Ovarian Hyperstimulation Syndrome and Arterial Stroke

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Case Description
A 29-year-old woman undergoing in vitro fertilization treatment for infertility presented to a rural hospital 7 days after embryo transfer with abdominal distension, nausea, headache, and paresthesias. General examination revealed a distended abdomen with moderate generalized tenderness. Neurological examination revealed a left-sided facial droop with mild dysarthria and a left pronator drift. The remainder of her examination was normal. Her National Institute of Health Stroke Scale Score was 3. Laboratory investigations showed a positive pregnancy test, a hemoglobin concentration of 165 g/L, a hematocrit of 0.46 L/L, and low albumin of 22 g/L. Hypodensities in the right frontal and parietal lobes were found on computed tomography. She was transferred to the Stroke Team at a tertiary care center for further workup and management.

On arrival, she was started on aspirin, clopidogrel, and prophylactic subcutaneous heparin. Computed tomographic angiography showed an intraluminal thrombus at the origin of the right internal carotid artery and a distal right M3 branch occlusion (Figure 1). Bilateral large pleural effusions were also noted. MRI with diffusion-weighted imaging showed a large, acute right middle cerebral artery territory ischemic infarct, with no findings on MR venography. Autoimmune and thrombophilia screenings were negative; she denied a family or personal history of coagulation disorders or stroke. Abdominal ultrasound showed enlarged ovaries and ascites in keeping with the diagnosis of ovarian hyperstimulation syndrome (OHSS). Because of the large internal carotid artery thrombus and clinical stability, she was transitioned to therapeutic intravenous unfractionated heparin. Three days after initial presentation, she experienced a worsening of her symptoms with complete left hemiplegia and anarthria. Her National Institute of Health Stroke Scale examination immediately returned to her previous baseline. Scattered new areas of infarction were demonstrated on a repeat MRI before discharge. She required a paracentesis for symptomatic relief of abdominal pain and dyspnea during her stay of the stroke unit. She was discharged home with outpatient rehabilitation follow-up and ongoing obstetric care.

Discussion
OHSS is a well-described consequence of ovulation induction therapies for fertility treatment. The reported incidence is 0.3% to 6%. Severe complications, namely venous occlusive disease and rarely arterial thromboembolic events, occur in <2% of cases of OHSS and result in significant morbidity and mortality. Although limited, the literature on incidence suggests that it happens more commonly and is simply overlooked by practitioners. Stroke neurologists need to include this possibility when assessing a young patient with acute neurological deficits in the setting of fertility treatment.

OHSS is classified as mild, moderate, and severe, based on ovarian size and associated symptoms. Thromboembolic complications are thought to be associated with severe OHSS. Severe cases of OHSS are characterized by significant enlargement of the ovaries with the formation of numerous cysts, massive ascites, pleural effusions, electrolyte imbalance, and severe hypovolemia. More common in the first trimester of pregnancy, symptoms typically present 5 to 10 days after human chorionic gonadotropin administration. Reported risk factors for severe OHSS include younger age, a high number of induced follicles, polymorphism in the follicle-stimulating hormone receptors, polycystic ovarian syndrome, and hypothyroidism. Surprisingly, thrombophilic disorders do not seem to be risk factors for severe OHSS.

In the few reported cases of cerebral arterial infarctions secondary to severe OHSS, a predominance of thrombi in the middle cerebral artery territory has been identified. There is some evidence that subclinical strokes may go undiagnosed, with case reports detailing old infarctions on imaging thought to be the consequence of previous fertility treatment cycles. Clinically, supraphysiological levels of estrogen and leukocytosis are commonly observed and thought to contribute to the risk of thromboembolic complications.

The pathophysiology of thromboembolic disease in OHSS is not fully elucidated, but multiple factors probably contribute. In response to human chorionic gonadotropin, the ovaries release vasoactive peptides causing fluid extravasation to the...
peritoneal space and consequent hemoconcentration.\textsuperscript{2,6} This altered permeability may be furthered by increased plasma renin and vascular endothelial growth factor levels observed with an increased number of follicles in OHSS.\textsuperscript{7} Ascites and enlarged ovaries can decrease venous return and promote stasis.\textsuperscript{3} The frequently observed leukocytosis in OHSS likely plays a role in endothelial injury. Cathepsin G released from activated neutrophils disrupts the endothelial integrity and exposes the thrombogenic extracellular matrix.\textsuperscript{2,6,7} Increased tissue factor and thrombin concentrations, as well as decreased inhibitory and fibrinolytic pathway factors, have also been observed in patients with OHSS when compared with control.\textsuperscript{8}

**Management**

Arterial strokes are rare in OHSS. Because strokes are typically a progression of severe OHSS, prevention of the syndrome itself would seem a prudent approach. However, much of the pathophysiology of OHSS remains unknown, and risk assessment tools are lacking.\textsuperscript{3} Thrombophilia screening before initiation of fertility treatments would intuitively make sense in assessing the risk of thromboembolic events, but it is unlikely to be cost-effective.\textsuperscript{2,5,7} Some authors have proposed early pregnancy termination to prevent stroke progression.\textsuperscript{4} This may be especially important in the event of multiples pregnancy where the complication risk may be higher in women with OHSS.\textsuperscript{3} Obstetricians generally initiate prophylactic heparin therapy on presentation of OHSS. Therapeutic heparinization might be a consideration to reduce stroke incidence although ischemic stroke was still reported in the 1 case that tried this approach.\textsuperscript{9} One also wonders whether heparin played a role in disrupting and dislodging the clot in this patient. Supportive interventions, such as intravenous hydration, human albumin, and electrolyte correction, comprise the mainstay of standard treatment of OHSS.\textsuperscript{3} Decreasing hypovolemia and hemoconcentration may ultimately decrease the risk of thrombus formation and may help in preventing subsequent strokes.

Perhaps because of its relative infrequency, best practices for management of acute arterial thromboembolic events in the setting of OHSS have not been established. Many cases reported favorable outcomes with therapeutic unfractionated heparin and aspirin administration at the onset of ischemic symptoms in addition to standard OHSS treatment.\textsuperscript{1,3} Intra-arterial tissue-type plasminogen activator has had mixed outcomes; 2 cases have demonstrated successful recanalization, one case had a demise of the pregnancy 7 days after embryo transfer.\textsuperscript{9,10} Typically, intravenous tissue-type plasminogen activator is contraindicated in pregnancy because of believed disruptive effects on placental stability, but in the face of significant morbidity or mortality it may be warranted on a case by case basis.\textsuperscript{2} No data currently support interventional clot retrieval measures in this patient population. Ultimately, individual therapies will have to be tailored to the parturient mother.

**TAKE-HOME POINTS**

- Acute ischemic stroke, although much more rare than venous complications, must be considered in a young patient with acute neurological dysfunction and recent ovarian stimulation.
- The complex pathophysiology of ovarian hyper-stimulation syndrome promotes hypercoagulability, stasis, and endothelial injury putting women undergoing fertility treatment at higher risk for thromboembolic complications.
- Immediate treatment with intravenous unfractionated heparin and aspirin on presentation of neurological symptoms generally yields good maternal neurological outcomes. Additional research is required to determine a role for systemic or intra-arterial tissue-type plasminogen activator and mechanical clot retrieval.
Acknowledgments
We acknowledge Dr Sheila Caddy for her careful review of the article.

Disclosures
None.

References

Key Words: complications ■ ovarian hyperstimulation syndrome ■ stroke
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Stroke. published online November 13, 2014;
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2014 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/2014/11/13/STROKEAHA.114.007476.citation

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