

Treatment of ovarian hyperstimulation syndrome

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Master's thesis / Diplomski rad

2015

Degree Grantor / Ustanova koja je dodijelila akademski / stručni stupanj: **University of Zagreb, School of Medicine / Sveučilište u Zagrebu, Medicinski fakultet**

Permanent link / Trajna poveznica: <https://um.nsk.hr/um:nbn:hr:105:112166>

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Download date / Datum preuzimanja: **2024-04-24**



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Zagreb, 2015

This graduate thesis was made at the Department of Human Reproduction and Endocrinology mentored by doc. dr. sc. Miro Kasum and was submitted for evaluation in 2015.

Abbreviations

ART: assisted reproductive technologies

OHSS: Ovarian Hyperstimulation Syndrome

VEGF: Vascular Endothelial Growth Factor

sVEGF: soluble vascular endothelial growth factor

VEGFR2: vascular endothelial growth factor receptor 2

hCH: human chorionic gonadotropin

GnRH: gonadotropin releasing hormone

ANGPT1: angiopoietin 1

i.v.: intravenous

INR: international normalized ratio

ASRM: American Society for Reproductive Medicine

HES: hydroxyethyl starch

IgG: immunoglobulin G

IgA: immunoglobulin A

IVF: in vitro fertilization

UTI: urinary tract infection

URTI: upper respiratory tract infection

ICU: intensive care unit

CRP: C- reactive protein

DVT: deep venous thrombosis

LMWH: low-molecular weight heparin

s.c.: subcutaneously

CVP: central venous pressure

ABGs: arterial blood gases

CPAP: continuous positive airway pressure

PT: prothrombin time

aPTT: activated partial thromboplastin time

PTT: partial thromboplastin time

JVP: jugular venous pressure

PCV: packed cell volume

RCC: red cell concentrate

FFP: fresh frozen plasma

1. Introduction

Ovarian hyperstimulation syndrome is a rare complication of controlled ovarian hyperstimulation and ovulation induction which can develop during the luteal phase or during early pregnancy. Controlled ovarian hyperstimulation is a treatment used as a part of assisted reproduction. Its aim is to induce the development of multiple ovarian follicles so that multiple oocytes can be obtained at follicular aspiration. “Ovulation induction” is more commonly used to refer to the treatment of menstrual disorders, for example anovulation and oligoovulation. (Federal Drug Agency). Different studies report the incidence of OHSS as ranging from 0.6% to 6% (European Society of Human Reproduction and Embryology, 2011; Elia EM et al, 2013).

The main pathophysiological mechanism in OHSS is the development of vascular hyperpermeability. A steep rise in hCG levels, whether exogenously administered or endogenously secreted after the onset of pregnancy, is the main cause of vascular hyperpermeability in OHSS. The main mediators of the hyperpermeability are VEGF and its receptor VEGFR2 (Hanevik HI et al 2012, Levin ER et al 1998). The VEGF protein is produced by human granulosa cells (Neulen J et al, 1995) and its expression is enhanced by administration or endogenous secretion of hCG (Neulen J et al, 1995, Wang TH et al 2002). Administration of GnRH agonists instead of hCG to trigger ovulation in controlled ovarian stimulation cycles has shown that those treated with GnRH as trigger showed a statistically significant decrease in VEGF in follicular fluid and in VEGF mRNA expression in granulosa cells. (Cerrillo M et al, 2011). VEGF increases vascular permeability by acting on adherens junctions and thus causing endothelial barrier breakdown. Fragments of adherens junctions can be used as markers of hyperpermeability. Indeed, women with severe OHSS have significantly higher levels of endothelium-derived sVE-cadherin fragments than patients without OHSS and thus sVE-

cadherin may be involved in the pathogenesis of severe OHSS (Villasante A et al 2008). It has also been suggested that ANGPT1 increases pathophysiological angiogenesis in patients at risk of OHSS by acting on tight and adherens junction proteins (Scotti L et al, 2014).

The clinical features of OHSS result from a fluid shift from the intravascular space into third spaces causing hemoconcentration. According to the Whelan and Vlahos classification, the symptoms and signs of OHSS can be classified into five grades. The presenting symptom in grade 1 of Mild OHSS is abdominal distension or discomfort. Grade 2 includes the symptoms of grade 1 and also nausea, vomiting, and/or diarrhea, and the ovaries are enlarged to a size of 5 to 12cm. Grade 3 is the Moderate stage of OHSS, and includes the characteristics of Mild OHSS plus ultrasonographic evidence of ascites. The severe stages of OHSS are grades 4 and 5. Grade 4 includes characteristics of moderate OHSS plus clinical evidence of ascites and/or hydrothorax or difficulty in breathing. Grade 5 includes all of the above plus change in blood volume, increased blood viscosity due to hemoconcentration, coagulation abnormalities, and diminished renal perfusion and function (Whelan and Vlahos 2000).

OHSS has the potential to occur at two separate and distinct times, depending on the source of hCG. If the OHSS develops shortly after administration of hCG for triggering of ovulation, the patient has early OHSS. If the patient develops OHSS after the confirmation of pregnancy, it is late OHSS, caused by the ongoing secretion of hCG from the syncytiotrophoblast cells of the blastocyst (O'Brien K et al 2009).

In 2011 there were 1683 OHSS cases recorded in 28 out of 33 European countries reporting to the European Society for Human Reproduction and Embryology, making up 0.6% of cycles. The incidence of severe OHSS is reported to be 0.2-1% (Binder H et al, 2007).

Alternatively, the incidence of OHSS requiring hospitalization has been calculated as 2.1% (Papanikolaou EG et al, 2006). The decreasing incidence of OHSS in recent years reflects the successful application of newer preventive measures aimed at reducing the number of cases of OHSS. However, OHSS can occur in some patients despite the most recent preventive measures. Therefore, treatment of OHSS continues to be a current issue in gynecology. The objective of this paper is to review the main points surrounding the treatment of OHSS and its complications.

2. Treatment of OHSS

2.1. Conservative treatment

Conservative treatment of OHSS is focused on 4 main areas: restoring intravascular volume, shifting fluid from the third space back to the vessels, improving circulatory hemodynamics and preventing hemoconcentration. (Delvigne and Rozenberg, 2003).

Women with symptoms of severe OHSS should be admitted to the hospital. If the patient cannot tolerate oral fluids, i.v. fluids such as normal saline should be started. The volume should be adjusted according to the hematocrit, with the aim to use correction of hemoconcentration as a marker of adequate fluid replenishment. It is important to note that excess i.v. fluids could cause a deterioration in the patient's status, with an increase the amount of ascites. The input and output of fluids should be measured repeatedly throughout the treatment. Rapid initial hydration with a bolus of 500-1000mL can be performed for patients with severe OHSS being admitted to hospital. Five percent dextrose in normal saline should be used instead of lactated Ringer's solution, due to the tendency of Ringer's lactate towards hyponatremia, as it is hypotonic compared to the plasma water. Overall, correction of hypotension, hypovolemia and oliguria is

the main goal. If the patient is oliguric she should be catheterized with hourly urine measurements and transferred to an intensive care unit.

Electrolyte imbalances include hyponatremia and hyperkalemia (ASRM Practice Committee, 2008). Hyperkalemia can be managed acutely with insulin and glucose, sodium bicarbonate, or albuterol which move potassium into the intracellular space or with calcium gluconate to prevent onset of arrhythmias. If there are electrocardiographic signs of hyperkalemia, patients should be treated immediately with calcium gluconate. Kayexelate is a cation exchange resin that removes potassium from the body and has an onset of action within 1-2 hours. It may be administered per os or as a retention enema. (Institute of Clinicians and Gynecologists, 2012; ASRM, 2008; Royal College of Obstetricians and Gynecologists, 2006; Shmorgun, D and Claman, P, 2011). Patients may require total parenteral nutrition if they cannot take enteral feeding (Talawar P et al 2011).

2.1.1. Volume expanders

Until recently, it was accepted that albumin should be the first line treatment for volume expansion in OHSS. Albumin creates plasma oncotic pressure, which depends on its high plasma concentration and its net negative charge. Its net negative charge pulls sodium ions and consequently water into the intravascular space. Albumin makes up 75% of the plasma oncotic pressure (Garcia-Martinez R et al, 2013).

Until recently albumin has been recommended only in specific cases such as in the case of hypo-albuminemia. Adverse outcomes that can occur with albumin administration are excessive albumin overload, renal function impairment and potential viral infection. It was also previously recommended that albumin is only useful during drainage of ascites (Institute of

Obstetricians and Gynecologists, 2012). The most recent protocols in hospitals such as the University of Colorado Hospital have concluded that ovarian hyperstimulation syndrome is an inappropriate indication for albumin treatment (2014). Without a reduction in vascular permeability, the effect of albumin on intravascular volume and hematocrit – specifically, an increase in intravascular volume and decrease in hematocrit – may be only temporary and may be followed by diffusion of albumin into the extravascular space thus increasing the formation of ascites as well as pleural effusions (Kasum M, Oresković S, 2010).

An alternative to albumin solution is HES. Patients with severe OHSS who received 6% HES had higher daily urine output, needed fewer abdominal and pleural paracenteses, and had a shorter hospital stay than those who received human albumin. (Abramov Y et al, 2001). HES 6% in isotonic sodium chloride solution can be used at a maximum daily dose of 33ml/kg in 250 - 500 mL per day, administered slowly to avoid lung congestion (Delvigne A et al, 2006).

2.1.2. Paracentesis

Paracentesis is a method of aspirating fluid from the abdomen. It is predominantly used to treat the moderate to severe stages of OHSS, including severe late-onset OHSS, with severe ascites and pulmonary effusion. (Chan CC et al, 2004).

Paracentesis lowers intra-abdominal pressure and improves renal function, leading to increased urine output and a reduction in BUN, especially in patients with severe OHSS. (Chen CD et al, 1998, Levin I et al, 2002). It is plausible that the beneficial effects of paracentesis on urine output in OHSS are due to improved renal blood flow from a direct decompression effect. Paracentesis lowers intra-abdominal pressure and decreases renal arterial resistance, and has been reported to increase the urine production by 65%. (Maslovitz S et al, 2004). With outpatient

paracentesis, the onset of diuresis has been found to occur, on average, 2.8 days and recovery 7.4 days after the first paracentesis in patients who were oliguric (Fluker MR et al, 2000).

Patients with severe early OHSS who were hospitalized and managed with multiple aspirations (≥ 3) had significantly lower days of hospitalization as compared with the control group (<3) and had a significantly higher pregnancy rate and significantly lower abortion rate compared with the control group (Qublan HS et al, 2012). In addition, paracentesis is equally effective if performed with the transvaginal technique as with the transabdominal technique (Raziel A et al, 1998; Kasum M and Oreskovic S, 2010) and both methods can be performed on an inpatient or outpatient basis, provided that outpatients are controlled by daily phone calls and frequent office visits (Abuzeid et al, 2014).

Case-control studies of patients receiving either outpatient or inpatient paracentesis have found that outpatient paracentesis minimized the need for hospitalization of patients with moderate to severe OHSS. The management of the patients ranged from outpatient paracentesis being performed every 1-3 days to a single paracentesis where 1-3 L was removed over 2-3 hours with patients staying in the hospital for a total of 6-7 hours during the day. The endpoints were resolution of symptoms or hospitalization. In the first study outpatient paracentesis was found to result in 91.6% of patients avoiding hospitalization, with a pregnancy rate in patients undergoing embryo transfer of 84.7%, and a spontaneous loss rate of 16%. In the second study, the symptoms of OHSS improved quickly and pregnancy was achieved in 68% of all patients. It is important to note that patients should be hydrated intravenously during paracentesis to avoid dehydration and its complications (Lincoln SR et al, 2002, Shrivastav P et al 1994). Similarly, after the initiation of aggressive outpatient transvaginal paracentesis in one clinic it was found

that a significantly smaller number of patients required hospitalization for OHSS in the years following the initiation of outpatient paracentesis (Smith LP et al, 2009).

Pigtail catheter placement for prolonged drainage in patients with moderate to severe OHSS is another option, and can be equally effective in the outpatient as in the inpatient settings. As an example of this type of paracentesis, studies report placement of the pigtail catheter in both outpatients and inpatients for mean of 7.8 -12.9 days, with one study reporting an average of 11.2 L of ascites removed from the abdominal cavity. Following catheter placement, improvement of symptoms and signs was noted after 24-48 h in all patients in both groups. The procedures were well tolerated and no complications developed. The conception rate for IVF patients who developed OHSS and were treated with pigtail catheter placement was reported in one study as 84%. Out of thirty-three IVF patients requiring pigtail catheter placement, the complications requiring hospital admission included work up for chest pain in one patient and critical OHSS with severe pleural effusion requiring thoracentesis and supportive treatment in nine patients. (Abuzeid MI et al, 2003; Abuzeid M et al, 2014).

There were no hospitalizations for OHSS symptoms and no complications. All women had viable intrauterine pregnancies (Fluker MR et al, 2000).

It has also been proposed that outpatient paracentesis, when appropriate, is more cost effective. The cost of conservative inpatient versus outpatient management with paracentesis for moderate to severe ovarian hyperstimulation syndrome when compared, resulted in an estimated cost savings of \$8145 with outpatient management with paracentesis. This model suggests early outpatient paracentesis for moderate to severe OHSS is the most cost-effective management plan when compared with traditional conservative inpatient therapy (Csokmay JM et al, 2010).

An increase in uterine perfusion was also observed. Average white blood cell count and the mean hematocrit value were also reduced. Generally no adverse effects on pregnancy were found (Chen CD et al, 1998, Levin I et al, 2002).

2.1.3. Antibiotics

Common interventions performed in patients with severe OHSS such as abdominal paracentesis, urinary catheterization and thoracic paracentesis, predisposes them to nosocomial infections. Less common procedures that increase the risk of infection are central vein catheterization, transabdominal aspiration of ovarian cysts, and transvaginal paracentesis (Abramov et al, 1998).

Several factors have been proposed as mechanisms of increased risk for infection in OHSS. Hypoglobulinemia of lower molecular weight immunoglobulins, including IgG and IgA may increase the risk of nosocomial infection. It is proposed that the immunoglobulins leak into the third spaced fluid. Supporting this, ascitic and pleural fluid aspirated from hypoglobulinemic patients was found to contain high concentrations of globulins. Pulmonary infections are commonly caused by *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, and *Streptococcus pneumoniae* (Delvigne and Rozenberg, 2003, Budev MM et al, 2005, Abramov et al 1998). *Proteus* and *Enterobacter* species can also be found as atypical organisms in OHSS associated infections (Abramov et al, 1998)

Febrile morbidity in patients with severe and critical OHSS as reported by Abramov et al was due to the following infections: 35% definite UTI , 5% probable UTI, 4% definite pneumonia, 4% probable pneumonia, 3% definite URTI, 4% probable URTI, 2% definite intravenous line phlebitis, 2% probable intravenous line phlebitis, 2% definite cellulitis at an

abdominal puncture site, 1% definite gluteal abscess at the site of progesterone injection, 2% postoperative wound infections with a total infection rate of 67% in severe and critical OHSS. For the 67 % of patients with an infection, 9% of patients were treated with intravenous antibiotics, and 58 % were treated with oral antibiotics. Mean duration of treatment was 5.2 days (Abramov Y et al, 1999).

Empirical antibiotics should be chosen based on the patient's endogenous flora, the severity of disease, risk factors for infection, and the existing types of local ICU antibiotic resistance (Budev, MM et al, 2005).

2.1.4. Anticoagulation

Thromboembolic events are the most serious complication of OHSS. The incidence of thrombosis in IVF cycles developing OHSS is reported as 0.2% up to 10% in severe cases of the syndrome (Serour GI et al, 1998, Delvigne et al.1993). In 74-79% of cases of thromboembolism following ovarian stimulation and ovulation induction, patients also had OHSS (Rao et al, 2005, Ou YC et al 2003). Furthermore, OHSS was found to be one of the most significant risk factors for internal jugular vein thrombosis, with the proportion of internal jugular vein thromboses due to OHSS being reported as 12.6%. In one case, OHSS was found to be the third most common cause of internal jugular vein thrombosis (Gbaguidi X, et al 2011). Thrombosis may occur during the course of treatment for OHSS or even weeks after resolution of symptoms (Rao AK, et al 2005).

The tendency towards thromboembolism in OHSS patients can be attributed to three main factors: hyperestrogenism, hypovolemia and hemoconcentration. The high concentration of 17β estradiol in the upper circulation has been suggested as the reason for tendency for upper

extremity thrombosis (Jóźwik M, 2012). The concentration of 17β -estradiol in the ascitic fluid from OHSS women is very elevated, being approximately 27 times higher than the serum concentration (Bauersachs R.M. et al, 2007). Furthermore, a combination of iatrogenic hyperestrogenism and established pregnancy may have a synergistic effect on the risk of thromboembolism (Ou YC et al, 2003). Other than high estradiol levels, the hypercoagulable state may be measured with changes in clotting factors, hemostatic markers, CRP, and the kinin system (Levin I, 2005, Bauersachs R.M et al, 2007).

Hemoconcentration is a crucial part of the tendency to thrombosis in OHSS patients. Hemoconcentration and hypovolemia result from the leaking of fluid from the vascular compartment to the third space, due to vomiting from pressure of intraperitoneal exudate on the bowel, and vasoconstriction due to vasoconstrictive factors of ovarian origin such as angiotensin, interleukins, and prostaglandins (Bauersachs R.M., et al 2007). Reduced venous return caused by enlarged ovaries may also play a role in the development of DVT (Rao et al, 2005).

Paradoxically, most thromboses in OHSS patients tend to occur in the upper extremities rather than the lower extremities. The tendency for venous thromboses to occur in the upper body has been attributed to the higher concentration of estrogens in the ascitic fluid going through the lymphatic drainage system and possible compression by branchial cysts (Kasum, M et al, 2014; Bauersachs et al, 2007). Salomon et al. detected in OHSS patients, clusters of rudimentary branchial fluid-filled cysts that mechanically compressed the jugular and subclavian veins (Salomon O et al, 2009).

Furthermore, thromboses most often occur in the venous vessels and less often in the arterial circulation. It is estimated that 67% of thromboses that appear during OHSS are venous

and only 33% are arterial. Of the venous sites, 71% of reported cases involve the upper limb, neck and head veins. (Rao et al, 2005). The clinical presentation of venous thrombosis in the upper extremities is usually of swelling accompanied by pain radiating from the arm to the neck on the affected side. The clinical presentation of thrombosis in the neck is pain at the site of thrombosis. (Alasiri SA & Case AM, 2008, Raw DM, 2007). Venous thromboses usually occur several weeks after the onset of OHSS. (Chan W.S., 2009; Kasum M et al, 2014). Of the arterial sites, the thrombosis is usually intracerebral (Rao AK et al, 2005) and usually occurring concurrently with the onset of OHSS (Chan W.S., 2009; Kasum M et al, 2014).

The sudden onset of neurological signs, such as sudden onset generalized seizure, is a sign of intracerebral thrombosis and can lead to ischemic stroke (Hassa H et al, 2013; Kasum M et al, 2014). Cerebral venous thrombosis with development of an acute stroke may present with left hemiparesis and headache, for example (Man BL & Hui AC, 2011). As another example, superior sagittal sinus thrombosis can present with a sudden onset generalized seizure, with post-ictal confusion and left-sided hemiplegia resulting 20min later, and a second grand mal seizure with projectile vomiting occurring subsequently. (Ou YC et al, 2003).

Pulmonary embolism can also occur in OHSS patients. The incidence of pulmonary thromboembolism in OHSS patients has been reported as 2% (Abramov et al, 1999). The risk of developing pulmonary embolism following upper extremity DVT rises to 4–12% (Rao AK et al 2005). Patients with pulmonary thromboembolism can present with severe hypoxemia. (Abramov Y et al, 1999).

Specific areas in which thrombosis can occur include the internal jugular, subclavian, axillary, ulnar, retinal, mesenteric, coronary and cerebral vessels. (Raw DM & Collins MC,

2007, Rao AK et al, 2005, Heinig J et al, 2001, Turkistani IM et al, 2001, Arikan I, Barut A, Harma M, Harma M, 2009, Edris F et al, 2007, Dorais J et al, 2011; van den Broek R et al, 2014; Rao et al, 2005) Acute myocardial infarction due to thrombosis in coronary artery is also a rare complication of OHSS (Akdemir R et al, 2002).

Anticoagulant therapy should be prophylactically administered in all OHSS patients (Bauersachs R.M. et al, 2007). Despite prophylactic anticoagulation in OHSS patients, it is possible for a patient to develop thrombosis even 14 days after a 2-week course of heparin (Rao AK et al, 2005; Raw DM & Collins MC, 2007). Treatment of such a patient with LMWH heparin has been shown to result in full recovery (Raw DM & Collins MC, 2007).

After an early diagnosis of OHSS is made, it is essential to start LMWH treatment as soon as possible (Kasum M et al, 2014). As the first line treatment of choice, dose-adjusted heparinization is recommended. Intravascular thrombolysis or operative thrombectomy is a possibility as well. (Ou YC et al, 2003). Heparin augments activity of antithrombin III and prevents conversion of fibrinogen to fibrin and does not actively lyse but can inhibit further thrombogenesis. It prevents reaccumulation of clot after spontaneous fibrinolysis (Kumar P et al, 2011). Prophylactic LMWH therapy of 5,000 Units s.c., every 24 hours can be given to patients during in-patient treatment. (Nouri K et al, 2014). LMWH have been used successfully in pregnancy because they do not cross the placenta, appear to cause less osteoporosis during long-term use than standard heparin, and do not require routine laboratory monitoring (Belaen B et al 2001). The suggested dosage of heparin to prevent DVT is 5000 IU s.c. every 12 hours. After deep vein thrombosis occurs, the patient can be placed on i.v. heparin to maintain a therapeutic PTT (Cil T et al, 2000). Although it is possible that anticoagulation with low molecular weight heparin may be beneficial in cases of severe OHSS, it is not a uniformly established practice to

give it to all women with OHSS (Rao AK et al, 2005). The duration of anticoagulation varies between case reports. In the review on OHSS by Navot (2001), it was concluded that fast correction of hemoconcentration is more important than prophylactic administration of heparin in OHSS patients. For sagittal sinus thrombosis operative thrombectomy has been reported involving catheterization of the superior sagittal sinus, after which urokinase was injected locally, and the blood clots macerated using a microballoon (Ou YC et al, 2003).

If hemodialysis becomes necessary due to renal failure, heparin may need to be stopped when inserting the hemodialysis catheter (Cil T et al, 2000).

2.1.5. Diuretics

The use of diuretics is contraindicated in patients with hypovolemia (Kumar P et al, 2011) and when hemoconcentration is present. Diuretics can be used only where renal output is decreased in the case of normal hematocrit (Royal College of Physicians of Ireland, 2012), with no significant hypotension present (Whelan and Vlahos, 2000). Furosemide, at 10mg to 20mg is the diuretic of choice in severe ovarian hyperstimulation syndrome (Yildizhan R, 2008, Chen, Chin-Der, 2013, ASRM) with persistent oliguria.

Diuretics are contraindicated in patients with hyponatremia (Bar-Hava I, 1993). The ASRM recommends that treatment with diuretics can be started only when an adequate intravascular volume has been restored, with a hematocrit <38%. Furthermore, if diuretics are given before the above requirements are satisfied, they may exacerbate hypovolemia, and hemoconcentration, thus increasing risk of thromboembolism (ASRM, 2008).

2.1.6. Intensive care unit

Patients should be transferred to the ICU when they have thromboembolic complications, renal failure, respiratory failure, and/or deterioration of circulation that cannot be corrected with supportive treatment and paracentesis (Jenkins JM, et al 2006). An elevated hematocrit indicates intravascular volume depletion and increased blood viscosity. A haematocrit of over 45% indicates severe hemoconcentration and a measurement greater than 55% is life threatening (Balén A, 2008).

Renal function should be monitored by careful attention to input and urine output (Balén A, 2008). Measurement of serum urea, creatinine and electrolytes should be performed (Balén A, 2008). In the case of oliguria, careful hydration of the patient with frequent CVP measurements should be performed. If the CVP rises above 15 cm H₂O and the urinary output is still not satisfactory, i.v. furosemide (5-10 mg) with careful hydration is recommended until urinary output improves (IVF-Worldwide, 2012). Renal failure will often respond to low-dose dopamine therapy (0.18 mg/kg/h) that will dilate renal vessels and increase renal blood flow (Chin-Der Chen, 2011; Talawar et al, 2011). In some cases, short-term dialysis is necessary (Chin-Der Chen MD et al, 2012).

Severe respiratory failure and refractory hypoxemia (Gentile M, 2009) due to pulmonary edema, pulmonary embolism, and massive pleural effusion are indications for ICU admission (BaHammam AS, 2005). Thus, ABGs and O₂ saturation should be measured. Patients tend to have a low PaO₂ and the blood gas examination can reveal a metabolic acidosis (Gentile M, 2009). Pulmonary intensive care involves oxygen supplementation, thoracentesis, CPAP support, and if necessary assisted ventilation (Chin-Der Chen, 2011; Talawar P et al, 2011). Reduction of

PCWP may improve the patient's condition significantly with an improvement in respiratory failure and oxygenation, especially in patients with capillary leakage into the alveoli due to high pressure pulmonary edema (Balasch J et al, 1994).

Patients with OHSS have a hyperdynamic circulation, similar to that seen in liver cirrhosis, with increased cardiac output and decreased systemic vascular resistance (Balasch J et al, 1994; Iwakiri Y and Groszmann RJ, 2006). The intravascular volume should be monitored by measurements of CVP, which will be elevated in cases of fluid overload (Balen A, 2008; Talawar P et al, 2011), leading to pulmonary edema and renal impairment. JVP as an indirect measure of CVP will also be elevated in these cases (Talawar P et al, 2011). Due to elevated CVP, some patients require inotropic support with noradrenaline (Talawar P et al, 2011).

2.2. Operative treatment

2.2.1. Laparoscopy

Laparoscopic operative treatment is generally only recommended for OHSS complicated by: ruptured ovarian cyst, ovarian torsion, and ectopic pregnancy. The laparoscopic approach has successfully been used in each of these cases.

The clinical presentation of a ruptured cyst is acute abdominal pain. Blood from ruptured cysts can cause peritoneal irritation and lead to localized or generalized peritonitis (Kumar P, et al, 2011). Ovarian bleeding leads to signs of acute hemorrhage such as hypotension, nausea, and a sudden drop in hematocrit (Gerris J and DeSutter P, 2006). There is a risk of ovarian rupture with bimanual examination of the ovaries therefore it is not recommended during physical examination. Pain and ascites can make ovarian rupture and acute intra-abdominal hemorrhage difficult to detect (ASRM, 2008).

The incidence of adnexal torsion after ART is around 0.2% or 1 in 500 ART patients (Spitzer D et al, 2012). In OHSS patients, the incidence rises to 2.3% in nonpregnant and 16% in pregnant patients (Mashiach S et al, 1990). This can be explained in part by the increased risk of ovarian torsion in pathologically enlarged ovaries (more than 6cm) which is commonly seen in OHSS. Ultrasound is the imaging modality of choice for ovarian torsion (Urbina A et al, 2014). The most consistent imaging finding is asymmetric enlargement of the twisted ovary (Baron KT et al, 2013). To preserve ovarian function and fertility it is important to make a timely diagnosis of ovarian torsion. Unfortunately, the symptoms of adnexal torsion are similar to those of OHSS or pregnancy, including abdominal pain, nausea and vomiting and can thus make the final diagnosis difficult (Spitzer D, 2012).

Evaluating the degree of ovarian ischemia is an important step in choosing the type of operative treatment, which will be detorsion for the ischemic ovary and salpingo-oophorectomy if gangrene has occurred (Munshi S, 2014) as the fallopian tube can also be significantly affected. Detorsion, which spares the ovary, is the preferred treatment despite the initial presentation of the ovary which can be swollen and with a bluish-black colour (Oelsner G et al, 2003). Detorsion has been shown to salvage 88% or more of ovaries with preservation of ovarian function, due to different parts of the ovary being ischemic to different degrees and the with collateral vasculature helping to preserve ovarian function (Tandulwadkar S et al, 2009; BMJ: Best Practice Guidelines, 2015). It is important to immediately treat ovarian torsion because, left untreated peritonitis may develop (Martin C and Magee K, 2006). When the patient has a viable pregnancy, laparoscopic detorsion has shown to result in uneventful pregnancy and delivery at term, with preservation of the ovaries and fallopian tubes (Spitzer D, 2012). Furthermore, in pregnant patients laparoscopic detorsion has been successfully performed up to 20 weeks'

gestation. (2015). Complications to the pregnant patient include possible injury to the enlarged uterus and ovaries and cardiovascular and respiratory disturbances caused by the pneumoperitoneum pressure and CO₂ absorption. It is recommended to observe the patient for 24 hours after the detorsion. (Giulini S et al, 2010).

If necrosis is present a salpingoophorectomy has to be performed. To illustrate this, Lazaridis et al presented a 39-year old IVF patient who at 12 weeks of gestation presented to the hospital with a 1-week history of worsening abdominal distension and pain in the right iliac fossa that would subside and then reappear. Nausea and vomiting was also present with several loose stools. In her surgical history was a hysteroscopic removal of an endometrial polyp. From her status she was afebrile with normal blood pressure, respiratory rate and oxygen saturation. On palpation the abdomen was soft, with no signs of peritonitis. The pain in the right iliac fossa increased with palpation and the abdomen was mildly distended. All other findings were normal. Laboratory tests showed Hb of 11.6g/dL, hematocrit of 0.332, white blood cells of $21 \times 10^9/L$ and CRP of 11.6. Albumin was 31g/L. all other tests were unremarkable. Bilateral enlarged ovaries were found on the Doppler ultrasound. Also on the Doppler ultrasound, fecal retention and fluid in the right lateral paracolic gutter could be seen. Supportive treatment was initiated but the patient's status continued to decline with increased abdominal pain and newly appearing signs of intestinal obstruction. She vomited bile-stained fluid and had complete absence of flatus.

Expectant treatment was initiated including antiemetics, iv fluids, analgesics and laxatives. Her albumin dropped to 28g/L and thus 2 units of human albumin were administered. Her abdominal distension continued to increase with a tenderness that was now generalized across the abdomen but reached a maximum in the periumbilical area and the right iliac fossa. An MRI was performed which revealed, in addition to the enlarged ovaries, also a small bowel

obstruction with a transition point in the distal third of the ileum very close to the right ovary. The right ovary itself had a hemorrhagic stroma.

Due to its size and presence of hemorrhage, ovarian torsion was suspected and a laparoscopy was planned. The laparoscopy was by open approach with creation of pneumoperitoneum. The findings on laparoscopy were that of ovarian torsion and necrosis in the right ovary, with a cystic but untorsed left ovary. The adhesions between the small intestine and the torsed ovary were first dissected, correcting the bowel obstruction. This was followed by a right salpingoophorectomy. The surgery was performed without complications and the patient received post-operative iv fluids and coamoxiclav thrice daily as a broad-spectrum antibiotic. The patient's pregnancy continued to be viable and was unaffected by the procedure. She continued to receive progesterone throughout the pregnancy until 34 weeks gestation (Lazaridis A et al, 2013).

In addition to ovarian cysts and ovarian torsion, ectopic pregnancy in an OHSS patient may be another indication for laparoscopy. Heterotopic pregnancy refers to simultaneous intrauterine and ectopic pregnancies and has an incidence of 1%–3% in ART patients. ART patients are also at an increased risk of rarer forms of ectopic pregnancy including interstitial and cervical ectopic pregnancies (Baron KT et al, 2013). The laparoscopic surgery performed depends on the location of the ectopic pregnancy. For ovarian pregnancies a laparoscopic organ-preserving removal can be performed (Einenkel J et al, 2000). For an actively bleeding ectopic tubal pregnancy, partial or complete salpingectomy can be performed (Hassa H et al, 2013, Fisher SL et al 2011).

2.2.2. Laparotomy

Exploratory laparotomy during torsion and intraperitoneal hemorrhage is lifesaving and recommended (Lucidi RS, 2015). Patients with an ectopic pregnancy may have a bleeding gestational sac that goes unnoticed due to the already existing symptoms of severe OHSS. In this case an emergency laparotomy may not only save the patient's life but also allow the preservation of fertility (Shiau CS et al, 2004). The decision to perform laparotomy should be based on the diagnosis. A ruptured ovarian cyst with hemoperitoneum should be diagnosed according to the anamnesis, laboratory tests and imaging of the abdomen using ultrasound and CT. Pre-operative tests should include Hb, PCV, WBC count, platelets, PT, INR, aPTT, liver function tests, renal function tests, and serum electrolytes. The patient should be transfused pre-operatively for example with RCC. Due to the significant nature of intra-operative bleeding the patient will probably have to be transfused intra-operatively according to the estimated amount of blood lost. Blood volume can be replaced intra-operatively using a combination of RCC, FFP, colloids and crystalloid solution. Tranexamic acid can be given iv intra-operatively for post-operative pain. Post-operatively the patient can be transfused again, with cryoprecipitate and RCC. Injections of tranexamic acid should be repeated in a dose of 500mg every 8 hours to maintain analgesia (Siddiqui AS et al, 2009).

Abdominal compartment syndrome may develop in patients with early onset severe OHSS, with intra-abdominal pressures of 25-35 cm H₂O. These patients will frequently but not always require surgical decompression via laparotomy. Patients with intra-abdominal pressure >35mm cm H₂O are even more likely to require decompressive laparotomy (Cil T et al, 2000).

2.2.3. Abortion

If a pregnancy is maintaining a life-threatening OHSS, therapeutic abortion must be considered. Some examples of such cases are patients with renal failure or thromboembolic events (Kovacs P, 2006). Opinions vary as to the necessity of termination of pregnancy as a treatment of OHSS with some authors finding OHSS not a sufficient indication for abortion (Zimmerman C, 2010). In the critical cases where it is necessary to perform an abortion it has been shown to improve the outcome of neurological, hematological, and vascular complications (Rizk B, 2006).

Conclusion

Ovarian hyperstimulation syndrome (OHSS) is a rare complication of controlled ovarian hyperstimulation and ovulation induction that despite better preventative methods, continues to develop in some patients undergoing assisted reproduction. Patients with mild to moderate OHSS can be managed conservatively by reducing ascites and restoring intravascular volume. Patients with severe OHSS are always treated as inpatients and may require admission to the intensive care unit where they can also be treated for the complications of OHSS, such as DVTs. Several complications such as ovarian torsion, ectopic pregnancy and ovarian cyst are indication for laparoscopy, with laparotomy being required in cases such as hemorrhage of ruptured ovarian cyst. In some cases, when the patient is refractory to other treatments, therapeutic abortion may result in a significant improvement of the patient's symptoms.

References

- (2014) Albumin Administration Guidelines. The Regents of the University of Colorado.
<http://www.ucdenver.edu/academics/colleges/medicalschoo/departments/surgery/divisions/Trauma/Trauma-at-UCH/Documents/SICU-Protocols/Albumin-Administration-Guidelines.pdf>.
Accessed 15 March 2015
- (2015) Ovarian Torsion. BMJ: Best Practice. BMJ Publishing Group Limited
- Abramov Y, Elchalal U, Schenker JG. (1998). Febrile morbidity in severe and critical ovarian hyperstimulation syndrome: a multicentre study. *Hum Reprod.* 13(11):3128-31.
- Abramov Y, Elchalal U, Schenker JG. (1999). Pulmonary manifestations of severe ovarian hyperstimulation syndrome: a multicenter study. *Fertility and Sterility.* 74(4): 645–651.
- Abramov Y, Fatum M, Abrahamov D, Schenker JG. (2001). Hydroxyethylstarch versus human albumin for the treatment of severe ovarian hyperstimulation syndrome: a preliminary report. *Fertility and Sterility.*; 75(6):1228-30.
- Abuzeid M, Warda H, Joseph S, Corrado MG, Abuzeid Y, Ashraf M, Rizk B. (2014). Outpatient Management of Severe Ovarian Hyperstimulation Syndrome (OHSS) with Placement of Pigtail Catheter. *Facts, Views and Vision in Obgyn.*; 6(1):31-7.
- Abuzeid MI, Nassar Z, Massaad Z, Weiss M, Ashraf M, Fakihi M. (2003). Pigtail catheter for the treatment of ascites associated with ovarian hyperstimulation syndrome. *Human Reproduction.* 18(2):370-3.
- Akdemir R, Uyan C, Emiroglu Y. (2002). Acute myocardial infarction secondary thrombosis associated with ovarian hyperstimulation syndrome. *Int J Cardiol.*; 83(2):187-9
- Alasiri SA, Case AM. Thrombosis of Subclavian and Internal Jugular Veins Following Severe Ovarian Hyperstimulation Syndrome: A Case Report. (2008). *J Obstet Gynaecol Can*; 30(7):590–597)
- Alper MM, Smith LP, Sills ES. (2009). Ovarian Hyperstimulation Syndrome: Current Views on Pathophysiology, Risk Factors, Prevention, and Management. *J Exp and Clin Assist Reprod.*; 6:3
- American Society for Reproductive Medicine. (2008). Ovarian Hyperstimulation Syndrome. *Fertil Steril.* 90: S188-93
- Arikan I, Barut A, Harma M, Harma M. (2009). The Internet Journal of Gynecology and Obstetrics. A severe case of ovarian hyperstimulation syndrome with pulmonary thromboembolism. 13(1)

Ata B, Seyhan A, Orhaner S, Urman B. (2009). High dose cabergoline in management of ovarian hyperstimulation syndrome. *Fertil Steril.*; 92(3):1168.

BaHammam AS. (2005). Pulmonary edema complicating ovarian hyperstimulation syndrome: low-pressure edema, high-pressure edema, or mixed edema? *Ann Saudi Med* 25(4):335-338.

Balasch J, Arroyo V, Fábregues F, Saló J, Jiménez W, Paré JC, Vanrell JA. (1994) Neurohormonal and hemodynamic changes in severe cases of the ovarian hyperstimulation syndrome. *Ann Intern Med.*; 121:27-33

Balen A. (2008). Ovarian hyperstimulation syndrome (OHSS): A short report for the HFEA. http://www.hfea.gov.uk/docs/OHSS_UPDATED_Report_from_Adam_Balen_2008.pdf.

Bar-Hava I, Homburg R. (1993). Correct timing of administration of diuretic agents for the treatment of ovarian hyperstimulation syndrome. *Gynecol Endocrinol.*; 7(1): 63–65

Baron KT, Babagbemi KT, Arleo EK, Asrani AV, and Troiano RN. (2013) Radiographics; 33(1):229-44.

Bauersachs R.M., Manolopoulos K., Hoppe I., Arin M.J., Schleussner E (2007). More on: the ‘ART’ behind the clot: solving the mystery. *J. Thromb. Haemost.*; 5: 438-439

Belaen B, Geerinckx K, Vergauwe P, Thys J (2001) *Hum Reprod.* Internal jugular vein thrombosis after ovarian stimulation. 16(3):510-2

Binder H et al (2007) Update on ovarian hyperstimulation syndrome: Part 1--Incidence and pathogenesis. *Int J Fertil Womens Med.*; 52(1):11-26.

Budev MM, Arroliga AC, Falcone T. (2005). Ovarian hyperstimulation syndrome. *Crit Care Med* Vol. 33, No. 10 (Suppl.)

Cerrillo M, Pacheco A, Rodríguez S, Gómez R, Delgado F, Pellicer A, Garcia-Velasco JA. (2011). Effect of GnRH agonist and hCG treatment on VEGF, angiopoietin-2, and VE-cadherin: trying to explain the link to ovarian hyperstimulation syndrome. *Fertility and Sterility.*; 95(8):2517-9.

Chan W.S. (2009) The ‘ART’ of thrombosis: a review of arterial and venous thrombosis in assisted reproductive technology. *Curr. Opin. Obstet. Gynecol.*, 21, 208-218

Chan C-C, Yin CS, Lan S-C, Chen I-C, and Wu G-J. (2004) Continuous Abdominal Paracentesis for Management of Late Type Severe Ovarian Hyperstimulation Syndrome. *Journal of the Chinese Medical Association.* 67:197-199

Chen CD, Chen SU, Yang YS. (2013). Prevention and management of ovarian hyperstimulation syndrome. *Reproductive Biomedicine Online.* 817 – 827. <http://www.iffs-uit.com/article/S1521->

6934(12)00072-7/aim/management-of-ovarian-hyperstimulation-syndrome/. Accessed April 10, 2015.

Chen CD, Yang JH, Chao KH, Chen SU, Ho HN, Yang YS. (1998). Effects of repeated abdominal paracentesis on uterine and intraovarian haemodynamics and pregnancy outcome in severe ovarian hyperstimulation syndrome. *Human Reproduction*.; 13(8):2077-81.

Cil T, Tummon IS, House AA, Taylor B, Hooker G, Franklin J, Rankin R, Carey M (2000). A tale of two syndromes: ovarian hyperstimulation and abdominal compartment. *Hum Reprod*. 15(5):1058-60.

Csokmay JM, Yaeger BJ, Henne MB, Armstrong AY, Queenan JT, Segars JH. (2010). Cost analysis model of outpatient management of ovarian hyperstimulation syndrome with paracentesis: "tap early and often" versus hospitalization. *Fertility and Sterility*; 93(1):167-73.

Delvigne A, De Sutter P, Dhont M, Gherris J, Olivennes F, Gosta Nygren K. (2006). Ovarian Hyperstimulation (OHSS) Guidelines ESHRE 2006.

Dorais J, Jones K, Hammoud A, Gibson M, Johnstone E, Peterson CM. (2011). A superior mesenteric vein thrombosis associated with in vitro fertilization. *Fertil Steril*. 95(2):804.

Edris F, Kerner CM, Feyles V, Leung A, Power S. (2007). Successful management of an extensive intracranial sinus thrombosis in a patient undergoing IVF: case report and review of literature. *Fertil Steril*. 88(3):705.

Einenkel J, Baier D, Horn LC and Alexander H. (2000). Laparoscopic therapy of an intact primary ovarian pregnancy with ovarian hyperstimulation syndrome: Case report. *Human Reproduction*. 15 (9): 2037-2040.

Elia EM et al. (2013). Metformin decreases the incidence of ovarian hyperstimulation syndrome: an experimental study. *Journal of Ovarian Research*. 6:62
<http://www.ovarianresearch.com/content/6/1/62>. Accessed March 15 2015.

Endo T, Kitajima Y, Hayashi T, Fujii M, Hata H, Azumaguchi A. (2004). Low-molecular-weight dextran infusion is more effective for the treatment of hemoconcentration due to severe ovarian hyperstimulation syndrome than human albumin infusion. *Fertility and Sterility*; 82(5):1449-51.

Fatemi HM, Popovic-Todorovic B, Humaidan P, Kol S, Banker M, Devroey P, García-Velasco JA. (2014) Severe ovarian hyperstimulation syndrome after gonadotropin-releasing hormone (GnRH) agonist trigger and "freeze-all" approach in GnRH antagonist protocol. *Fertil Steril*.; 101(4):1008-11

Federal Drug Agency.

Definitions.http://www.fda.gov/ohrms/dockets/ac/03/briefing/3985B1_03_Definitions.htm. Accessed April 20, 2015

Fisher SL, Massie JA, Blumenfeld YJ, Lathi RB (2011) Sextuplet heterotopic pregnancy presenting as ovarian hyperstimulation syndrome and hemoperitoneum. *Fertil Steril*; 95(7):2431.e1-3.

Fluker MR, Copeland JE, Yuzpe AA. (2000) An ounce of prevention: outpatient management of the ovarian hyperstimulation syndrome. *Fertility and Sterility*. 73(4):821-4.

Garcia-Martinez R et al (2013) Albumin: Pathophysiologic Basis of Its Role in the Treatment of Cirrhosis and Its Complications. *Hepatology*. 58(5): 1836-46

Gbaguidi X, Janvresse A, Benichou J, Cailleux N, Levesque H, Marie I. (2011). Internal jugular vein thrombosis: outcome and risk factors *QJM*; 104(3):209-19

Gentile M, Simeone S, Scaravilli G, Capuano S, Balbi C (2009). Severe ovarian hyperstimulation syndrome after intrauterine insemination: A case report. *The American Journal of Case Report*. 10: 59-61.

Gerris J and DeSutter P. (2006) Ovarian hyperstimulation syndrome. *J Obstet Gynecol India Vol*. 56 (1): 30-36.

Giulini S, Dante G, Xella S, La Marca A, Marsella T, Volpe A. (2010). Adnexal Torsion during Pregnancy after Oocyte In Vitro Maturation and Intracytoplasmic Sperm Injection Cycle. *Case Rep Med*. Epub 2010

Hassa H, Aydin Y, Oge T, Yavuz Tokgoz V (2013) Incompletely Evaluated ART Leading to Ectopic Pregnancy and Cerebral Thrombosis. *Int J Fertil Steril*. 7(2):138-41

Heinig J, Behre HM, Klockenbusch W (2001) Occlusion of the ulnar artery in a patient with severe ovarian hyperstimulation syndrome. *Eur J Obstet Gynecol Reprod Biol*. 96(1):126-7.

Hosseini MA, Mahdavi A, Aleyasin A, Safdarian L, Bahmaee F. (2012) Treatment of ovarian hyperstimulation syndrome using gonadotropin releasing hormone antagonist: a pilot study. *Gynecological Endocrinology*.; 28(11):853-5

Institute of Clinicians and Gynaecologists, Royal College of Physicians of Ireland and Directorate of Strategy and Clinical Programmes, Health Service Executive (2012) Clinical Practice Guidelines: Ovarian Hyperstimulation Syndrome (OHSS) Diagnosis and Management. <http://www.hse.ie/eng/about/Who/clinical/natclinprog/obsandgynaeprograme/guide8.pdf>. Accessed 13 March 2015

IVF-Worldwide (2012). Ovarian Hyperstimulation Syndrome. <http://www.ivf-worldwide.com/education/ivf-complications/ovarian-hyperstimulation-syndrome-ohss.html>. Accessed April 10, 2015.

Iwakiri Y and Groszmann RJ. (2006) The Hyperdynamic Circulation of Chronic Liver Diseases: From the Patient to the Molecule. *Hepatology*. Volume 43, Issue S1

Jenkins JM, Drakeley AJ, Mathur RS (2006). The Management of Ovarian Hyperstimulation Syndrome. Royal College of Obstetricians and Gynaecologists.
https://www.rcog.org.uk/globalassets/documents/guidelines/gtg5_230611.pdf. Accessed 15 March 2015

Jóźwik M. (2012). *Med Wieku Rozwoj*. The mechanism of thromboembolism in the course of ovarian hyperstimulation syndrome. 16(4):269-71

Junqueira JJM, Bammann RH, Mingarini Terra R, Pugliesi de Castro AC, Ishy A, Fernandez A. (2012) Pleural Effusion Following Ovarian Hyperstimulation. *Jornal Brasileiro de Pneumologia*.; 38(3):400-403.

Kasum M and Oreskovic S. (2010). Treatment of ovarian hyperstimulation syndrome: new insights. *Acta Clin Croat*. 49(4):421-7.

Kasum M, Danolić D, Orešković S, Ježek D, Beketić-Orešković L, Pekez M (2014). Thrombosis following ovarian hyperstimulation syndrome. *Gynecol Endocrinol*. 30(11):764-8

Kovacs, P. (2006) Management of Severe Ovarian Hyperstimulation Syndrome.
<http://www.medscape.com/viewarticle/524218>

Kumar P, Sait SF, Sharma A, and Kumar M. (2011). Ovarian hyperstimulation syndrome. *J Hum Reprod Sci*. 4(2): 70–75

Lazaridis A, Maclaran K, Behar N and Narayanan P. (2013). A rare case of small bowel obstruction secondary to ovarian torsion in an IVF pregnancy. *BMJ Case Report*. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3603835/>. Accessed May 15, 2015

Levin ER, Rosen GF, Cassidenti DL, Yee B, Meldrum D, Wisot A, et al. (1998). Role of vascular endothelial cell growth factor in ovarian hyperstimulation syndrome. *The Journal of Clinical Investigation*.; 102:1978–85.

Levin I, Almog B, Avni A, Baram A, Lessing JB, Gamzu R. (2002) Effect of paracentesis of ascitic fluids on urinary output and blood indices in patients with severe ovarian hyperstimulation syndrome. *Fertility and Sterility*.; 77(5):986-8

Levin I, Gamzu, R, Pauzner D, Rogowski O, Shapira I, Maslovitz S, and Almog B (2005) Elevated levels of CRP in ovarian hyperstimulation syndrome: an unrecognized potential hazard? *BJOG: An International Journal of Obstetrics and Gynecology*. 112: 952-955

Levy G, Lucidi RS. (2011) Thrombophilia and ovarian hyperstimulation syndrome: a case report. *Hawaii Med J*.; 70(5):97-8.

Lincoln SR, Opsahl MS, Blauer KL, Black SH, Schulman JD. (2002) Aggressive outpatient treatment of ovarian hyperstimulation syndrome with ascites using transvaginal culdocentesis and intravenous albumin minimizes hospitalization. *Journal of Assisted Reproduction and Genetics.*; 19(4):159-63.

Lucidi, RS (2015) Ovarian Hyperstimulation Syndrome Treatment and Management. <http://emedicine.medscape.com/article/1343572-treatment>. Accessed April 1st, 2015.

Man BL, Hui AC. *Hong Kong Med J.* (2011). Cerebral venous thrombosis secondary to ovarian hyperstimulation syndrome. 17(2):155-6

Martin C and Magee K. (2006). Ovarian Torsion in a 20 year old patient. *CJEM*; 8(2):126-129

Mashiach S, Bider D, Moran O, Goldenberg M, Ben-Rafael Z. (1990). Adnexal torsion of hyperstimulated ovaries in pregnancies after gonadotropin therapy. *Fertil Steril*; 53(1):76–80.

Maslovitz S, Jaffa A, Eytan O, Wolman I, Many A, Lessing JB, Gamzu R. (2004) Renal blood flow alteration after paracentesis in women with ovarian hyperstimulation. *Obstetrics and Gynecology.*; 104(2):321-6.

Maxwell KN, Cholst IN, and Rosenwaks Z (2008). The incidence of both serious and minor complications in young women undergoing oocyte donation. *Fertil Steril.* 90(6):2165-71

McClure N, Healy DL, Rogers PA, Sullivan J, Beaton L, Haning RV Jr, Connolly DT, Robertson DM. (1994). Vascular endothelial growth factor as capillary permeability agent in ovarian hyperstimulation syndrome. *Lancet.* 344(8917):235-6.

Munshi S, Patel A, Banker M, and Patel P. (2014) Laparoscopic detorsion for bilateral ovarian torsion in a singleton pregnancy with spontaneous ovarian hyperstimulation syndrome. *J Hum Reprod Sci.* 7(1): 66–68

Neulen J, Yan Z, Raczek S, Weindel K, Keck C, Weich HA, Marmé D, Breckwoldt M. (1995) Human chorionic gonadotropin-dependent expression of vascular endothelial growth factor/vascular permeability factor in human granulosa cells: importance in ovarian hyperstimulation syndrome. *The Journal of Clinical Endocrinology and Metabolism.* 80(6):1967-71.

Nouri K, Haslinger P, Szabo L, Sator M, Schreiber M, Schneeberger C, Pietrowski D. (2014) Polymorphisms of VEGF and VEGF receptors are associated with the occurrence of ovarian hyperstimulation syndrome (OHSS)-a retrospective case-control study. *Journal of Ovarian Research.* 7:54.

Nouri K, Tempfer CB, Lenart C, Windischbauer L, Walch K, Promberger R, Ott J. (2014) Predictive factors for recovery time in patients suffering from severe OHSS. *Reprod Biol Endocrinol.* 12:59

O'Brien K, Lazar E, Athanassiou A and Ravnika V (2009). Ovarian hyperstimulation syndrome associated with fetal trisomy 21. *Journal of Perinatology* 29: 388–390

Ou YC, Kao YL, Lai SL, Kung FT, Huang FJ, Chang SY, ChangChien CC. (2003). Thromboembolism after ovarian stimulation: successful management of a woman with superior sagittal sinus thrombosis after IVF and embryo transfer: case report. *Hum Reprod.*; 18(11):2375-81.

Papanikolaou EG et al (2006). Incidence and prediction of ovarian hyperstimulation syndrome in women undergoing gonadotropin-releasing hormone antagonist in vitro fertilization cycles. *Fertil Steril.* 85(1):112-20

Qublan HS, Al-Taani MI, Megdadi MF, Metri RM, Al-Ahmad N. (2012). Multiple transvaginal ascitic fluid aspirations improves the clinical and reproductive outcome in patients undergoing in vitro fertilisation treatment complicated by severe early ovarian hyperstimulation syndrome. *Journal of Obstetrics and Gynaecology* 32(4):379-82.

Rao AK, Chitkara U, Milki AA (2005) Subclavian vein thrombosis following IVF and ovarian hyperstimulation: a case report *Hum Reprod.*;20(12):3307-12.

Raw DM, Collins MC. (2007) Internal jugular vein thrombosis and ovarian hyperstimulation syndrome. *J R Soc Med.*; 100(7):339-40.

Raziel A, Friedler S, Schachter M, Strassburger D, Bukovsky I, Ron-El R. (1998) Transvaginal drainage of ascites as an alternative to abdominal paracentesis in patients with severe ovarian hyperstimulation syndrome, obesity, and generalized edema. *Fertility and Sterility.* 69(4):780-3.

Rizk B. (2006). *Ovarian Hyperstimulation Syndrome: Epidemiology, Pathophysiology, Prevention and Management.* Cambridge, UK: Cambridge University Press.

Rogolino A., Coccia M.E., Fedi S., Gori A.M., Cellai A.P., Scarselli G.F., Prisco D., Abbate R. (2003): Hypercoagulability, high tissue factor and low tissue factor pathway inhibitor levels in severe ovarian hyperstimulation syndrome: possible association with clinical outcome. *Blood Coagul. Fibrinolysis*, 14, 277-282

Royal College of Obstetricians and Gynaecologists (RCOG) (2006). The management of ovarian hyperstimulation syndrome.

Salomon O., Schiby G., Heiman Z., Avivi K., Sigal C., Levran D., Dor J., Itzhak Y. (2009). Combined jugular and subclavian vein thrombosis following assisted reproductive technology - new observation. *Fertil. Steril.* 92, 620-5

Scotti L, Abramovich D, Pascuali N, Durand LH, Irusta G, de Zúñiga I, Tesone M, Parborell F. (2014). Inhibition of angiopoietin-1 (ANGPT1) affects vascular integrity in ovarian hyperstimulation syndrome (OHSS). *Reproduction, Fertility and Development.* 11

Serour GI, Aboulghar M, Mansour R, et al. (1998). Complications of medically assisted conception in 3,500 cycles. *Fertil Steril*; 70: 638-42.

Shiau CS, Chang MY, Chiang CH, Hsieh CC, Hsieh TT. (2004). Severe ovarian hyperstimulation syndrome coexisting with a bilateral ectopic pregnancy. *Chang Gung Med J*. 27(2):143-7

Shmorgun, D and Claman, P. (2011). The Diagnosis and Management of Ovarian Hyperstimulation Syndrome. <http://sogc.org/guidelines/the-diagnosis-and-management-of-ovarian-hyperstimulation-syndrome/>. Accessed 13 March 2015

Shrivastav P, Nadkarni P, Craft I. (1994). Day care management of severe ovarian hyperstimulation syndrome avoids hospitalization and morbidity. *Human Reproduction*. 9(5):812-4.

Siddiqui AS, Ahmed J, Siddiqui SZ and Haider S.(2009). Perioperative anesthetic management for a patient with severe von Willebrand disease for major gynecological surgery. *Anaesth Pain & Intensive Care*; 13(1):19-22

Smith LP, Hacker MR, Alper MM. (2009). Patients with severe ovarian hyperstimulation syndrome can be managed safely with aggressive outpatient transvaginal paracentesis. *Fertility and Sterility*; 92(6):1953-9.

Spitzer D, Wirleitner B, Steiner H, Zech NH (2012). Geburtshilfe Frauenheilkd. 72(8):716-720. Adnexal Torsion in Pregnancy after Assisted Reproduction - Case Study and Review of the Literature

Tal Y, Haber G, Cohen MJ, Phillips M, Revel A, Varon D, Ben-Yehuda A. (2009). Superior vena cava syndrome and ovarian hyperstimulation syndrome. *Isr Med Assoc J*; 11(8):503-4

Talawar P, Rewari V, Sinha R, Tripathi A (2011). Severe ovarian hyperstimulation syndrome: Intensive care management of two cases. *Journal of Obstetric Anesthesia and Critical Care*. 1(2): 92-95.

Tandulwadkar S, Shah A, and Agarwal B (2009). *J Gynecol Endosc Surg*. 1(1): 21–26

Taniguchi LU, Jorge CG, de Oliveira LF. (2011). Spontaneous bacterial peritonitis complicating ovarian hyperstimulation syndrome-related ascites. *Clinics*; 66(12):2173-2175

The Practice Committee of the American Society of Reproductive Medicine. (2008). Ovarian Hyperstimulation Syndrome. 90:S188-93.

Tsunoda T, Shibahara H, Hirano Y, Suzuki T, Fujiwara H, Takamizawa S, Ogawa S, Motoyama M, Suzuki M. (2003). Treatment for ovarian hyperstimulation syndrome using an oral dopamine prodrug, docarpamine. *Gynecol Endocrinol*. (4):281-6.

Turkistani IM, Ghourab SA, Al-Sheikh OH, Abuel-Asrar AM. (2001) Central retinal artery occlusion associated with severe ovarian hyperstimulation syndrome. *Eur J Ophthalmol.* 11(3):313-5.

Urbina A., Andreu Rodríguez M., Ibañez M, Béliz IS, Hernandez Muñoz S, Soteras Roura C, Arevalo N, López MD, San Sebastian de los Reyes (2014) Adnexal Torsion: An uncommon but not exceptional diagnosis in an Emergency Radiology Department.
<http://dx.doi.org/10.1594/ecr2014/C-1349>

Villasante A, Pacheco A, Pau E, Ruiz A, Pellicer A, Garcia-Velasco JA. (2008). Soluble vascular endothelial-cadherin levels correlate with clinical and biological aspects of severe ovarian hyperstimulation syndrome. *Human Reproduction.*; 23(3):662-7.

Wang TH, Horng SG, Chang CL, Wu HM, Tsai YJ, Wang HS, Soong YK. (2002). Human chorionic gonadotropin-induced ovarian hyperstimulation syndrome is associated with up-regulation of vascular endothelial growth factor. *The Journal of Clinical Endocrinology and Metabolism.*; 87(7):3300-8.

Whelan JG, and Vlahos NF. (2000). The Ovarian Hyperstimulation Syndrome. *Fertility and Sterility.*; 73(5): 883-96.

Yan Z, Weich HA, Bernart W, Breckwoldt M, Neulen J. (1993) Vascular endothelial growth factor (VEGF) messenger ribonucleic acid (mRNA) expression in luteinized human granulosa cells in vitro. *The Journal of Clinical Endocrinology and Metabolism*; 77:1723–5.

Yildizhan R, Adali E, Kolusari A, Kurdoglu M, Ozgokce C and Adali F. (2008) Ovarian Hyperstimulation Syndrome with pleural effusion: a case report. *Cases Journal*; 1:323.
<http://www.casesjournal.com/content/1/1/323>

Zimmerman C. (2010) *Proceedings in Obstetrics and Gynecology.* 1(1):11