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Review Article

Anesthetic Considerations in the Ovarian Hyperstimulation Syndrome

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Abstract

Background: The ovary hyperstimulation syndrome (OHSS) is a rare iatrogenic complication, associated with drugs used for induction of ovulation and follicular development during the *in vitro* fertilization procedures.

Material and Methods: In this manuscript we performed a systematic review from medline, artemisa, pubmed, medigrafic, elsevier, current contents and the cochrane collaboration about ohss. A total of 112 articles were analyzed and finally 32 were included in the article.

With the data we review the risk factors, etiology, pathophysiology, diagnosis, anesthetic techniques for the management and associated complications.

Conclusion: With the increase in assisted reproductive procedures the OHSS syndrome is more prevalent and we have to know all about the risk factors, diagnosis and management for the integration of multidisciplinary groups that are going to treat those patients and prevent serious complications.

Keywords: *Anesthetic; Ovary Hyperstimulation Syndrome*

Introduction

The ovary hyperstimulation syndrome (OHSS) is a rare iatrogenic complication, associated with drugs used for induction of ovulation and follicular development during the *in vitro* fertilization procedures [1].

This phenomenon is reported in the worldwide literature, but in México there are no clear documented references in this respect actually.

With the increase in assisted reproduction centers in the country, an inadequate use of gonadotrophins by gynecologist without training in assisted reproduction have been described, probably increasing the incidence of OHSS; a syndrome that can decrease significantly with a proper and planned ovary stimulation by experts, in a controlled and meticulous way [1,2].

The OHSS is presented in patients in which there no exist organ or life compromise but can present in a severe way and a potentially fatal result. This clinical entity is an important problem, in the first place for the group of human reproduction physicians, the anesthesiologist as part of the team, is obligated to know this syndrome and their physiological consequences to achieve an adequate clinical practice[3]. This syndrome can be considered a consequence of the loss of control over a therapeutic ovary hyper-stimulation [3].

This syndrome was described for the first time in 1943 and was denominated massive hyper luteinization syndrome of the ovaries. The first fatal case was reported in 1951, with an oliguric renal failure as death cause [4].

The ovarian induction with gonadotrophins is one of the greatest advances in the modern treatment of infertility, and the goal is the recollection of a greater number of oocytes, subsequent embryos' and finally to improve the pregnancy rate, but in the last decades this situation has changed, and the stimulation cycles are individualized and adjusted according to each patient requirements [1,3].

In the last inform of the Society for Assisted Reproductive Technology and América Society for Reproductive Medicine, 134.260 of stimulation cycles were reported and the European commission for human reproduction and embryology reports 367.066 cycles. This huge increase in the number of cycles around the world was associated with a greater number of complications during the assisted reproduction treatments and particularly the OHSS [2,3].

It has been calculated that the human population around the globe is 7, 120, 000, 000 people and between 15 to 20% of the couples in reproductive age has some reproductive problem [4].

The exact etiology of the OHSS is not clearly known, but with the recent research, a group of new strategies for their control has been developed.

Some of this measure are empiric, but the advances in prevention are promising.

Objective

To know the adequate anesthetic management in patients with OHSS for a better medical attention.

Describe the OHSS syndrome in their epidemiology, etiology, physiopathology, clinical course, classification, diagnosis, treatment and prevention for the adequate comprehension by the physician.

Justification

Create a useful reference tool for the knowledge spread about the OHSS, because actually this is an uncommon pathology in our field but in the future, it will become a cause of medical attention in the emergency rooms, hospitalization, during surgery or in the intensive care units, but the increases in the assisted reproduction treatments.

Material and Methods

A systematic review of the literature was completed by the online searchers: Medline, artemisia, PubMed, medigrafic, elsevier, current contents and the Cochrane collaboration. A total of 112 articles about OHSS were reviewed, after language and relevance analysis, 32 were included in the for extensive review.

Epidemiology

Incidence

According to the consulted literature, the OHSS incidence is 0.5 - 1.4% along the assisted reproduction treatments. This is a range because it has been described that between 33 - 58% of the cases are grade 1 or mild, with abdominal distention as the only symptom and the more frequent one [2-4].

The moderate OHSS is presented in 4% and the severe in 5 - 10%. In our country, there are no reports about the incidence of OHSS, mostly because the majority of ovary hyperstimulation cycles are realized in the private practice and there is no a statistic that shows us the real incidence [2-4].

Mortality

The reported mortality in the literature is about 1:45,000-450,000 cases [4].

Risk factors

Age: Many studies have demonstrated that young patients (younger than 35 years) have an increased risk of OHSS, this probably secondary to the high number of gonadotropin receptors, increasing the ovary sensibility to stimulation or by the great number of follicles capable to response to gonadotropin stimulation [5].

Body mass index: The studies show an increase in the number of patients with OHSS when their body mass index under 18, but more studies are needed to confirm this data. Actually, it is not considered officially an independent risk factor [5].

Polycystic Ovary Syndrome: Patients with this pathology present hyperandrogenism, insulin resistance, and lipidic alterations, risk factors for OHSS. The presence of multiple intermediate or immature follicles has been associated with an increased risk of OHSS, probably for the high probability to be stimulated and develop an exaggerated response [5].

Allergies: It has been demonstrated that patients with OHSS have an increased prevalence of atopy compared with patients without it (56% vs 21%). It is possible that an increased inflammatory response is involved in patients with OHSS [5].

Pregnancy: This factor is very important because if conception is achieved in this patient, the risk to present OHSS in the severe form is increased notably, increasing the associated mortality. This is secondary to an increase of gonadotropins by the synthesis for the syncytium trophoblast [5].

Estradiol levels: Once the ovary stimulation is started, as part of the protocol the serif estradiol is quantified, and if this is higher than 3500 pg./ml, the risk of OHSS is increased [5].

The number of follicles: The presence of more than 10 follicles in the ultrasonography after the stimulation increases the risk of OHSS. Other ultrasound data related with the syndrome are the presence of antral follicles and "collar" sign or "Perl ring", and this must take the physician attention by the increased sensibility to gonadotropins [5].

Background of OHSS in the previous pregnancy: Those patients must be managed carefully and advertised about the increased risk factors.

Other risk factors. The SHEO must be presented in the course of a spontaneous pregnancy and multiple pregnancies. The OHSS have been described with a spontaneous and recurrent familiar form, inclusive with normal pregnancy [5].

Some cases of OHSS have been reported in patients with a gestational trophoblastic disease, multiple pregnancies and patients with mutations in the receptor of follicle stimulating hormone, or conditions with the important release of gonadotrophins. Other associated diseases are the hypothyroidism and patients with pituitary adenoma [2,4,5].

Etiology

One of the beliefs about OHSS is that an excessive follicular recruitment is present, in association with the Latinization mediated by the luteinizing hormone receptors, resulting in an ovarian hyperstimulation. The development of OHSS in patients with assisted reproduction treatments depends on the ovary presence and hCG administration, and this has been demonstrated by the absence of this syndrome in patients with bilateral oophorectomy [4-6].

This syndrome presents 3 to 8 days after the human chorionic gonadotrophins administration producing a massive follicular Latinization, with the release of intraovarian mediators that induces an increase of vascular permeability associated with an increased angiogenesis; those effects continue along the luteal phase and during the pregnancy [3,5,6].

The active component that produces this syndrome is generated in the ovaries, increasing the vascular permeability, and some of the implicated substances include vascular endothelial growth factor(VEGF), endothelin 1, histamine and prostaglandins [7,8].

Other substances implicated in the OHSS:

- Human chorionic gonadotropin
- Vascular endothelial growth factor
- Estradiol
- Angiotensin renin system
- Interleukin 6
- Prostaglandins
- Insulin
- Von Willebrand factor
- Cytokines
- Adhesion molecules of the vascular endothelium
- Angiotensin
- Histamine
- Endothelin 1
- Quinine-kallikrein system

Physiopathology

The OHSS is a consequence of the increase of vascular permeability and extravasation of liquid rich in proteins, mostly albumin, form the intravascular to the peritoneal, pleural and pericarpic space, with an increase in the oncotic pressure and the anasarca [9,10].

This phenomenon produces hemoconcentration, reduction in organ perfusion, clot alterations and increase in the risk of thromboembolism. The intensity of the syndrome is related with the grade of follicular response to the ovary induction agents [9].

The physiopathology of OHSS is extremely important actually, because the increase in the utilization of ovarian induction agents, and the development of more sophisticated techniques in the assisted reproduction influence the incidence of this pathology [9,11].

In the beginning, a correlation was founded between activated cytokines and the severity of OHSS, the endocrine, immune and metabolic mechanism involved [12,13].

This research allows us to understand the pathogenesis and develop strategies of treatment during the acute phase and convalescence. The vascular and endothelial growth factor, endothelin 1, renin-angiotensin-aldosterone system and other cytokines probable play a fundamental role in the capillary permeability increase that explains the majority of signs and symptoms [14,15].

The GCh and the agonist or antagonist hormones for gonadotrophin release do not cause OHSS, because these substances do not have vasoactive properties, but typically they are used in combination and can exacerbate the symptomatology [16].

The angiogenic molecule VEGF is the most important mediator of the ovary angiogenesis, and their production depends on the GCh [16,18]. The VEGF promotes the development of new vessels and is responsible for the regulation of vascular permeability [16].

The VEGF has 5 different isoforms and 2 different membrane receptors in the endothelial cells with biologic importance in the OHSS:

- The VEGFR-2 that is responsible for the increase in the vascular permeability [17].
- The VEGFR-1 that is responsible for maintaining the integrity of vascular vessel wall. It connects with the VEGF to avoid the increase in vascular permeability.

The gen for the tyrosine hydroxylase enzyme is considered characteristic in the OHSS because for the production of the syndrome this enzyme must be inhibited. This enzyme is the clue for the dopamine synthesis, and during the OHSS the dopamine synthesis at ovarian level is inhibited. The dopamine prevents the correct phosphorylation of VEGFR-2 and contributes to keeping vascular permeability, the reason why dopamine agonist Cb2 (cabergoline) is useful in the treatment of OHSS [17].

Clinical manifestations

The OHSS produces a hyperdynamic hemodynamic state, similar to the one presented in other diseases associated with edema, like the cardiac failure with high output, and others [18].

It is characterized by hypotension, an increase of the cardiac output, diminish in the vascular peripheric resistances, an intense activation of the renin-angiotensin-aldosterone, central nervous system and antidiuretic hormone. The consequence of this hormones activation is an important vascular fugue, with hemoconcentration, hypovolemia, severe arterial dilatation, finally producing systemic hypoperfusion and death [18,19].

One of the first clinical signs of a capillary fugue is the third space development and ascites, but finally, almost all cavities are compromised, with final anasarca creation. The renal failure is secondary to hypovolemia and increase in the intraabdominal pressure [18,19].

The symptoms: nausea, throwing, distention and abdominal pain are presented 48 hours after the administration of Gch. These symptoms increase after 7 to 10 days and the evolution depends on the presence or absence of pregnancy. The symptoms are very variable, but some are related to severity like intense nausea with threw up, intense abdominal pain secondary to ascites, ventilatory compromise, anuria, oliguria, thrombosis [20-23].

The ovarian cyst can reach diameters of more than 12 cm, with the subsequent risk of rupture and hemorrhage or torsion, and the secondary intense abdominal pain that could require surgical management [24].

Classification

The women that were treated with assisted reproduction techniques and develop OHSS could be evaluated according to their signs and symptoms according to the OHSS classification [14] (Table 1).

Grade	Severity	Clinical signs and symptoms
1	Mild	Abdominal distention
2	Mild	Grade 1 sign and nausea threw up and diarrhea. Ovary from 5 to 12cm.
3	Moderate	Grade 1 signs and symptoms and eco-graphic evidence of ascites.
4	Severe	Moderate signs and symptoms and clinical evidence of ascites, hydrothorax or respiratory distress.
5	Severe	Previous mentioned signs and hypovolemia, hemoconcentration, liver or kidney function alterations.

Table 1: *OHSS classification scale.*

According to the evolution of the OHSS could be classified too in:

- **Early:** It appears between 3 to 7 days after GCh administration.
- **Late:** It appears between 12 to 17 days after GCh administration, is related with pregnancy, depends on endogenous GCh produced by the syncytiotrophoblast.

Severe OHSS	*Life-threatening OHSS.*
Variable ovary growth	Variable ovary growth
Massive ascites with or without hydrothorax	Massive ascites with or without hydrothorax
Hematocrit higher than 45%	Hematocrit higher than 55%
More than 15000 leucocytes	More than 25000 leucocytes
Oliguria	Oliguria
Creatinine level 1.0 - 1.5 mg/dL	Creatinine level higher than 1.6 mg/dL
Creatinine clearance greater than 50 mL/min	Creatinine clearance greater than 50 mL/min
Hepatic dysfunction	Renal failure
Anasarca	Thromboembolic phenomenon
	Adult respiratory distress syndrome

Table 2*: Severity criteria in OHSS.*

Treatment

The management consists of support measures and waits until the clinical course to improve. In the majority of cases the evolution is auto limited according to the decrease of GCh seric levels in about 7 days in non-pregnant women, and 10 to 20 days in pregnant women, although some of them could evolve to the severe presentation very fast [20].

Although the moderate forms of OHSS usually resolve spontaneously with support management in 2 to 3 weeks, the patients could progress to a severe presentation very fast, especially if the pregnancy is achieved. The ambulatory treatment of this patients, according to the American Society of Reproductive Medicine, recommends that the mild cases receive oral analgesics. When the symptoms are worse the antiemetics could be added [23-25].

Mild cases could have an ambulatory management. This kind of management includes the daily weight measurement and urinary output, and abdominal diameter. If the abdominal diameter increase, with a weight increase of more than 900g or urinary output, reduces, it is recommended to complete an examination and an ultrasound to check the ovaries diameter [26].

Physical intense activity and sexual practices must be avoided; abundant liquids must be consumed and at least a litter of some beverage with electrolytes, with monitoring of hematocrit, electrolytes, and seric creatinine. The management of this patients must be a multidisciplinary one, and always have a reference hospital in case of intense abdominal pain, nausea, threw up, oliguria or anuria, tension ascites, dyspnea, tachypnea, hyponatremia, hypokalemia, or altered liver function [24-27].

Anesthetics considerations

It is extremely important to obtain an informed consent in this patient because most of them do not inform the parents about these treatments and when the complications occur, there exist some conflicts for the medical attention [26].

Is necessary to classify the patient in the correct OHSS grade to begin the management accordingly and establish if it could be an extra or intra hospital treatment.

An important point to take in account is the place to establish the treatment because, in our country and many others, the assisted reproduction centers work as ambulatory surgery centers, without all the infrastructure necessary to treat severe cases of OHSS. The participation of the anesthesiologist in the assisted reproduction process include oocyte capture, testicular biopsy, hysteroscopy, and cervical cerclage among others, including OHSS management [26-28].

For intraspinal treatment in cases of severe OHSS (grade 4 and 5), we have to be aware of other pathologies, allergies, previous medication for symptoms management, anesthetic complications and the presence of pregnancy [26].

The risk of thromboembolism is secondary to hemoconcentration, endothelial lesion, thrombocytosis, and immobility. The prophylaxis must be initiated with low molecular weight heparin 40mg/ 12h, a recommended scheme for those patients and must be administered when a grade 3-4 OHSS syndrome is diagnosed. In case of administration of Heparin 5,000 IU /24h is the indicated dose [26,27].

The thromboembolic processes in the severe cases are devastating and could appear although the indicated prophylactic treatment, this by the high estrogen levels, and hemoconcentration. This kind of complications during OHSS is estimated in 10% of the cases. In the 75% of the cases are venous thrombotic events and 25% arterial; any vascular territory could be affected, but the more frequent include arm, brain, and hearth [27].

Renal insufficiency. It is secondary to hypovolemia and increased intra-abdominal pressure.

Immunosuppression: There is an important decrease in immunoglobulins levels because the vascular leak allows the albumin fugue and other macromolecules especially IgG and IgA. The seric IgG is loosed through the peritoneal cavity, turning those patients into immunodeficient, with an increased infection potential.

The frequently isolated pathogens include Proteus mirabilis, Klebsiella pneumonia, Pseudomonas aeruginosa, Escherichia coli, Morganella morganii, and Proteus vulgaris. For this reason, the therapies with antibiotics specific to the pathogen are recommended [26,27].

A physical exam, the 4 extremities, head, and neck must be evaluated to discard deep venous thrombosis in severe cases. Some cases of visual acuity diminished have been reported and are explained by a thrombosis of the retina central artery.

During the airway, evaluation is very important to diagnose the mucous edema in the severe cases by the grade of difficulty to intubation that this factor could represent [26,27].

For the exploration of the cardiopulmonary system, we can find tachycardia, hypotension, tachypnea, dyspnea, hypotension according to the ascites grade [28].

In the grade 5, the cardiopulmonary manifestations include lobar pneumonia, pulmonary embolism, atelectasis, adult respiratory distress syndrome, hydrothorax and pericardic effusion [28].

When ventilatory distress is developed the possibility of pulmonary thromboembolism must be considered. Some cases of unilateral hydrothorax have been reported as the one extra-ovary manifestation of OHSS and must be considered in the pleuropulmonary syndromes [28].

The abdomen presents an increase in circumference, is painful, with or without acute abdomen signs. In patients with a moderate to severe disease, the pelvic exploration must be avoided for the risk of cystic rupture, lutein bodies rupture and friable ovaries, with the possibility of intra-abdominal bleeding and ovary torsion [26,27].

Laboratory test

The increase of hematocrit higher than 45%. When is reported between 45 - 50% the mortality risk is increased by the risk of thrombosis, venous in the majority of cases. A hematocrit higher than 55% is a factor of high severity and increased mortality too.

Leucocytes higher than 15,000/mm and more than 20000 are associated with an independent infectious process, and near 80% of the patients' present fever.

A third of the patients have *a* urinary infection, and antibiotics must be administered since the beginning [29].

Sodium lower than 135 mEq/L, potassium higher than *5.0* mEq/L. The hyponatremia founded could be explained by the liquid infusion, although in severe cases it could produce seizures. The hyperkalemia and metabolic acidosis are reflected in kidney and hemodynamic alterations.

Creatinine higher than 1.2 mg/dl and albumin < 3 g/dL. The increase in the creatinine levels constitutes a severity marker as the hypoalbuminemia [29].

Elevation of liver enzymes in 30% of the patients, with gamma-glutamyl transpeptidase and alkaline phosphatase in many cases, but these elevations use to disappear once the disease is resolved [26-29].

In the electrocardiogram, we can find tachycardia, pericarpic effusion data in severe cases, in patients with other cardiac disease decompensation data and hemodynamic instability.

Chest X-ray: Pleural effusion of some grade could be observed, and the atelectasis is the two most common findings. Control X-ray must be performed to evaluate the evolution and consider some other treatment in case of progression. For those reasons, the patients must be considered as ASA III, with a high thromboembolic risk, high respiratory risk and functional class between 2 and 4.

Those patients usually go to the operating room as an urgency, but a close follows up since the stimulation phase and during the cycle could allow those patients to enter the operating room in not complicated states, with a better short-term forecast [27].

Blood bank. Usually, during a culdocentesis or embryonic reduction blood derivatives are not needed, but if the surgical plan includes an instrumented curettage, laparotomy by ectopic pregnancy, ovary torsion or cyst rupture, the erythrocyte concentrates must be ready [27].

The anesthetic techniques described in the literature include the local anesthesia, conscious sedation, neuroaxial anesthesia and general anesthesia; the procedure to be performed must be individualized according to the patients by the pre-anesthesia assessment and decide the more convenient technique.

We have to consider the uterine and vaginal innervation for the administration of anesthesia, which covers from T12 to L2 and sacral segments S2-S4. The stimulus that occurs is an acute and nociceptive, generated by the needle across the vaginal wall and vaginal sack.

Local anesthesia

In the beginning, it was used but by the clear disadvantages like discomfort and inadequate analgesia, the use of this technique was abandoned [27,30].

Conscious sedation

It is described for the moderate cases when the surgeons have a lot of experience and skills, where the ascites liquid extraction is about 1000cc. It has the disadvantages in very anxious patients, because the movements of the patient during the procedure difficult the process and increase the risk of a lesion to adjacent structures, mainly vascular structures, compared with other techniques [30].

Neuroaxial Anesthesia

Is described as a very useful technique, associated with a great patient and surgeon satisfaction.

Some cases of moderate OHSS could be treated with culdocentesis by this technique, but unfortunately is not used in some centers for the dynamic of ambulatory procedures, or in other cases the patients refuse the procedure when other options are offered.

The peridural blockade with fractionated doses is preferred over the spinal blockade because it produces better hemodynamic stability.

The lidocaine, bupivacaine, and ropivacaine in different concentrations have been used with excellent results and variable times for recovery.

When the patients have been initiated in anticoagulation treatment this technique is contraindicated. Another contraindication is in the patients with tension ascites because the patients can't tolerate the positions to apply the blockade, referring dyspnea and pain; besides the abdominal compression must be avoided by the risk of ovary torsion or ovarian cyst rupture [31].

General Anesthesia

It gives adequate surgical conditions, the immobility diminishes the risk of adjacent organs injury, is safe and comfortable for patients and surgeon.

The total intravenous anesthesia is preferred over the general balanced when there exists pregnancy, by the mitosis inhibition of halogenated, they interfere the DNA synthesis and have been associated with abortion depending to the time of exposure.

There is no difference in the use of opioids for this procedure.

The propofol has been recommended for the induction and maintenance in this patient, with advantages in the recovery over other induction drugs.

For the use of neuromuscular blockade, the recommended drug is rocuronium in the case of a fast sequence intubation, in patients with respiratory distress secondary to tension ascites.

In patients with some kidney function alteration and/or liver dysfunction associated with the OHSS, the use of cisatracurium must be considered [30,31].

Airway instrumentation

Some of this patient can be treated with manual ventilation with facial mask, but it is not recommended when tension ascites exist.

A laryngeal mask is an excellent option, especially the Supreme®, because it allows the introduction of an orogastric tube, to an empty stomach and reduces the risk of Broncho aspiration.

The tracheal intubation is indicated in patients with ventilatory dysfunction by tension ascites. The controlled ventilation is recommended with 6.6 ml/Kg and P-max: ≤ 30 cm/H2O [30-32].

Preanesthesia medication: Is important to prevent the bronchoaspiration in anesthesiology, with a proper fast, prokinetic drugs, proton pump inhibitors, H2 inhibitors**,** and more important in patients with risk factors like reflux disease or a hiatal hernia, especially when ascites is present.

The administration of benzodiazepines is convenient because a great percentage of this patients have anxiety problems, emotional and psychological instability since the beginning of treatment and the presence of complications that could compromise their life [27,30,31].

Monitoring

It is performed with all the available devices in the operating room, in the conscious sedation techniques the bio spectral index allows us to complete an adequate drug titration.

The neuromuscular blockade monitoring gives the patient safety after extubation in the operating room for the post-anesthesia care.

The urinary output must be quantified by urinary catheter to evaluate renal function, and for the intra-abdominal pressure measurement to prevent the compartmental syndrome by ascites [27].

Fluid therapy

The therapy with liquids is an important problem in this patient, but the intravascular volume repletion represents the greatest challenge. Is important to maintain the parameters of pressure to guarantee the systemic perfusion. The goal is to resolve the hypovolemia, with a hematocrit around 36 - 38%. For this objective peripheral catheter of good caliber is needed, in the grade 5, a central line is needed for the central venous pressure measurement in the intensive care unit.

The treatment is directed to maintain the circulatory function and mobilize the intra-abdominal liquid, with a negative liquid balance in sodium and water.

The use of isotonic crystalloids is recommended more than the hypertonic fluids with the objective of accomplishing the redistribution of liquids forms the third space. The electrolytes must be adjusted constantly according to steric levels and renal function [27,30,32].

Albumin. The use is described since the prevention of moderate OHSS and in the treatment, during culdocentesis when is an absolute indication, especially when a great volume is removed (more than 5 litters) [6].

The described scheme in moderate OHSS is albumin 50%: 50 g in 500cc of NaCl 0.9% solution during the oocyte capture [7].

This dose must be administered 4 to 12 hours after the culdocentesis when necessary.

Another advantage of the albumin is the catchment of vasoactive substances, responsible for the genesis and development of OHSS [8].

The paracentesis with auto transfusion of ascites liquid has been described as an option for treatment in patients with severe OHSS[4]. The auto transfusion offers a fast and important decrease in symptoms without adverse hemodynamic effects or hematologic complications. An improve in the next parameters was observed: hemoglobin, el hematocrit and platelets. The steric albumin increase 55.5% their steric concentration [12].

Plasm: It has been used with limited success but sometimes is used in patients without response to traditional management.

Hydroxyethyl Starch. Is not recommended, especially in patients in the intensive care unit by the possible kidney damage, like in the OHSS grade 5.

Other plasma expanders like dextrans and mannitol have been used with limited success too [8,12].

With respect to surgical management, the drain of ascites liquid by paracentesis guided by ultrasound or culdocentesis are the options. Both methods offer a short hospital stay, fast symptoms reduction, and no adverse hemodynamic effects although big volumes were removed [27].

The diuretics theoretically are contraindicated, considering the relative hypovolemia in those patients, however many times are used in the management of this pathology once the intravascular volume is restored and when colloids are used for volume distribution. The treatment with diuretics must be considered after an adequate intravascular volume replacement (hematocrit < 38) because the early use in the management could increase the hypovolemia and the risk of thromboembolism [32].

The furosemide could be administered to evaluate renal function, in doses of 40 mg each 8 horas, with the proper albumin scheme.

The postsurgical analgesia must be with paracetamol and opioids, isn´t recommendable the use of NSAIDs, for the risk of renal failure.

Steroids, although in general terms their utility has not been proved in patients with OHSS, some cases have reported good results for a fast recovery [27].

The culdocentesis is the most used procedure in the treatment of OHSS grade 4, it must be performed in the operating room for better security conditions. The patient is placed in the lithotomy position with a fowler inclination of 45º, the liquid is calculated by ultrasound, important to calculate the amount of liquid to replenish. A vaginal asepsis is performed and by an ultrasound guide a 16 - 20 G needle is introduced 2 – 4 cm in the more decline area of the sack of Douglas, is connected to an aspiration system and drained with a pressure of 100 to 150 mm Hg or 100 ml per min, with a close monitoring of hemodynamic parameters.

After the procedure, the plasmatic proteins replacement for the patients is necessary, especially in repetitive aspirations taking into consideration that the content of ascites proteins is between 22 to 47 g/L [27,32].

Other procedures in which the anesthesiologist can intervene are:

- Puncture of lutein cysts to diminish the symptomatology.
- The embryonic reduction, defined as the selective reduction of gestational sacs when there are multiple pregnancies and constitutes a risk factor for the gonadotropins synthesis [27].
- The instrumented curettage, when the vitality of the embryo is confirmed.
- Exploratory laparotomy for ectopic heterotopic pregnancy, torsion or ovary rupture, and appendicitis secondary to intra-abdominal pressure increase by tension ascites.
- The oophorectomy has been described for the control of OHSS **[27,32].**

Management in the intensive care unit

After management in the intensive care unit to re-establish the intravascular volume, the laboratory parameters, symptoms, diuresis, and hemodynamic parameters improve significantly, and the use of albumin or furosemide could last 2 to 6 days be depending on the severity of the case. In the cases of severe ascites, the treatment includes liquid drain two or three times per week [5]. Although there exist some reports about the successful use of dopamine in the OHSS management to improve the diuresis it is not practiced frequently for the kidney damage in critical patients [19].

In patients with severe OHSS, the cardiopulmonary and hemodynamic parameters must be checked closely. The therapeutic thoracentesis is indicated in patients with respiratory distress and in the patients that develop ARDS the management with ventilatory neuroprotection (open lung technique) is the indicated [28].

In some cases, the therapeutic abortion is indicated with mifepristone, especially in severe cases refractory to initial management.

Once the hemoconcentration is resolved and the urinary output is normal, almost all the systemic alterations improve, and the patients can be discharged from intensive care unit in 7 to 8 days. When the disease is related to pregnancy, the hospitalization is prolonged for 3 weeks in average [11].

Prevention

For the previous we can establish the great importance of warning about OHSS in patients that are going to be managed with assisted fertilization treatments, with ovulation inductors [27].

Since the beginning in the attention to those patients, the background must be identified clearly, risk factors and special conditions that allow us to offer the best therapeutic options [1].

The intervention that prevents the OHSS does not exist actually, but some therapeutic indications could limit the symptoms and consequences to optimize the attention in patients with risk factors.

When a great number of oocytes (≥ 20) have been captured, the ovary hyperstimulation must be suspected and a close follows up of the patients performed.

The close quantification of steric estradiol is the most important risk factor, and a value above 4000 pg/dl would require strict vigilance in the evolution of the cycle.

The use of an agonist of GnRH for the induction of final maturation of oocytes in the protocol could reduce the OHSS [25].

The use of dopamine agonist like cabergoline has demonstrated good results in the treatment of OHSS. Cabergoline diminishes the correct phosphorylation of VEGFR-2 receptor, a critic step for the action of VEGF. The VEGF is a mediator of the hCG in the SHO. The Cb2 inhibits the increase in vascular permeability in the OHSS. It internalizes the R2-VEGF, preventing phosphorylation and their use improve the hemoconcentration, ascites and diminish the incidence of moderate-severe OHSS [2].

The quinagolide seems to prevent the cases of moderate-severe OHSS without affection of treatment results and their effect is more important in patients without a successful pregnancy [3,8].

The insulin resistance has been proposed as a factor related with ovary dysfunction and hyperandrogenism in polycystic ovary syndrome. Metformin has been used for this purpose in the prevention of OHSS because it does not affect the dose of gonadotrophins used, days of stimulation, number of recovered oocytes, number of transferred embryos or pregnancy rate.

In a recent meta-analysis, the infusion of albumin 25% in the capture of oocytes did not demonstrate a reduction in the incidence of grade 4 or 5 OHSS.

The quantification of steric antimalarial hormone level could be used to predict the OHSS in an effective way allowing to direct the protocols [29].

The adoption of the blastocyst transference strategy could allow us to have more time to evaluate the possibility of OHSS.

The verification of embryos with the postponement of their transfer could prevent the occurrence of OHSS, by improving clinical conditions of the patients in a new cycle.

The support of luteal phase with progesterone and estradiol, instead of hCG supplements, reduce the risk of OHSS.

The use of recombinant LH for oocyte maturation induction is essential for the prevention of OHSS in the future.

Some drugs that are frequently prescribed for reduction of vascular permeability like antihistamines, angiotensin-converting enzyme inhibitors or cyclooxygenase inhibitors, hasn´t probe efficacy for the reduction of symptoms [19].

Conclusions

With the recent advances in the Human Reproductive Medicine, the cases of ovary stimulation have increased, increasing the risk of complications like the ovary hyperstimulation syndrome.

The anesthesiology must know extensively the epidemiology, physiopathology, signs, symptoms and prevention maneuvers for the best anesthetic attention in this patients and better results.

The attention of this kind of patients must be according to clinical practice guidelines in the objective population.

The treatment of this OHSS is multidisciplinary, and the spread of knowledge about this pathology in the service of emergency, operating room, hospitalization and intensive care unit could improve the results in the management of the patients.

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