascular resistance, and increased blood-brain barrier permeability (61). Even more extreme disruptions have been observed in animal models of preeclampsia, including dramatic increases in blood-brain barrier permeability, disruption cerebral autoregulatory function, and impaired arteriolar response to neurovascular signaling (62,63). Small clinical studies have corroborated these findings, finding changes in cerebral autoregulatory function both in healthy pregnant women and women with HDP (64,65). Independent of immunomodulatory mechanisms, the altered cerebral autoregulation associated with HDP may elevate cerebral wall tension in the fragile vessel walls and increase vulnerability to maternal stroke (66,67) (Figure 3). A severe form of preeclampsia is characterized by hemolysis, elevated liver enzymes, and a low platelet count, known as HELLP syndrome. The combination of blood-brain barrier damage in the setting of hypertension enhances the risk of hemorrhagic stroke in women with HELLP (68). The pathogenesis of preeclampsia is thought to be linked, at least in part, to altered expression of placental anti-angiogenic factors which induces endothelial dysfunction, contributing to increased risk for proteinuria and hypertension (69). Endothelial dysfunction, both systemic and cerebral, is a pivotal mechanism that results in the disruption of vascular tone, increased vessel reactivity, and, in some cases, vasogenic edema (70). In addition, preeclampsia has been linked with enhanced platelet aggregation (71).

Clinically, preeclampsia and eclampsia are highly associated with the reversible cerebral vasoconstriction syndrome (RCVS) and the posterior reversible encephalopathy syndrome (PRES) (72), which may lead to ischemic stroke due to vasospasm-related hypoperfusion, as well as subarachnoid and intracerebral hemorrhage due to increased cerebral perfusion pressure, inflammation, and impaired compensatory autoregulatory mechanisms (73).

Cerebral venous thrombosis is another cause of maternal stroke, usually occurring in the postpartum period (28,74). During pregnancy and the post-partum period, hormonally mediated changes in the coagulation system shift the balance to a hypercoagulable state (75). Hypercoagulability, together with other mechanisms such as hypervolemic circulatory dynamics, venous stasis, and vascular endothelial injury in the setting of delivery increase the risk of thrombogenicity and may potentiate ischemic stroke risk (76), particularly in the

postpartum period. In addition, increased venous capacitance and venous pooling with resultant stasis, as well as reduced mobility, may play a role in the increased risk of thrombotic events during pregnancy and the post-partum period (77).

Management of maternal stroke

All randomized trials of therapies for acute ischemic stroke have excluded pregnant and postpartum women. In general, pregnant women with acute stroke are best managed in tertiary stroke centers whenever feasible (78). A multidisciplinary team approach including obstetricians, obstetric anesthesiologists, and neurologists is recommended (78). Emergent neuro-imaging should be obtained either with computed tomography (CT) or magnetic resonance imaging (MRI), in accordance with best practices for all acute stroke patients (79). Iodinated contrast for CT may be given when clinically indicated (80). Gadolinium contrast for MRI can cross the placenta and has been linked with still birth and neonatal death, and thus should be avoided; in any case it is rarely needed for management of acute stroke (81). Both pregnant women and their care providers often express concerns about the fetal risk associated with neuroimaging and ionizing radiation. Given the magnitude of maternal and fetal risk caused by potential delay in diagnosis of stroke, particularly given the higher proportion of hemorrhagic strokes among pregnant women, and the low risk to the fetus of CT, neuroimaging with CT scanning is acceptable and often the fastest or only available option (78).

Among pregnant women with acute ischemic stroke and no other contraindications to systemic thrombolysis, systemic intravenous thrombolysis with alteplase is recommended if they present within 4.5 hours of symptom onset when the benefit outweighs the risk (78). Since alteplase is a large molecule, it does not cross the placental barrier (78). Few case reports and series suggest that intravenous thrombolysis is associated with favorable outcomes during all trimesters including symptomatic improvement, uneventful deliveries and low incidence of symptomatic intracerebral bleed that is comparable with non-pregnant women (82). Thrombolytic therapy in the early postpartum period (≤ 48 hours) remains controversial because of increased risk of bleeding (79). A multi-disciplinary approach is needed to weigh the risks and benefits of thrombolytic strategy in such circumstances, and management needs to be individualized. Endovascular mechanical thrombectomy with stent retrievers has revolutionized the management of acute ischemic stroke among select patients with proximal large vessel intracranial arterial occlusions (83). In an analysis of 338 pregnant and post-partum women from the Get With the Guidelines Stroke-Registry treated with reperfusion therapy (i.e., systemic thrombolysis, catheter-based thrombolysis or thrombectomy), there was no difference in the short-term outcomes between pregnant and postpartum women compared with non-pregnant women (84), despite the maternal stroke group having more severe strokes.

In women with hemorrhagic stroke, for both ICH or SAH, treatment involves initial stabilization measures as blood pressure control (i.e., systolic blood pressure ≤160 mm Hg), reversal of anticoagulation, and identification of the etiology and source control if feasible (78). Emergent procedures like aneurysm clipping/coiling, arteriovenous malformation embolization, and surgical resection can be performed, regardless of pregnancy status (78).

Among patients with maternal stroke due to cerebral venous thrombosis, therapeutic anticoagulation with low molecular weight or unfractionated heparin remains the mainstay therapy (85), regardless of the presence of intracerebral hemorrhage. Intra-sinus thrombolysis or endovascular thrombectomy have been reported in some severe cases (86).

Mode of delivery among pregnant women with stroke:

Maternal stroke does not preclude vaginal delivery, provided that there is no other obstetric contraindication. The etiology of stroke and risks posed to the mother and the fetus by the Valsalva efforts are important considerations for decision making regarding the mode of delivery (78). In women for whom a mild increase in the intracranial pressure could be tolerated, vaginal births without assisted delivery can be a safe option (78). Women in whom increased intracranial pressure is a concern may be candidates for assisted vaginal delivery (78). Cesarean delivery is usually necessitated by standard obstetric indications, irrespective of severity of the stroke, which include maternal (e.g., pelvic deformity and abruptio placenta) and fetal (e.g., malpresentation and fetal asphyxia) indications. Additionally, cesarean delivery may also be considered in women with intracranial bleeding, or those who are at high risk of intracranial bleeding including those with unsecured aneurysm, untreated or partially treated symptomatic arteriovenous malformation (AVM) and acute ischemic stroke with hemorrhagic transformation (78). Data regarding the mode of delivery for women with intracranial aneurysms are limited. In an analysis of NIS years 1988–2009 including ~20 million pregnancies, the estimated risk of aneurysmal rupture was 1.4% during pregnancy and only 0.05% during delivery which were comparable with the risk in the general population (87). Though data is insufficient, vaginal delivery is generally recommended for most cardiac conditions including patent foramen ovale.

The process of decision-making regarding mode of delivery should be determined on an individualized basis. Maternal safety and outcomes should be prioritized, recognizing that what is best for maternal health is usually though not always best for fetal health as well (78). Important factors to consider include the viability of the fetus, the health of the mother and the health of the fetus, recognizing that death or disability of the mother is not in either her or her child’s interest (88).

Primary prevention of maternal stroke

Although maternal stroke is a relatively rare condition, it may lead to potential devastating consequences; thus, prevention remains of paramount importance. Since a number of maternal stroke risk factors are potentially manageable, a key aspect of prevention involves multidisciplinary careful recognition of these risk factors and addressing them appropriately in a timely manner. There are currently no available risk prediction tools to identify women with increased risk for maternal stroke.

With the rise in prevalence of traditional risk factors among pregnant women in the recent years, optimal management of these factors is a pivotal step in the prevention of maternal stroke. Early identification and optimal management of risk factors during pregnancy and postpartum period are important. Women with a history of chronic hypertension should be identified, monitored closely for superimposed preeclampsia and treated to a targeted blood

pressure goal depending on their other underlying cardiovascular conditions. With regards to obesity, excessive weight gain during pregnancy is commonly seen in women with a higher pre-pregnancy BMI and is associated with adverse pregnancy outcomes including HDP (89). These women will probably benefit most from lifestyle intervention strategies and counselling, including regular exercise, a healthy diet, achieving a desirable body weight and discontinuing smoking prior to conceiving. An increase in physical activity during and before pregnancy not only reduces blood pressure but might also reduce the incidence of preeclampsia (90).

Prevention, early recognition and treatment of HDP, especially preeclampsia, may be key for primary prevention of maternal stroke. Prophylactic use of aspirin, before 16 weeks of gestation, in patients with one high or two or more moderate risk factors for preeclampsia has been found to reduce the risk of preeclampsia (Table 2) (91,92). A meta-analysis of five trials with a total of 556 women concluded that aspirin initiated at or before 16 weeks of gestation was associated with a major reduction in the risk of preterm preeclampsia (RR 0.11, 95% CI 0.04–0.33), although no significant effect was seen on term preeclampsia (RR 0.98, 95% CI 0.42–2.33) (91). Another meta-analysis including the results of 13 studies, reported that low-dose aspirin (60–100 mg) use was associated with a 24% reduction in preeclampsia (RR 0.76, 95% CI 0.62–0.95), when initiated from 12 to 16 weeks of gestation (92). Results from the ASPRE trial, which enrolled 1776 women with singleton pregnancies who were at high risk for preterm preeclampsia, showed that low-dose aspirin (150 mg per day), initiated from 11–14 weeks of gestation until 36 weeks of gestation, reduced the risk of delivery with preeclampsia before 37 weeks of gestation, compared with placebo (OR 0.38, 95% CI 0.20–0.74), and without an increased risk of adverse events (93).

Systolic blood pressure rises between days 3–6 postpartum, typically peaking around day 6–7 (94). Up to 30% of HDP may occur postpartum, often associated with headaches and/or visual changes (95). The postpartum period is also the most common time for hemorrhagic stroke, most often associated with HDP (31,95). A study from Calgary, Canada identified that 6-week postpartum HDP are often not accurately identified and treated in the emergency department (95). Timely identification and treatment of blood pressure is recommended to reduce the risk of cardiovascular complications including stroke among women with HDP. Studies have revealed that a large proportion of deaths attributable to maternal stroke could possibly be prevented with earlier transfer to higher level of care and aggressive blood pressure treatment (78). However, unlike in hypertensive patients without HDP, there is no consensus on ideal target blood pressure goal in HDP. There is a need for robust studies to determine the impact of aggressive blood pressure control in HDP on the prevention of maternal stroke (96).

Epidemiological data suggest racial and ethnic disparities in the risk of maternal stroke, as Black and Hispanic populations have a higher incidence of maternal stroke than Whites (16,18,25). There are multiple possible reasons to account for these differences including socioeconomic differences, disproportionate access to health facilities, systemic racism, differences in prevalence of co-morbidities including obesity and high blood pressure (13,30). Additionally, non-hypertensive Black women remained at increased risk of stroke, suggesting the possibility of additional mechanisms contributing to increased maternal

stroke in this group, including the impact of systemic racism and clinician bias (18,22). This calls for coordinated efforts to explore the underlying reasons for these disparities, reduce overall maternal stroke burden by addressing modifiable risk factors in these populations, and address clinician biases which contribute to differences in the quality of care provided. Further efforts should be directed at developing an individualized prenatal care plan for high-risk populations, focusing on a more aggressive risk factor control strategies, careful counselling, and community-based preventive measures to modify the risk of maternal stroke.

The dynamics of preventive efforts may differ in low-and middle-income countries from those witnessed in developed countries, and besides the personalized primary preventive strategies, a community-based approach for the prevention of maternal stroke in low-and middle-income countries might be more effective. This includes improved healthcare infrastructure and facilities for the pregnant women, strong physician-patient dynamics in terms of extensive counseling and regular follow-up visits, and early screening and diagnosis of HDP. There is a need for community-based initiatives and public education regarding the importance of maternal health, and awareness campaigns with regards to symptoms of stroke and highlighting steps needed for the primary prevention.

Secondary prevention of maternal stroke

Women with a history of stroke in general are at risk for recurrent strokes. One study, of 441 young women with prior stroke, found that the overall risk of recurrent ischemic stroke was low in subsequent pregnancies (absolute risk 1.8%; 95%CI 0.5–7.5) (97). In a systematic review of 13 studies including 217 pregnant and post-partum women with cerebral venous thrombosis recurrence showed that the pooled estimate for recurrent cerebral venous thrombosis was 9 per 1000 pregnancies (98). Similar data on the subsequent risk of hemorrhagic stroke are lacking.

Long-term postpartum monitoring is crucial among women who develop maternal stroke for risk factor assessment and secondary prevention. While proper counseling is imperative, a history of maternal stroke should not be considered as a contraindication for subsequent pregnancy. These women should be encouraged to discuss their future pregnancy plans with their healthcare provider for adequate pre-pregnancy counselling. Lifestyle modification is a pivotal component of the secondary prevention strategy for all stroke subtypes, with emphasis on healthy diet, regular exercise, weight loss, smoking cessation, and blood pressure control. Secondary preventive strategies should be tailored to the stroke subtype and etiology. For women with a history of ischemic stroke, contraceptive counseling is important. Systemic estrogen-containing contraceptives or hormone replacement therapy can increase the risk of thromboembolic events, and therefore alternative methods of contraception should be considered (99). Women who develop maternal stroke secondary to cerebral venous thrombosis might benefit from low–molecular weight heparin thromboprophylaxis during subsequent pregnancies (99).

Conclusions and Future Directions:

Maternal stroke is an important cause of maternal morbidity and mortality and is potentially preventable. The prevalence of maternal stroke is higher in the US compared with other developed nations, and this prevalence appears to be rising. To address gaps in knowledge, further research is needed to broaden our understanding of the mechanisms, risk factors, and management options along with devising robust preventive strategies (Table 3). Thrombolytic therapy for ischemic stroke appears to be safe among pregnant women, but there is insufficient evidence to support thrombolysis for post-partum women within the first 48 hours. Mechanical thrombectomy can be safely performed in both pregnant and post-partum women. Future studies addressing therapies for ischemic stroke might consider enrolling pregnant and post-partum women. There is no current risk prediction tool to identify women at risk for maternal stroke, and studies are needed to risk stratify women for early identification and timely risk factor management of higher risk women. Prevention should focus on controlling traditional risk factors prior to conception and early recognition and treatment of HDP. Given our recognition of racial disparities in the risk of maternal stroke, the employment of aggressive strategies in terms of risk factor control, proper counseling, and community preventative measures are critically important in high-risk populations. The risk of recurrent stroke in future pregnancies depends on the initial stroke mechanism, and secondary prevention strategies must be individualized, ideally with the help of a multidisciplinary team including vascular neurologists, obstetricians, and other specialists depending on the stroke mechanism. There is also a need to implement aggressive healthcare policies that ensure accessibility of standardized healthcare for all pregnant women (Table 4). Filling these knowledge gaps could help provide physicians with better understanding of maternal stroke, make them better equipped to manage maternal stroke and improve outcomes for pregnant and post-partum women.

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Non-standard Abbreviations and Acronyms:

APS	antiphospholipid syndrome
AVM	arteriovenous malformation
aRR	adjusted risk ratio
CI	confidence interval
CT	computed tomography
HDP	hypertensive disorders of pregnancy
ICH	intracerebral hemorrhage
MRI	magnetic resonance imaging

NIS	National Inpatient Sample
OR	odds ratio
PRES	the posterior reversible encephalopathy syndrome
RCVS	reversible cerebral vasoconstriction syndrome
SAH	subarachnoid hemorrhage
TIA	transient ischemic attack
US	United States

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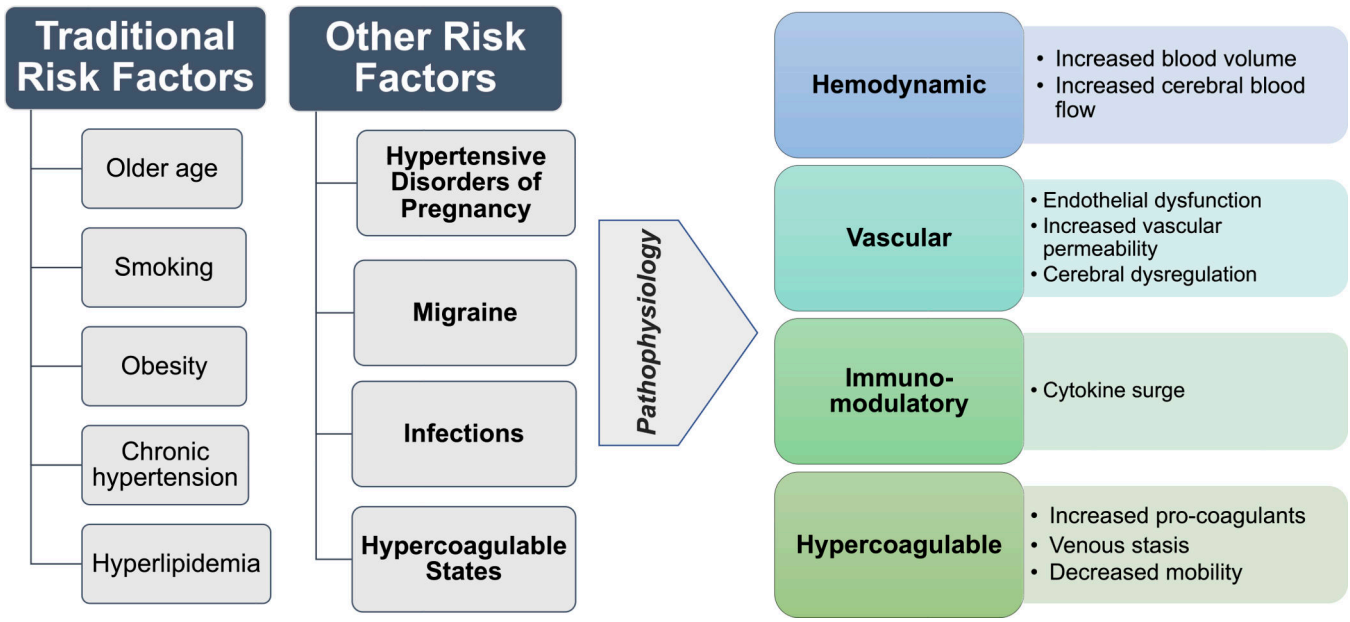

Figure 1:

Risk factors and pathophysiology of maternal stroke.

Risk factors for maternal stroke are traditional and other risk factors including hypertensive diseases of pregnancy, migraine, infections, and hypercoagulable states. The pathophysiological mechanisms implicated in maternal stroke involve hemodynamic, vascular, immune-modulatory, and hypercoagulable changes.

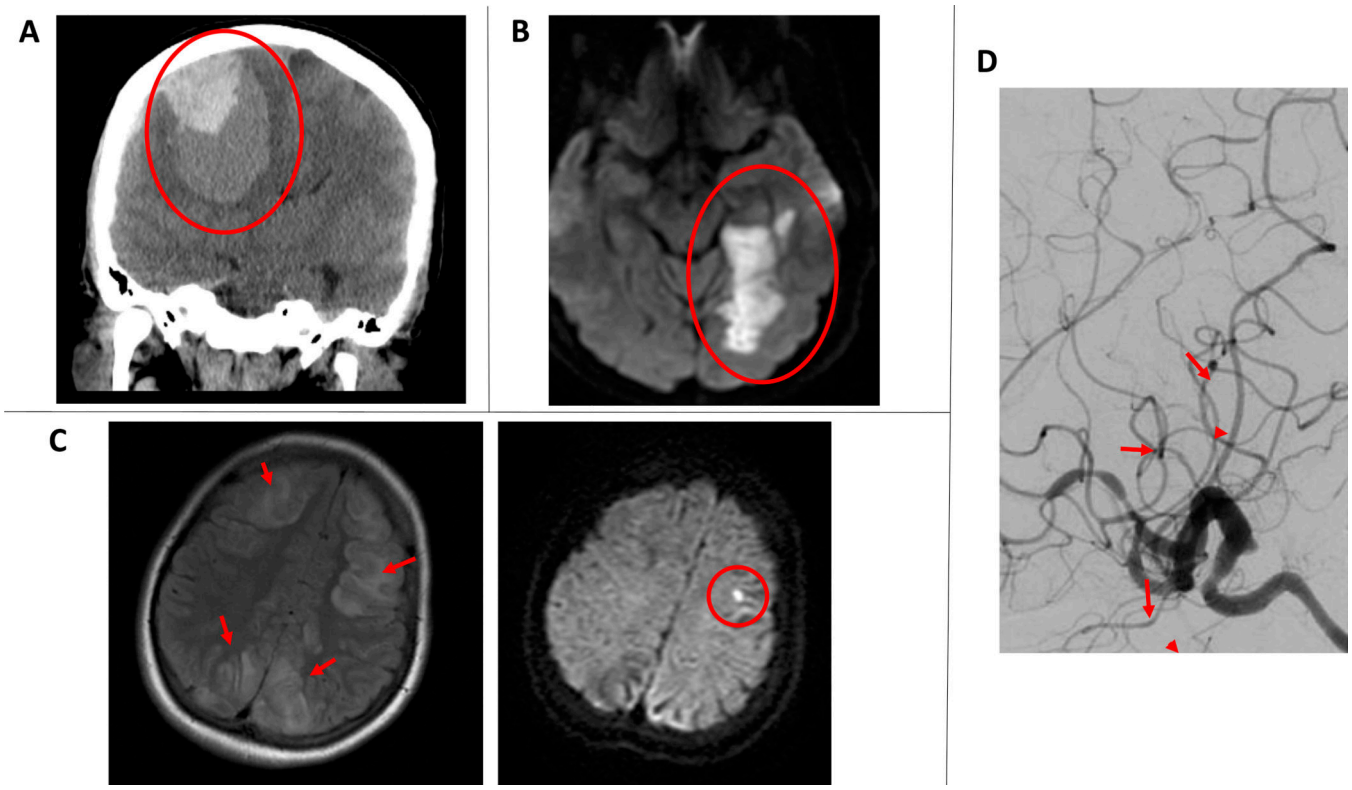

Figure 2:

Examples for cases of maternal stroke.

(A) Right frontal intracerebral hemorrhage with surrounding edema and brain herniation in a post-partum woman with the HELLP syndrome. No underlying vascular lesion was identified, and the stroke was felt like due to hypertension and HELLP-related coagulopathy; (B) Arterial ischemic stroke due to paradoxical embolus related to patent foramen ovale, although no deep venous thrombosis was identified to left posterior cerebral artery in a post-partum woman; (C) Multifocal vasogenic edema due to the posterior reversible encephalopathy syndrome (PRES) in a woman with eclampsia. Note that not all lesions are posterior. A small area of infarction on diffusion-restricted imaging is noted, occasionally seen in association with PRES. (D) Cerebral angiogram demonstrating multifocal vasospasm due to reversible cerebral vasoconstriction syndrome in a postpartum woman with pre-eclampsia. She developed ischemic strokes distal to the areas of vasospasm, as well as intracerebral hemorrhage.

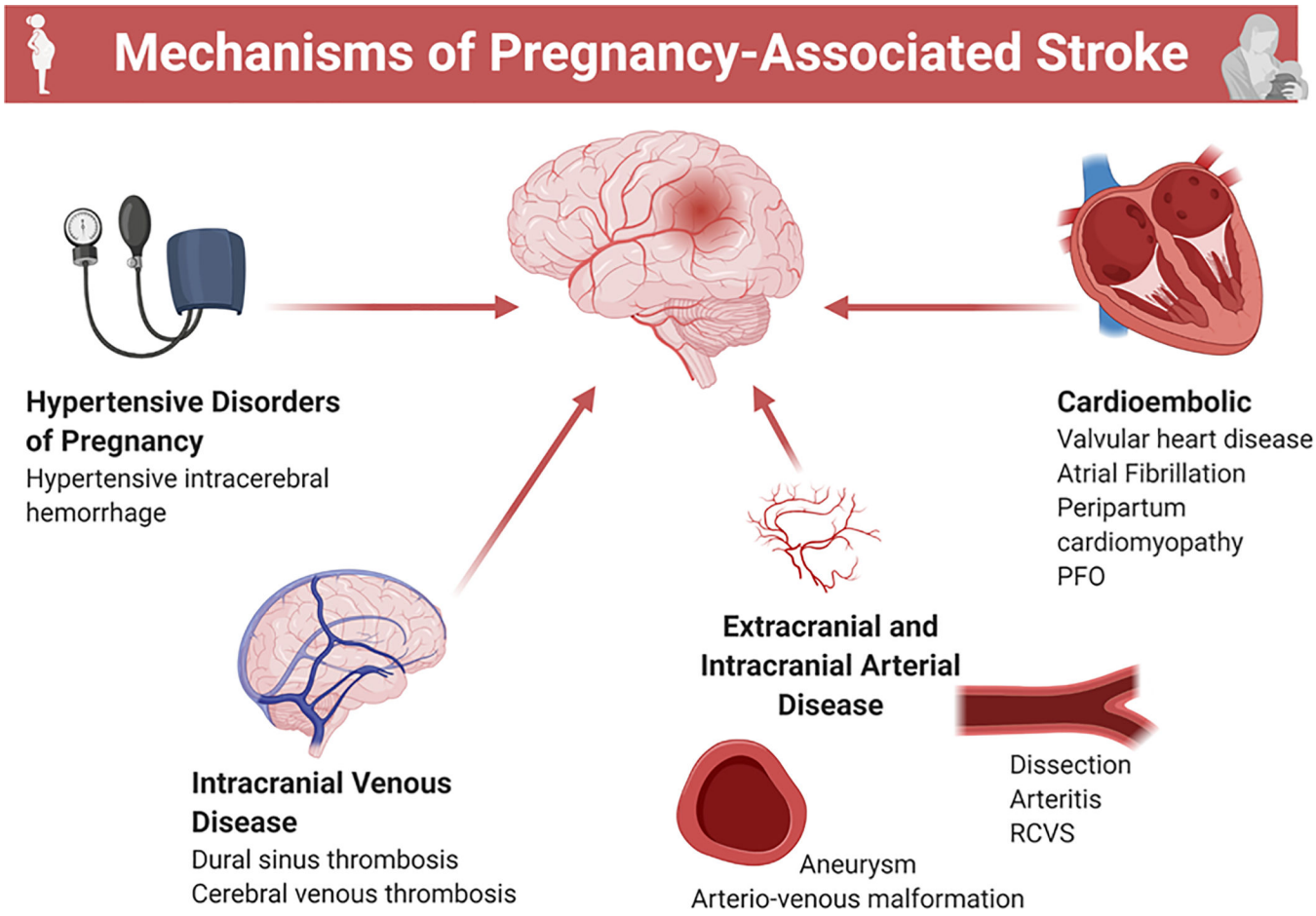

Figure 3:

Potential mechanisms of maternal stroke.

Summary of possible mechanisms of maternal stroke.

PFO= patent foramen ovale; RCVS= reversible cerebral vasoconstriction syndrome

Table 1:

Rates of maternal stroke across different nations

Study	Country	Enrollment period	Pregnant/post-partum women, n	Incidence of maternal stroke (per 100,000)	Mean age of women with stroke, years
Elgendy et al.[16]	USA	2007–2015	37,360,772	45	30
Liu et al.[17]	Canada	2003–2016	3,907,262	13.4	NR
Yoshida et al.[19]	Japan	2012–2013	2,115,949	10.2	32.2
Sharshar et al.[8]	France	1989–1992	669,680	4.6	30.6
Bashiri et al.[20]	Israel	1988–2004	173,803	9.2	35.5
Liang et al.[21]	Taiwan	1992–2004	66,781	47.9	30.1
Prabhu et al.[12]	India	2006–2008	39,211	66	22

NR: not reported

Table 2:

Risk factors for preeclampsia

High risk factors:
History of preeclampsia
Multifetal gestation
Renal disease
Autoimmune disease
Type 1 or type 2 diabetes
Chronic hypertension
Moderate risk factors:
First pregnancy
Maternal age of 35 years or older
Body mass index greater than 30
Family history of preeclampsia
Sociodemographic risk factors (African American race, low socioeconomic status)
Personal history factors (low birth weight or small for gestational age, previous adverse pregnancy outcome, more than 10-year pregnancy interval)

Prophylactic low dose aspirin is recommended before 16 weeks of gestation until the day of delivery among women with one high risk factors or two or more moderate risk factors

Table 3:

Knowledge gaps related to maternal stroke

1.	Mechanisms of maternal stroke A. Understanding mechanisms related to known risk factors including HDP, migraine and infections B. Identification of other risk factors.
2.	Development and validation of risk prediction tools to identify women who are at increased risk for maternal stroke.
3.	Consideration of enrollment of pregnant and post-partum in future randomized controlled trials of therapies for acute ischemic stroke.
4.	Risk factor control strategies, including individualized blood pressure goals, prenatal care plan and preventive approaches for high-risk groups and racial groups.
5.	Investigating the impact of aggressive blood pressure control in HDP on the prevention of maternal stroke.
6.	Need for large-scale studies to evaluate the risk of stroke recurrence in women with maternal stroke, especially hemorrhagic stroke.

HDP= hypertensive disorders of pregnancy

Table 4:

Call for action- Clinical practice and healthcare settings

1.	Improved prenatal patient education of cardiovascular risk factors, symptoms of cardiovascular complications of pregnancy, and the importance of long-term preventative care among reproductive age women.
2.	Implementation of multidisciplinary healthcare team education and maternal stroke toolkits to improve recognition of cardiovascular complications and standardization of maternal healthcare delivery.
3.	Reduction of socioeconomic disparities in maternal cardiovascular outcomes, through increased access to healthcare coverage for pregnant and postpartum women, increased access to maternal healthcare in rural areas, and efforts to address systemic racism.
4.	Targeted efforts to reduce knowledge gaps in maternal cardiovascular health, through increased funding for maternal cardiovascular research and increased inclusion of pregnant and postpartum women in clinical trials.