EDITORIAL

THE MECHANISM OF THROMBOEMBOLISM IN THE COURSE OF OVARIAN HYPERSTIMULATION SYNDROME

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Abstract

Ovarian hyperstimulation syndrome (OHSS) is an uncommon complication of controlled ovarian hyperstimulation. Although principal risk factors for OHSS have been determined, unfortunately, to date we are unable to precisely predict the appearance of OHSS. Still more infrequent are thromboembolic complications of OHSS. The background for the increased blood clotting in such cases includes, but is not limited to, increased permeability of blood vessels in response to excessive vasoactive substances of ovarian origin, vasoconstrictive effects of some other agents of ovarian origin, hemoconcentration and hypovolemia with resultant arterial hypotension, gonadotropin administration, supraphysiological concentrations of 17β-estradiol following ovulation induction, and inherited thrombophilias. Arterial events are predominantly cerebrovascular accidents, usually occuring concurrently with the onset of OHSS. Venous thromboses occur several weeks later and are mostly reported in unusual yet specific sites such as large veins of the upper extremities and neck. There is some evidence that arterial events may be rather embolic by their nature. Thus, the mechanisms standing behind arterial and venous events are likely to be different. Laboratory studies on hypercoagulability in OHSS indicate a broad array of possible changes, from the disturbed balance between tissue factor and tissue factor pathway inhibitor to elevated levels of D-dimer, thrombin-antithrombin complexes, prothrombin fragment 1 + 2, plasmin-antiplasmin complexes, and von Willebrand factor antigen. Increased levels of factors I, V, and VIII, thrombocytes, and decreased levels of tissue plasminogen activator and plasminogen activator inhibitor type I have also been reported. The quite unique localization of venous thrombi requires further careful attention for understanding. Although thromboembolic events are not frequently encountered in the course of OHSS, they are strikingly serious in a proportion of affected patients, and we agree with the recommendation by Grygoruk et al. from the current issue of the Journal that anticoagulant therapy should be prophylactically administered in all OHSS patients. As we discuss it, a precautionary good practice point could be the combined administration of low-dose aspirin and low-dose heparin in all controlled ovarian hyperstimulation patients.

Key words: female, ovarian hyperstimulation syndrome, pathogenesis, thromboembolism

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Ovarian Hyperstimulation Syndrome (OHSS) is considered by many authors as the most serious complication of ovulation induction as it is potentially lethal. In the course of OHSS, thromboembolic events are infrequently observed but may substantially contribute to the aggravation of the patient's condition. In this issue of the Journal, *Grygoruk* et al. present a case report on such a patient with a thrombus situated at the junction of the left external jugular and subclavian veins, and recommend an early routine administration of anticoagulant therapy with heparin in every OHSS patient as a prophylactic measure (1). Such a prudent suggestion is highly commendable, especially in the light of the fact that a recent review on OHSS management did not prompt any precise clinical step to be undertaken to avoid or treat thrombosis (2).

As we were involved in the process of blind review and copy-editing of the manuscript by *Grygoruk* et al., with time we became more and more intrigued by the presented case (1). This case, together with the cited literature, poses two important questions lacking the exact answers to date: Why is OHSS associated in a high proportion of patients with such a peculiar form of thromboembolic event like a clot at the junction of the left external jugular and subclavian veins? Why are other venous vascular system locations, like veins of the lower extremities, or vena cava inferior, or pulmonary microcirculation, not as frequently involved? In young women of good general health, the thrombus formation before pregnancy and after conception is generally low (3).

Looking at the possible risk factors for thromboembolism in severe OHSS, increased permeability of blood vessels in response to excessive vasoactive substances produced by the ovaries definitely plays an important role (1). The escape of body fluid from the vascular compartment to the third space (ascites, hydrothorax, hydropericardium) contributes to both hemoconcentration and hypovolemia. Vomiting in OHSS - the result of the pressure of intraperitoneal exudate on the bowel - can similarly contribute to them.

When arterial hypotension is present, then the blood flow velocity is less. Vasoconstrictive agents of ovarian origin include some potent compounds, such as angiotensin, interleukins and prostaglandins. For many years, a role of gonadotropin administration has been implicated (4, 5). Supraphysiologic 17β-estradiol concentrations in the patient's serum at the end of ovulation induction are a risk factor for OHSS and, moreover, could be responsible for the increased blood clotting. Obviously, presence of antiphospholipid antibody syndrome, factor II G20210A mutation or factor V Leiden G16191A mutation, or protein C, protein S or antithrombin III deficiencies are all per se other factors associated with the increased risk for hypercoagulability following controlled ovarian hyperstimulation (COH). In fact, several papers in support of this contention have been published (6-11). *Nowicka* et al. found direct correlations of elevated C-reactive protein concentration in the OHSS patients' blood with abdominal circumference measured at admission and ovarian size measured by ultrasound (12). This is of importance since the protein is well known to promote thrombosis following vascular injury, and such impairment is present in OHSS. Among others, C-reactive protein could have a role in OHSS hypercoagulability via the thromboxane A_2 pathway, as indicated in studies with transgenic mice (13).

In regard to laboratory findings, in 1991, Norwegian authors were among the first to study changes in the hemostasis following hormonal stimulation with human chorionic gonadotropin (14). They found a marked increase in plasma fibrinogen concentration, a reduction in antithrombin III concentration, and an increase in the clot lysis time. In 2003, *Rogolino* et al. reported a carefully controlled study on hemostatic markers in severe OHSS patients (15). In such women, tissue factor, D-dimer, thrombin-antithrombin complexes, prothrombin fragment 1 + 2, plasmin-antiplasmin complexes, and von Willebrand factor antigen levels in plasma were significantly higher than those observed both in the case-controls and in healthy controls. In contrast, tissue factor pathway inhibitor (TFPI) levels were significantly lower. Interestingly, D-dimer levels were tightly related with serum 17β-estradiol concentrations and number of recovered oocytes. The authors concluded that the disturbed balance: tissue factor-TFPI is present in OHSS and that there is a correlation between the magnitude of COH and hypercoagulability. They thought that a chronic depletion of the TFPI endothelial pool may be due to endothelial injury in OHSS. Earlier, increased levels of factors I and V, thrombocytes, and fibrinolytic inhibitors have been reported (4). In 2009, Chan presented an excellent review of English-language articles on thromboembolism associated with COH and OHSS and reported until December 2008 (16). The analysis of longitudinal studies allowed to conclude that activation in both the coagulation and fibrinolysis systems occurs in patients who undergo ovarian stimulation, and that this activation is greatly exaggerated with the development of OHSS. However, there is no one strictly defined picture of laboratory alterations in all patients. Besides possible changes already mentioned, in some studies increased activated protein C resistance, increased levels of factor VIII, and decreased levels of tissue plasminogen activator and plasminogen activator inhibitor type I have also been reported (16). In summary, from the last two paragraphs, all components of Virchow's triad can be affected in OHSS.

Further important information is that arterial events are predominantly cerebrovascular accidents, usually occuring concurrently with the onset of OHSS. Venous thromboses occur several weeks later and are mostly reported in unusual sites such as the large veins of the upper extremities and neck (16). There is some evidence that arterial events may be rather embolic in nature and less frequent than venous. Thus, with different timings, incidences and localizations, the mechanisms standing behind arterial and venous events are likely to be different (16). In 2007, *Bauersachs* et al. reported that the concentration of 17β-estradiol in the ascitic fluid from OHSS women is very elevated, being approximately 27 times higher than the serum concentration (17). Since the thoracic duct drains into the junction of the left subclavian vein and left jugular vein, and the right lymphatic duct into the venous angle on the right side at the jugular vein and the subclavian vein, thus, an explanation for the unusual predisposition for upper extremity thrombosis in patients who undergo COH could be in part in the anatomy of the lymphatic system. *Bauersachs* et al. attributed this predisposition to the lymphatic drainage of high levels of ascitic 17β-estradiol via the major lymphatic vessels into the major neck veins. On the other hand, *Salomon* et al. detected in OHSS patients clusters of rudimentary branchial fluid-filled cysts that mechanically compressed the jugular and subclavian veins (11). The quite unusual localization of venous thrombi requires further careful attention for understanding.

As assisted reproductive technology has increased tremendously over the past three decades, the medical community deals with patients who underwent COH more and more often. Although thromboembolic events are not frequently encountered in the course of OHSS, they can be strikingly serious and most saddening in a proportion of affected patients. For instance, some sequelae described in articles cited in the Chan review included: fatality, cerebral infarctions, amputation of the extremity, all this in young women who just wished to have a child. With our current better understanding of a predilection for hypercoagulation in OHSS, we should do our best to prevent thromboembolism associated with this entity. This makes us think that patients selected for COH should have an early checkup for abnormalities of blood clotting (at least such as control of basic coagulation and fibrinolysis markers, supplemented by protein C, protein S, and antithrombin III levels) included in their routine infertility workup. A careful history towards family thrombophilias should be taken. In a meta-analysis from 2007, aspirin was found to be not particularly beneficial, but also harmless for the course of pregnancy following in vitro fertilization (18). Yet, a 2010 study from Hungary presented data on high efficacy of low-dose aspirin treatment (starting from the first day of COH) in the prevention of OHSS ocurrence (19). A recent meta-analysis of observational

studies on women undergoing in vitro fertilization and receiving heparin compared with placebo demonstrated a significant increase in the clinical pregnancy rate in the heparin group (20). From the world review of case reports, the overall risk of progression of thrombosis in OHSS despite administration of anticoagulation is not small: 7.5% (16). Bilateral internal jugular venous thrombosis following COH has been reported even in the absence of OHSS (21). Therefore, it is reasonable to think now that a precautionary good practice point could be the combined administration of low-dose aspirin and low-dose heparin in all COH patients on a regular basis.

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