THE MECHANISM OF THROMBOEMBOLISM IN THE COURSE OF OVARIAN HYPERSTIMULATION SYNDROME

Maciej Jóźwik, MD, PhD
Department of Gynecology, Medical University of Białystok, Białystok, Poland

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 occurring 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
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 A₂ 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 occurring 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 sequelaes 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 occurrence (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.

REFERENCES


Received: November 04, 2012
Accepted: November 12, 2012

Address for correspondence:
Maciej Jóźwik
Department of Gynecology, Medical University of Białystok, Skłodowskiej 24 A, 15-276 Białystok, Poland
E-mail: jozwikmc@interia.pl