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## THE RISK OF HYPERCOAGULABILITY IN OVARIAN HYPERSTIMULATION SYNDROME

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**SUMMARY** – Ovarian hyperstimulation syndrome (OHSS) is a rare and potentially life-threatening complication of infertility treatment occurring during either the luteal phase or early pregnancy. An increasing number of thromboembolic complications associated with the increased use of assisted reproductive techniques have been reported in the literature. Identification of the risk factors is crucial for prevention of thromboembolic events in OHSS patients. Alterations in the hemostatic system cause hypercoagulability in women affected by severe OHSS. Coexistence of inherited hypercoagulable conditions increases the risk of thromboembolism. The role of clinical parameters that can help predict development of thrombosis is controversial. Patients with a personal or family history of thrombosis undergoing infertility treatment should be considered for thrombophilia screening, while routine examination of inherited thrombophilic mutations is not indicated in infertile patients. Antithrombotic primary prevention is not indicated in healthy women undergoing assisted reproductive procedures or in women with thrombophilia. Anticoagulant therapy is indicated if there is clinical evidence of thrombosis or laboratory evidence of hypercoagulability. In this review, the risks of hypercoagulability in the OHSS are discussed.

Key words: *Ovarian hyperstimulation syndrome; Thrombophilia; Thrombosis*

### Introduction

Ovarian hyperstimulation syndrome (OHSS) is one of the most frequently reported complications of infertility treatment occurring during either the luteal phase or early pregnancy. It is usually associated with the use of exogenous gonadotropins for ovarian stimulation, or occasionally with the use of clomiphene citrate. Some forms of OHSS are rarely associated with a spontaneous ovulatory cycle. The incidence of

OHSS varies according to different studies. The overall incidence of OHSS is estimated at 0.6%-14% of all ovarian stimulation cycles<sup>1</sup>. Severe OHSS accounts for 0.5% to 5% of all cases of OHSS<sup>1</sup>. The risk factors for developing severe form of OHSS include high or rapidly rising estradiol levels (with serum concentration >2500-3500 pg/mL), great numbers of large and medium-sized follicles and the number of oocytes retrieved during *in vitro* fertilization (IVF; >14), previous episodes of OHSS, age under 30 years, use of gonadotropin releasing agonist protocol, higher or repeated dose of human chorionic gonadotropin (hCG), and polycystic ovarian syndrome (PCOS)<sup>2,3</sup>.

Thromboembolic phenomena are an uncommon complication of OHSS and sometimes fatal despite appropriate treatment<sup>4</sup>. It is estimated that one of 128

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women with severe OHSS develops thromboembolic disease<sup>5</sup>.

### Pathophysiology of Thrombosis

The etiology of OHSS is complex, but hCG, either exogenous (to induce ovulation or as a luteal phase support) or endogenous (pregnancy derived), is believed to be a main promoter of OHSS. First step in the pathophysiology of OHSS is hCG stimulation of granulosa-lutein cells, leading to the increased production of vascular endothelial growth factor (VEGF)<sup>6,7</sup>. A number of other molecules, including angiogenin, interleukin(IL)-1, IL-2, IL-6, IL-10, IL-18, tumor necrosis factor-alpha, insulin-like growth factor 1, epidermal growth factor, transforming growth factors, von Willebrand's factor (vWF), endothelial adhesion molecules, endothelin-1, histamines and ovarian kinin-kallikrein and ovarian-renin angiotensin system, take part in the increased capillary permeability, ovarian neovascularization, inflammatory response and inhibition of hepatic albumin production, which explains most of the symptoms and signs of OHSS<sup>8,9</sup>. VEGF is the pivotal cytokine involved in the pathophysiology of OHSS. It acts dominantly through the VEGF receptor-2 increasing vascular permeability with loss of fluid, proteins and electrolytes into the extravascular compartment. Severe OHSS is a potentially life-threatening iatrogenic complication accompanied by massive ovarian enlargement, intravascular volume depletion with accompanying development of edema, ascites, hydrothorax, abdominal distension, electrolyte disturbance, hypoalbuminemia, hemoconcentration and ultimately thromboembolism, liver and renal insufficiency and multiple organ failure with adult respiratory distress syndrome<sup>2</sup>. The exact pathogenesis of thrombosis in OHSS has not yet been elucidated entirely. It has been surmised that the hypercoagulable state is created due to hemoconcentration, as a result of the increased capillary permeability, which leads to the loss of protein-rich fluid from the intravascular compartment into the third space, and blood viscosity together with changes in coagulation parameters. Both arterial and venous thrombosis in OHSS demonstrate predilection for head and neck manifestation. Bauersachs *et al.*<sup>10</sup> offer a pathophysiological explanation for this

phenomenon. Estrogen-rich lymph collected from ascites into the lymphatic system, which further drains into the junction of the subclavian vein and jugular veins, can cause local high estrogen content, triggering thrombosis in these neck veins<sup>10</sup>. The concentration of estradiol in the ascites fluid is 27 times higher than the serum concentration<sup>10</sup>. Other substances drained from the lymphatic system into the veins may cause additional prothrombotic output. Salomon *et al.* hypothesize that the development of thrombosis early in pregnancy is the result of mechanical compression mediated by rudimentary brachial cysts filled with fluid during OHSS<sup>11</sup>. Further studies are required to fully understand this phenomenon.

### Thrombotic Risk Factors

In a cross sectional study, Henriksson *et al.*<sup>12</sup> analyzed 23,498 women who gave birth after IVF and 116,960 individually matched women with natural pregnancies and showed an increased risk of thromboembolism and pulmonary embolism in pregnant women after IVF, especially during the first trimester. In their study, venous thromboembolism (VTE) occurred in 4.2/1000 women after IVF *versus* 2.5/1000 in women with natural pregnancies. The risk of VTE after IVF was significantly increased throughout pregnancy, especially during the first trimester. Pulmonary embolism occurred in 3.0/10 000 women after IVF during the first trimester, compared with 0.4/10 000 in women with natural pregnancies. The absolute risk of pulmonary embolism was low<sup>12</sup>. Their results are in accordance with the findings reported by Rova *et al.*<sup>13</sup>, on the risk of first-trimester VTE in women after IVF being tenfold that recorded in women without IVF. Pregnant women after IVF in the absence of OHSS had a fivefold risk of VTE, while pregnancies after IVF that were complicated by OHSS had a 100-fold risk of VTE. There was no increased risk of VTE after the first trimester<sup>13</sup>.

Several studies investigated the alterations of the hemostatic system in women affected by severe OHSS. Considering laboratory findings, increased levels of factors I and V, platelets and fibrinolytic inhibitors have been reported in patients with OHSS<sup>14</sup>. Aune *et al.*<sup>15</sup> analyzed the effects on blood coagulation and fibrinolytic activity during ovarian stimulation. They

found a marked increase in the clot lysis time, a rise in plasma fibrinogen concentration and reduction in antithrombin III concentration. The blood fibrinolytic activity was significantly reduced. Rogolino *et al.*<sup>16</sup> report that D-dimer, tissue factor (TF), thrombin-antithrombin complexes, prothrombin fragment 1 + 2 (F1+2), plasmin-antiplasmin complexes (PAP), and vWF antigen plasma levels were significantly higher in patients with severe OHSS as compared with those observed in both case-control group and healthy controls. Plasma levels of the tissue factor pathway inhibitor (TFPI) were significantly lower. They also found that D-dimer levels were related to serum estradiol levels and number of recovered oocytes. The authors concluded that marked hypercoagulability with alterations in TF and TFPI levels determined the clinical outcome of severe OHSS. In addition to these changes, there is a reduced protein C and protein S activity and decreased levels of tissue plasminogen activator and plasminogen activator inhibitor type I (PAI-1) as well<sup>17</sup>. These results indicate an increased risk of hypercoagulability following ovarian stimulation for IVF. In the analysis of longitudinal studies, Chan<sup>17</sup> concludes that activation in both the coagulation and fibrinolysis systems occurs in patients undergoing ovarian stimulation, and that this activation is greatly exaggerated with the development of OHSS. Besides the laboratory findings mentioned, the possible risk factors for thromboembolism in severe OHSS are elevated serum estradiol levels at the end of ovulation induction, presence of antiphospholipid antibody syndrome, factor II (FII) G20210A mutation and factor V Leiden (FVL) G16191A mutation<sup>17</sup>. Some authors recommend screening for genetically determined risk factors before ovulation induction, especially in patients with personal and family history of thrombosis<sup>2</sup>. Febregues *et al.*<sup>18</sup> report that screening for FII and FVL mutation in an IVF general population is not cost-effective and that the prevalence of thrombophilia is not increased in patients with severe OHSS, which is in contrast to the results of a previous study by Dulitzky *et al.*<sup>19</sup>, who found an increased prevalence of thrombophilia in women with severe OHSS. Machac *et al.*<sup>20</sup> found an increased heterozygous form of FVL mutation in infertile patients. However, carriers of this mutation did not have an increased risk of developing severe form of OHSS during stimulation. Ricci

*et al.*<sup>21</sup> compared the prevalence of FII and FVL mutation between women undergoing IVF and women with spontaneous pregnancy; and the IVF outcomes and the risk of complications in FVL and FII carrier *versus* non-carrier women. No thrombotic complications occurred in either group. They conclude that the presence of FVL and FII mutations in asymptomatic women and in the absence of other risk factors does not influence IVF outcome, does not represent a risk factor for OHSS, and does not favor thrombosis after IVF. Although the coexistence of thrombophilia and OHSS can have fatal consequences, routine examination for inherited thrombophilic mutations is not indicated in infertile patients<sup>20,21</sup>. Only patients with a personal or family history of thrombosis undergoing IVF should be considered for thrombophilia screening<sup>22</sup>. Identification of the risk factors is crucial for prevention of OHSS.

### Thromboembolic Complications

The incidence of thromboembolic events in assisted reproductive techniques (ART) has been estimated to 0.08%–0.11%<sup>23</sup>. Rao *et al.*<sup>24</sup> performed a review of thromboembolic cases associated with ovarian stimulation, including 54 cases between 1964 and 1997, previously reported by Stewart *et al.* Sixty-seven percent of the 97 cases with thrombotic events after ovulation induction were of venous origin, while 33% were arterial thromboses. Seventy-four percent of these cases were associated with OHSS and 77% were associated with pregnancy<sup>22</sup>. In pregnancy, venous thrombosis is often located in lower extremities, most commonly in the iliofemoral region<sup>24</sup>, while venous thrombosis in OHSS usually involves veins in the neck and upper extremities (71%–80%)<sup>17,24</sup>. Pulmonary thromboembolism occurs in 4%–12% of OHSS patients, complicated with deep vein thrombosis<sup>25,26</sup>. Venous thrombosis often presents several weeks after resolution of OHSS, while arterial event usually occurs concurrently with OHSS development<sup>14,24</sup>. Of the arterial thromboembolic events, most common are cerebrovascular accidents (60%), followed by extremities (17%) and myocardial infarction (11%)<sup>17</sup>. Chan<sup>17</sup> has presented a review of 96 English-language articles on thromboembolism associated with OHSS reported until December 2008. In Chan's review,

mortality among reported arterial thrombosis cases was 9%. There was no mortality reported among venous thrombosis cases<sup>17</sup>. Our literature review using the Medline database identified additional 14 well documented cases of venous and arterial thrombosis associated with ART (January 2009-August 2014). We found additional 12 articles reporting on venous thrombosis<sup>27-38</sup>, and two articles reporting on arterial thrombosis after ovarian stimulation<sup>39,40</sup>.

Of the arterial thromboembolic reports, one patient had cerebrovascular accident and another one right femoral artery thrombosis<sup>39,40</sup>. The predominant sites of venous thrombosis involvement were the internal and external jugular veins<sup>27-29,31,36,38</sup>, sporadically combined with subclavian vein thrombosis<sup>27,36</sup>. One patient had combined jugular vein thrombosis, subclavian vein thrombosis and right brachiocephalic vein thrombosis after IVF and embryo transfer<sup>30</sup>. Three patients had cerebral venous thrombosis<sup>32,34,37</sup>, while one of them had dual cerebral vein thrombosis affecting rectal sinus and left transverse sinus<sup>37</sup>. In patients that develop progressive abdominal pain during and after ART, mesenteric vein thrombosis and portal vein thrombosis should be considered on differential diagnosis<sup>33,35</sup>, even in the absence of OHSS<sup>33</sup>.

### Thrombosis Prevention and Treatment

Based on the existing literature, antithrombotic primary prevention is not indicated in healthy women undergoing assisted reproductive procedures, or in women with thrombophilia<sup>41</sup>. Women with severe OHSS require hospitalization for careful monitoring and appropriate treatment. The main interventions are fluid management and correction of hypovolemia and hemoconcentration. Intravenous hydration should be started with a crystalloid solution to alleviate hemoconcentration and provide adequate end-organ perfusion. If end-organ perfusion is not maintained, an alternate colloid solution should be administered<sup>42</sup>. Transvaginal ascitic fluid aspiration should be performed in patients with tense ascites to alleviate their discomfort, and according to Qublan *et al.*<sup>43</sup>, if repeated (>3) it significantly increases pregnancy rate along with a significant decrease in the abortion rate. Anticoagulant therapy is indicated if there is clinical evidence of thrombosis or laboratory evidence of

hypercoagulability<sup>2</sup>. Thromboprophylaxis should not be prescribed for women with a family history of thrombosis and early start of OHSS after ET with no other risk factors (previous VTE, thrombophilia, age over 35, obesity, parity >4, gross varicose veins, paraplegia, inflammatory disorders, e.g., inflammatory bowel disease, nephrotic syndrome, certain cardiac diseases, myeloproliferative disorders, hyperemesis and dehydration). To prevent thrombosis in severe OHSS, subcutaneous heparin 5000-7500 IU/day and use of thromboembolic deterrent stockings should be instituted and continued until discharge<sup>25,42</sup>. Thromboprophylaxis in severe form of OHSS does not always prevent thrombosis<sup>44-46</sup>. Acute management of patients that develop venous thrombosis involves the use of adjusted-dose low molecular weight heparin (LMWH) or intravenous unfractionated heparin (IV UFH) for at least 5 days, followed by adjusted-dose UFH or LMWH for the remainder of pregnancy and at least 6 weeks postpartum<sup>47</sup>. The preferred option for most patients is LMWH due to better bioavailability, longer plasma half-life, and better safety profile with regard to osteoporosis and thrombocytopenia compared to UFH<sup>48,49</sup>. LMWH and UFH are safe for the fetus, due to the inability to pass placental barrier. Bleeding at the uteroplacental junction is possible<sup>49</sup>. For cerebrovascular accidents and myocardial infarction, specific treatment with LMWH and UFH is the same as in the general population<sup>17,47,50</sup>. Acute reperfusion in selected patients with myocardial infarction may be achieved with percutaneous coronary intervention and/or fibrinolytic agents under strict protocols<sup>17,47</sup>. The rate of thrombosis progression in OHSS despite administration of anticoagulant therapy is 7.5%<sup>17</sup>. Multidisciplinary approach in the treatment of critical OHSS is required for its appropriate management.

### Conclusion

Ovarian hyperstimulation syndrome is the main risk factor for thrombosis complicating controlled ovarian hyperstimulation and ovulation induction. Prevention of the syndrome is the most important aspect of its management. Apart from cycle canceling, all other preventive methods may reduce but not eliminate OHSS. Antithrombotic treatment is crucial

if there is clinical evidence of thrombosis or laboratory evidence of hypercoagulability.

Further studies will complement our knowledge of thromboembolic phenomena in OHSS, which may advance our ability to predict, prevent and treat this rare, but life-threatening complication of ART.

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## Sažetak

## RIZIK HIPERKOAGULABILNOSTI KOD SINDROMA HIPERSTIMULACIJE JAJNIKA

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Sindrom hiperstimulacije jajnika je rijetka i za život opasna komplikacija liječenja neplodnosti koja se javlja u lutealnoj fazi menstrualnog ciklusa ili tijekom rane trudnoće. Povećanjem zastupljenosti tehnika potpomognute oplodnje povećava se broj prijavljenih slučajeva tromboembolijskih komplikacija. U prevenciji tromboembolijskih događaja kod bolesnica sa sindromom hiperstimulacije jajnika ključno je određivanje rizičnih čimbenika. Promjene u sustavu hemostaze uzrokuju hiperkoagulabilnost, a nasljedne trombofilije dodatno povećavaju rizik tromboembolije. Sporna je uloga kliničkih parametara koji mogu pomoći u predviđanju razvoja tromboze. Žene podvrgnute liječenju neplodnosti koje su preboljele tromboembolijsku bolest ili u obitelji imaju slučajeve tromboembolijske bolesti treba testirati na nasljedne trombofilije, dok se rutinsko testiranje kod neplodnih žena ne provodi. Antitrombotska terapija je indicirana samo ako su prisutni klinički znakovi tromboze ili laboratorijski dokazana hiperkoagulabilnost, a nije indicirana kod žena s nasljednom trombofilijom u postupku medicinski potpomognute oplodnje bez kliničkih i/ili laboratorijskih znakova tromboze. U ovom preglednom članku opisani su rizici hiperkoagulabilnosti u sindromu hiperstimulacije jajnika.

Ključne riječi: *Ovarijski hiperstimulacijski sindrom; Trombofilija; Tromboza*