Pregnancy and Cardio-embolic Stroke: To Recanalize or Not?

Sir,

Acute ischemic stroke (AIS) is the fifth leading cause of death and disability worldwide.[1] AIS associated with pregnancy and puerperal period is a rare but devastating complication, with an incidence of 1.5–67.1 strokes/100,000 deliveries,[2-4] and pregnant women are more prone to stroke than non-pregnant counterparts.[2] Approximately, 10 percent of strokes occur in the antepartum period, 40 percent occur proximate to delivery, and 50 percent occur in the postpartum period.[2-4] The predisposing mechanisms for AIS include altered hemodynamics, pre-eclampsia/eclampsia, peripartum cardiomyopathy, amniotic fluid embolism, and cerebral angiopathy, over and above the traditional risk factors.[5]

However, pregnancy was an exclusion criterion for all recanalization trials (thrombolysis and endovascular thrombectomy [EVT]), leading to the absence of evidence for AIS management in these patients. Therefore, treatment was based on data gathered from case reports and series that have proven that thrombolysis and mechanical thrombectomy are both safe and efficacious in this patient population.[5,6] We report three cases of pregnancy-associated stroke with good functional outcomes in the two who underwent EVT and thrombolysis.

CASE 1: A 26-year-old lady, G1P0L0, known case of rheumatic heart disease (RHD) with atrial fibrillation for the past 5 years, post mitral valve replacement one year ago, on warfarin 4 mg daily; International normalized ratio (INR)-1.6, presented to our emergency at 28 weeks period of gestation with sudden onset dizziness and altered sensorium of 3 h duration. She had an irregularly irregular pulse, and her Glasgow Coma Scale (GCS) score was E2V1M5 at presentation, and was intubated because of poor GCS. Reflex movements of all limbs were noted, but ill-sustained on painful stimuli application (National Institute of Health Stroke Severity [NIHSS] score - 21; modified Rankin Scale score [mRS] - 5). Non-contrast computed tomography (NCCT) head with abdominal shield showed normal brain parenchyma [Figure 1a] with craniovertebral junction abnormality in the form of basilar invagination and atlantoaxial dislocation [Figure 2]. CT angiography of head and neck vessels revealed a filling defect in the region of basilar top and proximal P1 segments of both posterior cerebral arteries [Figure 1b]. Both vertebral arteries had an anomalous course, and the left vertebral artery was hypoplastic. She was thrombolyzed with alteplase and taken up for EVT using a Solitaire device [Figure 1c and d]. The procedure was partially successful with the distal run-off of the embolus into the right posterior cerebral artery [Figure 1d]. Post-procedure she improved to E4VtM6 status and was weaned off her ventilatory support and extubated. Three days post-EVT, her NIHSS score improved to 2 and mRS to 1, and she was discharged on low molecular weight heparin. She delivered a healthy girl child by elective cesarean section at 38 weeks of gestation. She is planned for surgery for the craniovertebral junction anomaly.

CASE 2: A 26-year-old lady, G5P0L0A4, known case of RHD and atrial septal defect (ASD) for the past 10 and 18 years respectively, who underwent mitral valve repair and ASD closure 5 years back, was on anticoagulation (warfarin 3 mg once daily; INR-2.5) and single antiplatelet (aspirin 150 mg OD). She was admitted to the department of gynecology and obstetrics at 36 weeks +1 day of gestation for heparin switchover for term preparation as her probability of requiring a cesarean section was high. Warfarin was switched to unfractionated heparin (UFH) infusion with coagulation parameter monitoring. She went into labor at 38 weeks but had poor progression, and the decision for an emergency cesarean section was made, and UFH stopped. Three hours after stopping heparin, she developed sudden onset right upper limb weakness (power - 2/5) and numbness (70% decrease in sensations) (NIHSS-6). NCCT head with the abdominal shield was normal. Her two-dimensional echocardiography (2D-ECHO) showed a normal ejection fraction without any clots/vegetation. She had to be managed conservatively for AIS, was taken for emergency cesarean section, and delivered a healthy male child. Six hours post-surgery, UFH was restarted, followed by a switch back to warfarin on discharge (NIHSS-6). Her power gradually improved to 4-/5 with complete resolution of numbness in the ensuing 3 months (NIHSS-3, mRS-2).

CASE 3: A 25-year-old lady, G1P0L0, known case of RHD for 8 years, post percutaneous balloon mitral valvotomy, not on treatment, presented to our emergency with twin pregnancy of 20 weeks period of gestation and sudden onset left hemiplegia of 30 min duration. Her NIHSS and mRS at presentation were 13 and 3, respectively. NCCT head (with abdominal shield) was normal [Figure 3a] and CT angiography of head and neck vessels revealed a distal right M1-middle cerebral artery (MCA) occlusion [Figure 3b]. She was thrombolyzed by tissue plasminogen activator (t-PA) followed by EVT

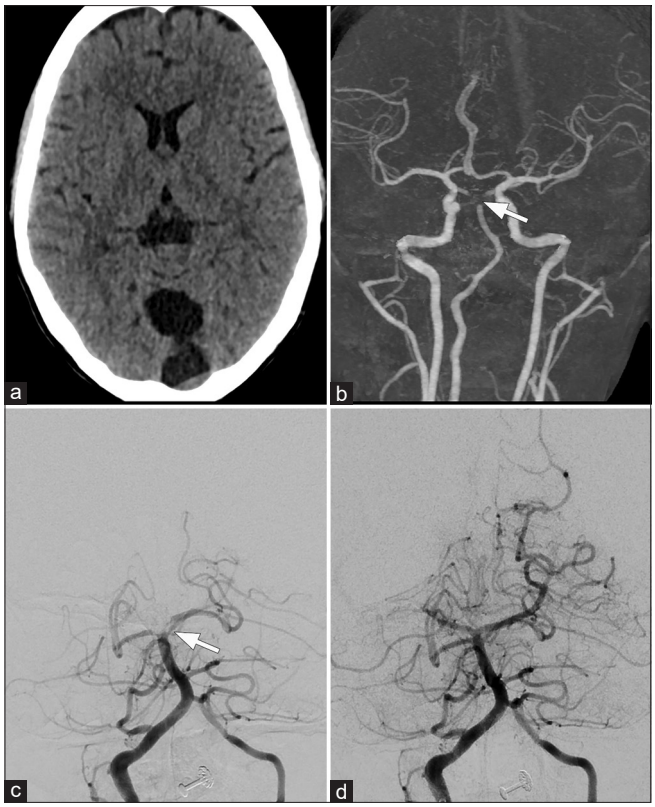

Figure 1: Axial non-contrast CT head (a) at the level of basal ganglia is normal. MIP images of CT angiogram (b) and right vertebral artery angiogram (c) images reveal a filling defect (arrows in b and c) in the region of basilar top and proximal posterior cerebral arteries. Post-thrombectomy right vertebral angiogram (d) shows resolution of filling defect; however, there is a paucity of right PCA cortical branches in the occipital region

using the Solitaire device and showed improvement in the power of left upper and lower limbs (power-5/5 and 4/5, respectively; NIHSS-1 and mRS-1), within 24 h post-procedure [Figure 3c and d]. 2D-ECHO did not reveal any clot or vegetations and she was in sinus rhythm. She was discharged on day 3 on warfarin (INR-2.2). Warfarin was switched to low molecular weight heparin at 36 weeks of gestation, and she delivered healthy twin boys at 37 weeks.

Managing an AIS during pregnancy or puerperium is complicated due to inherent risks to both the mother and the fetus/child and limited scientific evidence. This patient population was excluded from all major stroke trials, and through our case series, we emphasize the safety and efficacy of thrombolysis and EVT during pregnancy and the puerperal period. All our patients had a cardio-embolic stroke, and those who underwent recanalization improved post-treatment, delivered healthy children, and had no treatment-related adverse events.

Recombinant t-PA given to the mother does not reach fetal circulation as its large molecular size prevents it from crossing the placental barrier.[7] Maternal hemorrhagic and mortality risk was found to be approximately 8% and 1.2%, respectively, with its use.[8] American Heart Association (AHA)/American

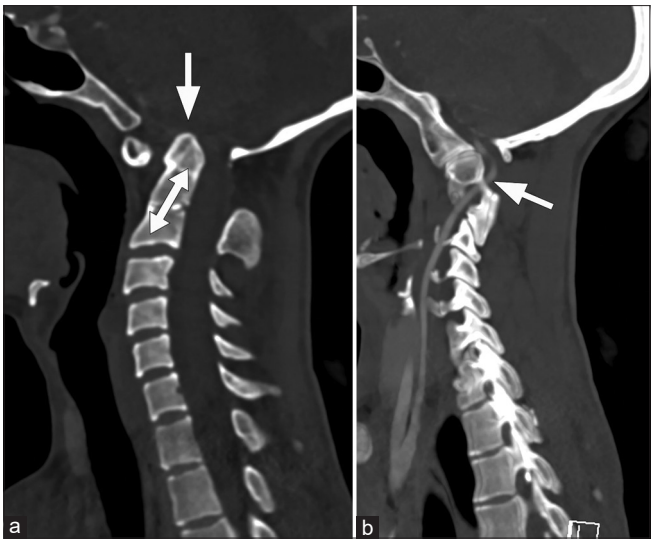

Figure 2: Sagittal reconstructed images of the cervical spine (a) show basilar invagination (arrow), atlantoaxial dislocation (small arrowhead), a fusion of the body of C2 and C3 vertebra (double-head arrow), and occipitalization of the posterior arch of C1 vertebra (arrowhead). Parasagittal image of CTA (b) shows the anomalous course of the right vertebral artery below C1

Stroke Association (ASA) guidelines recommend (Class IIb, grade C) its administration when anticipated benefits outweigh the risk of uterine bleeding.[9] Our patient developed a stroke during labor and was not thrombolyzed because she needed an operation within the next 24 h. She Post-delivery heparin was restarted and did not develop any bleeding manifestation (systemic or intracranial).

Two of our patients underwent EVT (one each for anterior and posterior circulation) with good functional outcomes and without adverse events. A study by Dicpinigaitis *et al*.[5] evaluated pregnancy-related strokes between 2012 and 2018 and found 180 cases that underwent EVT. These patients were found to have lower intracranial hemorrhage rates when compared to non-pregnant female patients (11% versus 24%, *p*-0.069) and similar rates compared to medically managed pregnant AIS patients. After adjusting for age, stroke, and illness severity, the multivariable analysis revealed pregnancy/puerperium to be independently associated with a lower likelihood of intracranial bleeding (adjusted odds ratio-0.26, *p*-0.008). Compared to medically managed pregnant women, EVT-treated women experienced a higher frequency of venous thromboembolic events (17% versus 0%, *p*-0.001) but lower pregnancy-related complications (44% versus 64%, *p*-0.034). Importantly, none of the pregnant/puerperal women who underwent EVT experienced a miscarriage or mortality during hospital admission.

Another study by Limaye *et al*.[6] described seven patients who underwent EVT, three of which received pre-EVT thrombolysis. They all had a good functional outcome (mRS 0-2 at 3 months), and most achieved mTICI 2b or higher grade post-EVT

Figure 3: Axial non-contrast CT head (a) shows focal hyperdensity (arrow in a) in the region of the right sylvian fissure suggestive of thrombus. Frontal projection of CTA (b) shows abrupt cutoff of right distal M1 with a poor filling of proximal MCA divisions. Right ICA angiogram (c) shows a focal filling defect in the distal M1 segment, which resolved following thrombectomy using stent-retriever (d)

recanalization. These good outcomes are possible because of the younger age of this patient population and the relative absence of vascular risk factors. They also reported the absence of any fetal abnormalities or issues secondary to treatment or exposure to iodinated contrast. Animal studies revealed an absence of contrast-induced teratogenic or mutagenic effects, and human studies did not demonstrate an inhibitory effect on the thyroid function of the neonate.[10]

The radiation exposure to the fetus is minimal with CT scans done outside the abdomen and pelvis as scatter radiations are very minimal with thin-beam of CT scans. Though not necessary, we used a lead shield over the abdomen to provide reassurance and protection to the patient.[11] We used the automatic exposure control to modulate CT tube current automatically in response to variations in x-ray intensity at the detector to reduce radiation dose by up to 40%. In addition, a lower tube potential of 80 kV was used to reduce radiation (a high contrast-to-noise ratio (CNR) technique allows us to lower kV).[12,13] Advanced Modeled Iterative Reconstruction (ADMIRE) algorithm was also employed in our scanner to reduce radiation dose while maintaining image quality during CT examination. The effective radiation dose during CT angiography of the head and neck is between 1.12 and 1.34 mSv (360–440 mGycm) in our set-up. We did not advise medical termination of pregnancy as the radiation from a CT scan is in a very thin beam, and there is very little, if any, scattered radiation below the neck.

Thrombolysis and EVT are safe and effective for treating carefully selected pregnant patients with AIS. We strongly recommend considering AIS during pregnancy or puerperium, especially due to large vessel occlusion. However, more extensive multi-center collaborative studies are required before they can be incorporated as the standard of care in this population of patients.

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Conflicts of interest

There are no conflicts of interest.

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