Patent foramen ovale (PFO), stroke and pregnancy

Lei Chen,[1,2] Wenjun Deng,[1] Igor Palacios,[3] Ignacio Inglessis-Azuaje,[3] David McMullin,[1] Dong Zhou,[2] Eng H Lo,[1] Ferdinando Buonanno,[1] MingMing Ning[1]

[1]Department of Neurology, Cardio-Neurology Clinic, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA
[2]Department of Neurology, West China Hospital in Sichuan University, Chengdu, China
[3]Department of Cardiology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA

Correspondence to
Dr MingMing Ning, Cardio-Neurology Clinic, Department of Neurology, Massachusetts General Hospital, Harvard Medical School, 175 Cambridge Street, Suite 340, Boston, MA 02114, USA;
mmning@mgh.harvard.edu

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ABSTRACT

Patent foramen ovale (PFO)-related stroke is increasingly recognized as an important etiology of ischemic embolic stroke—accounting for up to 50% of strokes previously considered 'cryptogenic' or with an unknown mechanism. As a 'back door to the brain,' PFO can allow venous clots to enter arterial circulation via interatrial right-to-left shunting, potentially resulting in ischemic stroke. We observe that clinically, PFO-related stroke affects women of childbearing age, and that pregnancy—owing to major changes in hemocoagulative, hormonal, and cardiovascular parameters—can enhance stroke risks. However, no systematic study has been performed and little is known regarding complications, pregnancy outcomes and treatment for PFO-related stroke during pregnancy. To identify and characterize the complications and clinical outcomes related to PFOs during pregnancy, we performed a literature review and analysis from all reported cases of pregnancy with PFO-related complications in the medical literature from 1970 to 2015. We find that during pregnancy and postpartum, PFO is associated with complications affecting multiple organs, including the brain, heart and lung. The three principal complications reported are stroke, pulmonary emboli and myocardial infarction. In contrast to other pregnancy-related stroke etiologies, which peak during later pregnancy and postpartum, PFO-related stroke peaks during early pregnancy (first and second trimester—60%), and most patients had good neurological outcome (77%). In patients with PFO with recurrent stroke during pregnancy, additional key factors include high-risk PFO morphology (atrial septal aneurysm), larger right-to-left shunt, multiple gestation and concurrent hypercoagulability. Compared to strokes of other etiologies during pregnancy, most PFO stroke patients experienced uneventful delivery (93%) of healthy babies with a good clinical outcome. We conclude with recommended clinical treatment strategies for pregnant patients with PFO suggested by the data from these cases, and the clinical experience of our Cardio-Neurology Clinic.

BACKGROUND

Patent foramen ovale (PFO), a congenital heart abnormality resulting from failed closure of the antenatal interatrial communication, may allow transit of embolic particles from venous sources to directly injure the brain.[1 2] PFO has been an important emerging risk factor for stroke and is recognized as an independent risk factor for stroke.[2 3] While congenital heart defects such as atrial septal defect and ventricular septal defect are detected in childhood due to cyanotic cardiac symptoms, PFO—facilitating only right-to-left (venous to arterial) shunting—is largely asymptomatic, usually remaining undetected until a stroke or change in coagulation status occurs, such as during pregnancy.

While it has recently been established as an independent risk factor for stroke, PFO is found in 20–30% of all healthy adults, and therefore risk stratification, diagnosis and treatment remain under rigorous debate and investigation. We observe that clinically, PFO-related stroke affects women of childbearing age, and that pregnancy, owing to major changes in hemocoagulative, hormonal, and cardiovascular parameters, can enhance stroke risks.[1 2] However, the risks of PFO during pregnancy have not been systematically analyzed and their importance is not well understood. We performed an extensive literature review and analysis of PFO-related clotting complications including stroke over 45 years (1970–2015), using Medline and Pubmed with keywords of arterial stroke, ischemic stroke, venous stroke, venous sinus stroke, venous sinus thromboembolism, hemorrhagic stroke, cranial thromboembolism, pregnant, pregnancy, delivery, PFO, and right-to-left shunt, vascular complications related to heart, lung and peripheral vasculature, and all variations related to these and clinical outcome.

Here, we summarize the clinical features and outcomes of reported PFO-related complications during pregnancy or after delivery. We also present clinical recommendations based on these data and our experience over the past 30 years in treating patients with neurovascular disease related to cardiac structural abnormalities in the Cardio-Neurology Clinic at the Massachusetts General Hospital. While causation cannot be conclusively established except in rare instances, throughout this discussion we follow the convention of designating a stroke to be PFO related if a PFO is present and other stroke etiologies can be ruled out (ie, the stroke is classified as cryptogenic). We will focus on characterizing stroke reported to be associated

with PFO in the peripartum period, but will also report other vascular events associated with pregnancy, PFO, and other relevant clotting disorders to provide a wider context.

COMPLICATIONS OF PREGNANCY IN PATIENTS WITH PFO

Stroke

PFO-related strokes affect more than 150,000 people per year in the USA, and are found in up to 50% of all cryptogenic strokes.[2 4] Pregnant women are at threefold increased risk of ischemic and hemorrhagic stroke, and fivefold increased risk of venous thromboembolism compared to non-pregnant women.[5 6] From our clinical experience, PFO is associated with an even higher risk of stroke during pregnancy, most likely due to the increased risk of venous thromboembolism and other physiological changes related to the heart and peripheral vasculature. To the best of our knowledge, there have been no reports in the medical literature systematically analyzing the clinical features of stroke in pregnant patients with PFO. While larger prospective studies are direly needed to understand complications related to PFO in pregnant patients, this is the first compilation of PFO-related complications during pregnancy in the literature over the past 45 years.

In performing an extensive review of the literature, we found 16 reports of PFO-related pregnancy complications: 13 patients with stroke, including 15 instances of stroke as two patients had recurrent strokes; and three patients with other vascular complications including pulmonary embolism (PE) and myocardial infarction (MI).[7–18] We compiled descriptions of all reports in table 1, including pregnancy age, time complication occurred, delivery outcome, additional stroke risk factors (such as hypercoagulable state or migraine with aura), stroke subtype with information on vascular territory (anterior vs posterior circulation), treatment modality (medical vs endovascular closure—and if endovascular closure, whether it was done under fluoroscopy with exposure to radiation during pregnancy) and clinical outcome. To understand the mechanism of stroke, we summarized detailed clinical features of all stroke cases in table 2 (13 patients, 15 instances of stroke due to recurrence in 2 patients).

We found that 60% of these strokes occurred in the first two trimesters of pregnancy (1st trimester 7 of 15, 47%; 2nd trimester 2/15, 13%, both recurrences) and 20% postpartum (3/15; 20%) (table 2). Since previous studies show that the incidence of pregnancy-related stroke peaks in the third trimester and puerperium,[19–23] and may extend as long as 12 weeks postpartum,[24] this finding is important to alert clinicians to be aware of high-risk patients with PFO early on during pregnancy. Clinicians should be also aware of patients with PFO postpartum, when women remain at risk for stroke even if they have been discharged from labor and delivery without complication.

Our analysis indicates that about half of the pregnant PFO stroke patients (7 patients of 13; 54%) (table 2) had additional stroke risk factors such as hypercoagulable state, additional right-to-left shunting (pulmonary arteriovenous malformation—AVM), or migraine with aura. Hypercoagulable state includes positive anticardiolipin antibodies, decreased protein S activity, and the HELLP (hemolysis, elevated liver enzyme levels, and low platelet levels) syndrome. This is in agreement with the literature in non-pregnancy-related stroke, which shows an inherited hypercoagulable state such as protein C resistance, factor V Leiden mutation, and elevated anticardiolipin antibodies to be more prevalent in patients with PFO-related stroke.[25–34] Thus, testing for an inherited hypercoagulable state is very important for patients with PFO, especially in pregnancy, which is associated with elevated estrogen and progesterone levels, elevated venous blood pressure, slowed deep venous circulation,[35] and prothrombotic changes in the hemostatic system, with substantially increased levels of coagulation factors II, VII, and X, and a decline in anticoagulant protein S levels.[36] Patients with PFO with a known inherited hypercoagulable state may need to be evaluated carefully for the risk/benefit of anticoagulation.

Other risk factors include high-risk PFO morphology such as atrial septal aneurysm (ASA), additional right-to-left shunting (pulmonary AVM), smoking, and use of oral contraceptives immediately prior to pregnancy. The presence of ASA, an outstretched atrial septum that can increase right to left shunting, has also been reported to increase the risk of stroke in all patients with PFO.[37] Other common stroke risk factors during pregnancy and after delivery, including pre-eclampsia and older age, were also found in our review.[5]

While previous studies found pregnancy-related hemorrhagic strokes (likely related to preeclampsia) to be more common than ischemic strokes in the postpartum period, the PFO-related strokes reported here are all ischemic, and are likely due to paradoxical embolic phenomena related to PFO.[5 23 38] Vascular territories affected by stroke were predominantly in the anterior circulation (2/3 anterior circulation ischemic stroke vs 1/3 posterior circulation ischemic stroke), in accordance with previous reported vascular territories of cardioembolic stroke. There were no hemorrhagic strokes or cerebral venous sinus thrombosis in this cohort. Previous literature reports that maternal mortality rate for hemorrhagic events was 1.5 times greater than that for ischemic events.[5 39 40] Moreover, venous thromboembolism during pregnancy is also a leading cause of maternal mortality.[41 42] In this cohort, clinical outcomes were favorable (as measured by neurological improvement, delivery outcome and resolution of complications) in 10 of 13 patients (77%). This is much higher than previously reported pregnancy-related stroke outcomes, likely due to ischemic stroke subtype and prompt intervention.

Recurrent stroke

Approximately 25% of the estimated 750,000 strokes each year in the USA are recurrences. There are many predictors of recurrent stroke, such as older age, hypertension, heart disease, atrial fibrillation, heavy alcohol use, diabetes, and medication non-compliance. Previous literature notes lower stroke recurrence rates in the PFO stroke population,[37 43] and within this population, concurrent stroke risk factors such as hypertension, diabetes, higher body mass index (BMI), ischemic heart disease and atrial fibrillation are risk markers of recurrence.[44] In our study, there were two patients (cases 6 and 13, 15%) with recurrent stroke; we summarize their special clinical features in table 3. These patients with recurrent stroke had more stroke risk factors

Table 1 Detailed description of all cases reported for complications in pregnant women with PFO

Study (year)	Complication occurrence time	Delivery outcome	Additional stroke risk factors	Complication details	Treatment modality (Medical vs PFO closure)	Clinical outcome
Case 1 Giberti *et al* (2005)	31-year- old 2 months before delivery	Uneventful cesarean section at 32 weeks gestation	anticardiolipin antibodies (+)	Posterior circulation ischemic stroke	325 mg aspirin *without PFO closure*	NR
Case 2 Hidalgo *et al* (2010)	31-year-old (2nd pregnancy) 3 days postpartum	Uneventful cesarean section	NO	Posterior circulation ischemic stroke	NO	NR
Case 3 Szydełko *et al* (2006)	22-year-old 1 h postpartum	Uneventful vaginal delivery	NR	Anterior circulation ischemic stroke	Percutaneous closure 10 months later	Improvement* (rehabilitated)
Case 4 Bodur *et al* (2008)	21-year-old (G4P3) 1 week postpartum	Cesarean section at 32 weeks gestation for fetal distress and abruption placenta	NO	Anterior circulation ischemic stroke; DVT; Tonic–clonic seizures	LMWH and warfarin *without PFO closure*	Improvement* (neurological deficit completely resolved by the end of the first week)
Case 5 Kozelj *et al* (1999)	39-year-old (2nd pregnancy) 41 weeks gestation	Uneventful Vaginal Delivery	NO	Anterior circulation ischemic stroke	Heparin and then warfarin *without PFO closure*	Improvement* (complete neurological improvement 6 months later)
Case 6-1† Daehnert *et al* (2001)	<25-year-old (2nd pregnancy) 10 weeks gestation	spontaneous abortion at 12 weeks gestation	NR	Anterior circulation ischemic stroke	*No PFO closure*, aspirin and enoxaparin	Improvement* (resolved completely within 14 days)
Case 6-2† Daehnert *et al* (2001)	25-year-old (5th pregnancy) 18 weeks gestation	Uneventful cesarean section at 38 weeks gestation	Protein S activity decreased 45%	Anterior circulation ischemic stroke	Percutaneous PFO (15 mm) closure 4 weeks later without fluoroscopy; maintain LMWH+ enoxaparin until 6 weeks postpartum.	Improvement* (no residual atrial shunt and postinterventional course was uneventful)
Case 7 Schrale *et al* (2007)	34-year-old (5th pregnancy) 5 weeks gestation	Uneventful vaginal delivery	Smoking; oral contraceptive; ASA	Anterior circulation ischemic stroke	Aspirin; then percutaneous (large) PFO closure 13 weeks later under fluoroscope	Improvement* (shunt abolition at 23 weeks)
Case 8 Schrale *et al* (2007)	39-year-old <16 weeks gestation	Uneventful Vaginal delivery at 37 weeks gestation	HELLP syndrome; Pre-eclampsia	Anterior circulation ischemic stroke (TIA)	Percutaneous closure at 16 weeks gestation under fluoroscope and aspirin	Improvement* (no residual shunt after PFO closure)
Case 9 Schrale *et al* (2007)	27-year-old (2nd pregnancy) 9 weeks gestation	Uneventful Vaginal delivery at 36 weeks gestation	Migraine	Anterior circulation ischemic stroke	Enoxaparin twice daily, percutaneous closure 8 weeks later under fluoroscope	Improvement* (symptom resolved over 1 week)
Case 10 Dark *et al* (2011)	24-year-old 6 weeks gestation	Uneventful cesarean section	NO	Posterior circulation ischemic stroke	Percutaneous closure under fluoroscope; aspirin	Improvement* (negative for right to left shunting at 6 months)
Case 11 Vij *et al* (2008)	37-year-old (G3P2) 8 weeks gestation	Uneventful vaginal delivery at 38 weeks	ASA	Seizure; anterior circulation ischemic stroke	Percutaneous closure 3 months postpartum under fluoroscope; aspirin and LMWH	Improvement* (her repeat CT scan of the head was normal)
Case 12 Vij *et al* (2008)	27-year-old (G2P0A1) 12 weeks gestation	Uneventful cesarean section at 40 weeks gestation	NO	Posterior circulation ischemic Stroke (TIA)	Plan to get PFO closure but no further information	NR
Case 13-1† Li *et al* (2012)	24-year-old (G4P3) 11 weeks gestation	Uneventful vaginal delivery at 39 weeks gestation	Decreased protein S; ASA; Pulmonary AVM	Anterior circulation ischemic stroke	rt-PA was infused into the thrombus starting at 4 h after stroke onset.	Improvement* (stroke symptoms recovered soon after rt-PA using)

Continued

Table 1 Continued

Study (year)	Complication occurrence time	Delivery outcome	Additional stroke risk factors	Complication details	Treatment modality (Medical vs PFO closure)	Clinical outcome
Case 13-2† Li *et al* (2012)	24-year-old 13 weeks gestation	Uneventful vaginal delivery at 39 weeks gestation	Decreased protein S; ASA; Pulmonary AVM	Posterior circulation ischemic stroke	Percutaneous closure without fluoroscope at 13 weeks gestation but right-to-left shunt persisted	Improvement* (16 months later no further ischemic events occurred)
Case 14 Ramineni *et al* (2010)	29-year-old 5 days postpartum	Uneventful vaginal delivery	NO	PE MI No stroke	Heparin, plavix, aspirin, B-blocker, acetylcholinesterase inhibitor; percutaneous closure 8 weeks later under fluoroscopy	Improvement* (did well after PFO closure)
Case 15 Agostoni *et al* (2004)	19-year- old 22 weeks gestation	Uneventful cesarean section at 31 weeks gestation	smoking; factor V Leiden mutation; ASA	MI No stroke	Patient declined percutaneous closure	NR
Case 16 Krenz *et al* (2011)	38-year-old 32 weeks gestation (G6P5)	Uneventful cesarean delivery at 34 weeks gestation	NO	Idiopathic pulmonary hypertension	Heparin without PFO closure	Died 6 months postpartum due to cardiac arrest (with potential concurrent cerebrovascular event)

*Clinical symptoms of these complications disappear or recover after treatment.
†Same patient with recurrent stroke.
ASA, atrial septal aneurysm; AVM, arteriovenous malformation; DVT, deep vein thrombosis; HELLP, hemolysis, elevated liver enzyme levels, and low platelet levels; LMWH, low-molecular-weight heparin; MI, myocardial infarction; NR, not reported; PE, pulmonary embolism; PFO, patent foramen ovale; rt-PA, recombinant tissue plasminogen activator.

Table 2 Clinical features of all stroke cases included

Variables	Pregnant patients with PFO-related stroke (n=13 patients, 15 strokes)
Average age (years)*	28.93*
Additional stroke risk factor (number/%)	7 (54%)
Time of stroke (number/per cent)	
First trimester	7 (47%)
Second trimester	2 (13%): both recurrent strokes
Third trimester	2 (13%)
Postpartum	3 (20%)
Unknown (<16 weeks)	1 (7%)
Stroke type (number/%)	
Anterior circulation ischemic stroke	10 (67%): 9 initial, 1 recurrent
Posterior circulation ischemic stroke	5 (33%): 4 initial, 1 recurrent
Hemorrhagic stroke	0 (0%)
Venous sinus thromboembolism	0 (0%)
% underwent closure	8 (62%)
% complication from closure	0 (0%)
Clinical outcome of stroke (number/%)	
Recurrent stroke during pregnancy	2 (15%) 1 in same pregnancy, 1 in a later pregnancy
Good neurological outcome	10 (77%)
Unknown	3 (23%)
Delivery (number/%)	
Uneventful delivery	13 (87%)
Vaginal	8 (53%)
Cesarean section	6 (40%)
Spontaneous abortion/fetal distress	2 (13%)

*We did not include the age of case 6-1 in the calculation of average age as her age of first stroke was not clear from the report. She was 25 at the time of her second stroke (case 6-2), three pregnancies later.

including larger shunting by PFO, additional right-to-left shunting (pulmonary AVM), higher-risk features (ASA) in PFO, hypercoagulability, and multiple previous pregnancies. One of these patients was treated with medical therapy only (no PFO closure), and the other patient had a PFO closure procedure that was unsuccessful, leaving persistent right-to-left shunting. Clinicians should take into account these factors when assessing recurrent stroke risks.

Table 3 Risk factors and treatment choice in recurrent stroke in pregnant women with PFO

Risk factors	Case 6	Case 13
PFO with large amount of right to left shunting	+	+
Additional right to left shunting—pulmonary AVM	–	+
ASA with PFO	–	+
Medical treatment (aspirin or LMWH)	+	+
Multiple pregnancy	+	+
PFO endovascular closure after first event	–	+*
Protein S activity decrease	+	+

*PFO endovascular closure attempted, but unsuccessful with residual right to left shunting post procedure.
AVM, arteriovenous malformation; ASA, atrial septal aneurysm; LMWH, low molecular weight heparin; PFO, patent foramen ovale.

Successful PFO endovascular closure may offer the best chance to prevent recurrence in high-risk patients.

Other complications

While the focal point of our inquiry is PFO-related stroke, we also looked for venous thromboembolic events (VTE), such as deep vein thrombosis (DVT) and PE. The literature has reported PE and DVT to be important markers of venous clotting, which elevates the risk of PFO-related stroke.

Deep vein thrombosis

Pregnant women have an increased risk of VTE—fourfold to fivefold higher in pregnancy and with a further increase in the postpartum period—compared with non-pregnant women of similar age.[45 46] 80% of pregnancy-associated VTE is represented by DVT.[47 48] In view of DVT's relation to pregnancy and to PFO, it may be surprising that only one patient in this cohort had a DVT. However, in most of the literature, DVT is not commonly found after PFO-related stroke, probably due to delay in timing of imaging or lack of sensitivity for detection of smaller venous clots that may trigger paradoxical events.[2] In fact, pelvic venous abnormalities such as the May-Thurners syndrome—compression of the left common iliac vein by the right common iliac artery (the reason why DVT is more common in the left leg)—resulting in pelvic venous stasis and pelvic venous clotting are likely more important markers of peripheral venous stasis during pregnancy due to the increase in abdominal girth.[49]

In this case, the patient's DVT was discovered after cesarean delivery,[10] consistent with the usual VTE occurrence time (postpartum period) in all pregnant women. This case may also be complicated by the fact that cesarean section itself doubles VTE risk compared to vaginal delivery. However, this case highlights the importance of VTE, which in conjunction with PFO may elevate postpartum risk of paradoxical embolic events. All VTEs, including DVTs, are markers that may trigger evaluation for the presence of PFO; appropriate medical treatment such as short-term anticoagulation (3–6 months at our institution) may be considered in the clinical setting to prevent future events.

Pulmonary complications

PE and pulmonary hypertension are other important morbidities associated with PFO in pregnancy.[50] PE has long been reported as a concurrent finding in some patients with PFO.[51–53] PE serves as a marker for venous clotting, as well as a cause of elevated pulmonary pressure which can facilitate right-to-left shunting. Increased pulmonary artery pressure from a large PE can propagate in a retrograde fashion to the right ventricle and atrium, creating a gradient of pressure across the PFO that leads to a right-to-left shunt. Pulmonary hypertension can also have the same effect, to 'pop open' the PFO. We found two case reports of pulmonary complications in women with PFO, at 32 weeks of gestation and 5 days after vaginal delivery.[17 54] Although PE is a serious complication which can cause 10% of maternal deaths,[55] the patients reported here recovered well and underwent percutaneous PFO closure 8 weeks later. However, one of these patients had pulmonary hypertension with very poor prognosis and died 6 weeks postdelivery from cardiac arrest. It was unclear whether a cerebral vascular event also occurred at the time of death, but it was thought that back pressure from pulmonary hypertension had opened the PFO, making treatment extremely difficult. In such patients, in our experience, PFO endovascular closure appears to be safe and effective in preventing further paradoxical events. However, in patients with PE or other VTE, an extensive hypercoagulable workup should be done and additional medical therapy such as anticoagulation may need to be instituted, as PFO closure will not prevent in situ venous thrombi.

Myocardial infarction

Acute MI was reported in two patients with PFO.[2 56] The most likely mechanisms underlying these MIs are not clear from the reports. In general, the risk of MI is three to four times higher in pregnant women than in non-pregnant women.[57 58] The prior literature shows the most common mechanisms of MI in pregnancy to be coronary dissection secondary to hormonal changes, coronary artery spasm and thrombosis.[59] Paradoxical coronary embolic events can be a potential etiology, but an incidental finding cannot be excluded, given the lack of mechanism studies.

WOMAN OF CHILDBEARING AGE WITH PFO

Pre-conception counseling and pregnancy care

Pre-conception counseling should be offered to all women of childbearing age with known PFO, prior complications with PFO or congenital heart disease. Post-PFO-related complications, a multidisciplinary specialist team with neurology, cardiology, peripheral vascular, hematology and obstetrics/gynecology has been successful in preventing recurrent events at our center.[1] However, since PFOs are often clinically asymptomatic, most women with PFO do not have the opportunity to receive pre-conception counseling. Thus, PFO screening may be important in high-risk patients with a venous hypercoagulable state. Akin to other monitoring such as blood pressure, blood glucose, and BMI, close follow-up and screening are even more important in women with PFO-related stroke who are planning a pregnancy. Keeping in mind that PFO is not just a 'hole,' but a mobile valvular structure which becomes more dynamic during pregnancy, serial cardiac echography may be indicated in patients with prior events without PFO closure.

From our experience in treating patients with PFO-related complications over the past 30 years and the analysis of literature from this field, we conclude with some recommendations for PFO stroke patients who wish to become pregnant (box 1). Since PFO is also associated with non-cerebral systemic embolic events such as MI, PE, DVT, renal infarction, or limb ischemia, in addition to PFO intervention, systemic anticoagulation either in the short term or long term may be indicated.[60–62] Low molecular weight heparin (LMWH) is routinely administered during pregnancy for patients with prior complications or a hypercoagulable state. As reviewed elsewhere, clinical management should also include the treatment of important concurrent risk factors such as obstructive sleep apnea, migraine with aura, and May-Thurner anatomy.[1 49 63–72]

Box 1 Recommendations for clinical treatment and workup for patent foramen ovale (PFO) stroke patients who wish to undergo pregnancy

1. Pre-conception counseling from a specialist multidisciplinary team with neurological, cardiac, hematological, and obstetric experts, along with the primary care physician.
2. Delivery planning should be a multidisciplinary effort (among, eg, the obstetrician, cardiologist, anesthesiologist, neurologist, hematologist, and patient) communicated well in advance of the due date.
3. Hypercoagulable panel blood testing to stratify clotting risk (eg, D-dimer, partial-thromboplastin time, activated partial-thromboplastin time, protein C, protein S, antiphospholipid antibodies, anti-β2glycoprotein, lupus anticoagulant, prothrombin gene mutation, antithrombin III, homocysteine, Factor V Leiden)
4. Pelvic magnetic resonance venography or CT venography to look for the May-Thurner Syndrome (MTS)—increased abdominal girth during pregnancy can worsen MTS due to compression of abdominal vasculature, increasing the risk of pelvic venous thrombosis
5. Cardiac workup including EKG to detect myocardial infarction and arrhythmia; Holter monitoring or extended cardiac monitoring to detect cardiac arrhythmia, especially atrial fibrillation; Transthoracic echocardiograph to assess PFO features, such as atrial septal aneurysm (ASA) and the degree of shunting during valsalva.
6. For patients with high-risk status such as hypercoagulation state, consider ASA+/−low molecular weight heparin during pregnancy.
7. PFO endovascular closure may be considered for secondary prevention of stroke in patients with PFO

A multidisciplinary clinical team should follow the patients in conjunction with high-risk OB during pregnancy.

Delivery outcome

In our review of the literature (table 2), all but one case report included information in detail on delivery. The majority of patients with stroke (9 of 12; 75%) had uneventful deliveries of healthy newborns, and three patients had fetal distress or spontaneous abortion (25%). While vaginal delivery is often considered to have fewer or lower risks in patients without PFO,[73] patients with PFO may deserve special considerations. An elective cesarean section delivery may have logistical advantages and prevent a Valsalva maneuver, which may increase right-to-left shunting of PFO during delivery.

The results of our review suggest that despite the higher risk of stroke in patients with PFO, a majority of women after PFO-related stroke can successfully give birth to healthy infants. It is not clear whether vaginal delivery and cesarean section are comparable for PFO stroke patients; more studies are needed and, most importantly, individualization is imperative for each patient. Patients should be followed from pre-pregnancy planning to postpartum. We suggest that delivery planning should be a multidisciplinary decision made by a team of clinicians (eg, obstetrician, cardiologist, anesthesiologist, neurologist, hematologist and primary care physician) in conjunction with the patient. Care should be taken to identify obstetric drugs that may cause cardiac instability, and limitations should be set regarding the duration of the second stage if contemplating a vaginal delivery.[73] Plans should be made and communicated well in advance of the due date. In women with PFO, it is particularly important that the extended team understand the patient's anatomy and physiology.

PFO treatment

Treatment for PFO-related injury has been under active investigation, but there is still little consensus regarding optimal clinical management in general, and no published study has addressed pregnant PFO patients in particular. For prevention of recurrent stroke in patients with PFO, some experts advocate medical treatments targeting either platelets or coagulation cascades, while others recommend obliteration of the PFO by endovascular closure. Since PFO-related injuries are inherently complex, affecting multiple organs and the circulatory system as a whole, a myriad of associated risks differ widely between individual patients. We have therefore advocated an integrated multidisciplinary team approach to individualize treatment for each patient.[1]

The two main large-scale trials of endovascular PFO closure completed to date, CLOSURE I and RESPECT, have tested different devices and were designed to detect different effects with respect to different end points in differently selected patient cohorts.[74 75] Accordingly, the tentative clinical guidance to be gleaned from the two studies' findings is different but not contradictory. In the CLOSURE I trial, while the PFO closure group had 22% less risk of recurrent stroke, this difference was not statistically significant, as the study was powered to detect only a rather ambitious two-thirds reduction of risk. Furthermore, the CLOSURE study excluded many high-risk patients (eg, patients with hypercoagulable states), so its conclusions apply only to patients already at a lower risk of recurrent stroke.[74] In contrast to the CLOSURE I trial, the RESPECT trial showed significant risk reduction in the PFO closure arm compared to the medical arm in the per-protocol and as-treated analysis, while statistically significant risk reduction was not quite attained in the primary intention-to-treat analysis due to patient crossover and spurious events: a number of medical group patients underwent off-label closure, and three of nine patients in the device group had strokes while awaiting device placement.[75] However, in a subsequent 10-year follow-up analysis, the RESPECT investigators found that in the intention-to-treat population, the relative risk for recurrent cryptogenic stroke was reduced by more than half (54%) after PFO closure, and that PFO closure reduced the relative risk of recurrent cryptogenic stroke by 70% compared with medical therapy.[76] The 10-year follow-up results also demonstrated safety and efficacy of PFO endovascular closure.[76]

We have offered a more detailed assessment and comparison of these trials elsewhere;[1] suffice it to say here that further study is required to better understand the risks and benefits of endovascular PFO closure. Most importantly, the vital question to answer is not whether PFO closure is

good or bad in general, but rather for which individual patients the risk/benefit profile would make closure the best treatment. In our experience, when performed by experienced cardiologists, non-invasive endovascular closure can be safe and effective, especially for patients at high risk for recurrent stroke.[12 13 77–80] Systemic reviews of PFO with stroke also indicate a trend in favor of percutaneous intervention for younger patients,[77 79] which would by definition include pregnant patients with PFO. In our clinic, we have seen that PFO closure is often chosen by young patients with PFO who prefer to undergo vaginal delivery or lactation, but the cost of PFO closure without medical insurance coverage is often a deterrent to such therapy.

While we wait for new and ongoing clinical trials to clarify the risk/benefit profiles of PFO closure for individual stroke patients in general, there are still no data available about PFO closure during pregnancy. Pregnant women, particularly in the puerperium, are at significantly increased risk of thrombotic events and catastrophic anticoagulation associated hemorrhage compared to non-pregnant women of similar age. At our center, we routinely place patients on LMWH during pregnancy if they have PFO-related stroke with a hypercoagulable state, and it has been safe without adverse delivery outcome.

In the cases we reviewed, eight patients with stroke who received percutaneous closure of PFO did not have any further complication during a few months postpartum (tables 1 and 2). Of the two patients with recurrent stroke, one was on medical therapy only, and the other had undergone a failed endovascular closure procedure (with residual shunting). Radiation exposure is an important concern to address when considering percutaneous device closure during pregnancy. The International Commission on Radiological Protection, British National Radiological Protection Board and others have concluded that there is no substantial effect on the risk to an individual pregnancy regarding incidence of fetal death, malformation, or the impairment of mental development with the low exposures from medical radiation.[81–83] It is reported that intracardiac echocardiography (ICE) can minimize fluoroscopy requirements and procedure time. Furthermore, placement of the retroflexed ICE catheter in the right atrium provides excellent visualization of the PFO and device during the closure procedure. In this series, most patients received the traditional method of percutaneous PFO closure under fluoroscopy. Two patients underwent PFO closure without fluoroscopy, which provides no radiation exposure.[12 16] However, this methodology requires more experience.[84] Thus, development of new techniques is also of paramount importance.

CHALLENGES

While the literature reviewed here is rich with some descriptive details, this is a relatively small case series. With millions of pregnancies in the USA each year and 20–30% prevalence of PFO in the population, we found only 16 case reports published since 1999, and none from 1970 to 1998. This is most likely due to the relatively recent recognition of the relevance of PFO to stroke and pregnancy, and to increased PFO screening only in the past 5–10 years. The true prevalence of PFO-related complications in pregnancy is probably much higher than a count of 16 reports over 45 years might be taken to suggest. This case-report review also lacks quantitative measures of neurologic outcome such as the NIHSS score or Barthel index, or mRankins for long-term outcome characterization. While all infants born were reported to be healthy at birth, no long-term follow-up is reported. One case did not report the patient's age at the time of stroke, another did not report the time of stroke with respect to the pregnancy, and three cases did not report neurological outcomes. More work is called for in this field, including more detailed prospective studies.

CONCLUSION

PFO-related complications during pregnancy can injure multiple organs, including the brain, heart, lung, and peripheral vasculature, but we found stroke to be the predominant complication reported in the existing literature. There is unfortunately not any systematic clinical or translational research in this field. Our analysis of case reports finds PFO-related stroke to occur during early pregnancy—a majority during the first and second trimesters. So early recognition and diagnosis of PFO is crucial in preventing long-term complications with PFO. Recurrent strokes during pregnancy are associated with additional risk factors such as a larger degree of right-to-left shunting, multiple gestation or hypercoagulable states. Pre-conception counseling should be offered to all women with PFO who are of child-bearing age. We have had success following patients with a multidisciplinary team. While the literature remains scant, we are optimistic with the data so far that women with PFO-related stroke can have an uneventful delivery of a healthy baby.

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