Clinical Reasoning:

An unusual case of blurry vision in a young woman after ovarian induction

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SECTION 1

A 38-year-old woman presented to our emergency department with blurry vision and headache. She developed her symptoms insidiously 8 days into ovarian induction for in vitro fertilization (IVF), consisting of recombinant follicular stimulating hormone, gonadotropin, and a gonadotropin-releasing hormone antagonist. The headache was mild, constant, diffuse, nonpositional, and minimally alleviated with ibuprofen. She described binocular difficulty “focusing her vision” but denied a field cut or diplopia. A community ophthalmologist reported a normal dilated fundusoscopic examination but noted a subtle right homonymous hemianopia only present on formal Humphrey visual field testing and brought her to neurologic attention. She denied a history of headaches, muffled hearing or whooshing sounds, or prior symptoms suggestive of demyelinating disease. She did not have a history of immunocompromising conditions. She had not undergone any invasive gynecologic procedures nor did she have fevers. She had a history of Gilbert syndrome and hypothyroidism. Her only additional

medications were levothyroxine, fish oil, and iron supplements.

Vital signs were normal. The initial physical and neurologic examinations were unrevealing. She had a normal pupil examination, normal acuity, and intact extraocular movements. The hemianopia noted on formal field testing by the ophthalmologist was not present on bedside examination. Laboratory testing revealed a mild transaminitis, mild mixed bilirubinemia, and mild normocytic anemia, which were attributed to her history of Gilbert disease and menstruation, respectively. Of note, the patient’s platelet count was 214,000 cells per microliter (normal 150,000–450,000 cells per microliter), her international normalized ratio was 1.1 (normal 0.9–1.1), and her activated partial thromboplastin time was 31.1 seconds (normal 26.0–37.0 seconds).

Questions for consideration:

1. What is the differential diagnosis for vision changes and headache in a woman of childbearing age?
2. What disorders are unique to this population?

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SECTION 2

Given the patient's homonymous hemianopia localizing to the retrochiasmal visual tracts, we considered processes that produce focal lesions: demyelinating

Figure MRI brain with multifocal infarctions

(A) Diffusion-weighted imaging sequence reveals multiple diffusion-restricting lesions in a multifocal pattern. (B) Apparent diffusion coefficient map correlates with the diffusion-weighted image.

disease, ischemic or hemorrhagic stroke, cortical vein or cerebral venous sinus thrombosis, brain abscess, and primary brain tumor. In this population, one should additionally be vigilant for features of eclampsia, posterior reversible encephalopathy syndrome, and reversible vasoconstrictive syndrome.¹ Other diagnoses to consider in a woman of childbearing age include migraine with aura, idiopathic intracranial hypertension, and leptomeningitis.

A brain MRI (figure) demonstrated multiple, bilateral cortical and subcortical infarcts with the largest in the left parieto-occipital lobe. On hospital day 1, her physical examination changed and was notable for multiple splinter hemorrhages on her digits and a dusky area on her left fifth digit.

Questions for consideration:

1. What are the broad mechanisms of disease that could result in her MRI findings and evolving examination?
2. What are the appropriate next steps in evaluation?

GO TO SECTION 3

SECTION 3

Given the multifocal infarcts on MRI and the cutaneous stigmata of peripheral thromboembolism, our diagnostic evaluation focused on cardioembolic, vasculitic, and hypercoagulable disorders. The brain imaging pattern was also consistent with watershed infarctions; however, the patient had not had any known antecedent episodes of hypotension.

Standard stroke evaluation including hemoglobin A1c level, lipid profile, transthoracic echocardiogram with bubble study, telemetry, and head and neck magnetic resonance angiography was unremarkable. Transesophageal echocardiography, cardiac MRI, and prolonged cardiac monitoring did not reveal a source of embolization. Blood cultures were negative. Contrast-enhanced CT of the chest, abdomen, and pelvis did not reveal evidence of visceral ischemia or infarction nor was an occult malignancy revealed. The ovaries were mildly enlarged, which was radiographically consistent with recent ovarian induction, and no pleural effusions were found. The liver and spleen were unremarkable in size and appearance. Autoimmune markers including antinuclear, double-stranded DNA, Smith, ribonucleic acid, and Sjögren antibodies were negative. Erythrocyte sedimentation rate and C-reactive protein levels were normal. In light of this and as the patient's findings were not confined to the CNS, we

did not expect a lumbar puncture to reveal signs of primary CNS inflammation and therefore a lumbar puncture was not performed. Additionally, given the low suspicion for a primary CNS vasculitis, a formal diagnostic angiogram was not pursued.

An elevated D-dimer level of 988 ng/mL (<150 ng/mL) in the absence of a patent foramen ovale prompted an arterial hypercoagulability analysis.² Homocysteine and antiphospholipid syndrome markers were normal or negative, with the exception of phosphatidylserine immunoglobulin G and immunoglobulin M levels, which were mildly elevated: 12 U/mL (normal 0–10 U/mL) and 37 U/mL (normal 0–24 U/mL), respectively. Additionally, factor II prothrombin gene mutation and factor V Leiden mutation testing was negative.

In the absence of positive markers for a specific, known hypercoagulable disorder, we deemed the patient's stroke and systemic embolization to be due to presumed hypercoagulability in the setting of recent ovarian induction.

Questions for consideration:

1. What constitutes appropriate treatment for this syndrome?
2. Through what mechanisms might ovarian induction be associated with thromboembolism?

GO TO SECTION 4

SECTION 4

Stroke in the setting of ovarian induction is rare and was thought to exclusively occur in patients with ovarian hyperstimulation syndrome (OHS), which our patient did not manifest.³ Our patient did not have typical OHS symptoms of abdominal pain, vomiting, diarrhea, or dyspnea, and imaging did not demonstrate pleural effusions. There are no evidence-based therapeutic approaches specifically for stroke in OHS. Treatment options include standard stroke treatment with aspirin monotherapy or dual antiplatelet therapy in addition to heparin products if appropriate.^{3,4} Some physicians initiate prophylactic heparin treatment on signs of OHS.⁴

Our patient was initially given aspirin and high-intensity statin therapy. Ovarian induction drugs were stopped. On this regimen, she developed the aforementioned cutaneous stigmata of embolization. Aspirin therapy was therefore switched to therapeutic enoxaparin anticoagulation. She had no further signs of embolization, and her D-dimer level decreased to normal; however, she redeveloped a mild transaminitis, which was attributed to the enoxaparin. In consultation with hematology and given the patient's preference to avoid warfarin due to monitoring requirements, enoxaparin was substituted with apixaban. She had no further thromboembolic events while on apixaban, and her transaminitis resolved rapidly after discontinuation of enoxaparin.

DISCUSSION A review of IVF-associated arterial thrombosis reported arterial thrombosis to occur exclusively in the setting of OHS.³ OHS is characterized by marked enlargement of the ovaries and an increase in capillary permeability, which leads to pleural effusions, ascites, and oliguria, as well as symptoms of dyspnea, nausea, vomiting, and abdominal pain.⁵ OHS occurs in 3%–20% of patients undergoing IVF, but venous and arterial thromboembolic complications are rare and occur in severe OHS.⁵ Of reported arterial thrombotic events in OHS, 60% were ischemic stroke, occurring on average 8–11 days after administration of ovulation inducers or embryo implantation.³ Our patient was notably free of signs and symptoms of OHS. Similar pathophysiology may nonetheless be implicated.

Several mechanisms for thromboembolism in OHS have been proposed. Human chorionic gonadotropin administration may increase interleukin-6 and vascular endothelial growth factor levels, which may contribute to increased vascular permeability and thereby hemoconcentration.⁵ Multiple perturbations in the coagulation and fibrinolysis systems found in OHS may also predispose to thrombosis.³

Additionally, ovulation induction causes estradiol levels to peak at 20–50 times normal levels.³

Other treatments that increase estradiol levels, including hormonal contraception and hormone replacement therapy, increase the risk of thromboembolic events, including arterial stroke.^{6,7} This may be an additional mechanism of thromboembolism in ovarian induction, even in the absence of OHS.

We could only find one report of ischemic stroke in a patient undergoing ovarian induction in the absence of OHS.⁸ However, common causes of stroke were not exhaustively excluded, and the patient had polycystic ovarian syndrome, which may be associated with stroke.⁹ Our patient had mild elevations of antiphosphatidylserine antibodies, which may also be weakly associated with stroke.¹⁰ Ovarian induction may therefore pose a stroke risk even in the absence of OHS, especially in patients with underlying potentially prothrombotic disorders. With the increasing prevalence of IVF use, awareness of neurologic complications is warranted. Additionally, our findings may influence IVF counseling and hypercoagulability screening practices.

AUTHOR CONTRIBUTIONS

Neal S. Parikh conceived and designed the study and drafted and revised the manuscript for intellectual content. Darya Khazanov drafted and revised the manuscript for intellectual content. Antonio Moya drafted and revised the manuscript for intellectual content. Ulrike W. Kaunzner drafted and revised the manuscript for intellectual content. Baxter B. Allen drafted and revised the manuscript for intellectual content. Babak B. Navi conceived and designed the study and drafted and revised the manuscript for intellectual content.

STUDY FUNDING

No targeted funding reported.

DISCLOSURE

N. Parikh, D. Khazanov, and A. Moya report no disclosures relevant to the manuscript. U. Kaunzner received a fellowship grant from Biogen. B. Allen reports no disclosures relevant to the manuscript. B. Navi is supported by NIH grant K23NS091395 and the Florence Gould Endowment for Discovery in Stroke. The sponsors had no involvement in any aspect of study design; writing the report; or the decision to submit the report for publication. Go to Neurology.org for full disclosures.

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Neurology 2016;87:e49-e53

DOI 10.1212/WNL.0000000000002915

This information is current as of August 1, 2016

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