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Ovarian Hyperstimulation Syndrome

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Abbreviations

AFC	anfral follicle count
AMH	anti-müllerian hormone
ARDS	acute respiratory distress syndrome
ART	assisted reproduction technologies
BMI	body mass index
Ca	calcium
COS	controlled ovarian stimulation
DIC	disseminated intravascular coagulation
DOPAC	3,4-dihydroxyphenyl-acetic acid
FSH	follicle-stimulating hormone
GC	granulosa cell
hCG	human chorionic gonadotropin
HES	hydroxyethyl starch solution
IO	induction of ovulation
IVF	in vitro fertilization
IVM	in vitro maturation
Kp	kisspeptin
OHSS	ovarian hyperstimulation syndrome
VEGF	vascular endothelial growth factor
VPF	vascular permeability factor

DEFINITION AND PREVALENCE

Ovarian hyperstimulation syndrome (OHSS) is the most serious complication resulting from the medical manipulation of the ovary. It occurs in anovulatory patients wanting to conceive who need full ovulation induction (OI), and in controlled ovarian stimulation (COS) in women undergoing assisted reproduction technologies (ART) in whom the retrieval of a certain number of oocytes is desired. Thus, OHSS is an iatrogenic condition, which affects young healthy individuals mainly as a consequence of fertility treatments.

OHSS consists of a broad spectrum of signs and symptoms that include abdominal distention and discomfort, enlarged ovaries, ascites, and other complications of enhanced ovarian vascular permeability [1,2]. In its severe form, OHSS is a life-threatening condition because it can cause renal failure and venous or arterial thromboembolic events, which include stroke and loss of perfusion to an extremity. It has also been associated with maternal death [3]. In addition, there is an important economic burden associated with OHSS due to absence from work, bed rest, and hospitalization, as well as the intensive medical management of severe cases.

The true incidence of OHSS is difficult to determine as there is no generally accepted definition of the syndrome. Moreover, it depends upon the clinical setting (OI or COS), the drugs employed, and the type of patient treated (either at risk or not at risk). When ovulation is induced with clomiphene citrate or aromatase inhibitors, either for timed intercourse or intrauterine insemination, a mild form of OHSS may occur, but moderate to severe OHSS is rarely seen [4]. In COS, the overall incidence of moderate and severe OHSS is 3%–6% and 0.1%–2%, respectively [1,5,6]. Hospitalization due to OHSS has been reported to range between 0.3% and 1.1% [7,8]. There was an alarming increase in the incidence of OHSS in the 1990s. However, the introduction of risk markers and a series of preventative measures, the most important of which is the freezing the embryos avoiding pregnancies, has resulted in a substantial decrease of this iatrogenic complication.

PATHOGENESIS

OHSS is the result of multiple follicular development with gonadotropins and subsequent ovulation triggering with hCG. If pregnancy follows, trophoblast-derived hCG will worsen the symptoms. Also, it has to be recognized as a phenomenon localized to the ovaries. In fact, although increased peripheral arteriolar dilatation in the entire body was proposed [9], it is today accepted that OHSS is a local phenomenon of the ovary, since oophorectomy restores normality and OHSS does not develop in experimental conditions in which ovaries are not present [10,11]. Similarly, if as a result of COS with gonadotropins many follicles develop and hCG for ovulation triggering is withhold, OHSS does not occur [12–14],

showing that hCG is the driver of all the pathophysiological events in OHSS. Since hCG has no direct vasoactive properties, investigations have aimed to detect the vasoactive substance responsible for this condition.

Initial investigations suggested that high estradiol levels was the determinant of OHSS [15,16]. However, women with enzymatic mutations in the steroid pathway and low estrogens levels in the blood can develop OHSS [17]. Others have pointed to substances present in follicular and ascitic fluid of hyperstimulated women such as cytokines and growth factors (interleukins (IL): IL-2, IL-6, IL-8, IL-10, IL-18) [18], as well as other substances such as histamine, prolactin, prostaglandins, and renin-angiotensin as participants in OHSS pathophysiology [19].

The true candidate must fulfill a number of prerequisites. Its expression should be enhanced by hCG and should be higher in cases of OHSS. It must have a clear and strong effect on vascular permeability, and inhibition of this candidate mediator should inhibit the clinical manifestations of OHSS. Today, it is accepted that the hCG mediator is vascular endothelial growth factor (VEGF), originally described as a vascular permeability factor (VPF) because of its ability to cause substantial vascular leakage [20] when secreted by tumor cells. Compared with histamine, VEGF/VPF enhances endothelial permeability by 50,000 times [21].

The human VEGF gene has been mapped to chromosome 6p12 [22] and is made up of eight exons. The VEGF gene shows the same exonic structure in rodents and humans, with 95% protein homology between them [23]. Similar to the human [24], hybridization studies in the rat ovary have demonstrated significant VEGF mRNA expression, which are mostly seen after the LH surge [25].

VEGF exerts its biological actions by binding to receptors present on the endothelial cells surface that belong to the tyrosine kinase receptor family [26], VEGFR-1 (Flt-1) and VEGFR-2 (Flk1/KDR) [26,27]. The receptor Flk1/KDR appears to be involved in regulating vascular permeability, angiogenesis, and vasculogenesis, while VEGFR-1 seems to work against VEGFR-2 by controlling the assembly and maintenance of tight junctions between endothelial cells in existing vessels [28]. In addition, VEGFR-1 is produced as a soluble receptor (sVEGFR-1) by alternative splicing of the precursor mRNA [29]. This truncated receptor appears to compete with the full-length VEGF receptors for binding VEGF, and also heterodimerizes with VEGFR-2 to inhibit vascular permeability [30].

Given indirect evidence that VEGF is augmented by hCG in COS patients [24,25,31], some experiments have induced ovarian enlargement and ascites using gonadotropins similar to COS in humans and showed that ovarian VEGF, VEGFR-2 mRNA, and protein levels increased even before hCG administration [11,32]. The administration of hCG further augmented all these parameters to their maximum [11,32]. These effects were specific to the ovary and not to surrounding tissues. In fact, COS did not induce ascites in oophorectomized animals [11].

In women who develop OHSS, VEGF is overexpressed and produced by granulosa-lutein cells [24,33], and then released into the follicular fluid in response to increased capillary permeability induced by hCG [24,34,35]. hCG induces the expression of VEGF in cultured granulosa-luteal cells, which is higher in women developing OHSS [36] than in women who do not develop the syndrome. Plasma [37] and ascitic [38] VEGF levels correlate with the clinical picture of OHSS. It has also been demonstrated that hCG administration increases VEGFR-2 expression in granulosa-lutein cells, mainly in patients at risk of OHSS [37] (Fig. 1).

In addition, other studies have determined soluble receptor sVEGFR-1 serum levels to be a modulator of VEGF bioactivity. It was found that women who did not develop OHSS had significantly higher sVEGFR-1 plasma levels, while hyperstimulated women had significantly higher amounts of free and bound VEGF and lower sVEGFR-1 levels [39].

The endothelial cell-to-cell junctions are the downstream targets of VEGF. An increase in cadherin expression with increasing VEGF levels and changes in the conformational arrangements of endothelial cells have been described, which represent the morphological confirmation of increased vascular permeability [40].

Among women who display OHSS, the most important group are women with polycystic ovary syndrome (PCOS). Recent studies have provided important information about the reasons why these women are at high risk. One interesting observation is the relationship between dopaminergic system and VEGF secretion. Early studies using the murine model showed that administration of a dopamine agonist was able to reverse increased capillary permeability due to gonadotropins by inactivation of VEGFR-2 phosphorilation [41]. Subsequent studies in humans employing different dopamine agonists showed that these drugs can be used to reduce ovarian capillary permeability in hyperstimulated patients [42,43], showing the potential relevance that dopamine might have in the development of OHSS.

Dopamine and its receptors have been explored in normal and PCOS patients. As shown in Fig. 2, the dopamine receptor D2 (Dr2) is present in the theca cells of antral and preovulatory follicles as well as in granulosa-lutein cells [44]. The Dr2 is significantly higher in normo-ovulatory women compared with PCOS. Moreover, granulosa-lutein cells also secrete dopamine in much higher amounts in normal subjects than in PCOS [44]. In contrast, the secretion of 3,4-dihydroxyphenyl-acetic acid (DOPAC), the primary metabolite of dopamine, is

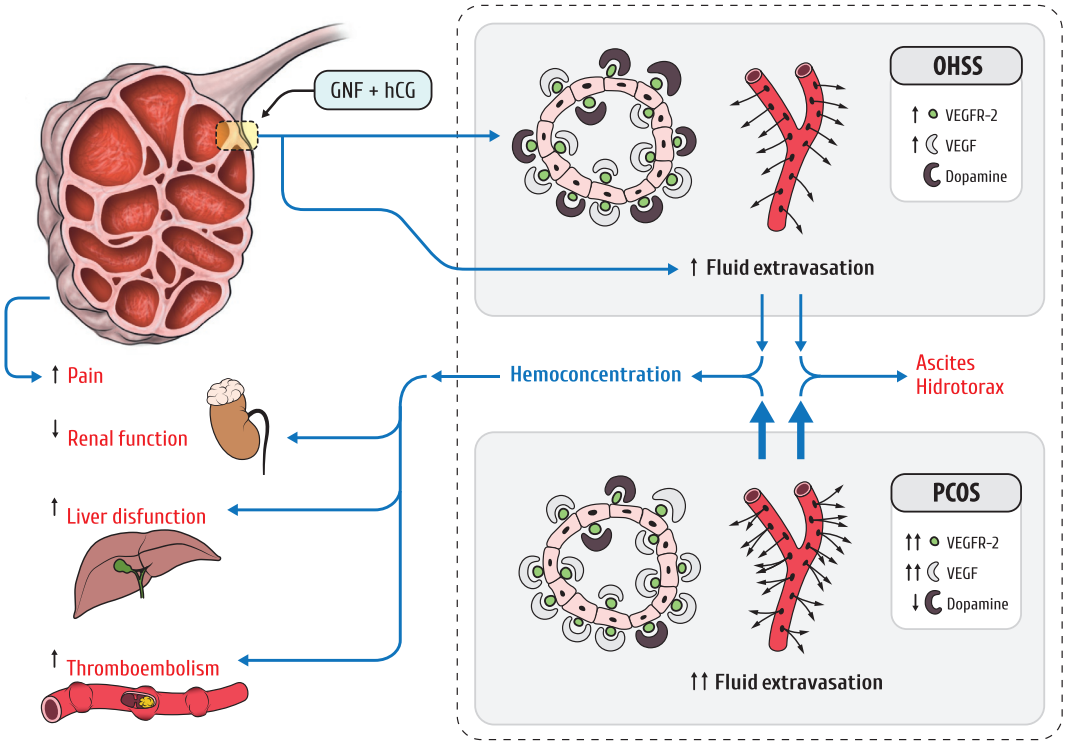

FIG. 1 Pathophysiology of OHSS in women treated for controlled ovarian stimulation (COS) with gonadotropins and in women with polycystic ovarian syndrome (PCOS).

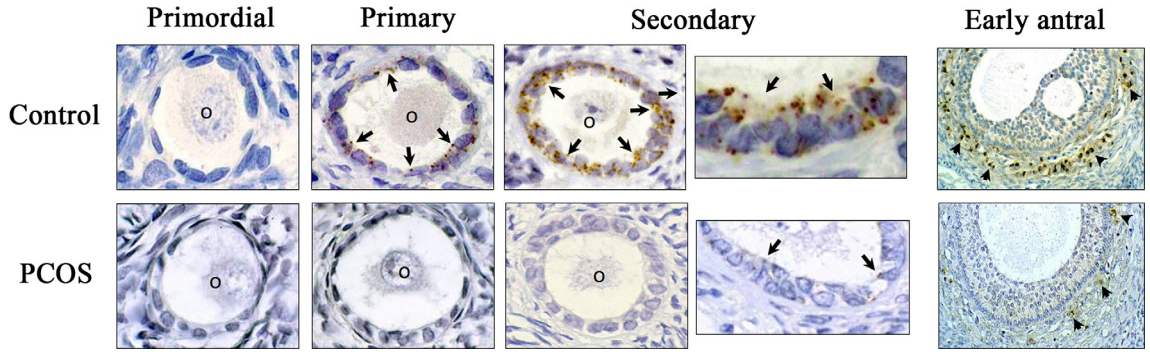

FIG. 2 Expression of dopamine receptors in cycling and PCOS human ovaries. In control ovaries, immunostaining was absent in primordial follicles and showed a punctate immunostaining pattern in the granulosa cell (GC) (arrows) of primary and secondary follicles. In contrast, in PCOS ovaries, immunostaining was absent or barely detectable (arrows) in the GC of small follicles. In early antral follicles, dopamine receptor expression was also more evident (arrows) in control than PCOS ovaries. (Adapted with permission from the Endocrine Society, Ref. [44].)

significantly increased in PCOS, suggesting that the metabolism of dopamine was faster in PCOS than in normo-ovulatory women. All in all, it seems that PCOS women display an increased vascularization [44], which could be explained by higher serum and follicular VEGF levels compared with normal ovulatory subjects [33,45]. In PCOS, the dopaminergic system is different than in normal individuals, with lower presence of dopamine receptor D2 and deregulated dopamine metabolism, which results in higher expression of the signs and symptoms of the syndrome (Fig. 1).

Administration of a dopamine agonist (Cabergoline) reduces, in a dose-dependent manner, VEGF secretion by granulosa-lutein cells [46]. The mechanism by which dopamine and its agonists reduce vascular permeability seems to be even more complex than a simple blockage of VEFGR-2 phosphorilation. in vitro and in vivo studies have revealed that dopamine agonist action over Dr2

in granulosa-lutein cells is posttranscriptional [46–48]. Recent genomic association studies have shown that several pathways are affected in granulosa-lutein cells by dopamine agonists such as the VEGF signaling pathway, as well as apoptosis and ovarian steroidogenesis [49].

Rarely, OHSS may occur in the absence of ovarian stimulation, generally appearing in weeks 8th to 14th of spontaneous pregnancies [50]. There are four major causes of spontaneous OHSS. First, ovarian hypersensitivity to gonadotropins as the consequence of mutations in the FSH receptor, which allows hCG binding [51–54]. In such instances, a family history is found [52,53].

Second, OHSS has been described after abnormally high levels of endogenous gonadotropins in molar pregnancies and diandric or digynic triploids [55] or multiple pregnancies. This phenomenon is known as hyperreactio luteinalis [50].

Third, high levels of molecules structurally similar to gonadotropins, such TSH in hypothyroid states, may occupy their receptors and lead to hyperstimulation during pregnancy [56,57].

Forth, spontaneous OHSS can occur in women with pituitary adenomas, even where high serum FSH levels are not found. In these cases, the ovaries appear particularly sensitive to the ligand secreted by the pituitary, and this higher biologic activity induces massive multicystic formations and high serum estradiol levels [58].

RISK FACTORS

In theory, OHSS could develop in any patient undergoing COS with gonadotropins. However, the reality is that there are some women who are at a much higher risk. Identifying these women is essential for lowering and even eliminating OHSS in clinical practice [59] (Table 1).

TABLE 1 Identification of Patients at Risk of Developing OHSS

Before COS
– Previous epidosde of OHSS
– PCOS or PCO-like ovaries
– Black race
– Young woman <35 years
– Number of antral follicles >2 mm ≥24
– Serum AMH > 3.4 ng/mL
During COS
- Development of ≥19 follicles
- Serum E2 > 3500 pg/mL
After ovum pick-up
- Retrieval >15 oocytes

Before COS Begins

Not much can be said about the phenotype. However, ovulatory disorders, particularly PCOS, are the most prevalent characteristic of women at risk of OHSS. Similarly, women who have previously developed OHSS should be considered at high risk of experiencing a similar clinical picture [60–65]. Black women also appear to be at higher risk of OHSS [60]. In addition, younger age (<35 years) has been associated with OHSS [63,66]. In contrast, the relationship between body weight and OHSS is less clear. Some studies have indicated the relevance of BMI in the appearance of OHSS [66,67], whereas others found BMI to have no predictive value [62,64,68,69].

The use of markers for ovarian reserve has improved the risk assessment of OHSS. A cut-off value of 3.36 ng/mL serum antimüllerian hormone (AMH) levels has been considered a good predictor of OHSS, with a sensitivity of 90.5% and specificity of 81.3% [69]. Levels >10 ng/mL are associated with a threefold increase in the incidence of OHSS [70].

Antral follicle count (AFC) is also predictive of OHSS [68,71]. The risk of OHSS increases from 2.2% to 8.6% in women with an AFC <24 or >24 [61].

During COS

Once COS has started, there are a series of parameters that can predict OHSS if ovulation is triggered. It is well documented that a high number of growing follicles is an independent predictor of OHSS [62–64,66–68,72–77]. Specifically, >20 follicles during COS significantly increases the risk of OHSS [75]. In fact, a model has been developed to predict OHSS with 82% sensitivity and 90% specificity: >19 large-/medium-sized follicles before ovulation triggering; >25 follicles at oocyte retrieval; and >24 oocytes retrieved [73].

Serum estradiol concentrations >3500 pg/mL are also associated with OHSS [62–64,66–69,78,79].

After Ovum Pickup

The number of oocytes retrieved is the most direct measure of the ovarian response, although in some cases there are difficulties in obtaining eggs. Retrieval of >15 oocytes significantly increases the chance of OHSS in cycles in which hCG has been used to trigger ovulation [72].

CLINICAL MANIFESTATIONS

The variety of clinical manifestations of OHSS is the consequence of the processes that define the syndrome

(Fig. 1). Enlarged ovaries may themselves produce abdominal discomfort. Increased ovarian vascular permeability leads first to fluid accumulation in the abdomen and other body cavities, which then leads to abdominal heaviness and breathing difficulties due to limited diaphragmatic mobility [80]. Furthermore, this shift in serum from the intravascular to the extravascular space causes haemoconcentration and reduced blood perfusion, resulting in reduced general organ perfusion. Oliguria and renal insufficiency may occur, and liver function may also be affected. Moreover, haemoconcentration increases the risk of thromboembolic events. In very severe forms, renal failure and reduced perfusion in other vital organs, such as the brain and heart, may have fatal consequences [81].

There are two clinical forms of OHSS, both hCG related: the early onset, occurring 3–7 days after hCG administration; and the late onset, occurring 12–17 days after hCG administration, which is related to pregnancy-induced hCG production [82]. The early onset is usually mild to moderate, while late OHSS is more severe as the rising hCG during pregnancy exacerbates the course of the syndrome.

In order to define an increasing degree of severity in the establishment of OHSS, different classifications have been published [83,84] based upon the severity of symptoms, signs, and laboratory findings. OHSS classification is employed for academic reasons, but is also used as a guideline to establish who should receive outpatient management and who should be hospitalized.

A widely employed classification is described in Table 2 [85]. Here, *mild* OHSS is characterized by bilateral ovarian enlargement with multiple follicular and corpus luteum cysts, abdominal distention and discomfort, mild nausea, and less frequently, vomiting and diarrhea. There are no biochemical abnormalities. No special care is necessary, but surveillance of the patient is indicated.

The clinical features of *moderate* OHSS include ultrasonographic evidence of ascites. Ovaries are frequently enlarged up to 12 cm. Abdominal discomfort and gastrointestinal symptoms such as nausea, vomiting, and diarrhea are more frequent and intense than in mild OHSS. A sudden increase in weight of >3 kg (6.6 lb) might be an early sign of moderate OHSS (Table 2). Laboratory features include a hematocrit >41% and white blood cell concentration (WBC) >15,000/mL along with hypoproteinemia.

To consider OHSS as *severe,* clinical evidence of ascites with severe abdominal pain and, in some patients, pleural effusion is pathognomonic. Ascites and pleural effusion may compromise pulmonary function, resulting in hypoxia (Table 2) [86]. Women with severe OHSS can gain as much as 15–20 kg (33–44 lb) over 5–10 days and display progressive leukocytosis. Hypovolemia, oliguria, or anuria, and intractable nausea and/or vomiting are frequently present.

TABLE 2 Clinical Classification of OHSS (Adapted From Ref. [85].)

OHSS Stage	Clinical Features	Laboratorial Features
Mild	Abdominal distention/discomfort Mild nausea/vomiting Diarrhea Enlarged ovaries	No main laboratorial alterations
Moderate	Mild features + ultrasonographic evidence of ascitis	Elevated hematocrit (>41%) Elevated WBC (>15,000) Hypoproteinemia
Severe illness	Mild + moderate features +: Clinical evidence of ascitis Hydrothorax Severe dyspnea Oliguria/anuria Intractable nausea/vomiting Tense ascitis Low blood/central venous pressure Rapid weight gain (>1 kg in 24 h) Syncope Severe abdominal pain Venous thrombosis	Hemoconcentration (Htc > 55%) WBC > 25,000 Creatinine clearance <50 mL/min Creatinine >1.6 mg/dL Hyponatremia (Na^+ < 135 mEq/L) Hypokalemia (K^+ < 5 mEq/L) Elevated liver enzymes
Critical	Anuria/acute renal failure Thromboembolism Arrhythmia Pericardial effusion Massive hydrothorax Arterial thrombosis Adult respiratory distress syndrome Sepsis	Worsening of severe findings

Creatinine levels are >1.6 mg/dL. Reduced liver perfusion results in the depletion of anticlotting factors and transaminases are increased [87]. Other laboratory findings include a hematocrit >55%, WBC count >25,000/mL, hyponatremia, and hyperkalemia [2,88,89]. Hemoconcentration increases the risk for thromboembolism.

In *critical* OHSS, the function of vital organs and systems is seriously compromised. A series of catastrophic events could occur presenting a life-threatening situation. First, OHSS can be complicated with hemoconcentration, with a risk of venous (75%) and arterial (25%) thrombosis that may lead to permanent neurological injury or death [90,91]. High levels of factor V, platelets, fibrinogen, profibrinolysin, fibrinolytic inhibitors, and increased thromboplastin generation are observed in women with OHSS [92]. Moreover, altered liver function can lead to disseminated intravascular coagulation (DIC) and liver failure with hepatic encephalopathy [87].

Thromboembolic complications of OHSS have been reported in the internal jugular, subclavian, axillary, and mesenteric vessels [86,93]. Cerebrovascular thrombosis is typically present as an ischemic infarct. In 40% of cases, these complications are associated with an underlying thrombophilia [94]. It is important to rule out thrombophilia before COS begins in order to consider low-dose heparin prophylactic therapy [95].

Other catastrophic events characteristic of severe OHSS include acute kidney injury with anuria, sepsis and acute respiratory distress syndrome (ARDS), and cerebral edema/acute ischemia/encephalopathy [2,3,84,96–98]. Rarely, OHSS results in death. The precise risk of mortality from OHSS is unknown, but ranges between 0 and 3/100,000 in some reports [3,99,100].

Other potential complications of OHSS include ovarian torsion and hemorrhage from ovarian rupture. Ovarian torsion is the potential consequence of increased ovarian volume. It is characterized by ovarian enlargement, abdominal pain, nausea, vomiting, hypotension, progressive leukocytosis, and anemia. Ovarian torsion may demand surgical correction [101].

DIAGNOSIS

The diagnosis of OHSS is based on clinical features (Table 3) [102]. The symptoms of OHSS are not specific and there are no diagnostic tests for the condition. Although patients may come to the clinic with abdominal distension and discomfort following ovulation triggering, the typical patient appears 2–3 days after oocyte retrieval with abdominal discomfort and gastrointestinal symptoms such as nausea, vomiting, and diarrhea and perhaps reduced urinary output and/or constipation.

Therefore, it is important to get an idea of the severity of the suspected OHSS in the initial interview by asking whether the patient has undergone COS recently, if she has experienced OHSS before, if she has been diagnosed with PCOS, the number of eggs retrieved, if embryo replacement was performed, and the time of presentation following ovulation triggering. This is important because early onset is usually self-limited without many complications, while late onset could be associated with critical events.

A series of exams should be performed at this point (Table 3) to determine the severity of the syndrome (Table 2) and whether the patient should initially be managed as an outpatient, remain hospitalized, or even be admitted to an intensive care unit (ICU). There is not obvious and rigorous compartmentalization of patients, and the decisions should be made considering signs, symptoms, laboratory and image testing, as well as the special characteristics of the patient, including her sensitivity to pain, her compliance to treatment and difficulty accessing the clinic if her condition worsens.

Since OHSS symptoms are not specific, care must be taken to exclude other serious conditions that may be present in a similar manner but require very different management. The most frequent is peritonism, which is associated with some hemoperitoneum induced by blood loss from punctured ovaries. While OHSS is associated with elevated hematocrit and reduced serum osmolality and sodium, hemoperitoneum is accompanied by low hematocrit. Pyrexia is not typically present in OHSS,

TABLE 3 Relevant History, Symptoms, and Exams to be Taken in a Woman With Suspected OHSS Development (Adapted From Ref. [102], With the Permission of the Royal College of Obstetricians and Gynecologists.)

History
Diagnosis of PCOS
Previous episode of OHSS
Time of onset of symptoms relative to trigger of ovulation
Medication used for trigger ovulation (hCG or GnRH agonist)
Number of follicles developed on final monitoring scan
Number of oocytes retrieved
Embryo replacement performed?
Symptoms
Abdominal bloating
Abdominal discomfort/pain, need for analgesia
Nausea and vomiting
Breathlessness, inability to lie flat or talk in full sentences
Reduced urine output
Leg swelling
Vulvar swelling
Associated comorbidities such as thrombosis
Examination
General: assess for dehydration, edema (pedal, vulvar, and sacral); record heart rate, respiratory rate, assess for pleural effusion, blood pressure, body weight
Abdominal: assess for ascites, palpable mass, peritonism; measure girth
Laboratory and imaging tests
Full blood count
Hematocrit
C-reactive protein
Urea and electrolytes (Na, K)
Serum osmolality
Liver function tests
Coagulation profile
D-dimers
hCG (if embryo replacement)
Ultrasound scan: ovarian size, pelvic, and abdominal free fluid
Chest X-ray
Other tests that may be indicated (in critical OHSS)
Arterial blood gases
Electrocardiogram (ECG)/echocardiogram
Computerized tomography pulmonary angiogram (CTPA) or ventilation/perfusion (V/Q) scan

and therefore pelvic infections, including appendicitis or bowel perforation after blind transvaginal oocyte retrieval, must be ruled out in the case of elevated temperature. Ovarian torsion is associated with progressive leukocytosis and anemia, and should also be considered a potential differential diagnosis. If the pregnancy test is positive, a rare complication could be an ectopic pregnancy from the preceding cycle, which should also be kept in mind.

PREVENTION

Before COS Begins

Planning COS in patients at risk is the most important step in the prevention of OHSS [103]. The characteristics defined in Table 1, which identify women at high risk of developing OHSS, should be carefully considered in order to avoid further complications.

Selecting the Stimulation Protocol

There are different reasons to recommend stimulation protocols utilizing GnRH antagonists for ovulation suppression, namely similar pregnancy rates to protocols employing long-GnRH agonist suppression, lower costs, and lower risk of developing OHSS. This appears to act at two levels: lower serum levels of estradiol during ovarian stimulation, and the possibility of triggering ovulation with a GnRH agonist by taking advantage of the flare-up mechanism [104,105].

In fact, a main issue for the generalized use of pituitary suppression with an antagonist was lower pregnancy rates, which is probably associated with the lack of experience with GnRH antagonists. Today, there are reassuring data from 29 randomized clinical trials (RCTs) showing that GnRH antagonist protocols display similar pregnancy rates as long-agonist protocols. Moreover, they employ a smaller amount of gonadotropins, which reduces the costs of the cycle, and are also associated with less incidence of OHSS [106].

The use of a GnRH antagonist protocol, per se, reduces the risk of OHSS compared with protocols that use a GnRH agonist, most likely due to a reduction in circulating estradiol levels seen with GnRH antagonist suppression. Large randomized studies using long-agonists versus antagonists protocols in ART triggering ovulation with hCG have shown a significantly reduced incidence of severe OHSS in the antagonist group (5.1%) compared with the agonist (8.9%) [107]. Furthermore, in women with PCOS, it was observed that suppression with antagonist as opposed to agonist also reduced the incidence of moderate OHSS from 60% to 40% after ovulation triggering with hCG [108].

It is also worth to stress that the dose of gonadotropins to be employed in women at risk should not be higher than 150 IU/day.

Another possible approach is to substitute GnRH antagonists with progestogens in COS with cycle segmentation. No RCT has been established to test the role of these stimulation protocols in preventing OHSS, but they are widely employed and the published experience using 4–10 mg/day medroxyprogesterone acetate simultaneously with gonadotropins shows good-quality oocytes and pregnancy rates without LH surges or OHSS [109,110].

Finally, in vitro maturation (IVM) can also be considered in these patients. When IVM was described, avoidance of OHSS was always mentioned as one of the main advantages [111]. Monitoring PCOS patients after spontaneous or induced menses and administering 10,000 IU hCG when endometrial thickness is >6 mm has been associated with high yields of oocytes (>15), as well as acceptable implantation and pregnancy rates (30% and 50%, respectively) without OHSS development [112]. IVM remains unpopular, however, because results have not been replicated in many centers.

Adjuvant Therapies

ASPIRIN

Increased VEGF levels in women at risk of developing OHSS results in platelet activation and release of histamine, serotonin, platelet-derived growth factor, and/or lysophosphatidic acid, which can further potentiate the physiologic cascade of OHSS. Based on this theory, aspirin has been considered a possible therapy in OHSS [113].

In one set of randomized studies, the incidence of severe OHSS was reduced (1.7% vs 6.5%) in patients who received a daily dose of 100 mg aspirin plus prednisolone in varying doses (10–30 mg) from the first day of stimulation until the day of the pregnancy test [114]. In another study including women at high risk of OHSS, 100 mg aspirin/day were administered from the first day of the cycle (during COS) until the next menses in the case of a negative ART outcome or the ultrasonographic detection of embryonic cardiac activity. Aspirin significantly reduced the incidence of OHSS from 8.4% to 0.25% compared with no treatment [113].

METFORMIN

Metformin may improve intraovarian hyperandrogenism, and it can affect the ovarian response by reducing the number of nonperiovulatory follicles, thereby reducing estradiol secretion. By employing 500 mg three times daily or 850 mg twice daily during COS in PCOS patients, the incidence of OHSS was significantly reduced from 20.4% to 3.8% [115]. A meta-analysis including 12 studies showed that OHSS risk was significantly lower

with metformin use (relative risk (RR) 0.44, 95% CI: 0.26–0.77), while maintaining the same ART outcomes as controls without metformin [116]. Apparently, metformin works better in obese than in nonobese patients [117].

During COS

Coasting

Coasting consists of withholding the administration of gonadotropins at the end of COS for up to 4 days to decrease the risk of OHSS. Although extensively employed in the past, several studies have shown that coasting does not decrease the risk of OHSS, but is associated with fewer oocytes retrieved [118], and prolonged coasting might even hurt oocytes quality and reduce implantation [119].

Ovulation Triggering With a GnRH Agonist

hCG has been widely employed to mimic the mid-cycle surge of LH to trigger final oocyte maturation and ovulation for more than 60 years. hCG has a longer half-life than LH and it is known to initiate the cascade of events leading to OHSS. hCG stimulates VEGF release in granulosa-lutein cells that bind to VGEF-R2, which increases vascular permeability in the ovaries [11,32].

Administration of a GnRH agonist is associated with an initial "flare-up" effect in which both serum LH and FSH are increased [104]. It has been shown that a so-called GnRH agonist-induced surge of gonadotropins can last for 24–36 h and induce oocyte maturation [104,105]. Since then, multiple studies have assessed the development of OHSS in women who receive GnRH agonist trigger compared with hCG trigger for final oocyte maturation, resulting in a significant reduction in the development of OHSS. An analysis of 17 RCTs that assessed GnRH agonist compared with hCG trigger found that the agonist resulted in a lower incidence of OHSS in fresh autologous cycles (OR 0.15, 95% CI: 0.05–0.47), as well as in donor-recipient cycles (OR 0.05, 95% CI: 0.01–0.28) [120] compared with hCG.

These studies also reported, however, that agonist trigger was associated with a lower live-birth rate (OR 0.47, 95% CI: 0.31–0.70) in fresh autologous cycles due to a luteal phase insufficiency [120]. That said, several strategies have been implemented to overcome this problem when embryo replacement is performed in the same cycle. An alternative consists of inducing corpus luteum function with low-dose (1500 IU) hCG. When used in women at risk of OHSS, a single 1500 IU hCG injection administered the day of oocyte retrieval is associated with no OHSS and sustainable pregnancy rates [121]. If the patient is not at risk, a second 1500 IU hCG injection can be administered 5 days later. However, some cases of late-onset OHSS have been described, highlighting the fact that embryo transfer is a major driver of OHSS regardless of the number of follicles developed [121]. Therefore, the "freeze-all" policy should always be considered as a viable option in these cases.

It is advisable to measure serum LH on the day of triggering, as the chance of having a suboptimal response to GnRH agonist triggering 12 h after administration (LH < 15 UI/mL) is as high as 25% if serum LH is undetectable, compared with 5% in the general population [122]. The suboptimal response is particularly evident in women with anovulatory irregular cycles and when taking oral contraceptives for a long period of time.

Another option for overcoming a potential luteal phase defect is supplementing the luteal phase with both estrogens and progesterone according to the standard steroid replacement protocols. We usually employ 6 mg/day oral estradiol valerate and 800 mg/day vaginal micronized progesterone as in the oocyte donation cycles [123]. Using this luteal phase support, pregnancy rates are similar regardless of the triggering done with hCG or GnRH agonists [124].

Lowering or Withholding hCG

Another alternative that has been tried in women with high risk of OHSS is to reduce the dose of hCG used to trigger ovulation, which has traditionally been 5000–10,000 IU of urinary hCG, and more recently 2500 IU recombinant hCG. Different studies have compared 5000 IU vs 10,000 IU, as well as 4000 IU vs 6000 IU, without any beneficial effect on the incidence of OHSS [125,126]. The only way to prevent OHSS if ovulation triggering must be performed with hCG (e.g., in long-GnRH agonist cycles) is to withhold hCG administration and avoid sexual intercourse. This decision is sometimes difficult as patients have already invested substantial time, money, and energy in the process, but many times it is worth canceling the cycle to avoid putting the patient at high risk.

Kisspeptin (Kp)

Kisspeptins are a group of hypothalamic peptides that are essential for normal human fertility [127]. Within the hypothalamus, Kp is released from kisspeptin-neurokinin B-dynorphin (KNDy) which directly projects to GnRH neurons, subsequently activating the secretion of LH and FSH [128,129]. Peripheral injection of Kp has been shown to potently stimulate gonadotropin secretion in humans through a GnRH-dependent mechanism [130–132].

Initial proof-of-concept studies have shown that Kp-54 administration has an effect on egg maturation in women undergoing in vitro fertilization (IVF). Following superovulation with recombinant FSH, women were administered a single subcutaneous injection of different doses of Kp-54 to induce an LH surge and egg maturation. Oocyte maturation was observed in response to each tested dose

of Kp-54, and the mean number of mature eggs per patient generally increased in a dose-dependent manner [133]. In a subsequent study, the authors challenged the concept that Kp-54 would effectively trigger oocyte maturation and also have a low risk of inducing OHSS [134]. Following a standard recombinant FSH/GnRH antagonist protocol, patients were randomly assigned to receive a single injection of Kp-54 to trigger oocyte maturation using different doses. Women were routinely screened for the development of OHSS. Oocyte maturation occurred in 95% of women, with the highest oocyte yield following 12.8 nmol/kg Kp-54. No woman developed moderate, severe, or critical OHSS [134]. Kisspeptin is not yet commercially available.

After Egg Retrieval

Oocyte/Embryo Cryopreservation

One of the main advances that has changed clinical practice in ART has been the substantial and reproducible improvement in oocyte and embryo vitrification in terms of survival and overall health of newborn infants [135]. As a result, many cycles are associated with freezing all available oocytes or embryos. The policy is referred to as a "freeze-all policy" or "cycle segmentation."

The best OHSS preventive measure is oocyte/embryo cryopreservation, although there is not much literature on this method [136,137]. The reason is clear: avoiding pregnancy is the best way to avoid late-onset OHSS, the most dangerous form of the syndrome. Oocytes might be frozen or, alternatively, some can be fertilized and cryopreserved as embryos. Cryopreservation has also been shown to be more effective than coasting in early-onset OHSS prevention [138].

Thus, a widely employed strategy in women at risk of OHSS is to use a combination of GnRH agonist triggering and cryopreservation of oocytes (the so-called freeze-all strategy). But even in the absence of embryo replacement, some cases of OHSS have been described in high-risk populations [139–141]. Therefore, it might be worth exploring other initiatives during the luteal phase in order to prevent OHSS in the absence of embryo replacement.

Dopamine Agonists

As previously described, an increased vascular permeability of the ovarian capillaries caused by ovarian hypersecretion of VEGF and increased VEGFR-2 expression is the main pathophysiology of OHSS [11,32,41]. We introduced the concept of targeting VEGF by administering dopamine agonists in the murine model [41]. Our first study in humans employed cabergoline 0.5 mg/day from the day of hCG for 8 days. The study was performed in oocyte donors and showed a significant reduction of moderate OHSS in the dopamine agonist group compared with controls [42]. A subsequent study included women undergoing a full IVF treatment including embryo replacement [43]. In this study, women were treated with different doses of the dopamine agonist quinagolide (0, 50, 100, or 200 mg/day until the day of pregnancy test). Quinagolide reduced ascites formation and moderate-severe OHSS in women who did not get pregnant, but it was ineffective in women who became pregnant. This may be either because the amount of trophoblast-derived hCG was too elevated to be compensated by the doses of quinagolide administered, or because pregnancy stimulates other pathways that also affect vascular permeability irrespective of VEGF blockage by a dopamine agonist. Subsequent analysis of the literature confirmed that administration of dopamine agonists reduced the incidence of OHSS compared with no treatment (RR 0.38, CI: 0.29–0.51) without affecting pregnancy rates (RR 1.02, 95% CI: 0.78–1.34) [142]. It was also more effective in early-onset than late-onset prevention, showing the difficulty of targeting pregnant women with this therapy [143].

Whether a more aggressive intravenous administration of dopamine in women developing severe/critical OHSS will work has not been studied, but there are some reports in which this strategy has successfully rescued renal output in compromised cases [144,145].

Albumin

The rationale for the use of albumin in women at risk of OHSS is its ability to increase plasma oncotic pressure and counteract the permeability effect of angiotensin II. Moreover, albumin may also bind to vasoactive substances such as VEGF. However, the data evaluating the efficacy of albumin in the prevention of OHSS are contradictory.

Initial early RCTs demonstrated that 20% human albumin administered at oocyte retrieval decreased the incidence of moderate-to-severe OHSS compared with no treatment [146]. In an RCT involving almost 500 patients per arm, patients received either 40 g of 20% human albumin intravenously just after pick up for 30 min, or no treatment [147]. The incidence of moderate (7.1% vs 6.7%) and severe OHSS (5.0% vs 4.7%) was similar between treatment and nontreatment groups, as well as the patients that needed culdocentesis. There was also no difference in blood parameters and hypercoagulability state. It was concluded that albumin was not useful for preventing hCG-induced OHSS when administered after oocyte retrieval [147]. Subsequent systematic reviews also concluded that albumin does not prevent OHSS [148,149].

Moreover, other studies have compared the use of human albumin to other methods of reducing OHSS risk such as hydroxyethyl starch solution (HES), coasting, or placebo and found that human albumin does not offer a

significant benefit [150,151]. It is also worth noting that albumin is a blood-derived product, and can lead to allergic and anaphylactic reactions, and potentially to the transmission of viral or unidentified diseases.

Calcium

The rationale for calcium (Ca) administration has been to inhibit cAMP-stimulated renin secretion, which decreases angiotensin II synthesis and in turn might impair VEGF production. Thus, intravenous Ca infusion (10 mL of 10% Ca gluconate in 200 mL normal saline) on the day of oocyte retrieval and on days 1, 2, and 3 after oocyte retrieval, has been tested in an RCT of women at risk for OHSS. Results showed a significant reduction in the incidence of moderate and severe OHSS compared with saline (23% vs 7%) [152]. Ca seems to be as effective as dopamine agonists [153].

Letrozole

Letrozole is a potent aromatase inhibitor that also effectively lowers serum estradiol levels in the luteal phase [154]. Thus, there is a strong rationale for employing letrozole as a luteolytic agent, and in fact a pilot study successfully employed letrozole to prevent OHSS [155]. An RCT has compared the use of letrozole (5 mg/day for 5 days starting the day of oocyte retrieval) with aspirin (100 mg/day for 5 days after pickup) in women at high risk of developing OHSS who received hCG to trigger ovulation and all the embryos were frozen. The incidence of ascites formation and overall moderate early-onset OHSS was reduced in the letrozole group compared with the aspirin-treated group 7 days after hCG (19.6% vs 35.3%, respectively), and the luteal phase was shortened by almost 3 days [156]. The study intended to show that letrozole might decrease serum VEGF levels as had been described [157], but in fact women treated with letrozole had higher serum VEGF levels than those treated with aspirin. It was inferred that letrozole might have luteolytic actions through different unknown mechanisms, which may be related to its androgenic effects on granulosa cells [156].

GnRH Analogs in the Luteal Phase

GnRH analogs can be employed in two different directions during the luteal phase. One approach to induce luteolysis in women in whom a freeze-all policy has been applied is to continue GnRH antagonist administration during the luteal phase. In one report, 2 days of GnRH agonist administration plus dopamine agonists for 7 days prevented OHSS in a short series of patients [158]. Although no RCTs have been published, the potent luteolytic action of GnRH antagonists suggests that it may help to prevent OHSS after a freeze-all strategy.

A different strategy is to perform embryo replacement in cycles at high risk of OHSS in which triggering has been induced with an agonist. The luteal phase has been supported in a study including 46 patients with 200 mcgs for 2/day during the luteal phase until the day of the pregnancy test, where it was discontinued regardless of the results. No OHSS was observed, while the pregnancy rate was 52% [159].

Combination of Treatments

Based on the information reported above, different steps should be considered to prevent OHSS. The first step is to always perform COS with GnRH antagonists protocols, unless the patient systematically develops an asynchronic follicular growth that cannot be managed with steroids or oral contraceptives [160,161]. This is especially important in women with elevated serum AMH, a high AFC, or for those who have experienced OHSS in previous cycles.

GnRH antagonists protocols are associated with similar outcomes as GnRH agonists protocols [106], less gonadotropin consumption, and lower OHSS incidence, even if hCG is employed to trigger maturation [107]. In the course of COS, the clinician will determine the number of follicles developed and serum estradiol levels to move to step 2. Special attention should be paid to those individuals producing >19 follicles or serum estradiol >3500 pMol/L, but to be on the safe side we would recommend continuing to step 2 when >14 follicles have developed and serum estradiol >2500 pMol/L.

In those patients, step 2 will consist of administering a GnRH antagonist to trigger ovulation and counting the number of oocytes retrieved. If >15 oocytes are obtained, step 3 will consist of freezing all the oocytes/embryos and perhaps the administration of either dopamine agonists, letrozole, GnRH antagonist, or a combination of those during the luteal phase, depending of the number of oocytes finally displayed and the signs and symptoms of OHSS.

If the number of eggs collected is <15, we can carefully consider embryo replacement in step 3. In this case, single blastocyst transfer is preferred because it allows more time to reevaluate the patient in the first few days without risking twin pregnancies. To support the luteal phase, 1500 IU the day of oocyte retrieval and an additional 1500 IU 5 days later will sustain the corpus luteum. As mentioned, none of the measures will ever be 100% effective, and therefore patient counseling and surveillance is always of paramount importance.

MANAGEMENT

When managing OHSS, the first thing to consider is that it is a self-limited disease, although symptoms may be prolonged if pregnancy has occurred. The management of OHSS is described in Fig. 3 and should be

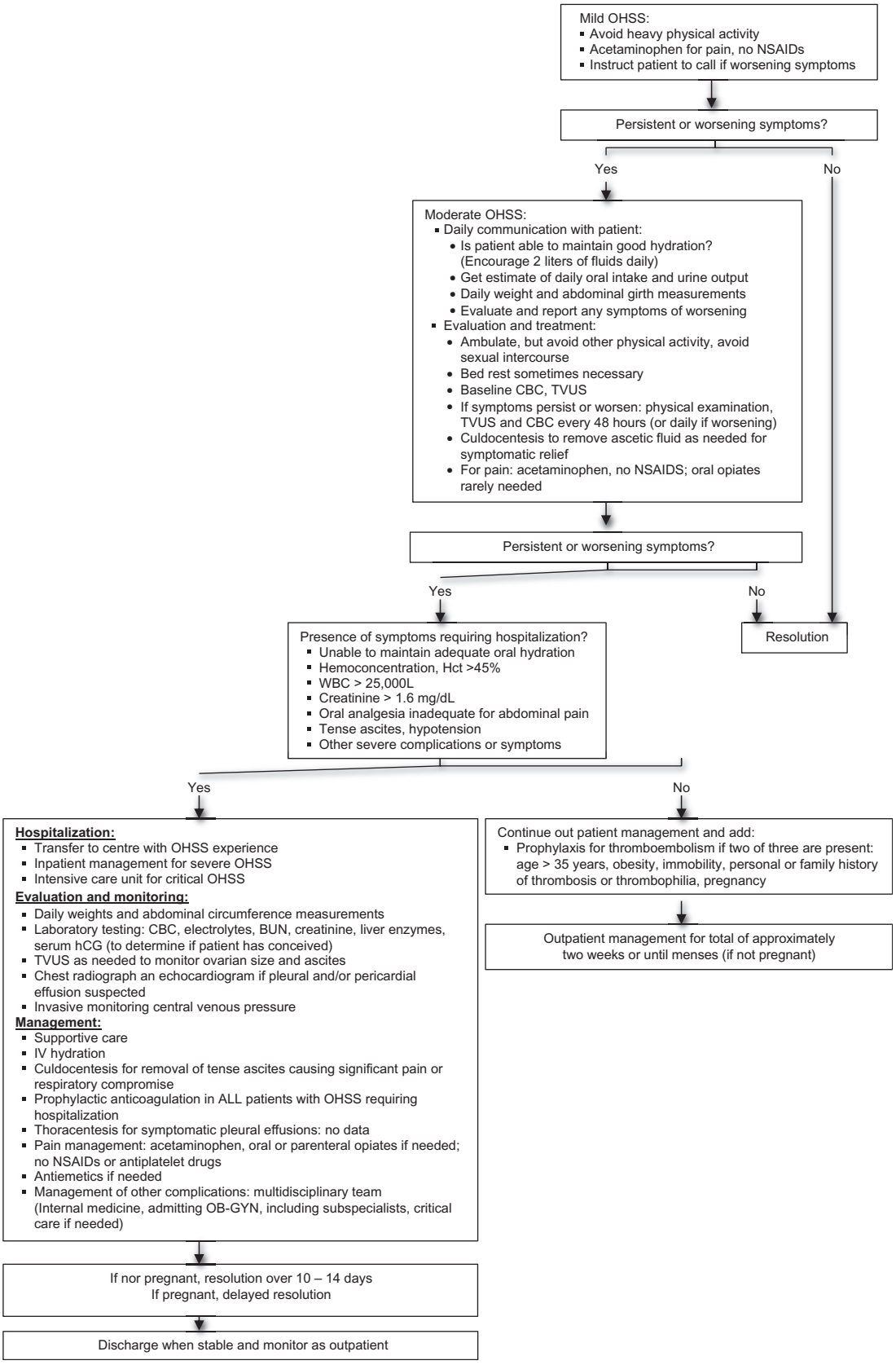

FIG. 3 Management of OHSS. (Reproduced with permission from Ref. [162], http://www.uptodate.com.)

considered conservative and directed to treat symptoms. Most people can be managed as outpatients, but some women with severe or critical OHSS will require hospitalization, possibly in the ICU [162].

Mild OHSS

Most OHSS cases are mild or moderate and can be managed on an outpatient basis with the goal of relieving symptoms because they are self-limited. For mild OHSS, analgesics and avoidance of heavy physical activity are usually enough. Nonsteroidal antiinflammatory drugs are contraindicated because they can compromise renal function, and therefore acetaminophen is usually administered. Patients should be instructed to call if any signs or symptoms become worse, especially with oliguria, abdominal distention, shortness of breath, or weight gain (>1 kg/day) because progression to moderate or severe forms can be expected in case of pregnancy (Fig. 3) [162].

Moderate OHSS

For women with moderate OHSS, recommendations include oral fluid intake of 1–2 L/day (Fig. 3) [162]. Diuretics are contraindicated because they can further decrease intravascular volume. It is important to instruct patients to perform daily recordings of weight, abdominal circumference, and urinary output. Regarding physical activity, they can ambulate but bed rest is sometimes necessary. Avoid other physical activity and especially sexual intercourse.

Patients should be monitored in the clinic every 48–72 h, although any worsening should be reported and the patient should go to the clinic, as this often occurs when women become pregnant. These visits should control vital signs and perform a physical examination, an ultrasound to evaluate ascites, and laboratory testing of complete blood count, electrolytes, creatinine, serum albumin, and liver enzymes. In addition, three important measures should be considered.

The first relates to reducing the volume of liquid accumulated in the abdomen. Although transabdominal paracentesis is reported to be successful [163], most centers use transvaginal aspiration of the ascitic fluid from the cul-de-sac using ultrasound to provide symptomatic relief. Even on an outpatient basis, culdocentesis is often performed in women with tense ascites, orthopnea, rapid increase of abdominal fluid, or any other sign that may indicate worsening [162]. Antibiotic coverage should also be used to avoid infections.

The volume of fluid to be removed is a matter of controversy. In general, after aspiration of 500 mL of fluid, patients report resolution of abdominal discomfort. Aspiration of 2000 mL of ascites results in intraabdominal pressure reduction and renal artery resistance, followed by an increase in urine output [164]. Aspiration of >4 L of fluid at once is not recommended. It has been reported than >90% of patients will benefit from culdocentesis, and that a mean of 3.4 procedures are necessary until the syndrome is resolved [60,72].

The second aspect to be consider is replacement of at least part of the fluid removed. Culdocentesis must be always accompanied by intravenous hydration with isotonic crystalloid solutions (e.g., normal saline, Ringer's lactate).

The third important measure is thromboembolism prophylaxis. It should be considered in hospitalized patients and for women with OHSS being managed as outpatients with two of the following risk factors: age >35 years, obesity, immobility, personal or family history of thrombosis, thrombophilias, and pregnancy.

We employ prophylactic low molecular weight heparin 20 mg subcutaneously every 12 h, or heparin 5000 units subcutaneously every 12 h [165].

Severe and Critical OHSS

Hospitalization is mandatory in women with severe OHSS and any of the following criteria: a hematocrit >55%, leukocytes >25,000/L, and creatinine >1.6 mg/dL. Also, women with severe abdominal pain, intractable vomiting, severe oliguria/anuria, tense ascites, dyspnea or tachypnea, hypotension, dizziness or syncope, severe electrolyte imbalance, or abnormal liver function tests must also be hospitalized (Fig. 3) [162].

Management of severe and critical OHSS is complicated, and therefore patients should be hospitalized in units with experience treating this condition. Alternatively, in the benefit of the patient or because of the severity of the syndrome, direct hospitalization in an ICU is strongly advised.

Treatment will consist of supportive care, monitoring, and prevention and treatment of complications. The first goal is to maintain intravascular blood volume. Although isotonic crystalloids are typically used, some clinicians employ intravenous albumin due to its osmotic properties in order to shift the direction of fluid from the extravascular to the intravascular space. It has been shown, however, that intravenous albumin provides no additional benefit when compared with crystalloid solutions. The only indication for using albumin is when there is concomitant oligoanuria. In this case, it is advised to administer intravenous albumin (25% in 250 mL) and subsequently furosemide (20 mg) in order to augment urine output. Also, intravenous dopamine (2–3 μg/kg/min) can be employed to force urinary output and repeated every 8 h, but these measures are performed by the ICU staff [144,145].

Critical OHSS cases should be managed in an ICU because they can be complicated with massive

hydrothorax, pericardial effusion, arterial thrombosis, pulmonary embolism, sepsis, acute renal failure, ARDS, and DIC, all of which need to be managed by specialized staff [165]. Oophorectomy is never an option in life-threatening conditions, but pregnancy interruption might be necessary in uncontrolled cases after unsuccessful application of available therapeutic approaches.

As already mentioned, OHSS is self-limited and increased ovarian vascular permeability regresses spontaneously in 10–14 days. The fluid in the third space slowly reenters the intravascular space, hemoconcentration reverses, and natural diuresis ensues. As a result, hematocrit is normalized, ultrasound shows no signs of ascites, and in general clinical symptoms alleviate.

If pregnancy occurs, resolution may take longer [166]. Some studies suggest that pregnancies complicated with OHSS have a higher rate of miscarriage, gestational diabetes, and pregnancy-associated hypertension [167,168], but these complications have not been confirmed in other studies [169].

CONCLUSIONS

OHSS is a complication of infertility treatments that is totally avoidable today. The syndrome consists of a series of signs and symptoms which are the consequence of increased ovarian capillary permeability after hCG administration. Pain and discomfort due to enlarged ovaries, ascites, hypercoagulability, and reduced renal function are common findings. OHSS is usually mild, but can be complicated seriously and become a life-threatening condition, especially in women who become pregnant.

Some phenotypic characteristics, such as race, PCOS, and biomarkers of ovarian reserve (AFC and AMH levels) predict the risk of developing OHSS in infertile patients. Special protocols for ovarian stimulation using low-dose gonadotropins, GnRH antagonists to prevent endogenous LH surges, and GnRH agonists to trigger ovulation, should be employed to minimize risk. Moreover, cryopreservation of oocytes/embryos and deferring pregnancy for a subsequent cycle is a very important step in the prevention of OHSS.

When OHSS develops, treatment consists of the management of symptoms and monitoring of vital signs, including culdocentesis of ascitic fluid, intravenous liquid replacement, antithrombotic measures, and pain reduction. These patients should be managed in specialized units to ensure the best possible outcomes.

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