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Ovarian hyperstimulation syndrome and the risk of internal jugular vein thrombosis

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Abstract

Introduction: Thromboembolic events are a rare complication of severe ovarian hyperstimulation syndrome (OHSS). In contrast to the classical left ilio-femoral deep vein thrombosis casesduring pregnancy,atypical localization in upper extremity, including internal jugular vein (IJV)is also reported. **Review of the literature:** We reviewed 39 cases of IJV thrombosis associated with OHSS mostly during assisted reproductive treatment. The diagnosis was made during first trimester, mainly with Doppler ultrasound, and treatment with heparin was initiated in all cases. In 14 patients another risk factor for thromboembolic event was reported (50% had FV-Leiden mutation). The IJV was extended in upper extremityincluding axillary, subclavian or superior vena cava in 46%, whereas pulmonary embolism was reported in 10% of cases. **Discussion:** Obstetricians should be aware of the rare complication of deep vein thrombosis in upper extremity including thrombosis of IJV, even weeks after OHSS symptoms have resolved.Patients with OHSS after assisted reproductive treatmentshould be prescribed heparin in prophylactic dose during the first trimester.

Key words: Internal jugular vein, ovarian hyperstimulation syndrome, thrombosis

Introduction

Ovarian hyperstimulation syndrome (OHSS) is an uncommon but serious complication associated with controlled ovarian stimulation during assisted reproductive treatment (ART). Classic physiologic changes of OHSS include arteriolar vasodilation and an increase in capillary permeability that results in fluid shifting from intravascular to extravascular spaces which may lead to ascites formation, pleural effusion and peripheral edema. In its severe form, which occurs in less than 5% of ACT cycles, OHSS is characterized by massive ovarian enlargement, hypovolemia, hemoconcentration, and hypoalbuminemia. Thromboembolic events area rare complication of OHSS andcould be related to the associated hemoconcentration in the hyperestrogenic environment.[1]

Pregnancy increases the risk of venous throm-

boembolic events (VTE), especially during the third trimester and the first 6 weeks postpartum. Few studies provided evidence that ART could represent an independent risk factor for VTE during pregnancy, especially during first trimester. However, there is no evidence of increased VTE risk after ART in unsuccessful cycles.[2]

Spontaneous and isolated internal jugular vein (IJV) thrombosis is a rare and atypical localization for VTE in upper extremity (UEDVT) and OHSS is included in the underlying factors that should be investigated after diagnosis.

Review of the Literature

A Pubmed search of English literature was performed in order to review all reported cases of IJV associated with OHSS. Cases without clinical overt OHSS were not included for analysis.

Thirty-nine cases of IJV thrombosis were reported in 32 manuscripts.[3-34] The median age of the patients was 31 years (range, 23-37). In 2 cases OHSS was spontaneous[7,26] whereas in all other cases there was history of ART.[3-34] The IJV thrombosis was diagnosed during first trimester (median 7 weeks of pregnancy with range, 4-13 weeks). It is interesting to note that the thrombosis was provoked in some casesweeks after resolution of the clinical syndromewith median value 3.5 weeks after OHSS diagnosis (range, 2-8).Nineteen pregnancies were multiparous.[3-5,10-12,14,17-19,21-23,27-30 33] One patient had past history of thrombosis[34] whereas another had a positive family history of a thromboembolic event[12]. When screening for thrombophilia was performed, 7 patients were found with F-V Leiden mutation[4,6,13,26,27 29] 2 of whom with homozygocity[13,27]. One patient was diagnosed with low antithrombin levels[7] and 3 patients with detectable antiphospholipid antibodies[6,8,14]. Protein S was also referred low in some cases; however, due to normal decrease due to pregnancy low levels were not evaluated.

The IJV thrombosis diagnosis was mostly made by Doppler ultrasound, whereas in few cases other imaging diagnostic scans like CT or MRI were performed.[7,13,24,31] The localization of IJV thrombosis was at the right side in 13 patients,[4,5,7,9,11,13,15,20,22,24,29 30 33] left in 14 patients[4,8,10,14,16-18,22,23,25,26,31,32,34] and in both sides in 6 patients[12,13,19,21,27,28] (in 7 cases the localization was not mentioned[3,6,25]). The IJV thrombosis was extended in subclavian vein in 7 patients,[8,12-14,19-21] in axillary vein in 4 patients[13,20,21,26] (2 patients had both suclavian and axillary vein thrombosis[20,21]), in superior vena cava (SVC) in 2 patients[24,33] and extended UEDVT not specified was reported in 5 patients.[7,20,21,26,28] The IJV thrombosis was associated with concurrent pulmonary embolism (PE) in 4 patients,[4,6,32] while 1 patient was diagnosed with PE before the diagnosis of IJV thrombosis, which occurred after discontinuation of anticoagulation for PE.[34]

After the diagnosis of IJV thrombosis anticoagulation was initiated and consisted of heparin in all patients: Unfractioned- heparin (UFH) in 13 patients,[7,14,19,25-34] low-molecular weight heparin (LMWH) in 22 patients,[3-6,8-11,13,16,17,20-24] both UFH and LMWH in 4 patients[12,13,15,18]). Heparin was co-administered with antibiotics in 4 patients[14,17,21,28] and SVC filter in 2 patients[7,15] (in 1 patient after insertion of SVC filter urokinase was also infused[7]). The IJV thrombosis had been occurred despite anticoagulation (mostly prophylactic dose) in 9 cases after diagnosis for OHSS[4,8,20,22,26,27,29,30] and in three patients the thrombosis occurred after insertion of a central venous catheter for treatment of OHSS.[10,21,31] In 3 patients the thrombosis was diagnosed after discontinuation of anticoagulation when OHSS was resolved.[10,12,28]

Discussion

During ART, in an attempt to maximize the number of embryos available for transfer and freezing, women are exposed to high doses of exogenous gonado-

trophins with a concurrent increase in thrombotic risk. The alterations in coagulation and fibrinolysis observed during ovarian stimulation are similar to those observed during pregnancy,due to rapid increase of estradiol levels potentially more than 100-fold within a 2-week period. However, despite significant alterations in hemostatic parameters, thromboembolic disease associated with ovarian stimulation is an uncommon complication, with an incidence of 0.08 –0.11% of treatment cycles-representing and increased risk of 20–40-fold.[11,35] Other risk factors for VTE disease should always be carefully investigated such as pasthistory of VTE event orpositive family history, concurrent medical conditions andobesity.

UEDVT in association with OHSS has been described despite prophylactic and even therapeutic anticoagulation. This resistance to anticoagulation may reflect localized excessive activation of coagulation and elevated concentrations of estradiol impairing the endothelium's antithrombotic properties.The predominance of UEDVT including the IJV, which is in contrast to the classical left ilio-femoral DVT during pregnancy, is possibly attributed to the unique drainage of the lymphatic system, with high levels of abdominal fluid containing estrogen drained via the thoracic duct.[36]

Data regarding the risk of VTE or development of OHSS in women with thrombophilia who undergo ART are lacking. In one case-control study, thrombophilia was associated with an increased risk of this complication. However, thrombophilia may have been overdiagnosed because blood samples were obtained while the patient was symptomatic for severe OHSS and the results of non-genetic factors may be affected.[37]

There have been no randomized trials demonstrating that prophylactic anticoagulation prevents VTE in patients with severe OHSS. Though, based on the risk of thrombosis due to OHSS and the generally low risks of bleeding associated with prophylactic LMWH in pregnancy, several guidelines recommend short-term prophylaxis in these patients. Dosage and duration of thromboprophylaxis has not been well studied and women that are more likely to benefit are those with higher-risk thrombophilias or hormone-associated VTE.[38]

Conclusion

OHHS represent a serious and potentially fatalcomplication of ART and earlydiagnosis and treatment is critical for both maternaland fetal safety. Obstetricians should be aware of the rare complication of UEDVT including thrombosis of IJV even weeks after OHSS symptoms have resolved.IJV thrombosis is asymptomatic in most patients, thus clinicians should carefully evaluate swelling, erythema, or tenderness in the angle of the jaw or the side of the neck and pregnant patients complaining of these symptomsshould undergo a systematicclinicalevaluation with doppler ultrasound in order to initiate anticoagulation treatment with LMWH. Patients with OHSS after ART should be prescribed LMWH during the first trimester which should be continued 3 months after resolution of their symptoms. Women with prior unprovoked or hormone-related VTE and those with higher-risk thrombophilias (eg, mutations in FV-Leiden or prothrombin, family history of VTE) should also be candidates for prophylactic LMWH. Other pregnant women after ART should be given thromboprophylaxis based on the same risk factors as other pregnant women.

Conflict of Interest and Funding

None

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