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Taiwanese Journal of Obstetrics & Gynecology 50 (2011) 2–10
www.tjog-online.com

Review Article

Update on management of ovarian hyperstimulation syndrome

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Accepted 7 September 2010

Abstract

Ovarian hyperstimulation syndrome (OHSS) is a relatively common complication of ovarian stimulation and can be life threatening. The pathophysiology of OHSS is characterized by increased capillary permeability, leading to leakage of fluid from the vascular compartment, with third-space fluid accumulation and intravascular dehydration. The increased intra-abdominal pressure indicated that OHSS may be considered a compartment syndrome. Vascular endothelial growth factor, also known as vascular permeability factor, has emerged as one of the mediators intrinsic to the development of OHSS. Conventional management is focused on supportive care until the spontaneous resolution of the condition. The standard of care for treatment—monitoring of appropriate clinical parameters, fluid balance management, thrombosis prophylaxis, and ascites treatment—should prevent severe morbidity in most cases. This review will cover inpatient and outpatient management. The potential therapeutic approach targeting the vascular endothelial growth factor system will be discussed.

Keywords: Abdominal compartment syndrome; Dopamine agonist; Intra-abdominal pressure; Ovarian hyperstimulation syndrome; Paracentesis

Introduction

Ovarian hyperstimulation syndrome (OHSS) is a relatively common complication of ovarian stimulation and can be life threatening [1]. In severe cases, a critical condition develops with massive ascites, marked ovarian enlargement, pleural effusion, electrolyte imbalance, and hypovolemia with hypotension and oliguria [2].

Unlike tumor angiogenesis, OHSS is self-limiting and will undergo gradual resolution with time. Conventional management is focused on supportive care until the spontaneous resolution of the condition. This review will explore the pathophysiology of OHSS and its management. The potential therapeutic approach targeting the vascular endothelial growth factor (VEGF) system will be discussed. Improved understanding of the pathogenesis of OHSS should facilitate more individualized *in vitro* fertilization (IVF) treatment protocols and minimize the occurrence of OHSS [3].

Pathophysiology

The pathophysiology of OHSS is characterized by increased capillary permeability, leading to leakage of fluid from the vascular compartment, with third-space fluid accumulation and intravascular dehydration [4]. The cause of OHSS is unknown, but it may be mediated by vasoactive cytokines secreted in excess by hyperstimulated ovaries [5], and it is believed that these ovarian factors are secreted by corpora lutea in response to human chorionic gonadotropin (hCG) stimulation [6–8].

Proinflammatory cytokines [interleukin-1β (IL-1β), IL-6, IL-8, and tumor necrosis factor-α] have been implicated as mediators of the acute-phase response [9], which is characterized by capillary leakage similar to that seen in OHSS. VEGF, also known as vascular permeability factor, has emerged as one of the factors most likely involved in the pathophysiology of OHSS [10]. VEGF is an angiogenic cytokine, which is a potent

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1028-4559/$ - see front matter
doi:10.1016/j.tjog.2011.01.014

stimular of the vascular endothelium and appears to play an integral role in follicular growth, corpus luteum function, and ovarian angiogenesis. In human, hCG administration increased VEGF expression in granulose-lutein cells [11]. High serum, peritoneal fluid, and follicular fluid VEGF, IL-6, and IL-8 concentrations have been correlated with the development of OHSS and its severity [7,12−15]. Hence, the inhibition of vascular permeability appears to be an attractive and novel therapeutic approach to preventing and treating OHSS (Fig. 1).

Hemodynamic changes of OHSS

The clinical manifestations originate from the combination of decreased intravascular space and the accumulation of protein-rich fluid into body cavities and interstitial space. This "third spacing" causes depletion of the intravascular space. Loss of intravascular volume leads to hemodynamic changes manifested as hypotension, severe tachycardia, and decreased renal perfusion as well as hemoconcentration. Hemoconcentration with increase in blood coagulability is responsible for arterial and venous thrombotic phenomena in patients with OHSS [16]. Loss of intravascular volume combined with decreased renal perfusion results in electrolyte abnormalities (hyperkalemia, hyponatremia), increase in hematocrit and white cell count, and decrease in creatinine clearance.

The most common symptom of OHSS (abdominal discomfort) is because of the development of ascites. Accumulation of protein-rich fluid in the peritoneal cavity leads to abdominal distention and increased intra-abdominal pressure (IAP).

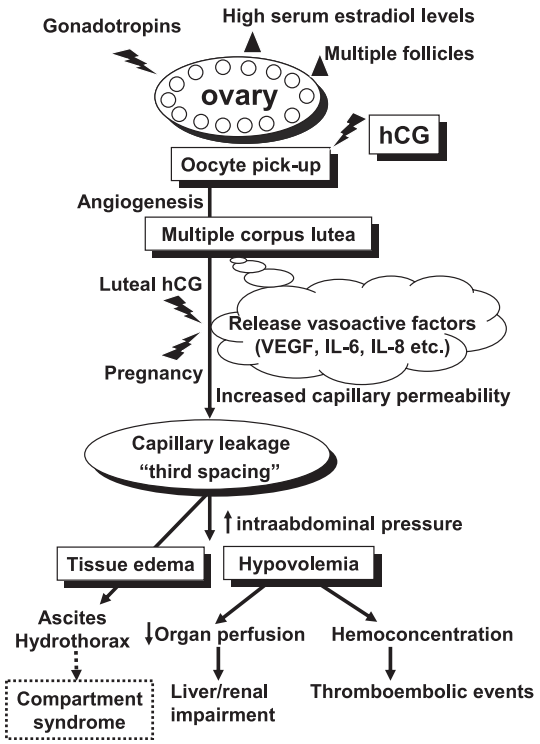

Fig. 1. Pathophysiology of ovarian hyperstimulation syndrome. hCG = human chorionic gonadotropin; IL-6 = interleukin-6; IL-8 = interleukin-8; VEGF = vascular endothelial growth factor.

Increased IAP has deleterious effects on end-organ function and may compromise respiratory, cardiovascular, renal, gastrointestinal, and hepatic system homeostasis [17,18]. An understanding of the pathophysiology of increased IAP is useful in the management of OHSS.

Changes in IAP have a great impact on renal function and urine production. One of the first visible signs of intra-abdominal hypertension (IAH) is oliguria, which occurs at an IAP of 15−20 mmHg [19]. Renal dysfunction secondary to increased IAP results from the decrease in cardiac output, direct compression of renal vessels and parenchyma with decreased renal blood flow, increased renal vascular resistance, and redistribution of renal blood flow from the cortex to the medulla. Experimental studies demonstrated that IAP >15−20 mmHg was associated with decreased glomerular filtration rate and oliguria, which progressed to anuria when IAP values exceeded 30 mmHg [20]. The same is true for all the intra-abdominal low-pressure vessels that supply the intestines. Initial venous compression results in parenchyma edema. Intestinal edema is responsible for the nausea and the diarrhea, which often occurs in patients with OHSS.

Increased IAP leads to decreased splanchnic and hepatic perfusion with tissular hypoxia. Animal studies showed a significant impairment of hepatic artery and portal vein blood flow at IAP of 10 mmHg and decreased mesenteric blood flow at IAP of 20 mmHg [17]. Liver edema is manifested with an increase in liver function tests [15]. The increase in IAP leads to elevation of the diaphragm with increased intrathoracic and pleural pressures, resulting in progressive reduction in lung and chest wall compliance. Pulmonary function may be compromised in cases of severe OHSS by several mechanisms that act synergistically: elevation of the diaphragm, accumulation of fluid in the pleura, and interstitial edema [21]. Although pleural effusion is generally thought to be a consequence of pronounced ascites, associated with a shift of liquid from the peritoneal cavity to the pleura, isolated pleural effusion without concomitant ascites has been reported as the only symptom of OHSS [22−24]. The pathogenesis of isolated hydrothorax in cases of OHSS remains unclear.

OHSS may be considered as an abdominal compartment syndrome

The increased IAP indicates that OHSS may be considered a compartment syndrome. IAH is defined by a sustained or repeated pathologic elevation of IAP ≥12 mmHg. Abdominal compartment syndrome (ACS) is defined as a sustained IAP >20 mmHg that is associated with new organ dysfunction/failure [25,26]. Primary ACS is a condition associated with injury or disease in the abdominopelvic region. Secondary ACS refers to conditions that do not originate from the abdominopelvic region, such as sepsis and capillary leak syndrome, major burns, and other conditions requiring massive fluid resuscitation, yet resulting in the signs and symptoms commonly associated with the ACS [25].

The most important factor responsible for the development of ACS might be excessive fluid administration, which can