Objective: To raise awareness of the potentially adverse consequences of postpartum cerebral vasoconstriction, which is typically considered benign and self-limiting, by describing 4 fulminantly fatal cases.

Design: Retrospective case series.

Setting: Tertiary referral center.

Patients: Four postpartum women aged 15 to 33 years developed acute neurologic deficits 1 to 8 days after uncomplicated deliveries. One had a history of migraine headaches and 2 had histories of spontaneous abortion. Two of the patients had uneventful pregnancies and 2 had preeclampsia, 1 of whom had acute hepatic failure. Presenting symptoms included severe headache (n=3), focal deficit (n=1), seizure (n=1), and encephalopathy (n=1). Initial brain imaging results demonstrated cortical ischemia and global edema in 2 patients, lobar hemorrhage in 1, and normal findings in 1. All had rapid clinical deterioration from hours to days with multiterritorial infarctions and global brain edema on imaging. All had angiographic findings of diffuse, severe, segmental multifocal arterial narrowings.

Interventions: Aggressive treatment was attempted with most patients including intravenous magnesium sulfate, corticosteroids, calcium channel blockers, balloon angioplasty, vasopressors, and osmotic agents. Two patients underwent serial angiography, with results showing severe, recurrent proximal vasoconstriction involving all major intracranial vessels.

Results: All patients had fulminant, accelerating courses leading to their deaths within 8 to 24 days after delivery.

Conclusions: Postpartum vasoconstriction can be fatal, with rapid progression of vasoconstriction, ischemia, and brain edema. Clinicians need to be aware of the potential consequences of this condition. Postpartum women with acute neurologic symptoms require prompt investigation with noninvasive cerebrovascular imaging and close monitoring for possible secondary deterioration.


The sudden appearance of neurologic deficits following delivery may be indicative of postpartum cerebral vasoconstriction. This poorly understood clinical entity is characterized by acute neurologic symptoms (recurrent thunderclap headaches, stroke, or encephalopathy) and radiologic findings of arterial vasoconstriction. It is often grouped with other disorders in the category of reversible cerebral vasoconstriction syndrome because vasoconstriction usually resolves spontaneously and prognosis is generally considered favorable. However, 3 fatal cases have been reported.1-3 It is unclear whether they represent an extreme in the spectrum of cerebral vasoconstriction syndromes or a distinct disorder. In 13 months, we encountered 4 cases of fulminant cerebral vasoconstriction.

REPORT OF CASES

CASE 1

A 33-year-old woman with a history of protein S deficiency developed a sudden headache and left facial droop 4 days after uncomplicated cesarean delivery of twins. On postpartum day (PPD) 17, she developed new left upper extremity weakness. The results from a head computed tomographic (CT) scan were normal. Severe headaches recurred, and she was admitted to a local hospital. Brain magnetic resonance imaging (MRI) showed a subacute left putaminal hemorrhage, areas of subcortical T2 hyperintensity in both pari-
etal lobes, and a minimal amount of left frontal convexal subarachnoid hemorrhage. Magnetic resonance venography showed no evidence of dural venous thrombosis. She was subsequently transferred to our institution for further evaluation.

Her medical history included migraine headaches and 3 miscarriages. Her blood pressure was 115/77 mm Hg. Results from a neurologic examination revealed a moderate left spastic hemiparesis with associated hyperreflexia and Babinski sign. During the first day of her hospitalization, she developed right lower extremity weakness. Findings from repeated brain MRI on PPD 20 revealed new areas of restricted diffusion in multiple vascular territories, and intracranial magnetic resonance angiography showed multifocal segments of vascular narrowing and dilatation involving all major intracranial vessels. High-dose intravenous methylprednisolone sodium succinate treatment was empirically initiated for consideration of vasculitis. Cerebrospinal fluid examination revealed 4 total nucleated cells/mL and a protein level of 58 mg/dL.

The patient became increasingly agitated and confused. Cerebral angiography was conducted on PPD 22, at which time balloon angioplasty was performed on both M1 segments of the middle cerebral arteries and intrarterial verapamil hydrochloride treatment was administered to all 4 major intracranial vessels with radiographic improvement. Following the procedure, treatment with intravenous vasopressin was started for hemodynamic augmentation.

During the following day, she stopped following commands and blinking to visual threat. On PPD 24, repeated cerebral angiography showed recurrence of severe proximal stenoses involving bilateral distal internal carotid arteries and proximal middle cerebral arteries (Figure 1). There was also severe involvement of the posterior circulation. Treatment with intra-arterial verapamil was administered, followed by balloon angioplasty to both M1 segments, with no substantial radiologic improvement shown. Following the procedure, the patient’s family requested withdrawal of life-sustaining measures.

![Image](image-url)
Postmortem brain examination showed flattening of gyri indicative of diffuse global cerebral edema and a small area of convexal focal subarachnoid hemorrhage. Axial sections revealed a dusky-colored brain with indistinct gray-white junction and bilateral uncal herniation. Microscopic examination of formalin-fixed paraffin-embedded sections of major cerebral blood vessels (internal carotid artery, A1, A2, M1, M2, P1) with hematoxylin-eosin and Movat pentachrome staining revealed normal arterial wall structure. In 1 section of the right M1 segment, there was subtle focal attenuation of the media of uncertain significance (Figure 2). There was no evidence of active inflammation or vasculitis. Evaluation of multiple neocritical and subcortical regions of brain parenchyma revealed widespread patchy acute ischemic infarcts, primarily in the distribution of the right and left posterior cerebral arteries. Subacute ischemic and hemorrhagic infarcts in the right and left basal ganglia, as well as a small amount of focal left frontal subarachnoid hemorrhage were also present. There was no evidence of intravascular microthrombosis or venous thrombosis.

CASE 2

A 32-year-old woman developed a gradual headache 5 days after uncomplicated cesarean delivery at the term of her fourth pregnancy. The following day, her headache worsened and she was admitted to a local hospital. Head CT showed acute right subcortical intraparenchymal hemorrhage. Initial cerebral angiography performed on PPD 7 showed no vascular abnormality. Four days later, she became somnolent and developed new left hemiparesis. Cerebral angiography revealed widespread patchy acute ischemic infarcts, primarily in the distribution of the right and left posterior cerebral arteries. Balloon angioplasty was performed to the left internal carotid artery. Intra-arterial verapamil was infused into the bilateral carotid and basilar territories with mild angiographic improvement. A ventriculostomy was inserted with plans for intrathecal sodium nitroprusside treatment. Head CT showed new areas of focal brain ischemia in addition to global cerebral edema and brain herniation (Figure 1). Following the procedure and on reexamination, the patient was found to be apneic and had no brainstem reflexes or motor response to noxious stimulus. She met brain death criteria on PPD 16.

CASE 3

A 30-year-old woman with a history of 1 miscarriage underwent urgent cesarean delivery at term for preeclampsia and fetal distress. On PPD 2, she was drowsy, confused, and unable to recognize people around her. She developed thrombocytopenia, elevated hepatic transaminase levels, coagulopathy (international normalized ratio up to 8), and acute kidney injury. Findings from a urine screen test for drug abuse were negative. A 5-day course of plasmapheresis was completed. She was intubated for airway protection because of somnolence on PPD 5. Brain

Figure 2. Photomicrographs from postmortem examination in case 1. A, Movat pentachrome staining reveals normal structures of the arterial wall in a section of the M1 segment of the right middle cerebral artery (original magnification ×200). B, Movat pentachrome staining shows subtle focal attenuation and thinning of the media of uncertain significance (arrow) in a section of the A1 segment of the right anterior cerebral artery (original magnification ×200).
MRI the following day showed diffuse cortical restricted diffusion in the vascular territories of the bilateral anterior cerebral and middle cerebral arteries as well as sulcal and basilar cistern effacement indicative of global edema. Intracranial magnetic resonance angiography showed multifocal narrowings, primarily involving the middle cerebral artery (Figure 3). There was no evidence of venous thrombosis on magnetic resonance venography. The patient was transferred to our institution.

On her arrival, she was comatose, intubated, and mechanically ventilated. There was no eyelid opening or motor response to noxious stimulation. Brainstem reflexes were preserved. An intracranial pressure monitor was placed. During the next 12 hours, episodic intracranial hypertension developed and was treated with hyperventilation, intravenous mannitol, and induced hypothermia. Electroencephalography showed generalized suppression.

Despite undergoing orthotopic liver transplantation on PPD 11, intracranial hypertension was refractory to treatment with hyperventilation, mannitol, hypertonic saline, intravenous pentobarbital sodium, and hypothermia. A neurologic examination performed while the pa-
Patient was not sedated revealed absent pupillary, corneal, and oculocaloric reflexes. Her pupils were anisocoric (left pupil, 4 mm; right pupil, 5 mm). Limbs were flaccid, with no motor response to noxious stimulation. She breathed spontaneously. Head CT on PPD 12 showed worsened cerebral edema, effacement of basilar cisterns, infarction of the left mesial temporal and occipital lobes, and early transtentorial herniation with brainstem compression. With a likely certainty of poor outcome, the patient’s family requested withdrawal of life-sustaining measures on PPD 14.

CASE 4

A 15-year-old nulliparous adolescent was hospitalized with preeclampsia at 35 weeks’ gestation. She was treated with intravenous magnesium sulfate and labetalol hydrochloride. Labor was induced, and she delivered a healthy girl. The patient had a generalized tonic-clonic seizure minutes after delivery. Hypertension was controlled with oral labetalol, and she was discharged from the hospital on the fourth day. On PPD 8, she was brought to our emergency department for lethargy and recurrent seizure. She had a headache during the prior few days, began vomiting the day before, and developed right lower extremity numbness. Vital signs showed blood pressure of 191/96 mm Hg and a heart rate of 93 beats/min. Within hours, her level of alertness deteriorated. Noxious stimulation produced no eyelid opening, grimacing, or other motor response. Pupils were anisocoric (right pupil, 5 mm; left pupil, 3 mm), with no reactivity to light on the right. Corneal reflexes were absent on the right and weakly present on the left. Breathing was regular with adequate oxygen saturation. She was intubated and hyperventilated to a PaCO₂ of 31 mm Hg, and she received 1 g/kg of intravenous mannitol, 20%.

Head CT showed diffuse global edema with basilar cistern effacement. Initial intracranial pressure measured on placement of an intraparenchymal monitor was 200 mm Hg, which decreased to 31 mm Hg. Computed tomographic angiography showed diffuse narrowing of all intracranial arteries (Figure 3). She became hypothermic, polyuric, and hypotensive. Reexamination revealed loss of all brainstem reflexes and no motor response to stimulation. After apnea testing, she was pronounced brain-dead on PPD 8. The results from a urine drug abuse survey were negative.

Postmortem brain examination showed evidence of brain death with diffuse cerebral edema with gyral flattening, ventricular effacement, and bilateral uncal and cerebellar tonsillar herniations. Microscopically, acute ischemic cell change was present in a patchy distribution as well as a focal acute microinfarct of the left superior frontal gyrus. Examination of major cerebral blood vessels (A1, M1, P1, internal carotid artery, basilar artery) showed nonspecific focal mild intimal hyperplasia (Figure 4) and focal mild medial attenuation. There was no evidence of active inflammation, vasculitis, microthrombosis, or sinus thrombosis.

We describe 4 women who developed rapidly fatal neurologic deterioration from massive brain edema caused by postpartum cerebral vasoconstriction and ischemia. It is possible that this disorder is not only underrecognized but worse than previously believed. Postpartum women with acute neurologic symptoms require prompt investigation with brain and cerebrovascular arterial imaging and close monitoring for possible secondary deterioration. Although our aggressive treatment failed to provide favorable outcomes in these patients, improved awareness that this poorly understood syndrome may have a malignant course can allow clinicians to recognize the potential for deterioration and arrange for appropriate neurologic monitoring. The condition is often benign but can quickly become severe with devastating results, making it difficult to decide when to initiate aggressive therapies.

Postpartum vasoconstriction is often included within the scope of reversible cerebral vasoconstriction syndrome, where poor outcomes are reported in a minority of patients. In the largest prospective study of patients with reversible cerebral vasospasm syndrome, which included 5 postpartum cases, only 4% of patients were
disabled due to strokes and there were no fatal cases. However, as noted earlier, 3 previous cases of fatal postpartum vasoconstriction have been described on an individual basis (Table). In the absence of large prospective studies on postpartum patients with vasoconstriction, the frequency of these fulminant, unremitting cases remains unknown.

The etiology of this disorder also remains unknown. The results from postmortem examination performed in 2 of our cases showed only minimal focal changes (focal medial attenuation and intimal proliferation) of unknown significance. This may support the previously described theory that functional vasoconstriction, rather than inflammatory vasculitis, underlies its pathophysiological course. Vasoactive medications (eg, sympathomimetics, selective serotonin reuptake inhibitors, and bromocriptine mesylate) have been implicated in the onset of postpartum cerebral vasoconstriction, but causality is difficult to prove. It has been theorized that the postpartum cerebral vasculature has enhanced susceptibility to sympathomimetic medications due to hormonal fluctuations. Nevertheless, cases have been reported in the absence of vasoactive medication administration. If this theory were comprehensive, one might expect this disorder would be more common with the high frequency of postpartum women receiving vasoactive medications.

Postpartum cerebral vasoconstriction and eclampsia share clinical and radiographic similarities, leading to speculation that they may also share a common pathophysiological course. Both conditions can be associated with transient vasogenic cerebral edema best visualized on MRI (posterior reversible encephalopathy syndrome). Although more commonly presenting with seizures during late pregnancy, about 25% of patients develop eclampsia in the postpartum period. In preeclampsia, there are several circulating factors that are elevated compared with healthy pregnant women, including levels of antiangiogenic proteins and placental proteins. It is not known whether these are of pathogenic significance or merely markers of the disease. However, there is experimental evidence that some antiangiogenic proteins (eg, soluble fms-like tyrosine kinase and endoglin) cause endothelial dysfunction. In a recent case of fatal postpartum vasoconstriction, a functionally low level of soluble fms-like tyrosine kinase 1 was found, perhaps contributing to the disease process. Two of our patients had preeclampsia, further supporting an overlap between the 2 conditions.

It is conceivable that the infarcts seen in this condition may not be exclusively caused by hypoperfusion due to vasoconstriction. In addition to delayed vasospasm, it has been suggested that intravascular microthrombosis could play a role in the pathogenesis of brain ischemia after subarachnoid hemorrhage, but microthrombosis was absent from the autopsy results in our cases as well as prior reports. It is well established that there is an increased risk of stroke in the postpartum period, and certain physiologic changes during the puerperium could be responsible for this predisposition. A hypercoagulable state is created by increasing concentrations of von Willebrand factor, factor VIII, and fibrinogen as well as increased resistance to protein C and reduced levels of protein S. Higher prolactin con-

<table>
<thead>
<tr>
<th>Case</th>
<th>Age, y</th>
<th>G/P, No.</th>
<th>Cesarean Delivery</th>
<th>PPD</th>
<th>Symptoms</th>
<th>Initial Imaging</th>
<th>Treatment</th>
<th>PPD at Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geraghty et al, 1991</td>
<td>27</td>
<td>1/1</td>
<td>+</td>
<td>4</td>
<td>Headache, focal</td>
<td>Normal</td>
<td>Verapamil, steroids</td>
<td>22</td>
</tr>
<tr>
<td>Williams et al, 2007</td>
<td>40</td>
<td>4/2</td>
<td>-</td>
<td>2</td>
<td>Headache, focal, seizure</td>
<td>Mild subcortical enhancement</td>
<td>Surgery, magnesium, calcium channel blocker, cyclophosphamide, hypertonic therapy</td>
<td>14</td>
</tr>
<tr>
<td>Singhal et al, 2009</td>
<td>36</td>
<td>2/3</td>
<td>+</td>
<td>10</td>
<td>Headache, seizure</td>
<td>Normal</td>
<td>Magnesium, BP augmentation, fludrocortisone acetate, nimodipine</td>
<td>27</td>
</tr>
<tr>
<td>1</td>
<td>33</td>
<td>5/2</td>
<td>+</td>
<td>4</td>
<td>Headache, focal</td>
<td>Normal</td>
<td>Magnesium, nimodipine, BP augmentation, steroids, IA verapamil, angioplasty</td>
<td>24</td>
</tr>
<tr>
<td>2</td>
<td>32</td>
<td>4/4</td>
<td>+</td>
<td>5</td>
<td>Encephalopathy</td>
<td>Subcortical IPH</td>
<td>Steroids, nimodipine, BP augmentation, IA verapamil, angioplasty, hypertonic therapy</td>
<td>16</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>1/1</td>
<td>+</td>
<td>0</td>
<td>Headache</td>
<td>Cortical ischemia at 6 d</td>
<td>Steroids, magnesium, PLEX, BP augmentation, hypertonic therapy, hypothermia</td>
<td>14</td>
</tr>
<tr>
<td>4</td>
<td>15</td>
<td>1/1</td>
<td>-</td>
<td>0</td>
<td>Seizure, headache</td>
<td>Global brain edema at 8 d</td>
<td>Hypertonic therapy</td>
<td>8</td>
</tr>
</tbody>
</table>

Abbreviations: BP, blood pressure; G, gravida; IA, intra-arterial; IPH, intraparenchymal hemorrhage; P, para; PLEX, plasma exchange; PPD, postpartum day.
centrations may also lead to increased platelet aggregation.23 Nevertheless, the degree to which these changes contribute to increased stroke risk is unclear because they also occur during pregnancy itself, and the increased risk of stroke during this period has not been found as consistently as in the postpartum period.24,25

In addition to ischemic stroke, cerebral vasoconstriction is often associated with intracranial hemorrhage.23-29 A variety of patterns can be seen, including convex subarachnoid hemorrhages, intraparenchymal hematomas, and subdural hematomas. In a prospective cohort of 89 patients with reversible cerebral vasoconstriction syndrome, female sex and history of migraines were found to be independent risk factors for hemorrhage, and those with hemorrhage tended to have a more severe clinical spectrum.25

We acknowledge limitations in these cases. The patient in case 3 was diagnosed as having postpartum cerebral vasoconstriction only when the case was reviewed by an expert panel during a mortality conference, highlighting the underrecognition of this disorder. This patient’s clinical course was confounded by acute hepatic failure, but after careful review there was evidence of cortical-restricted diffusion and arterial narrowing on her initial brain MRI. In case 4, there was no arterial imaging until intracranial pressure had already begun to increase. Radiographically, the differentiation of functional vasoconstriction from arterial narrowing secondary to elevated intracranial pressure may be difficult.

There is an acute need for further research because of many unanswered questions regarding fulminating postpartum vasoconstriction, including investigations to determine whether vasoconstriction is the only mechanism responsible for the development of severe ischemia in these patients. Clinicians should be aware that cerebral vasoconstriction syndromes may have a malignant course and should maintain a low threshold for noninvasive vascular imaging and close neurologic monitoring for postpartum women with acute neurologic symptoms.

Accepted for Publication: June 13, 2011.

Correspondence: Alejandro A. Rabinstein, MD, Mayo Clinic 8-W, 200 First Street SW, Rochester, MN 55905 (rabinstein.alejandro@mayo.edu).

Author Contributions: Study concept and design: Fugate and Rabinstein. Acquisition of data: Fugate, Kallmes, and Giraldo. Analysis and interpretation of data: Fugate, Wijdicks, Parisi, Cloft, Flemming, and Rabinstein. Drafting of the manuscript: Fugate and Rabinstein. Critical revision of the manuscript for important intellectual content: Wijdicks, Parisi, Kallmes, Cloft, Flemming, Giraldo, and Rabinstein. Study supervision: Wijdicks, Parisi, Kallmes, Cloft, Flemming, Giraldo, and Rabinstein.

Financial Disclosure: None reported.

REFERENCES