Thrombolytic Therapy for Ischemic Stroke Secondary to Paradoxical Embolism in Pregnancy A Case Report and Literature Review

Yuebing Li, MD, PhD, John Margraf, MD, Bryan Kluck, DO, Donna Jenny, RN, and John Castaldo, MD

Introduction: Thrombolysis for acute ischemic stroke has been rarely administrated during pregnancy. Paradoxical embolism through a patent foramen ovale (PFO) or pulmonary arteriovenous malformation (AVM) is an identified risk factor for ischemic stroke.

Case Report: We report a 24-year-old woman at 11 weeks gestation who developed a sudden onset of dysarthria, hemiparesis, and hemisensory loss. She was diagnosed as having an ischemic stroke in the left middle cerebral artery (MCA) territory. She was treated with intra-arterial recombinant tissue plasminogen activator with subsequent resolution of her neurological deficits. Further workup revealed the presence of a PFO with a large right-to-left shunt. After being put on antithrombotic therapy, she presented again at 13 gestational weeks with a new ischemic infarction in the vertebrobasilar territory. Her PFO was closed percutaneously under ultrasonic guidance but the right-to-left shunt persisted. After a normal delivery, she was found to have a large pulmonary AVM which was successfully resected without complication.

Conclusions: This report describes the successful usage of intraarterial tissue plasminogen activator for acute ischemic stroke during early pregnancy. In patients with presumed paradoxical embolism, careful attention should be paid to rule out a coexistence of PFO and pulmonary AVM.

Key Words: stroke, cerebrovascular disease, pregnancy, patent foramen ovale, pulmonary arteriovenous malformation

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Thrombolytic therapy with recombinant tissue plasminogen activator (rt-PA) is an approved therapy for ischemic stroke. However, there are no data about the efficacy and safety of rt-PA in pregnant patients from randomized controlled trials. A tendency for hypercoagulation is generally observed during pregnancy, so pregnant patients have a stronger risk for venous and arterial thromboembolism.¹ Recent studies indicate that embolic stroke could be caused by paradoxical emboli through either a patent foramen ovale (PFO) or pulmonary arteriovenous malformation (AVM) during pregnancy.^{2,3}

CASE REPORT

A 24-year-old white female suddenly collapsed at 8 PM. She arrived at our hospital at 10:32 PM. Her blood pressure was 120/75 mm Hg. She was alert and able to name objects with a moderate dysarthria.

Reprints: Yuebing Li, MD, PhD, 1250 S. South Cedar Crest Boulevard, Suite 405, Allentown 18103, PA. E-mail: Yuebing.Li@lvhn.org.

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She had a mild right facial weakness, plegia in the right arm and leg, and dense right-sided sensory deficits. Her initial noncontrast computed tomography (CT) image (Fig. 1) showed a dense left MCA without intracranial hemorrhage. She was diagnosed with an acute ischemic stroke, with a National Institute of Health stroke scale score of 13. She was found to be 11 weeks pregnant (G4P3) and she reported sexual activity immediately before the onset of her symptoms. Her only past medical history included gestational diabetes during a previous pregnancy. She had no previous history of excessive bleeding or recent surgery. Her platelet count, prothrombin time, and serum glucose were all normal.

A plan to perform urgent cerebral arteriography and treat with intra-arterial rt-PA or mechanical removal of the clot was discussed and consent obtained. A left carotid arteriogram demonstrated a thrombus at the left M1 bifurcation without evidence of arterial dissection. Recombinant tissue plasminogen activator was infused into the thrombus starting at 4 hours after the stroke onset. A total of 25 mg was given intermittently over a period of 2 hours, leading to a complete lysis of the thrombus. After procedure she had a normal strength in the right leg and a very mild drift in the right arm. Head CT 24 hours later showed a small area of low attenuation in the left corona radiata without hemorrhage.

Her electrocardiogram was normal. There was no family history of stroke, deep venous thrombosis, or pulmonary embolism. Her blood tests were normal except for a minimally decreased protein S level. Her sedimentation rate, prothrombin gene mutation assay, protein C, antiphospholipid antibody, and antinuclear antibody were all normal. Her echocardiogram with bubble contrast revealed the presence of a PFO with a significant right-to-left shunt and an atrial septal aneurysm (ASA). Her lower extremity duplex scan was normal. Pelvic magnetic resonance venogram was not performed.

Enoxaparin injections twice daily and aspirin daily were started considering the hypercoagulable state associated with pregnancy. She was discharged with a mild right facial weakness and slight ataxia on the right heel-to-shin test (National Institute of Health stroke scale score of 2). One week later, she presented with a sudden onset of right facial numbness and a normal neurological examination. Magnetic resonance imaging of her brain showed restricted diffusion in the left cerebral peduncle, left anterior medial thalamus, and the posterior limb of the left internal capsule (Fig. 2).

Because of the occurrence of strokes in separate arterial (left carotid then vertebrobasilar) territories, it was felt that the source of her stroke could be a central embolism such as paradoxical emboli through a PFO. She underwent a percutaneous PFO closure under intracardiac echocardiographic guidance at 13 weeks gestation. No cinefluoroscopy was used to minimize fetal radiation risk. Two days after the procedure, an echocardiogram with bubble contrast showed a persistent right-to-left shunt that was felt to be trans-device. Enoxaparin injections were continued throughout the remainder of her pregnancy but aspirin was discontinued in the third trimester.

The patient delivered a healthy baby girl at 39 weeks gestation under induction by vaginal delivery. A repeat echocardiogram with bubble contrast showed a persistent right-to-left shunt. Subsequent cardiac catheterization and intracardiac echocardiogram revealed a well-seated PFO-closing device without any identifiable atrial septal defect with catheter probing. However, a large amount of bubble flow

From the Division of Neurology, Department of Medicine, The Lehigh Valley Health Network, Allentown, PA. The authors declare no conflict of interest

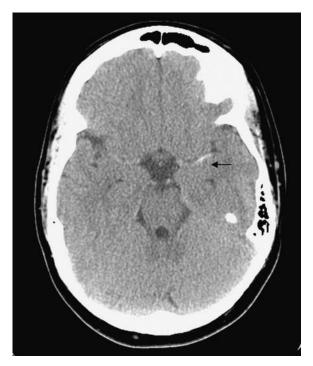


FIGURE 1. Noncontrast computed tomographic (CT) scan of the head. The CT scan shows a thrombus in the left middle cerebral artery (arrow).

was again seen in the left atrium after a delay of 3 cardiac cycles. A plain chest x-ray was normal. A pulmonary arteriogram demonstrated a large left lower lobe pulmonary AVM measuring approximately 5.5×3.4 cm (Fig. 3). The patient underwent a left lower lobe segmentectomy at 7 months postpartum. Her anticoagulation was eventually discontinued after segmentectomy. Sixteen months after the resection no further ischemic events have occurred.

DISCUSSION

Because of a series of prothrombotic changes in the hemostatic system, pregnancy is associated with an increased risk for both venous and arterial thromboembolism. Approximately 20% of the vascular events occurring during pregnancy are arterial and 80% venous. The risk of venous thromboembolism

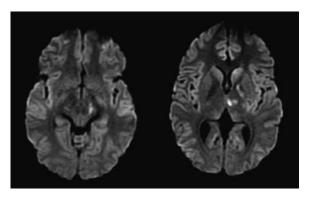


FIGURE 2. Magnetic resonance imaging scan of head. On diffusion-weighted imaging, foci of new ischemia can be seen in the left cerebral peduncle, the left anterior medial thalamus, and the posterior limb of the left internal capsule.



FIGURE 3. Pulmonary arterial angiography. A large arteriovenous malformation is shown.

is the highest in the third trimester and immediately postpartum, but an increased risk of venous thromboembolism is clearly present from the first trimester.¹ The incidence of stroke during pregnancy has been estimated to be 5 to 15 per 100,000. A significant portion of the strokes occur later in pregnancy, with the highest occurrence around the third trimester and immediately postpartum.⁴ Nearly 5% of maternal deaths are the result of stroke and approximately half of pregnancy-associated stroke survivors have residual neurological deficits.⁵ Fetal complications from maternal stroke include premature delivery and death. Thus, treatment and prevention of stroke in pregnancy may have a significant impact on the morbidity of both the mother and fetus.

When used appropriately, thrombolytic therapy decreases the morbidity of acute ischemic stroke in nonpregnant patients.⁶ No controlled trials have been performed using thrombolytic agents such as streptokinase, urokinase, or rt-PA for treatment of pregnancy-related thromboembolic events. Turrentine et al⁷ summarized a total of 172 patients receiving mostly streptokinase during pregnancy for predominant venous thromboembolism. There were 10 (5.8%) pregnancy losses and 2 (1.2%) maternal mortalities.

Newer agents such as rt-PA may add a margin of safety because of their fibrin specificity, absence of antigenicity, and shorter half life. Although studies using rt-PA have listed pregnancy as an exclusion criterion, rt-PA is a category C drug indicating it could be used when benefits justify potential risk. A literature review demonstrated that more than 30 pregnant women received rt-PA for myocardial infarction, pulmonary embolism, prosthetic valve thrombosis, deep venous thrombosis, or cerebral venous thrombosis. Complication rates were similar when compared with nonpregnant patients.⁸ Animal studies did not find evidence for teratogenicity and rt-PA does not cross the placenta.⁹ So far, limited usage of rt-PA in humans does not support a teratogenic risk.⁸

A literature review of all available cases focusing on using rt-PA for acute ischemic stroke in pregnancy suggests a very favorable outcome (Table 1).^{9–15} Complete or significant neurological recovery was seen in 10 of 11 mothers and 8 of 8

TABLE 1. (TABLE 1. Cases of Using rt-PA for Stroke During Pregnancy	or Stroke Durin	ig Pregnancy						
Patient				Stroke	Location of				
No.	References	Trimester	Route of rt-PA	Etiology	Stroke	SSHIN	Hemorrhage	Mother Status	Infant Status
1	Dapprich and Boessenecker ¹⁰	First	Intravenous	Low protein S	Left MCA	N/A	Small left basal-ganglia hemorrhage	Markedly improved	Healthy infant
7	Elford et al ¹¹	First	Intra-arterial	Ovarian hyperstimula- tion syndrome	Right MCA	11	Small right basal- ganglia hemorrhage	Markedly improved neurological status	Healthy Infant
з	Johnson et al ¹²	Third	Intra-arterial	Probable low protein S	Right MCA	20	No hemorrhage	Marked improvement with persistent MCA occlusion	Healthy infant
4	Leonhardt et al ⁹	Third	Intravenous	Antiphospholi- pid antibody	Left MCA	N/A	No hemorrhage	Good	Healthy infant
S	Wiese et al ¹³	Second	Intravenous	Mechanical valve prosthesis	Left MCA	13	No hemorrhage	Residual NIHSS of 4	Healthy infant
9	Murugappan et al ¹⁴	First	Intravenous	Mechanical valve prosthesis	Right MCA	19	Minor complication of intrauterine hematoma	Recovered well	Medical termination of pregnancy
٢	Murugappan et al ¹⁴	First	Intravenous	Decreased protein S activity	Left MCA	19	No hemorrhage	Recovered well	Medical termination of pregnancy
×	Murugappan et al ¹⁴	First	Intravenous	Mechanical valve prosthesis	Right MCA	13	Significant intracranial hemorrhage	Death from dissection during angioplasty	Fetus died with mother
6	Murugappan et al ¹⁴	Third	Intra-arterial	Low protein C and S protein level and antithrombin III level	Left MCA	25	No hemorrhage	Recovered well	Healthy infant
10	Yamaguchi et al ¹⁵	Second	Intravenous	Elevation of factor VIII level	Left MCA	6	No hemorrhage	Complete recovery	Healthy infant
11	Current case	First	Intra-arterial	PFO/ASA and/ or pulmonary AVM?	Left MCA	13	No hemorrhage	Complete recovery	Healthy infant
ASA indi tissue plasmin	ASA indicates atrial septal aneurysn tissue plasminogen activator.	n; AVM, arteriove	nous malformation; MCA	, middle cerebral artery;	N/A, not available; N	IHSS, Nationa	ASA indicates atrial septal aneurysm; AVM, arteriovenous malformation; MCA, middle cerebral artery; N/A, not available; NIHSS, National Institute of Health stroke scale; PFO, patent foramen ovale; rt-PA, recombinant te plasminogen activator.	PFO, patent foramen ov	ıle; rt-PA, recombina

continuing pregnancies ended with normal delivery. In 1 case (Case no. 8), both the mother and the fetus suffered a poor outcome which may be attributed to cerebral angioplasty rather than the usage of rt-PA alone. These cases seem to suggest that benefits of rt-PA thrombolysis outweigh risks when given to pregnant women for ischemic stroke. Awaiting large controlled studies, rt-PA should not be withheld in pregnant patients with acute ischemic stroke who otherwise fit criteria for rt-PA treatment.

There are 3 options for using rt-PA for acute ischemic stroke: standard dose of intravenous (IV) rt-PA with no further treatment, IV rt-PA followed by endovascular treatment, or endovascular treatment without previous IV rt-PA. The first 2 options minimize the time to treatment, and effectiveness of rt-PA has been shown to be strongly related to time to the initiation of therapy.¹⁶ The intra-arterial usage of rt-PA, although extending the treatment window of ischemic stroke from 0-3 to 0-6 hours, might delay treatment but allow less concern of teratogenic effects and hemorrhagic complications with a lower dosage. Altogether 7 of the 11 reported cases received IV rt-PA and 4 received intra-arterial.

The most common causes of stroke in the young population are cardioembolism, arterial dissection, migrainous stroke, drug use, and vasculitis. Pregnancy has its own unique risks of stroke especially in the peripartum period during which venous sinus occlusions, eclampsia, and vasculopathy of the peripuerium are the most common causes. Cardioembolism occurs in >30% of young patients with an identifiable cause of stroke, and is a common cause of pregnancy-related stroke as well.¹⁷ Paradoxical embolism has become an increasingly recognized cause of stroke, particularly in young patients without vascular risk factors. Abnormal venous-arterial channels include PFO, congenital cardiac defect, patent ductus arteriosus, and pulmonary AVMs. A significantly increased role of paradoxical embolism could exist for stroke pathogenesis during pregnancy because of the increased risk of venous thromboembolism. Elevation of intracardiac or intraabdominal pressure such as Valsalva maneuver or straining may invert the pressure gradient between the arterial and venous systems, facilitating the right-to-left shunting of emboli.

Because of the relatively high incidence of PFO in the general population, an etiological link between PFO and stroke should be interpreted with caution. Predictors for recurrent paradoxical embolism in PFO include a history of more than 1 embolic event or the coexistence of an ASA. The 2004 American Academy of Neurology practice parameter concluded that the combination of PFO and ASA possibly confers increased risk for subsequent stroke in medically treated patients younger than 55 years old compared with other cryptogenic stroke patients without atrial septal abnormalities.¹⁸ There is no clear evidence that PFO closure is better than medical therapy. Robust data are pending with several large randomized controlled clinical trials currently recruiting. Recent American Stroke Association guidelines recommend the use of aspirin for secondary stroke prevention, with warfarin reserved for high-risk patients with PFO. Consideration of PFO closure is an option for patients with recurrent cryptogenic stroke despite of optimal medical therapy.¹⁹

This case dealt with a young healthy female without other identifiable causes of stroke. Both of her strokes occurred during early pregnancy. The first episode occurred during vigorous physical activity. Evidence of a large right-to-left shunt was detected and it was initially felt to be secondary to the presence of a PFO. Because of the coexistence of a PFO and ASA, and because the second ischemic episode occurred on full-dose anticoagulation, it was felt that the risk of a recurrent thromboembolic event during her remaining pregnancy, labor, and delivery would markedly increase. The treating neurologist, cardiologist, and obstetrician agreed that her PFO should be corrected promptly while her anticoagulation continued. Such a PFO device closure in pregnancy presents specific challenges due to the fear of fetal radiation exposure. The procedure was successfully performed under the guidance of intracardiac echocardiography and limited fluoroscopy. Both the patient and the fetus tolerated the procedure well.

However, it is important to recognize that the appearance of left atrial bubbles on contrast-echocardiography indicates a shunt but does not necessarily specify its location. Pulmonary AVM can produce early appearances of bubbles in the left atrium and can be misinterpreted as a PFO. In general, bubbles through a right-to-left shunt at the pulmonary level appear in the left atrium 3 to 5 beats after it is seen in the right atrium, whereas bubbles through an intra-atrial shunt appear in the left atrium on the same or subsequent cycle as the right atrium.²⁰ Shunts beyond the left atrium should have a longer delay of bubbles appearing in the left atrium. The continued presence of a shunt after PFO closure should prompt careful review of the echocardiogram with particular attention to the timing of bubbles. In this patient, the successful PFO closure unveiled the presence of a large pulmonary AVM as another possible channel of paradoxical embolism.

Pulmonary AVMs are caused by abnormal artery-to-vein connections that result in a right-to-left shunt. Pulmonary AVMs may be isolated or seen within the context of hereditary hemorrhagic telangiectasia, also known as Rendu-Osler-Weber syndrome. The lesions usually enlarge with age and many become clinically apparent in adulthood. Pulmonary AVMs may expand during pregnancy because of increased pulmonary blood flow and increased venous distensibility due to high levels of estrogen and progesterone. Pulmonary AVMs can be suspected based on transcranial Doppler findings with saline contrast medium that detects microembolic signals through the MCA and a transesophageal echocardiogram that does not demonstrate a PFO. Selective pulmonary angiography and/or enhanced chest CT then can be performed to confirm the presence of pulmonary AVMs. For pregnant patients, a ventilation and perfusion scan can be used to diagnose, minimizing radiation. When a PFO coexists with pulmonary AVM, the early passage of contrast bubbles through the PFO may prevent identification of a concomitant pulmonary AVM, as in this case.

The association of stroke with hereditary hemorrhagic telangiectasia-associated pulmonary AVMs is well described in the literature, with prevalence varying from 10% to 18% for stroke and 6.5% to 37% for transient ischemic attack.²¹ The association of isolated pulmonary AVMs is less well documented. A recent study analyzing a population of 747 middle-aged patients with ischemic stroke disclosed the presence of isolated pulmonary AVMs in only 4 cases.²² Our patient had no history of recurrent nose-bleeds or telangiectasia and no positive family history. Embolization was not an option because of the size of her pulmonary AVM and a surgical resection was performed successfully after pregnancy without complication.

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