A 27-year-old right-handed woman who was 2 weeks postpartum awoke with left-sided weakness and dysarthria. In the emergency room, her National Institutes of Health stroke scale was 4 with points received for a left-sided hemiparesis. Computed tomography of the brain was negative for hemorrhage and she was given aspirin 325 mg. Magnetic resonance imaging showed an ischemic stroke in the centrum semiovale. Magnetic resonance angiography of the head and neck showed no intracranial or extracranial atherosclerosis. Transthoracic echocardiography revealed a patent foramen ovale (PFO) with right to left shunt (Figure). Echocardiography was otherwise unremarkable. She had a low-density lipoprotein level of 153 mg/dL. A hypercoagulable workup (Factor V Leiden, methylenetetrahydrofolate reductase mutations 677C>T and 1298A>C, prothrombin factor II, antinuclear antibody, extractable nuclear antigens, anticardiolipin antibody, β2-glycoprotein, C-reactive protein, homocysteine, protein C and S, and protein electrophoresis with immunofixation) was unremarkable. She was started on aspirin and a statin. Anticoagulation was not considered because of persistent vaginal bleeding. The mechanism of the stroke was felt to be either small vessel disease or paradoxical embolism. She was discharged home with physical therapy. One week later she complained of pain in the left lower extremity with calf tenderness. A venous duplex ultrasound was negative for deep vein thrombosis (DVT). However, 2 weeks later the left calf became swollen and a repeat ultrasound showed acute DVT involving the distal femoral, popliteal, and posterior tibial veins. She was admitted to the hospital and treated with intravenous heparin followed by oral warfarin. An intrauterine device was placed for birth control. She came to her follow-up appointment with questions about the increased volume of blood during pregnancy. Protein S activity is decreased and there is increased resistance to protein C activity. In addition, fibrin concentration is increased and intrinsic fibrinolysis is reduced, thereby limiting the anticoagulants within the blood.1

Hypercoagulability during pregnancy and the postpartum period compounded with relative patient inactivity results in increased thrombosis, most commonly seen in the venous system. Interestingly, DVT occurs more commonly in the left lower extremity, which is felt to be because of compression of the left femoral vein by the right femoral artery.2 Known as May–Thurner syndrome, this compression results in reduced venous return and is worsened by pregnancy. Importantly, DVT is not limited to the extremities. Compression of the pelvic venous plexus during pregnancy can result in increased stasis, and, in the setting of a hypercoagulable state, lead to thrombus formation.1 Pelvic vein thrombosis will not be found on lower extremity duplex but can be detected with magnetic resonance venography.3 The incidence of pelvic vein thrombosis in patients with cryptogenic stroke and PFO is increased4 and should be considered as a potential source of emboli in the setting of PFO.

PFO in Cryptogenic Stroke
The prevalence of PFO in autopsy studies is between 20% and 26%, whereas the incidence in patients aged <55 years with cryptogenic stroke is 56%,4 implicating PFO as a potential cause of stroke. Secondary stroke prevention guidelines from the American Heart Association5 suggest lower extremity ultrasound screening and pelvic vein imaging in young patients with stroke with PFO to evaluate for DVT. When DVT is present, anticoagulation is recommended along with consideration of PFO closure. If anticoagulation is not an option, an inferior vena cava filter is indicated with antiplatelet therapy. When DVT is not present, either antiplatelet or anticoagulation therapy without closure of the PFO should be initiated. There are not enough data to distinguish between the efficacy of aspirin versus warfarin in this setting.5

Multiple clinical trials have examined the effectiveness of PFO closure in preventing recurrent stroke, but fail to demonstrate significant benefit. All of these trials examined stroke

Received May 16, 2015; final revision received May 16, 2015; accepted May 19, 2015.

From the Neurological Institute, University Hospitals Case Medical Center, Cleveland, OH (B.R.M., S.S.); and Department of Neurology and Stroke Unit, Helsinki University Central Hospital, Helsinki, Finland (D.S.).

Correspondence to Sophia Sundararajan, MD, PhD, Neurological Institute, University Hospitals/Case Medical Center, 11100 Euclid, Ave, Cleveland, OH 44106. E-mail sophia.sundararajan@UHhospitals.org

(Stroke. 2015;46:00-00. DOI: 10.1161/STROKEAHA.115.009632.)

© 2015 American Heart Association, Inc.

Stroke is available at http://stroke.ahajournals.org

DOI: 10.1161/STROKEAHA.115.009632
reurrence in patients aged <60 years with cryptogenic stroke and PFO. Patients were randomized to either endovascular closure of their PFO or medical management. Evaluation of the STARFlex Septal Closure System in Patients With a Stroke and/or Transient Ischemic Attack Due to a Presumed Paradoxical Embolism Through a Patent Foramen Ovale (CLOSURE I) used a STARFlex septal closure system and found no difference in stroke recurrence for 2 years. The Percutaneous Closure of Patent Foramen Ovale (PFO) Using the Amplatzer PFO Occluder with Medical Treatment in Patients With Cryptogenic Embolism (PC) Trial used the Amplatzer PFO occluder and required that the recurrent event be associated with evidence of ischemia on magnetic resonance imaging. The PC Trial found no difference between PFO closure and medical therapy in ischemic events, death, or peripheral embolism for 4 years. Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment (RESPECT) also used the Amplatzer PFO occluder and required neuroimaging confirmation of ischemic stroke as an end point. The study design of RESPECT was to analyze data after 25 recurrent strokes had occurred. Importantly, it took ≈7 years before this point was reached, underlining the relatively small number of recurrent events. Intention to treat analysis failed to demonstrate a difference between the 2 groups. Unfortunately, there was significant dropout in the medical arm and crossover within the study. An analysis of treated patients showed a significant reduction in events in patients treated with PFO closure; however, because of the potential for bias in this analysis, these results remain controversial. Systematic meta-analyses of available studies fail to show benefit for PFO closure. Interestingly, an increased rate of atrial fibrillation was associated with PFO closure in CLOSURE I and in a meta-analysis of the trials. It has not been determined whether PFO itself is a risk factor for the development of atrial fibrillation.

Efforts have been made to identify subsets of patients who may be more likely to benefit from PFO closure. The Risk of Paradoxical Embolism (RoPE) Study compiled several large multicentered trials to form a pooled database and model recurrence risk. This scoring metric has been proposed to estimate the probability that a PFO is the cause of ischemic stroke. The score takes into account the absence of other potential risk factors for stroke including hypertension, diabetes mellitus, smoking, and prior transient ischemic attack or stroke. The score also includes the presence of cortical infarction on imaging, which would be more likely to be caused by an embolic mechanism. In addition, patients receive points depending on their age with more points assigned for younger ages (18–29 years, 5 points; 30–39 years, 4 points; 40–49 years, 3 points; 50–59 years, 2 points; 60–69 years, 1 point; >70 years, 0 points). A score of ≥6 is thought to represent a high probability that a stroke is because of paradoxical embolus secondary to PFO. High RoPE scores are associated with a higher prevalence of PFO within the database. It should be noted that the RoPE score has not been validated as a method to predict the likelihood of paradoxical embolization and the benefit of PFO closure.

Structural differences in the PFO have been suggested to increase the likelihood of paradoxical embolus. The RESPECT trial found that PFO closure may have provided a greater benefit in patients with a large (grade 3) PFO and those with an atrial septal aneurysm. However, although a recent meta-analysis of patients with cryptogenic stroke and PFO found an associated atrial septal aneurysm in 33.9% of patients, subgroup analysis failed to demonstrate a significant difference in stroke recurrence between those with an atrial septal aneurysm and those without. Another meta-analysis evaluating PFO size and increased risk of recurrent stroke, with a larger study population, failed to demonstrate a relationship between PFO size with risk of recurrent stroke.

TAKE-HOME POINTS

- A transient hypercoagulable state occurs during pregnancy and the postpartum period, which increases the risk for venous thrombosis and to a lesser extent, ischemic stroke.
- There is no clear consensus about optimal management of patent foramen ovale and stroke, although there may be select populations that benefit from endovascular patent foramen ovale closure.
- The Risk of Paradoxical Embolism score may identify patients whose cryptogenic stroke is more likely secondary to paradoxical embolism.
- The presence of an atrial septal aneurysm or large patent foramen ovale size may be associated with increased likelihood of paradoxical embolism, but is controversial.
Although PFO characteristics may provide an additional means to stratify risk in patients with cryptogenic stroke and PFO, this remains controversial.

In our patient only her postpartum state, her PFO, and hyperlipidemia were identified as potential risk factors for stroke. The finding of DVT soon after the stroke raises concern that it may have been present earlier but not detected and may be a source of paradoxical emboli. Her RoPE score was 9 having received maximal points for every item except cortical location of her stroke, suggesting a relatively high likelihood that the PFO contributed to her infarct. The fact that her stroke occurred in the postpartum period suggests that a transient hypercoagulable state may have contributed. At this point the patient remains on warfarin for her DVT. Transesophageal echocardiogram is planned to better define the PFO with respect to atrial septal aneurysm and PFO size. If there is an atrial septal aneurysm, the PFO is large, or if the patient decides to become pregnant again, consideration will be given to PFO closure.

Acknowledgments
We would like to thank Dr Furlan for reviewing the article and helpful discussions as well as Dr Jun Li for help with the figure.

Disclosures
None.

References
Stroke in the Young: Patent Foramen Ovale and Pregnancy
Benjamin R. Miller, Daniel Strbian and Sophia Sundararajan

Stroke. published online June 16, 2015;
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2015 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/early/2015/06/16/STROKEAHA.115.009632.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/