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Overview of Diagnosis and Management of Ovarian Hyperstimulation Syndrome

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Abstract: **Ovarian hyperstimulation syndrome (OHSS) is a major frequently dangerous, iatrogenic complication of assisted reproduction. Moderate & severe OHSS has actually been reported to happen in 0.2 - 2% of all ovarian stimulation cycles. This review aimed to discuss the Ovarian hyperstimulation syndrome (OHSS) from different clinical aspects, we intended to overview the diagnostic approaches and proper treatment of OHSS. A detailed search was conducted through electronic; PubMed/MIDLINE, and Embase databases, to find a relevant article to the aim of this study, this was conducted to search studies that were published in English language up to December 2016, with human subjects only. Prevention of OHSS begins with tailoring an individual's ovarian stimulation protocol based on their risk profile, through managed ovarian stimulation. Selecting one standardized preventative method for all patients or a big cohort of patients undergoing regulated ovarian stimulation is difficult, since the risks and advantages related to each technique vary between individuals. Recognition of hormonal, practical and hereditary markers of ovarian action will help with regulated ovarian stimulation.**

Keywords: **Ovarian hyperstimulation syndrome (OHSS), patients, Diagnosis, treatment, PubMed/MIDLINE.**

1. INTRODUCTION

Ovarian hyperstimulation syndrome (OHSS) is a major frequently dangerous, iatrogenic complication of assisted reproduction. Moderate to severe OHSS has actually been reported to happen in 0.2 - 2% of all ovarian stimulation cycles [(1)]. The syndrome is identified by an acute shift of protein-rich fluid from the vascular compartment into the 3rd area causing hemoconcentration, decreased renal perfusion, oliguria, thrombo-embolism, ultimately kidney shut down, and death in the most extreme cases [(1,2)]. OHSS has actually been categorized as early - taking place 3 - 5 days after the human chorionic gonadotrophin (hCG) trigger and late - taking place 5 - 7 days after embryo transfer. The exact pathophysiology of this syndrome is still not entirely illuminated. Mediators linked in the development of the syndrome include vascular endothelial development factor (VEGF), interleukins (IL1, IL2, IL6, IL8, endothelin 1, and tumor necrosis factor -alpha), prostaglandins, and renin angiotensin aldosterone system [(2)]. VEGF is presently thought about to be the most essential mediator as it increases vascular permeability leading to the fluid shift which is responsible for the symptomatology of OHSS, that is, abdominal distension, breathing distress, oliguria, and thromboembolic phenomenon [(3)].

The pathophysiology of OHSS is unknown, but the process is related to increased vascular permeability in the area surrounding the ovaries and their vasculature [(4)]. The core is a balance between antiangiogenic and proangiogenic factors present in follicular fluid. β-hCG and its analogs, estrogen, estradiol, prolactin, histamine and prostaglandins have all been implicated in OHSS and now it is significantly better comprehended that the vasoactive compounds such as interleukins, tumor necrosis factor (TNF)-α, endothelin-1 and VEGF produced by the ovaries have been implicated in increasing vascular permeability [(5)]. Prostaglandins, inhibin, the renin-angiotensin-aldosterone system and inflammatory mediators have all been implicated in the aetiology of OHSS [(6)]; nevertheless, vascular endothelial growth factor (VEGF) has actually been recognized as the major arbitrator (**Figure 1**) [(7,8)]. The expression of VEGF and VEGF receptor 2 (VEGFR-2) mRNA increases significantly in response to hCG, and peak levels coincide with maximum vascular permeability [(7)].

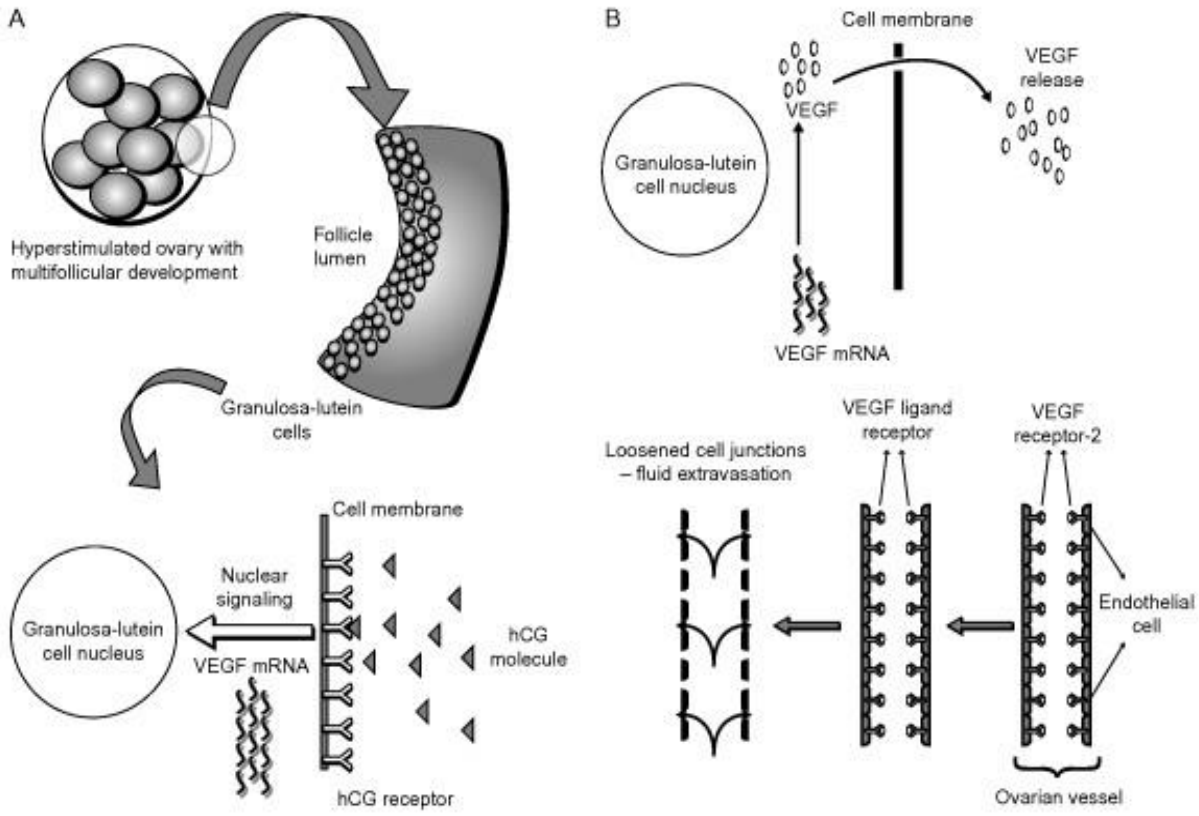

Figure 1: The pathogenesis of OHSS. Human chorionic gonadotropin (hCG) stimulates a high number of granulosa-lutein cells leading to the increased production of vascular endothelial growth factor (VEGF) mRNA VEGF receptor-2 (VEGFR-2) mRNA production in the granulosa-lutein and endothelial cells is also increased in response to hCG. High amounts of VEGF are produced and released from the granulosa-lutein cells and bind to VEGFR-2 on the endothelial cell membranes. Adapted from Soares et al [8]

hCG is Because of its resemblance to luteinizing hormone (LH) and its long half-life, utilized to activate last oocyte maturation in ovarian stimulation. It has also been determined as the trigger for the development of OHSS [9]. hCG causes the stimulated enlarged ovaries to produce the angiogenic particle VEGF [10]. Since, the development of gonadotropin-releasing hormonal agent (GnRH) villain protocols in vitro fertilization (IVF) it has become possible to utilize GnRH agonist as an ovulation trigger. GnRH agonist trigger works in installing an appropriate LH surge for final oocyte maturation furthermore it minimizes the risk of OHSS [11]. Various other methods have actually also been aimed to avoid OHSS. Use of the agonist trigger with elective cryopreservation of all embryos - the division method - has been promoted as a way to have an OHSS free center [12].

OBJECTIVES:

This review aimed to discuss the Ovarian hyperstimulation syndrome (OHSS) from different clinical aspects, we intended to overview the diagnostic approaches and proper treatment of OHSS.

2. METHODOLOGY

Search strategy: A detailed search was conducted through electronic; PubMed/MIDLINE, and Embase databases, to find a relevant article to the aim of this study, this was conducted to search studies that were published in English language up to December 2016, with human subjects only.

We used “Ovarian hyperstimulation syndrome (OHSS)” as Mesh terms for searching through Midline database combined with “diagnosis”, OR “prediction” OR “screening” AND “management”, OR “Treatment”. we included these studies which discussed the OHSS, with excluded studies with animal subjects.

3. RESULTS & DISCUSSION

➢ Classification of OHSS:

There has been a quick increase in the variety of couples receiving treatment for infertility with assisted reproductive innovation (ART) in recent years [13]. While there is robust proof supporting the effectiveness and safety of ART, it is very important to be familiar with the risks, the most severe which is OHSS. OHSS is an uncommon, iatrogenic issue of regulated ovarian stimulation (COS). Serious OHSS happens in roughly 1.4% of all cycles [14], impacting roughly 6020 patients per year in the United States and Europe [15]. The mortality risk is approximated to be 1 in 450000 to 500000 cases [16].

The medical manifestations of OHSS show the level of the shift of fluid into the 3rd area and the resulting hemoconcentration due to intravascular volume deficiency. Symptoms vary from mild stomach distention due to bigger ovaries alone or with an accompanying fluid shift into the abdomen, to kidney failure and death as a result of hemoconcentration and lowered perfusion of organs such as the kidneys, heart and brain (**Table 1**) [7,17,18]. Undoubtedly, as the severity of OHSS boosts, so does the variety of organs impacted [17].

Table 1: Classification of OHSS symptoms (adapted from Navot et al [18])

OHSS stage	Clinical features	Laboratory features
Mild	Abdominal distension/discomfort	
	Mild nausea/vomiting	
	Diarrhea	
	Enlarged ovaries	No important alterations
Moderate	Mild features +	Elevated hematocrit (>41 %)
	Ultrasonographic evidence of ascites	Elevated WBC (>15000)
		Hypoproteinemia
Severe	Mild and moderate features +	Hemoconcentration (Hct >55 %)
	Clinical evidence of ascites	WBC >25000
	Hydrothorax	CrCl <50 mL/min
	Severe dyspnea	Cr >1.6
	Oliguria/anuria	Na+ <135 mEq/L
	Intractable nausea/vomiting	K+ >5 mEq/L
	Tense ascites	Elevated liver enzymes
	Low blood/central venous pressure	
	Rapid weight gain (>1 kg in 24 hours)	
	Syncope	
	Severe abdominal pain	
	Venous thrombosis	
Critical	Anuria/acute renal failure	Worsening of findings
	Arrhythmia	
	Thromboembolism	
	Pericardial effusion	
	Massive hydrothorax	
	Arterial thrombosis	
	Adult respiratory distress syndrome	
	Sepsis	

Cr = serum creatinine level; CrCl = creatinine clearance; WBC = white blood cell count.

OHSS can be "early" or "late" based upon the source of hCG. Early OHSS takes place in the luteal stage of COS after the administration of exogenous hCG to cause oocyte maturation. Late OHSS takes place when ART leads to pregnancy and is the consequence of a boost in endogenous hCG levels following conception. For the most parts, OHSS is self-limiting and resolves spontaneously within numerous days. OHSS may persist, particularly late OHSS due to pregnancy [7,17,18].

- **Overview of Pathophysiology of OHSS:**

Vascular endothelial growth factor increases VP, and transcapillary fluid characteristics studies in OHSS patients verified a reduction in the colloid osmotic gradient preferring leak to the extravascular space [19]. This "3rd spacing" results in depletion of the intravascular volume, ultimately leading to hypotension. The large fluid shift can cause tension ascites that can be sent into the thoracic cavity resulting in pleural effusions as first explained by Mozes et al. [20], other lung manifestations [21], or reliant edema [22].

Because hypotension causes reduced venous pressure and decreased venous return, a decreased heart output (CO) might be expected; nevertheless, research studies have discovered the CO was increased in OHSS [23,24]. In one study CO was found to increase to 2.6 L/min, indicate arterial pressure decreased by 16.6 mmHg, and peripherial vascular resistance was decreased [24]. These findings caused the determination that there is accompanying arterial vasodilation in OHSS [23]. Because of the decreased perfusion, the hypotension likewise impacts organ function. Decreased perfusion of the kidney causes a reduced glomerular purification rate (GFR), and can result in oliguria. In addition, changes in perfusion can impact liver function [25], consisting of synthesis of proteins, of which anticlotting factors are among the very first to become diminished. This, in addition to the hemocon centration because of diminished intravascular volume can result in thromboses, not occasionally in the upper extremities [25]. Both arterial thromboses [27] and venous thromboses in sites such as the remarkable vena cava [28], internal jugular vein [29,30,31], and subclavian vein [32] have actually been reported in patients with OHSS. Numerous affected patients had no other risk factors for apoplexy. Hemoconcentration may partially explain the boost in white blood cells and platelets, although some believe these elevations might be because of demargination related to tension [33].

- **Risk factors/biomarkers for OHSS could help in diagnostic procedure:**

Several primary and secondary risk factors for OHSS have actually been determined (**Table 2**). Nevertheless, their level of sensitivity and uniqueness for anticipating hyper-response/OHSS varies [34,35]. Despite this, as signs of risk, these risk factors/biomarkers assist in the recognition of patients that need customized COS (iCOS). There are a number of reputable main risk factors for the development of OHSS, consisting of young age, polycystic ovary syndrome (PCOS)--defined by ultrasound and the ratio of luteinizing hormone (LH) to hair follicle stimulating hormonal agent (FSH)-- and a history of an elevated reaction to gonadotropins, i.e. prior hyper-response/OHSS [34,36,37]. Research studies investigating the effect of low body weight/body mass index (BMI) on the advancement of OHSS report inconsistent outcomes [37,38]. For that reason, body weight/BMI does not currently appear to be a useful marker for increased risk of OHSS. Immunological sensitivity, i.e. hypersensitivity or allergies may likewise be predictive of OHHS. In a potential accomplice study, patients who established severe OHSS (n=18/428) had an increased frequency of allergic reactions (56% vs. 21% in the control group) (39). While a link in between OHSS and allergic reaction is plausible, as the pathophysiological changes in the ovaries during OHSS resemble an overactive inflammatory action, the impact of allergic reactions on the advancement of OHSS needs further study.

Research study has actually recognized extra hormone biomarkers that may likewise forecast a patient's reaction to COS and determine their risk of OHSS. In the very early follicular stage of the cycle, a variety of antral hair follicles (2-10 mm in size) are present that are easily found by transvaginal ultrasound as their appearance is marked by the development of a fluid-filled cavity adjacent to the oocyte (the antrum) [35,38]. The number of small antral roots at the beginning of a cycle is connected to age and might reflect the ovarian reserve [35,38]. In a research study by Kwee et al, an antral root count (AFC) > 14 had the greatest sensitivity (82%) and specificity (89%) to positively predict ovarian hyper-response [40].

TABLE 2: Risk factors/predictive factors for OHSS (adapted from [34,38])

Risk factor	Threshold of risk
Primary risk factors (patient related)	
· ***High basal AMH***	- >3.36 ng/mL independently predicts OHSS
· ***Young age***	- <33 years predicts OHSS
· ***Previous OHSS***	- Moderate and severe cases, particularly those with hospitalization
· ***PCO like ovaries***	- >24 antral follicles in both ovaries combined
Secondary risk factors (ovarian response-related)	
· **High number of medium/large follicles**	- ≥13 follicles ≥11 mm in diameter - >11 follicles ≥10 mm in diameter
· **High or rapidly rising E2 levels and high number of follicles**	- E2 5,000 ng/L and/or ≥18 follicles predictive of severe OHSS
· **Number of oocytes retrieved**	- >11 predicts OHSS
· **VEGF levels**	- Not applicable
· **Elevated inhibin-B levels**	- Elevated levels on day 5 of gonadotropin stimulation, at oocyte retrieval and 3 days before
· **hCG administration for LPS**	- Not applicable
· **Pregnancy (increase in endogenous hCG)**	- Not applicable

AFC = antral follicle count; AMH = anti-Müllerian hormone; E2 = estradiol; hCG = human chorionic gonadotropin; LPS = luteal phase support; OHSS = ovarian hyperstimulation syndrome; PCOS = polycystic ovary syndrome; VEGF = vascular endothelial growth factor.

- **Treatment approaches of OHSS:**

Administration of macromolecules:

A. Albumin administration

Prophylactic albumin administration might interrupt the development of OHSS by increasing the plasma oncotic pressure and binding conciliators of ovarian origin. This impact could be combated by increased capillary permeability. Prospective randomized trials and one retrospective research study with a control group show 39 cases of OHSS in 468 cured risk cycles (8.3%) vs 89 OHSS cases in 611 untreated risk cycles (14.6%). The Cochrane review likewise shows that intravenous albumin administration at the time of oocyte collection has a preventive effect in cycles with a serious risk for OHSS [41]. However, a current prospective randomized trial of 488 cases in each arm of the research study appears, to show the inadequacy of human albumin [42]. Albumin administration likewise has negative effects like viral transmission, nausea, vomiting, and febrile and allergic reactions. Albumin is pricey too.

B. *Hydroxyethyl starch solution*

Because of the risk of viral transmission with human albumin, some authors have actually evaluated the result of this much safer nonbiological replacement with equivalent physiological properties. Three studies recommend a beneficial result but the associates are too small to draw guaranteed conclusions [43] Further clinical research seems required.

Cryopreservation of all embryos: Instead of canceling the cycle, it is also possible to administer hCG to retrieve the ocytes and to freeze all embryos. This does not leave out the risk for the early kind of OHSS. The elimination of a large number of granulose cells from the roots most likely likewise decreases the risk. The Cochrane Review concludes that the present proof is insufficient to consider this method as the requirement of treatment [44].

GnRH antagonist:

GnRH agonists (GnRHa) are associated with a boost in the occurrence of OHSS [45]. One possible explanation is that pretreatment blockade of endogenous gonadotrophins demands an increased dosage of exogenous FSH for adequate ovarian stimulation. In contrast to the extended pretreatment phase with GnRHa, the quick competitive blockade of pituitary GnRH receptors by villains can be provided normally at a roots size of 12-14 mm. The differential action of GnRH villains at both pituitary and ovarian receptors recommends that antagonist-suppressed cycles may lead to a lower occurrence of OHSS compared with agonist cycles. A Cochrane review [46] showed that the incidence of serious OHSS was significantly lower in an antagonist protocol than in an agonist procedure [46].

Cancelling of hCG for luteal phase support:

The use of hCG in luteal phase support (LPS) has been shown to provide considerable advantages over placebo in agonist reduced cycles; however, hCG is likewise known to increase the risk of OHSS. The use of Progestogens (P) appears to halve this risk, while demonstrating comparable enhancements in pregnancy and miscarriage rates [47].

4. CONCLUSION

Prevention of OHSS begins with tailoring an individual's ovarian stimulation protocol based on their risk profile, through managed ovarian stimulation. Selecting one standardized preventative method for all patients or a big cohort of patients undergoing regulated ovarian stimulation is difficult, since the risks and advantages related to each technique vary between individuals. Recognition of hormonal, practical and hereditary markers of ovarian action will help with regulated ovarian stimulation. Undoubtedly, if the risk factors and biomarkers for OHSS are acknowledged and patients are properly treated with regulated ovarian stimulation, OHSS may not be a problem.

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