Treatment of ovarian hyperstimulation syndrome

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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, Oreskovi ć 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. Hypoglobluinemia 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 concentractions 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 (Balen A, 2008).

Renal function should be monitored by careful attention to input and urine output (Balen A, 2008). Measurement of serum urea, creatinine and electrolytes should be performed (Balen 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 distrubances 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 a 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 x10(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 the 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 it's 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 tortsed 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-opertively using a combination of RCC, FFP, colloids and crystalloid solution. Tranexamic acid can be given iv intra-opertively 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 H20 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.

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