

Case Studies

Young Ischemic Stroke in Association with Ovarian Hyperstimulation Syndrome

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Background: Ovarian hyperstimulation syndrome (OHSS) is a serious and potentially fatal complication of medical ovarian stimulation. Uncommonly, it is associated with thromboembolic complications with venous thrombosis being more common than arterial thromboembolic events. We present a case of cerebral infarction in the setting of severe OHSS secondary to in vitro fertilization treatment with no residual neurological deficits. **Materials and Methods:** We also performed a review of previously published ischemic cerebral infarction and cerebral venous sinus thrombosis (CVST) cases associated with OHSS to evaluate common patterns in presentations, commonly affected central nervous system sites, trends for therapeutic options in these cases, and outcomes. **Conclusion:** We have included 27 cases of ischemic cerebral infarction and 7 cases of CVST previously published in English literature. We have included cases of central retinal artery occlusion in the ischemic cerebral infarction group, and central retinal vein occlusion in the CVST group. Mean ages of presentation were 31 ± 4.84 and 34 ± 4.90 years for ischemic cerebral infarction and CVST, respectively. Ischemic strokes commonly affect large cortical areas with unilateral weakness, aphasia, unilateral sensory changes, and visual field deficits being the common presentations. Middle cerebral artery ($n = 7$) is the common site of vascular occlusion where vascular imaging has been reported, followed by internal carotid artery occlusion ($n = 5$). OHSS cannot be considered a direct risk for pathogenesis, but OHSS is frequently associated with hyperviscosity, which may add to the risk factors. **Key Words:** Ovarian hyperstimulation syndrome—ischemic stroke—in vitro fertilization—cerebral venous sinus thrombosis.

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Case Report

A previously healthy 36-year-old right-handed Caucasian woman presented with an episode of right upper

extremity weakness and expressive aphasia lasting for about 15-20 minutes. The patient was undergoing treatment for infertility and had egg retrieval for in vitro fertilization (IVF) 7 days prior to the onset of these symptoms. The patient developed abdominal pain, nausea, malaise, and dyspnea 2 days after egg retrieval. Abdominal ultrasound confirmed the presence of ascites and ovarian enlargement, and the patient was diagnosed with ovarian hyperstimulation syndrome (OHSS). Embryos were not implanted and were frozen. The result of the neurological exam was normal on initial evaluation (National Institutes of Health Stroke Scale score of 0). The white blood cell count was 17 (76% neutrophils, 19% lymphocytes, 6% monocytes); platelet count, 535; hemoglobin level,

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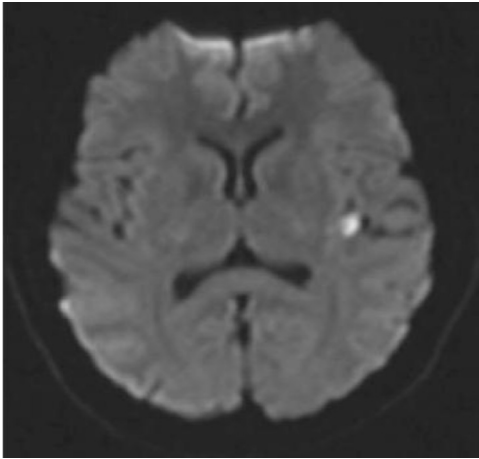


Figure 1. Diffusion-weighted magnetic resonance imaging of the brain showing acute infarction.

17.7; and hematocrit level, 52.5. Serum electrolytes were also deranged: Na, 130; K, 4.1; CO₂, 22; Cl, 100; blood urea nitrogen, 14, and creatinine, 1.4. Total estrogens level and total estradiol levels were 2730 and 1520 pg/mL, respectively. Repeat abdominal ultrasound showed an enlarged liver with moderate to severe ascites. The portal vein was patent. The patient was found to have a left posterior insular infarction on magnetic resonance imaging of the brain (Fig 1), and there was attenuation of the left middle cerebral artery vasculature on magnetic resonance angiography (MRA) of the head (Fig 2). Magnetic resonance venography of the head did not show any signs of venous sinus or cortical vein thrombosis. Fasting lipid profile showed a low-density lipoprotein level of 58. The hemoglobin A1c level was 5.3. The rest of the stroke workup including carotid duplex, 2-D echo, and telemonitoring were normal. The patient was treated with aggressive intravenous hydration and albumin infusions and had subsequent improvement in clinical status and electrolyte abnormalities. Aspirin, simvastatin, and subcutaneous heparin were started. The patient also had hypercoagulable workup including antithrombin III, protein C, protein S, factor V Leiden, antiphospholipid antibodies, beta-2 glycoprotein antibodies, Anti-nuclear Antibodies (ANA), and Extractable Nuclear Antigen Antibodies (ENA),

all of which had been normal. The patient was discharged home with aspirin and simvastatin. Repeat MRA of the head 2 months later showed improvement of the left MCA attenuation (Fig 2B).

The patient had mild occipital headaches after discharge, which was associated with mild photophobia. The patient did not develop any other neurological symptoms. The headaches improved spontaneously. Repeat MRA head 3 months later showed complete resolution of the MRA signal attenuation seen on the first study. The patient has been symptom free for about 6 months after the initial episode and has been taking aspirin 81 mg daily.

Discussion

OHSS is a serious and potentially fatal complication of ovarian stimulation for assisted reproduction technologies. Mild forms are common and reported frequencies for OHSS are approximately 20%-33% for mild cases, 3%-6% for moderate cases, and .1%-2.0% for severe cases. It is a broad spectrum of signs and symptoms that include abdominal distention and discomfort, enlarged ovaries, ascites, and other complications of enhanced vascular permeability. The pathophysiology is hypothesized to be increased capillary permeability with the loss of fluid into the third space, likely from overexpression of vascular endothelial growth factor in the ovary and release of vasoactive-angiogenic substances resulting in functional impairment of blood vessels systemically, often causing impairment of cardiac, renal, pulmonary, and liver functions. Clinically, OHSS has been classified as mild, moderate, severe, and critical. Thromboembolic complications are typically seen in the latter 2 forms with venous thrombosis (64.3%) being more common than arterial thromboembolic events (37.5%).¹

Major risk factors for OHSS are previous episode of OHSS, polycystic ovary syndrome, and younger age, which has been reported as a possible risk factor along with low body weight. Potential biomarkers of risk are a basal serum anti-Müllerian hormone concentration greater than 3.3 ng/mL and an antral follicle count greater than 8. Secondary risk factors related to ovarian response are the number of follicles (the risk rises with increasing number

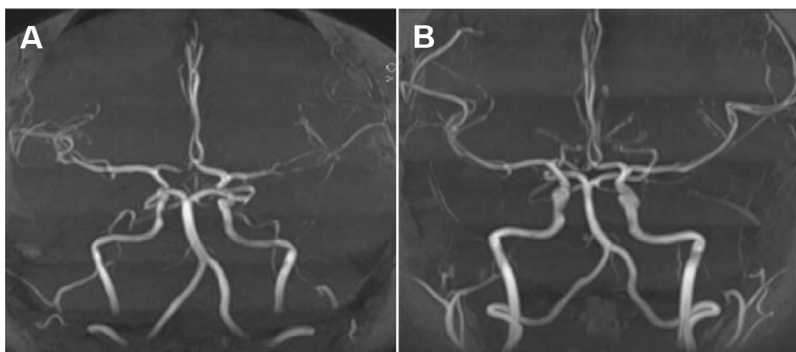


Figure 2. (A and B) Magnetic resonance angiography of the brain showing narrowing of the left middle cerebral artery with attenuated branches and follow-up scan 3 months later showing significant improvement.

Table 1. Ischemic cerebral infarction cases

Author	Year	Age (years)	Previous thromboembolism	Polycystic ovaries	Max estradiol level (pg/mL)	No. of mature follicles	Severity of OHSS	Days to development of stroke symptoms	Stroke symptoms
Mozes et al	1965	37	None	None	NR	NR	Severe	5 days post HCG injection	Left hemiplegia, coma
Rizk et al	1990	30	None	None	NR	NR	Severe	12 days post ET	Left hemiplegia, left hemisensory loss, left hemianopsia
Kermode et al	1993	34	None	Yes	NR	NR	Severe	9 days post ET	Right hemiplegia, right hemisensory loss, right hemianopsia, aphasia, left-sided Horner seizure
Inbar et al	1994	22	None	Yes	NR	Multiple	None	7 days post HCG injection	Headache, nausea, amnesia, dysarthria
Aurousseau et al	1995	34	None	None	NR	NR	None	3 days post ET transfer	Left hemiplegia
Cluroe et al	1995	40	None	None	NR	NR	Severe	6 days post ET	Left hemiplegia, left hemisensory loss, right gaze deviation, left tongue deviation, lethargy
Aboulghar et al	1998	33	None	None	2100	12	Moderate	11 days post ET	Left hemiparesis
Aboulghar et al	1998	25	None	None	2800	16	Moderate	9 days post ET	Left hemiparesis, seizure
Hwang et al	1998	22	None	None	NR	NR	Severe	12 days post ET	Left hemiparesis, left facial weakness, left hemisensory loss, dysarthria
El Sadek et al	1998	24	None	None	3000	34	Severe	6 days post ET	Right hemiparesis
Yoshii et al	1998	26	None	None	NR	NR	Severe	NR	Left hemiparesis, dysarthria,
Davies et al	1999	33	None	None	NR	NR	Moderate	NR	Left hemiparesis, headache
Worrell et al	2001	34	None	None	2663	NR	Mild	7 days post ET	Right hemiparesis, aphasia
Turkistani et al	2001	34	None	None	NR	NR	Moderate	NR	Left unilateral visual loss
Koo et al	2002	33	None	None	NR	NR	Severe	14 days post ET	Left hemiparesis, Left visual field deficit, right gaze preference, left hemineglect, dysarthria
Elford et al	2002	28	None	None	3132	NR	Severe	7 days post ET	Left hemiplegia, left facial weakness, dysarthria, drowsiness
Di Micco et al	2003	32	None	None	3800	NR	Moderate	NR	Right hemiplegia, right facial weakness, right visual field deficit
Togay-Isikay et al	2004	27	None	None	NR	NR	Severe	12 days post IUI	Sensory loss left face, right hemisory loss, ataxia, Horner syndrome, nystagmus
Demiroglu et al	2007	21	None	None	2118	16	None	2 days post HCG injection	Right hemisensory loss, aphasia, disorientation
Giner et al	2007	35	None	None	NR	NR	Severe	NR	Right hemiparesis, aphasia
Marti et al	2008	34	None	None	NR	NR	Moderate	3 days post ET	Left visual loss
Bartkova et al	2008	31	None	None	1440	NR	Severe	9 days post ET	Left hemiparesis, left facial weakness, right head deviation, left sided gaze palsy, drowsiness
Qazi et al	2008	30	None	None	NR	NR	Severe	NR	Left hemiparesis, dysarthria
Song et al	2008	31	None	Yes	4300	NR	Severe	NR	Left hemiparesis, left facial weakness, left visual field deficit, nystagmus
Jing et al	2011	30	None	None	4267	13	Severe	7 hours post ET	Right hemisensory loss, aphasia, disorientation, dizziness
Gervasi et al	2012	34	None	Yes	NR	NR	Severe	7 days post HCG injection	Right hemiparesis, aphasia
Current case	2013	36	None	None	1520		Severe	8 days post HCG injection	Right upper extremity weakness, aphasia

(continued on next page)

Table 1. (continued)

Author	Area of cerebral infarction on imaging	Vascular imaging findings	Other sites of thrombosis	Coagulation abnormalities	Maternal outcome	Fetal outcome	Treatment
Mozes et al	NR	Left extracranial ICA occlusion with intracranial extension	None	NR	Death	No pregnancy	Mechanical thrombectomy
Rizk et al	Right MCA territory	No abnormalities	None	NR	Recovery	Term delivery	Aspirin
Kermode et al	Left frontal and parietal	NR	Right internal iliac vein	NR	Residual motor and speech deficits	No pregnancy	NR
Inbar et al	Right temporoparietal	No abnormalities	None	None	Recovery	No pregnancy	Aspirin
Aurousseau et al	NR	Right ICA dissection and thrombosis	None	None	Recovery	Therapeutic abortion	Heparin
Cluroe et al	Right MCA territory	NR	None	NR	Death	No pregnancy	NR
Aboulghar et al	Cortical area, not specified	NR	None	None	Recovery	No pregnancy	Heparin
Aboulghar et al	Left parieto-occipital	NR	None	None	Recovery	No pregnancy	Heparin
Hwang et al	Right MCA territory	Right MCA occlusion	Myxomatous mitral valve	None	Residual motor deficits	Therapeutic abortion	NR
El Sadek et al	Left basal ganglia and corona radiata	Left choroidal artery occlusion	None	None	Recovery	No pregnancy	Heparin- > aspirin
Yoshii et al	Right internal capsular, bilateral corona radiata, bilateral parietal, right occipital	Right ICA occlusion	None	Temporary elevation of TAT and D-dimer, temporary reduction of protein S	Recovery	Therapeutic abortion	NR
Davies et al	Right MCA territory	NR	None	None	Recovery	NR	NR
Worrell et al	Left MCA territory infarction	Left distal ICA occlusion	Intracardiac thrombus	Mildly decreased protein S	Residual motor and speech deficits	Spontaneous miscarriage	tPA, heparin- > warfarin
Turkistani et al	Central retinal artery occlusion	NR	None	None	NR	Preterm labor	Heparin
Koo et al	Right MCA territory	Right MCA occlusion	None	Low protein S and high IgM anticardiolipin antibodies	Residual motor deficits	Therapeutic abortion	NR
Elford et al	Left MCA territory	Left MCA occlusion	None	None	Residual motor, visual, and sensory deficits	Normal vaginal delivery	intra-arterial tPA, dalteparin
Di Micco et al	NR	Left ICA occlusion	None	None	Improvement, not specified	No pregnancy	Heparin- > aspirin
Togay-Isikay et al	Bilateral PICA territory	Left vertebral occlusion	None	Activated protein C resistance, factor V Leiden mutation	Residual motor deficits	NR	Heparin, aspirin
Demiroglu et al	Left MCA territory	Left MCA occlusion	None	None	Recovery	No pregnancy	Aspirin, warfarin
Giner et al	Left parietal, left lenticular nucleus, right caudate	NR	See below	Antiphospholipid antibody syndrome	Recovery	No pregnancy	Anticoagulation, not specified
Marti et al	Left thalamus	Central retinal artery occlusion	None	None	Residual visual deficits	No pregnancy	Heparin- > warfarin- > aspirin
Bartkova et al	Left basal ganglia	Left MCA occlusion	None	None	Recovery	Term delivery	Heparin- > aspirin
Qazi et al	Right MCA territory	Carotid atherosclerosis	None	None	Recovery	No pregnancy	Heparin, aspirin
Song et al	Right MCA territory, left cerebellum	No abnormalities	None	Temporarily low protein S and antithrombin III	Residual motor and speech deficits	Therapeutic abortion	Heparin- > aspirin
Jing et al	Left MCA territory	Left MCA occlusion	None	homozygosity	Residual unknown deficits	NR	Ozagrel, aspirin
Gervasi et al	Left fronto-temporal-occipital	NR	Left ventricular thrombus, tetralogy of Fallot	MTHF reductase variant	NR	NR	NR
Current case	Left insula	Left MCA occlusion	None	None	Recovery	No pregnancy	Aspirin, heparin

Abbreviations: ET, embryo transfer; HCG, human chorionic gonadotrophin; ICA, internal carotid artery; IUI, Intra-uterine Insemination; MCA, middle cerebral artery; MTHF, methylenetetrahydrofolate; NR, not reported; OHSS, ovarian hyperstimulation syndrome; PICA, posterior inferior cerebellar artery; tPA, tissue plasminogen activator.

Table 2. Venous cerebral infarction cases

Author	Year	Age (years)	Previous thromboembolism	Polycystic ovaries	Max estradiol level (pg/mL)	No. of mature follicles	OHSS	Days to development of stroke symptoms	Stroke symptoms
Waterstone et al	1992	29	None	None	NR	2	Severe	12 days post HCG injection	Left hemiplegia, seizure, coma
Tang et al	2000	34	None	None	5668	NR	Severe	14 days post ET	Right hand weakness, seizure
Ou et al	2003	29	None	None	3707	7	Moderate	9 days post ET	Left hemiplegia, seizures
Edris et al	2007	38	None	None	3346	16	Severe	4 days post ET	Headache, lethargy, confusion, neck pain
Lee et al	2008	36	None	None	NR	NR	None	NR	Right visual loss
Santoro et al	2009	31	None	None	NR	NR	Moderate	NR	Hemiparesis unknown side, headache, visual complains
Man et al	2011	42	None	None	2616	NR	Severe	1 day post HCG injection	Left hemiparesis, headache

Author	Area of cerebral infarction on imaging	Vascular imaging findings	Other sites of thrombosis	Coagulation abnormalities	Maternal outcome	Fetal outcome	Treatment
Waterstone et al	NR	Right transverse sinus, internal cerebral vein, vein of Galen	None	NR	Residual motor deficits	Spontaneous miscarriage	Heparin- > warfarin
Tang et al	Left frontal hemorrhagic infarction	Cortical vein	Inferior vena cava, right common iliac, left femoral and left external iliac	No abnormalities	Recovery	Therapeutic abortion	Heparin- > warfarin
Ou et al	Right frontal, left frontoparietal	Superior sagittal sinus	None	Temporarily low protein S	Residual motor deficits, seizures	Term delivery	Mechanical thrombectomy, urokinase- > heparin
Edris et al	Periventricular white matter	Superior sagittal sinus, transverse sinus, cortical veins	None	No abnormalities	Recovery	No pregnancy	Heparin- > warfarin
Lee et al	None	Central retinal vein occlusion	None	No abnormalities	NR	NR	NR
Santoro et al	NR	Rectal sinus, transverse venous sinus	None	G20210A prothrombin mutation	Recovery	NR	Heparin- > warfarin
Man et al	Right frontal	Superior sagittal sinus, right cortical veins	None	No abnormalities	NR	NR	Heparin

Abbreviations: ET, embryo transfer; HCG, human chorionic gonadotrophin; NR, not reported; OHSS, ovarian hyperstimulation syndrome.

of follicles >20 over 10 mm in diameter) and high (or rapidly rising) serum estradiol concentration. In 1 study, the incidence of OHSS in women with preovulatory serum estradiol concentrations greater than 3500 pg/mL or greater than 6000 pg/mL was 1.5% and 38%, respectively. The commonly affected sites are the deep extremity veins, the internal jugular vein, and the subclavian vein. Mozes et al reported a fatal case of ischemic stroke associated with severe OHSS in 1965,² and there have been several other reports of ischemic cerebral infarction and cerebral venous sinus thrombosis (CVST) since then. We present another case of cerebral infarction in the setting of OHSS with no residual neurological deficits. We also performed a review of previously published ischemic cerebral infarction and CVST cases to evaluate common patterns in presentations, commonly affected central nervous system sides, trends for therapeutic options in these cases, and outcomes.

We have included 27 cases of ischemic cerebral infarction¹⁻²⁵ and 7 cases of CVST²⁶⁻³² previously published in English literature (Tables 1, 2). We have included cases of central retinal artery occlusion in the ischemic cerebral infarction group and central retinal vein occlusion in the CVST group. The mean ages of presentation were 31 ± 4.84 and 34 ± 4.90 years for ischemic cerebral infarction and CVST, respectively. Ischemic strokes commonly affect large cortical areas with unilateral weakness, aphasia, unilateral sensory changes, and visual field deficits being the common presentations. The middle cerebral artery ($n = 7$) is the common site of vascular occlusion where vascular imaging has been reported, followed by internal carotid artery occlusion ($n = 5$). Posterior circulation is rarely affected with only 1 reported case of vertebral occlusion.¹⁹ Ischemic strokes usually occur in association with moderate-severe OHSS (~85%), but there has been 1 case reported with mild OHSS and 3 cases without OHSS. These cases without OHSS happened also after IVF or ovulation induction without any determined etiology. By contrast, venous sinus thrombosis has always been associated with moderate-severe OHSS. The maximum serum estradiol level reported is 2831 ± 1000 pg/mL in ischemic strokes and 3834 ± 1304 pg/mL in CVST. The exposure to higher levels of estrogens in the women with other potential risk factors is the likely pathogenesis in these cases. In fact, other concomitant hypercoagulable risk factors have been found in 7 cases of ischemic strokes and in 2 cases of CVST. The true prevalence of hypercoagulable risk factors in these patients is difficult to estimate due to small numbers and as some of the case reports have not reported any testing for them.

It is difficult to definitely draw conclusions as very few of the reported cases of OHSS with ischemic stroke and CVST in our review were found to have concomitant coagulation abnormalities, primarily because of lack of hypercoagulability testing in the majority of the cases.

Out of 22 cases of ischemic stroke, 2 patients had mild protein S deficiency; 1 patient had protein S deficiency along with high anticardiolipin antibodies; 1 patient had protein C resistance along with factor V Leiden mutation; and 1 patient had antiphospholipid antibody syndrome. In patients with CVST and OHSS, 1 patient had temporarily low protein S deficiency and another patient had a G20210A prothrombin gene mutation. Because thromboembolic complications are relatively rare, routine screening for thrombophilia in women planning to undergo ovarian stimulation is not recommended. It is debatable whether women with an underlying known thrombophilia should receive prophylaxis or not prior to ovulation induction to prevent thromboembolic complications. OHSS is frequently associated with hyperviscosity, which may add to the risk factors. As there have been such few reports of high prevalence of inherited thrombophilias in patients with OHSS,^{33,34} whether it is cost effective to screen all women undergoing ovarian stimulation for these conditions is debatable.³⁵ We will suggest, though, a detailed discussion with the patients planning for IVF or ovulation induction who may have known risk factors.

Therapeutic options have been varied in the past with no particular trends. Two patients were treated with intravenous tissue plasminogen activator without any significant complications. All ischemic strokes in the acute setting should be treated with thrombolytics and/or mechanical intervention as per American Heart Association guidelines.³⁶ Secondary stroke prophylaxis in these cases is debatable. Previously antiplatelets, warfarin, and heparin products have been used in various regimens. Our patient has done well with only aspirin, and we will recommend an individualized approach on a case-to-case basis. About 48% of the ischemic stroke patients experienced complete recovery and 7% ($n = 2$) of the patients died. This outcome can be considered relatively good considering that most of these patients had large hemispheric strokes.

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