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REVIEW ARTICLE

# Ovarian Hyperstimulation Syndrome: contemporary approach to pathophysiology, risk stratification, prevention and management

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## Summary

Ovarian Hyperstimulation Syndrome (OHSS) is a potentially serious iatrogenic complication of controlled ovarian stimulation in assisted reproductive technology procedures (ART). Despite substantial progress in stimulation protocols and preventive strategies, OHSS remains an important clinical and safety concern in contemporary IVF practice. The purpose of this narrative review is to summarize and critically analyze current knowledge regarding the pathophysiology, risk factors, clinical presentation, prevention, and management of OHSS. Relevant literature was identified through searches of the PubMed/MEDLINE, Scopus, and Web of Science databases, including clinical studies, cohort analyses, systematic reviews, and professional society guidelines published between 2019 and 2026, with selective inclusion of earlier landmark studies essential for understanding the basic mechanisms of the syndrome. Current evidence indicates that the key pathophysiological mechanism of OHSS is increased vascular permeability mediated by vascular endothelial growth factor (VEGF), most commonly triggered by exposure to human chorionic gonadotropin. Identification of high-risk patients using ovarian reserve biomarkers, individualized gonadotropin dosing, the use of gonadotropin-releasing hormone (GnRH) antagonist protocols and GnRH agonist trigger, as well as freeze-all embryo strategies, have substantially reduced the incidence of moderate and severe forms of the syndrome. Contemporary management of OHSS is therefore primarily based on prevention and individualized stimulation strategies aimed at optimizing reproductive outcomes while ensuring maximal patient safety.

**Keywords:** ovarian hyperstimulation syndrome, controlled ovarian stimulation, IVF, prevention, VEGF, GnRH agonist trigger

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## INTRODUCTION

Ovarian hyperstimulation syndrome (OHSS) represents a potentially iatrogenic complication of controlled ovarian stimulation (COS), most commonly occurring within assisted reproductive technology (ART) procedures (1). This syndrome develops as a consequence of an excessive ovarian response to exogenous stimulation with gonadotropins, particularly following the administration of human chorionic gonadotropin (hCG) for final oocyte maturation. Although most cases are mild and self-limiting, moderate and severe forms may be associated with ascites, hemoconcentration, thromboembolic complications, respiratory distress, acute kidney injury, and hemodynamic instability (2,3). Owing to contemporary ART protocols, severe OHSS has become considerably less frequent. However, it remains an important clinical and safety concern in modern IVF practice (1,3). Its clinical relevance lies not only in the potential for rapid progression to severe and life-threatening forms, but also in the need for timely recognition, accurate severity assessment, and appropriate management in everyday reproductive practice. The contemporary approach to OHSS increasingly shifts the focus from treatment to prevention, to minimize moderate and severe forms and advance the concept of "OHSS-free" clinics (2,4). Current recommendations of the European Society of Human Reproduction and Embryology (ESHRE) emphasize that prevention of moderate and severe OHSS is an essential component of individualized COS protocols and a key outcome of ART treatment, alongside reproductive success (1,2). Despite significant advances in understanding its pathophysiology and in the development of preventive strategies, OHSS continues to occur, particularly in patients with a pronounced ovarian response and/or insufficiently precise risk assessment before the initiation of stimulation (5).

This narrative review aims to provide a critical analysis of current knowledge on OHSS, with particular emphasis on pathophysiological mechanisms, risk stratification, clinical presentation, and current preventive strategies in accordance with the latest ESHRE recommendations and the principles of contemporary IVF practice.

## MATERIAL AND METHODS

We present a narrative review of the contemporary literature on ovarian hyperstimulation syndrome (OHSS). The literature search was conducted in the PubMed/MEDLINE, Scopus, and Web of Science databases, using a structured but non-systematic approach tailored to the heterogeneity of available data on OHSS. The following keywords and their combinations were used: "ovarian hyperstimulation syndrome", "OHSS", "controlled ovarian stimulation", "IVF complications", "risk factors", "prevention", "GnRH agonist trigger", "freeze-all strategy", "dopamine agonists", "cabergoline", "assisted reproductive technologies".

The search included studies published between January 1, 2019, and February 1, 2026, in English and conducted with human subjects. Older studies were included selectively, exclusively when they were of fundamental importance for understanding the pathophysiology, classification, and basic concepts of OHSS.

### Inclusion criteria and study selection

Studies were included in the analysis if they met one or more of the following criteria: studies analyzing the pathophysiology of OHSS and mechanisms of vascular permeability; studies evaluating risk factors for the development of OHSS; studies addressing contemporary prevention and treatment strategies; recommendations issued by relevant professional societies (ESHRE, American Society for Reproductive Medicine (ASRM), and others); clinical studies; cohort studies; and relevant review articles. Titles and abstracts identified through the initial search were screened for relevance to the predefined thematic domains of this review. The authors then assessed full texts of potentially eligible studies, and final inclusion was based on their relevance to the clinical and pathophysiological understanding of OHSS and its contemporary prevention and management.

The following were excluded from the analysis: individual case reports without additional clinical or conceptual value; studies addressing only other complications of IVF procedures; studies without full-text availability; and studies not published in English.

A total of 479 records were identified through the initial search. After screening titles and abstracts, removing duplicates, and assessing relevance, 64 studies were included in the final narrative synthesis. The study selection process is presented in a PRISMA-like diagram **(Figure 1)**.

### Data extraction and synthesis

Data from the included studies were analyzed qualitatively and thematically. The analysis focused on the following domains: pathophysiological mechanisms underlying OHSS; identification of risk factors; clinical classification and diagnostic criteria; contemporary prevention strategies; therapeutic approaches; and clinical outcomes. Given the significant heterogeneity among studies, including differences in study design, populations, stimulation protocols, and outcomes, a quantitative meta-analysis was not performed.

A narrative approach was selected as the most appropriate methodological framework for integrating the available evidence, identifying clinically relevant patterns, and contextualizing contemporary recommendations in the field of OHSS.

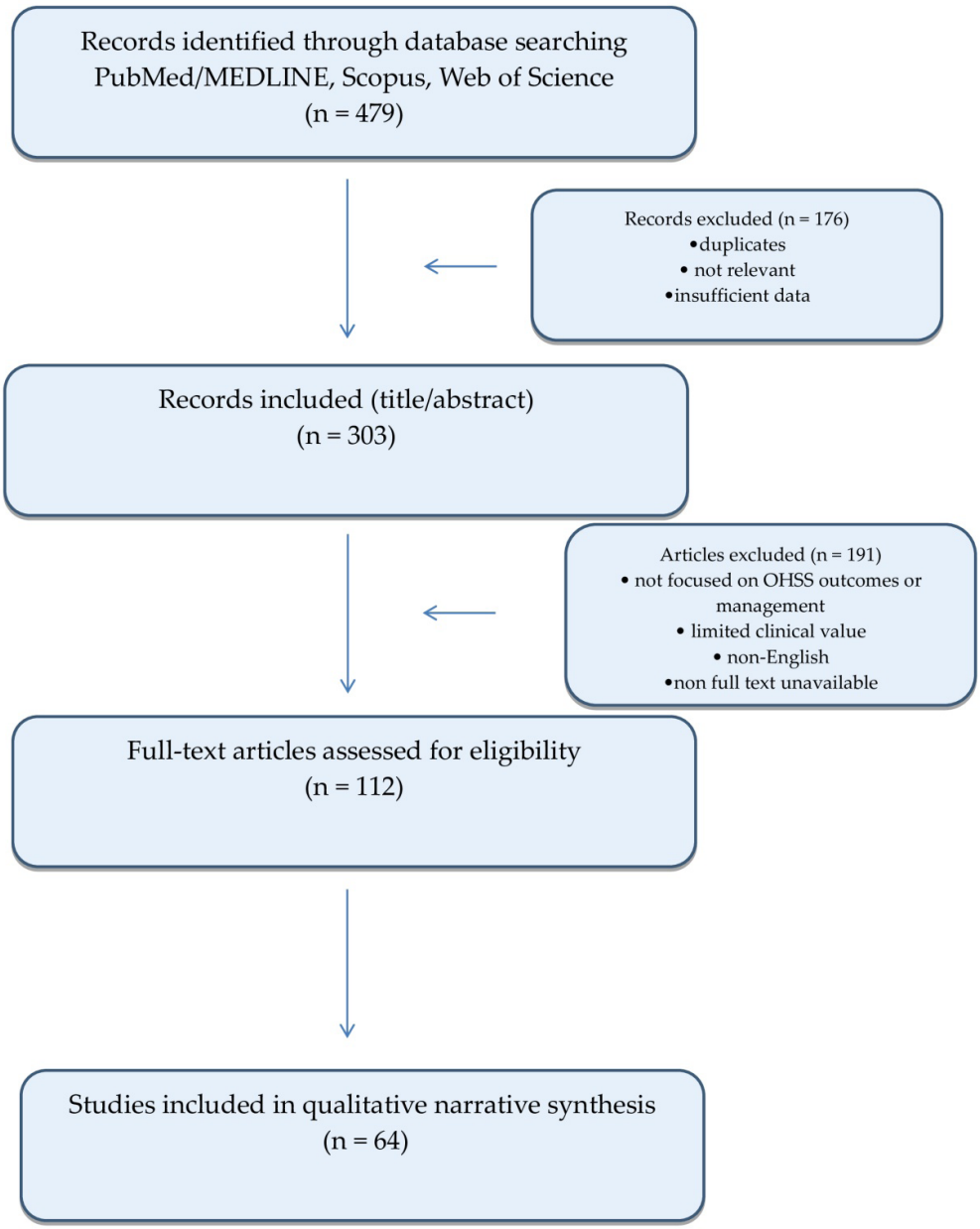


**Figure 1.** Prisma-like diagram

## Assessment and verification of included studies

The review and assessment of relevant studies were conducted independently by two authors. Potential disagreements in interpretation, methodological ambiguities, or possible data overlap were resolved through joint discussion and author consensus.

Due to the pronounced heterogeneity of the available studies, varying outcome definitions, variability in stimulation protocols, and the lack of homogeneous comparative studies, conducting a systematic review with quantitative synthesis would not have allowed for reliable conclusions. Therefore, a narrative review represents the most appropriate methodological framework for integrating contemporary evidence and recommendations from relevant professional societies. At the same time, this constitutes the principal limitation of our study **(Figure 1)**.

## CONTROLLED OVARIAN STIMULATION AND OVARIAN RESPONSE

COS is the cornerstone of ART procedures and involves the administration of exogenous gonadotropins to achieve the simultaneous development of multiple follicles and the retrieval of mature oocytes (6). The choice of stimulation protocol and the starting dose is crucial not only for procedural success but also for patient safety. In clinical practice, follicle-stimulating hormone (FSH) preparations are most commonly used, including both urinary and recombinant forms. At the same time, in certain protocols, FSH is combined with luteinizing hormone LH or hCG preparations (6,7). Supraphysiological concentrations of FSH enable the development of a greater number of antral follicles compared to the natural cycle, which constitutes a fundamental prerequisite for a

successful IVF cycle. However, this simultaneously increases the risk of an exaggerated ovarian response. The ovarian response to stimulation may be classified as poor, optimal, or exaggerated (6,8). An optimal response is considered to be the retrieval of approximately 10-15 oocytes. A poor response is defined as the retrieval of up to four oocytes. A suboptimal response includes 4 to 9 oocytes, whereas an exaggerated response is characterized by the development of a large number of follicles and/or the retrieval of ≥18 oocytes (6,7,8).

According to the ESHRE definition, an exaggerated response is defined as ≥18 follicles measuring ≥11 mm in diameter on the day of trigger administration or ≥18 oocytes retrieved during conventional stimulation (150–225 IU FSH). Patients with an exaggerated response ("high responders") are at a significantly increased risk of developing OHSS (8,9). At the same time, available data indicate that the highest live birth rate per fresh transfer is achieved within the range of 12–18 retrieved oocytes. In contrast, the cumulative live birth rate may increase further with a greater number of retrieved oocytes (6,10). This balance between efficacy and safety poses a clinical challenge in contemporary IVF practice and underscores the importance of precisely tailoring the stimulation protocol (7,9,10).

## CONTROL OF PREMATURE LH SURGE AND INDUCTION OF FINAL OOCYTE MATURATION

In the physiological menstrual cycle, rising estradiol concentrations, via positive feedback, trigger the preovulatory LH surge, which enables final oocyte maturation and ovulation. During COS, the simultaneous growth of multiple follicles results in significantly higher estradiol concentrations than in the natural cycle, which may lead to a premature and undesired LH surge, premature luteinization, and oocyte loss (11,12). Prevention of such events represents a key prerequisite for the successful implementation of assisted reproductive procedures and optimal timing of oocyte retrieval. To suppress endogenous gonadotropin secretion and control the timing of ovulation in IVF procedures, gonadotropin-releasing hormone (GnRH) analogs, including agonists and antagonists, are used (11-13). Following an initial stimulatory "flare-up" effect, GnRH agonists induce reversible desensitization and suppression of pituitary gonadotropin secretion.

In contrast, GnRH antagonists, through competitive receptor binding, rapidly and predictably inhibit LH secretion without an initial stimulatory effect (12). This pharmacological control of the gonadotropic axis allows precise regulation of folliculogenesis and constitutes the foundation of contemporary stimulation protocols (11,13). For the induction of final oocyte maturation, hCG has traditionally been used, as it stimulates final oocyte maturation and luteinization of granulosa cells via the LH/hCG receptor (14). However, the prolonged luteotropic effect of hCG and its potent stimulation of luteinized granulosa cells represent the central pathophysiological mechanism in the development of OHSS. Therefore, the choice of method for final oocyte maturation plays a crucial role in assessing and modifying the risk of OHSS (14). The contemporary approach increasingly involves the use of a GnRH agonist to induce an endogenous LH surge in patients at increased risk of an exaggerated ovarian response (11,15). Administration of a GnRH agonist trigger results in a shorter, more physiologically similar LH surge than hCG, accompanied by more rapid luteolysis and a significant reduction in the risk of moderate-to-severe OHSS (14,15). Although this approach is associated with a luteal phase defect, adequate luteal phase support or a deferred embryo transfer strategy allows preservation of reproductive outcomes while simultaneously enhancing patient safety. Therefore, the selection of the LH-suppression protocol and the method for final oocyte maturation are key elements in contemporary prevention of OHSS **(Table 1 and Table 2)** (11,14,16).

## PATHOPHYSIOLOGICAL BASIS OF OVARIAN HYPERSTIMULATION SYNDROME

The fundamental pathophysiological characteristic of the syndrome is a sudden increase in vascular permeability with extravasation of intravascular fluid into the "third space," primarily the peritoneal and pleural cavities, accompanied by the development of systemic hemodynamic and metabolic disturbances of varying severity. Although the clinical spectrum of OHSS ranges from mild and self-limiting forms to life-threatening conditions, the common pathophysiological denominator of all forms is a disturbance of microvascular regulation induced by hormonal ovarian stimulation (17).

Numerous clinical and experimental studies indicate that the development of OHSS is directly correlated with the administration of hCG for final oocyte maturation. Thus, hCG acts as the key trigger of a cascade of events leading to increased vascular permeability and is therefore considered the central pathophysiological factor in the development of the syndrome (18). The contemporary concept of OHSS does not view it solely as a consequence of a high follicle number or elevated estradiol concentrations, but rather as the result of a complex interaction between the ovarian response and the intensity of luteotropic stimulation by hCG (17,18,19).

According to the timing of onset in relation to hCG administration and the occurrence of pregnancy, OHSS is traditionally classified as early or late. Early OHSS occurs within the first few days after exogenous hCG administration and results from its direct luteotropic stimulation. In contrast, late OHSS develops after implantation as a consequence of continued ovarian stimulation by

**Table 1.** Stimulation protocols in IVF and their significance for the risk of OHSS

| Type of IVF Cycle | Ovulation Stimulation | Prevention of Premature LH Surge | Ovulation Trigger | Estimated Risk of OHSS |
|---|---|---|---|---|
| **Natural IVF cycle** | No pharmacological stimulation | Not required | Spontaneous LH surge | Minimal |
| **Modified natural cycle** | Low doses of gonadotropins in the late follicular phase | Usually not required or GnRH antagonist used | hCG or GnRH agonist | Low |
| **Mild IVF cycle** | Clomiphene, letrozole and/or low doses of gonadotropins | GnRH antagonists | hCG or GnRH agonist | Low–moderate |
| **Conventional IVF – antagonist protocol** | Standard doses of gonadotropins | GnRH antagonists | GnRH agonist (preferred in high-risk patients) or hCG | Low with adequate prevention |
| **Conventional IVF – agonist protocol** | Standard or high doses of gonadotropins | GnRH agonists | hCG | Increased risk |
| **Segmented IVF ("freeze-all") approach** | Individualized stimulation | GnRH antagonists | GnRH agonist | Minimal risk of severe OHSS |

**Notes**: This table summarizes commonly used IVF stimulation approaches and their relative association with OHSS risk. The estimated OHSS risk is qualitative (minimal/low/moderate/increased) and assumes contemporary good practice with individualized dosing and risk stratification; the actual risk depends on patient-related factors (e.g., AMH/AFC, PCOS, prior OHSS), gonadotropin dose, follicle number, estradiol levels, trigger choice, and whether pregnancy occurs after fresh transfer. GnRH antagonist protocols enable the use of a GnRH agonist trigger in high responders, which markedly reduces the risk of moderate–severe OHSS compared with hCG trigger. The "freeze-all/segmented" strategy primarily prevents late OHSS by avoiding exposure to endogenous hCG from early pregnancy. It is a cornerstone of the "OHSS-free" concept when combined with antagonist protocol and agonist trigger. **Abbreviations:** ART, assisted reproductive technology; IVF, in vitro fertilization; LH, luteinizing hormone; GnRH, gonadotropin-releasing hormone; hCG, human chorionic gonadotropin; OHSS, ovarian hyperstimulation syndrome (1,2,5,11,14,15,16).

**Table 2.** Contemporary clinical classification of the severity of Ovarian Hyperstimulation Syndrome

| Grade | Clinical Characteristics | Laboratory Parameters | Ultrasound / Radiological Findings | Clinical Management |
|---|---|---|---|---|
| **Mild** | Abdominal discomfort, bloating, mild pain | Findings within reference values | Enlarged ovaries without or with minimal ascites | Outpatient monitoring |
| **Moderate** | Nausea, vomiting, weight gain, abdominal distension | Mild hemoconcentration, possible leukocytosis | Free fluid in the pelvis | Intensified outpatient monitoring |
| **Severe** | Tense ascites, dyspnea, oliguria, tachycardia | Hematocrit >45%, creatinine>1.5 mg/dL, electrolyte imbalance | Massive ascites ± pleural effusion | Hospitalization |
| **Critical** | Hemodynamic instability, anuria, thromboembolic events, ARDS | Hematocrit >55%, severe renal failure, coagulopathy | Generalized effusions (ascites, pleural ± pericardial) | Intensive care treatment (ICU) |

**Notes:** This table provides a practical, clinically oriented severity classification of OHSS into mild, moderate, severe, and critical forms, integrating symptoms, laboratory markers of hemoconcentration/organ dysfunction, and imaging findings. Severity should be reassessed dynamically, as OHSS can progress rapidly; management should be guided primarily by hemodynamic status, fluid shift ("third spacing"), renal function, and thromboembolic/respiratory risk, rather than ovarian size alone (particularly after oocyte retrieval). Laboratory thresholds (e.g., hematocrit >45% for severe; >55% for critical) are intended as decision-support markers and must be interpreted in the overall clinical context. **Abbreviations:** ARDS, acute respiratory distress syndrome; ICU, intensive care unit; OHSS, ovarian hyperstimulation syndrome (1,2,5).

endogenous hCG from early pregnancy (18,20). This classification has important clinical implications, as it explains why strategies such as deferred embryo transfer and the "freeze-all" approach can effectively reduce the risk of late OHSS but cannot eliminate the early form of the syndrome. Early OHSS has been shown to be strongly associated with parameters of an exaggerated ovarian response, including high estradiol concentrations and a large number of follicles.

In contrast, late OHSS is more strongly determined by the intensity of endogenous hCG stimulation in early pregnancy and often presents in more severe clinical forms (17,18). At the molecular level, the central pathophysiological mechanism of OHSS is increased capillary permeability mediated by vascular endothelial growth factor (VEGF). VEGF is primarily synthesized in ovarian granulosa and luteal cells, and hCG strongly stimulates its expression. Activation of the VEGF signaling pathway leads to increased vascular permeability, loss of

intravascular fluid, and hemoconcentration, which underlies the systemic complications characteristic of severe forms of the syndrome. Experimental data indicate that neutralization of VEGF activity reduces the vasodilatory potential of ascitic fluid in patients with OHSS, thereby confirming the key role of this molecule in the pathogenesis of the syndrome (21,22). VEGF-A isoforms act through vascular endothelial growth factor receptors on endothelial cells, leading to disruption of endothelial barrier integrity, increased capillary permeability, and fluid extravasation. In addition, hCG may further enhance VEGF receptor expression, which helps explain the systemic nature of severe OHSS and the occurrence of pleural and pericardial effusions (18,22).

Even though a large number of patients undergoing controlled stimulation exhibit parameters of an exaggerated ovarian response, only a subset develops clinically manifest OHSS, suggesting the presence of additional regulatory mechanisms. One potential protective factor includes soluble forms of VEGF receptors (sVEGFR), which bind circulating VEGF and reduce its biological availability. Elevated concentrations of these proteins have been identified in patients who, despite intense stimulation, do not develop OHSS, suggesting their possible protective role (17,19). A similar effect may be exerted by α2-macroglobulin, which binds VEGF and modulates its activity, although its clinical significance remains unclear. In addition to VEGF-mediated mechanisms, numerous other mediators participate in the pathogenesis of OHSS, including proinflammatory cytokines (interleukin-1β, interleukin-6, interleukin-8, and TNF-α) and components of the ovarian renin–angiotensin system. The interaction of these factors contributes to alterations in microvascular circulation, enhances vascular permeability, and participates in the development of the systemic inflammatory response characteristic of more severe forms of the syndrome (21,23). At the molecular level, LH and hCG act via the shared LH/hCG receptor (LHCGR), activating the cAMP signaling pathway and increasing intracellular calcium concentrations in granulosa cells. Although they are often considered functionally equivalent, differences in pharmacokinetics and duration of luteotropic action result in significant differences in their potential to induce VEGF expression and vascular permeability. The prolonged and potent luteotropic effect of hCG makes it the principal pathophysiological trigger of OHSS (18,21).

Contemporary ESHRE recommendations clearly emphasize that a high number of follicles or oocytes alone is not sufficient for the development of the syndrome in the absence of a strong hCG signal. Understanding the pathophysiological mechanisms of OHSS forms the basis for modern preventive strategies, which are directed toward individualizing stimulation, minimizing hCG exposure, and developing safer IVF protocols that preserve reproductive outcomes while maximizing patient safety (20,21,24).

## RISK FACTORS AND CONTEMPORARY RISK STRATIFICATION FOR OVARIAN HYPERSTIMULATION SYNDROME

OHSS results from a complex interaction between individual patient characteristics and therapeutic factors related to the COS protocol. Although it is impossible to predict with absolute certainty the occurrence and severity of OHSS, the contemporary concept of reproductive medicine is based on the timely identification of patients at increased risk and the implementation of individualized preventive strategies before stimulation is initiated. For this reason, risk assessment currently represents a central element of a safe IVF procedure (25,26). Current ESHRE recommendations emphasize that assessing the likelihood of an exaggerated ovarian response is a key step in OHSS prevention, as it enables adjustment of the stimulation protocol, selection of the trigger, and the embryo transfer strategy before therapy is initiated. Biomarkers of ovarian reserve and ovarian sensitivity to gonadotropin stimulation form the basis of contemporary risk stratification. The most reliable and clinically relevant predictors of an exaggerated ovarian response are elevated anti-Müllerian hormone (AMH) levels and an increased antral follicle count (AFC). These parameters represent independent, the most accurate biomarkers of ovarian reserve, and have significantly greater predictive value than patient age, body mass index, basal FSH and estradiol concentrations, or inhibin B levels. Their routine use in pre-stimulation risk assessment is now considered a standard of contemporary IVF practice. High AMH and AFC values are directly associated with the likelihood of an exaggerated multifollicular response and represent the most important early indicators of potential OHSS development (24,26,27). In addition to biomarkers of ovarian reserve, numerous clinical factors have been identified that may modify risk. Younger age, particularly below 33 years, low BMI and asthenic constitution, polycystic ovary syndrome (PCOS), a history of previously manifested OHSS, as well as certain ethnic characteristics, are associated with an increased likelihood of an exaggerated ovarian response. Patients with PCOS represent a particularly high-risk group due to increased ovarian reserve and pronounced sensitivity of granulosa cells to FSH, resulting in a marked multifollicular response and increased estradiol production during stimulation.

Nevertheless, despite the presence of these factors, clinical practice demonstrates considerable interindividual variability in syndrome manifestation, indicating the existence of additional regulatory mechanisms that remain insufficiently clarified (25-29,30,31,32). Large cohort analyses of IVF cycles have identified additional factors, including tubal factor infertility, ovulatory disorders, and infertility of unknown origin, as potentially associated with a higher incidence of OHSS. However, their

value in individual risk assessment remains limited compared to biomarkers of ovarian reserve, which continue to represent the most sensitive and specific predictors of an exaggerated ovarian response (26,28,29,33). Therapeutic factors related to the stimulation protocol play an equally important role in risk modulation. Higher initial doses of gonadotropins, especially in patients already recognized as at risk for an excessive ovarian response, raise the likelihood of producing a large number of follicles and intensified steroidogenesis. Contemporary guidelines recommend individualized, reduced starting doses of FSH for predicted high responders, with careful monitoring of follicular growth dynamics and hormonal response (25,26,29,34). The use of hCG for final oocyte maturation represents the most significant and best-documented therapeutic risk factor for the development of OHSS. The prolonged luteotropic action of hCG leads to intense stimulation of luteinized granulosa cells, increased VEGF expression, and enhanced vascular permeability, thereby directly initiating the key pathophysiological mechanisms of the syndrome. The contemporary concept of OHSS therefore emphasizes that a high number of follicles or oocytes alone is not sufficient for syndrome development in the absence of a strong hCG signal (25). A markedly high number of developed follicles and/or retrieved oocytes during stimulation represents an important clinical indicator of increased OHSS risk and requires the implementation of preventive strategies. Although no universally defined threshold exists, a pronounced multifollicular response necessitates modification of the therapeutic approach, including selecting an alternative trigger, reducing luteotropic stimulation, and considering deferred embryo transfer (26,28).

The occurrence of pregnancy following fresh embryo transfer further increases the risk of late OHSS due to continued ovarian stimulation by endogenous hCG. For this reason, the "freeze-all" strategy is recommended in patients at increased risk as an effective method of preventing late forms of the syndrome (25,26). The contemporary approach to OHSS is based on an integrated assessment of individual and therapeutic risk factors and the application of personalized stimulation protocols aimed at achieving optimal reproductive outcomes while maximizing patient safety. Such an individualized and prevention-oriented approach represents the foundation of modern IVF practice and a key step toward the concept of "OHSS-free" reproductive medicine.

## CLINICAL PRESENTATION AND DIAGNOSIS OF OVARIAN HYPERSTIMULATION SYNDROME

The diagnosis of OHSS is primarily based on clinical assessment, with integration of data regarding the performed controlled ovarian stimulation, the timing of symptom onset in relation to hCG administration or the occurrence of pregnancy, as well as ultrasound and laboratory findings (35-37). Early recognition of OHSS is essential to prevent progression to severe and critical forms and to enable timely supportive management. In routine clinical practice, diagnosis relies on integrating recent stimulation history, symptom onset, physical examination, ultrasound findings, and laboratory assessment, with particular attention to hemoconcentration, ascites, oliguria, respiratory symptoms, and signs of hemodynamic compromise. Particular importance lies in distinguishing between early and late OHSS, given their different pathophysiological mechanisms, clinical course, and potential severity.

The clinical presentation of OHSS encompasses a broad spectrum of symptoms and signs, ranging from mild and self-limiting forms to life-threatening systemic complications (37,38). Initial symptoms are often nonspecific and include abdominal pain, abdominal distension, nausea, vomiting, and a general sense of discomfort. Due to the nonspecific nature of the presentation, differential diagnosis should exclude several conditions with similar clinical features, including pelvic inflammatory disease and abscess, ovarian torsion or rupture of an ovarian cyst, acute appendicitis, and ectopic pregnancy (37). A precise medical history regarding recently performed controlled ovarian stimulation and hCG administration is crucial for timely diagnosis.

The mild form of OHSS represents the most common clinical manifestation and occurs in approximately 20–30% of IVF cycles (36,39). It is characterized by lower abdominal pain and a sensation of pressure, mild abdominal distension, nausea, vomiting, and slight weight gain. Ultrasound examination reveals enlarged ovaries with multiple luteinized follicles, while laboratory findings usually remain within reference values (37). A small amount of free pelvic fluid may be present, but without signs of significant hemoconcentration or organ dysfunction. Although ovarian size is often associated with clinical severity, its accurate assessment after oocyte retrieval may be limited due to temporary volume reduction following follicular aspiration (37,39).

The moderate form of OHSS occurs in approximately 3–10% of stimulated cycles (36) and is characterized by more pronounced abdominal distension and ultrasound-confirmed ascites, most commonly in the pelvis and around the uterus. The clinical picture includes more marked nausea, vomiting, abdominal tension, and weight gain, often exceeding 1 kg per day (39). Laboratory findings may show initial hemoconcentration, leukocytosis frequently exceeding 15,000/mm$^3$, and mild elevations of creatinine (>1.5 mg/dL) and liver enzymes. Increased intra-abdominal pressure may result in subjective dyspnea and respiratory discomfort, while ultrasound confirms progressive accumulation of free fluid.

Severe OHSS occurs in approximately 0.1–3% of IVF cycles (34,36) and is characterized by massive fluid

extravasation into the "third space," resulting in marked ascites, pleural effusions, and significant hemoconcentration. A hematocrit greater than 45% represents an important laboratory marker of hemoconcentration and increased risk of thromboembolic complications (37). Reduced renal perfusion leads to oliguria, elevated creatinine levels, and electrolyte disturbances, including hyponatremia and hyperkalemia. Increased intra-abdominal pressure may lead to intra-abdominal hypertension, while values above 20 mmHg may be associated with the development of abdominal compartment syndrome and multiorgan dysfunction.

Respiratory manifestations of severe OHSS include dyspnea, tachypnea, and reduced exercise tolerance, most commonly due to pleural effusions, ascites, and hemoconcentration (37). In some cases, acute respiratory distress syndrome may develop. Increased blood viscosity, hemoconcentration, and venous stasis predispose to thromboembolic events, which occur in approximately 80% of cases within the venous system, often at atypical sites such as the jugular veins or the superior vena cava (34,37,40). Elevated C-reactive protein levels ≥12 mg/L have been associated with a higher likelihood of developing more severe forms of OHSS and may have additional prognostic value (37). Fever may occur in severe forms of the syndrome and has been reported in approximately 80% of cases. It may result from hemoconcentration and a systemic inflammatory response, as well as from secondary infections, most commonly of the urinary or respiratory tract (37). Reduced circulating immunoglobulin concentrations, due to their extravasation into the "third space," may contribute to increased susceptibility to infections (38).

The critical form of OHSS occurs in less than 0.1% of cases and is characterized by life-threatening complications, including severe hemoconcentration, acute kidney injury, respiratory distress, thromboembolic events, and hemodynamic instability. Various forms of hypovolemic shock may develop due to rapid loss of intravascular fluid into the "third space," while distributive and septic shock may occur in the context of systemic inflammatory response or secondary infections. The mortality associated with OHSS is estimated at 1:50,000 to 1:500,000 cycles (36), highlighting the potential severity of this syndrome despite its relatively low incidence.

Assessment of OHSS severity is based on the integration of subjective symptoms, objective clinical signs, ultrasound findings, and laboratory parameters. Standardization of assessment enables timely recognition of disease progression and identification of patients at increased risk of complications (37). For this purpose, various severity classifications have been developed, allowing patient stratification and facilitating clinical decision-making in everyday practice. From a practical perspective, mild OHSS usually requires outpatient monitoring and symptomatic treatment. In contrast, progressive abdominal distension, rapid weight gain, worsening ascites, oliguria, dyspnea, or significant hemoconcentration should raise suspicion of progression to severe disease and prompt closer surveillance or hospitalization.

The contemporary diagnostic approach to OHSS involves a systematic, dynamic evaluation of the clinical picture, taking into account the potential for rapid progression and the development of systemic complications (34,37).

## CONTEMPORARY APPROACH TO THE CLASSIFICATION OF OHSS SEVERITY

Over the past decades, several classification systems for OHSS have been proposed, initially based on clinical symptoms and ovarian size, and later supplemented with laboratory and ultrasound parameters (37). Although these systems differ in structure and terminology, their fundamental objective remains the same – stratification of disease severity and timely identification of patients at increased risk of developing complications (35,37). This severity-based classification is clinically relevant because it guides the intensity of monitoring, the need for hospitalization, and the choice of supportive therapeutic measures.

Contemporary clinical practice, in accordance with the ESHRE-oriented safety approach, favors a simplified classification of OHSS into mild, moderate, severe, and critical forms. This classification is based on the degree of fluid accumulation in the "third space," the presence of hemoconcentration, renal dysfunction, and systemic complications. The simplified stratification allows dynamic assessment of disease progression and represents a practical framework for clinical decision-making (35,37,41). It is important to emphasize once again that ovarian size alone does not reliably correlate with syndrome severity, particularly after oocyte retrieval (42). Therefore, the modern approach relies more on systemic parameters and hemodynamic status than on morphological criteria. Such a clinically oriented, simplified classification system enables standardization of severity assessment, facilitates communication between centers, and provides a basis for the timely implementation of preventive and therapeutic measures **(Table 3)** (35,37,43).

## PREVENTION OF OVARIAN HYPERSTIMULATION SYNDROME

Prevention of OHSS represents a central safety objective of contemporary ART and an integral part of the individualized approach to controlled ovarian stimulation (COS). The modern concept of IVF therapy implies achieving an optimal cumulative live birth rate while minimizing the risk of developing moderate and severe forms of OHSS

**Table 3.** Contemporary Strategies for the Prevention of OHSS According to Current Recommendations

| Prevention Domain | Strategy | Clinical Significance |
|---|---|---|
| **Pre-stimulation risk assessment** | AMH and AFC as the basis of stratification | Identification of high responders |
| **Selection of stimulation protocol** | GnRH antagonist protocol in at-risk patients | Greater safety compared to agonist protocols |
| **Individualization of gonadotropin dose** | Reduced starting doses in high-risk patients | Reduction of excessive ovarian response |
| **Ovulation trigger** | GnRH agonist trigger in high-risk patients | Most effective reduction of severe OHSS risk |
| **Avoidance of hCG trigger** | Not recommended in high-risk patients | Reduction of early and late OHSS |
| **Freeze-all strategy** | Cryopreservation of all embryos in at-risk patients | Prevention of late OHSS |
| **Pharmacological prevention** | Dopamine agonists (cabergoline) in selected cases | Reduction of VEGF-mediated permeability |
| **Strategies not routinely recommended** | Coasting, routine albumin use, aspirin, unselected metformin | Insufficient evidence of benefit |

**Note:** The strategies presented in this table summarize contemporary preventive measures to reduce the risk of ovarian hyperstimulation syndrome (OHSS) during controlled ovarian stimulation. Risk stratification based on ovarian reserve markers, particularly anti-Müllerian hormone (AMH) and antral follicle count (AFC), enables identification of patients at increased risk of excessive ovarian response. The use of GnRH antagonist stimulation protocols and GnRH agonist trigger in high-risk patients significantly reduces the incidence of severe OHSS. Additional preventive strategies include individualized gonadotropin dosing, avoidance of hCG trigger in susceptible patients, and the freeze-all approach to prevent late OHSS associated with pregnancy. In selected cases, dopamine agonists such as cabergoline may reduce vascular endothelial growth factor (VEGF)-mediated vascular permeability. Some strategies historically used for OHSS prevention, including coasting, routine albumin administration, aspirin, or unselected metformin use, are not routinely recommended due to limited or inconsistent evidence of clinical benefit. These recommendations are primarily based on current international clinical guidelines and consensus statements (2,3). **Abbreviations:** AMH – anti-Müllerian hormone; AFC – antral follicle count; GnRH – gonadotropin-releasing hormone; hCG – human chorionic gonadotropin; VEGF – vascular endothelial growth factor; OHSS – ovarian hyperstimulation syndrome.

(44). In this context, ESHRE recommendations emphasize that patient safety, primarily measured by the risk of OHSS, represents one of the key outcomes of the IVF procedure, equal in importance to reproductive success (2,3). Contemporary preventive strategies are based on early risk assessment, individualized stimulation protocols, and minimizing exposure to hCG (44,45). Although current guidelines do not formally distinguish between primary and secondary prevention, this approach provides a clear, clinically applicable framework for understanding preventive measures at different stages of the IVF process.

The literature highlights patients with PCOS, in whom increased ovarian reserve and heightened sensitivity of granulosa cells to FSH result in a pronounced multifollicular response (41,49). A history of prior OHSS is a strong predictive factor and requires the use of maximally safe stimulation protocols in subsequent cycles. Contemporary guidelines emphasize that risk assessment must be integrated and individualized, accounting for clinical, hormonal, and ultrasound parameters (44-46).

## PRIMARY PREVENTION: INDIVIDUALIZATION OF STIMULATION PROTOCOLS

Primary prevention encompasses measures implemented before the initiation of ovarian stimulation to prevent an exaggerated ovarian response. Individualization of the stimulation protocol and the starting dose of gonadotropins represents the foundation of the modern preventive approach (44).

In patients predicted to have a high ovarian response, the use of lower starting doses of FSH is recommended, while aggressive stimulation regimens should be avoided (46). ESHRE recommendations favor the use of GnRH antagonist protocols in patients at increased risk, including women with PCOS, due to their greater safety and the possibility of using a GnRH agonist trigger for final oocyte maturation (47,48). Such an approach significantly reduces the risk of developing moderate-to-severe OHSS (48).

The contemporary concept of individualized stimulation involves tailoring therapy to ovarian reserve and expected response, thereby achieving an optimal balance between reproductive efficacy and patient safety.

## SECONDARY PREVENTION DURING STIMULATION

Secondary prevention involves identifying risk factors during stimulation and promptly modifying therapy. The most important predictors of risk during stimulation are the number of growing follicles and the number of retrieved oocytes (44). The presence of ≥14–25 follicles>11 mm on the day of trigger administration has been shown to significantly increase the likelihood of developing OHSS. At the same time, retrieval of >15 oocytes represents a strong predictor of an exaggerated response (44).

Monitoring estradiol concentrations during stimulation has traditionally been considered an important parameter, with values in the range of 2,500–4,000 pg/mL associated with increased risk (44). However, contemporary ESHRE recommendations emphasize that combined hormonal monitoring (E2, progesterone, LH) is not superior to ultrasound monitoring of follicle number and size for safety and OHSS prevention (2,3).

Additional preventive strategies described in the literature include pharmacological approaches aimed at reducing vascular permeability and VEGF-mediated effects, most notably dopamine agonists such as cabergoline (46). Other pharmacological and metabolic interventions, including metformin or aromatase inhibitors in selected patients with PCOS, have also been investigated as potential strategies to reduce the risk of OHSS (47,52,53). Furthermore, embryo cryopreservation strategies, such as elective freeze-all cycles, may help prevent late OHSS associated with early pregnancy (42).

## TRIGGER MODIFICATION AND EMBRYO TRANSFER STRATEGY

Replacement of the hCG trigger with a GnRH agonist trigger represents the most significant single advancement in the prevention of OHSS and a key measure of secondary prevention (49,50). A GnRH agonist trigger induces a shorter endogenous LH surge and reduces luteotropic stimulation, thereby significantly decreasing VEGF-mediated vascular permeability and the risk of syndrome development (51).

The "freeze-all" strategy constitutes an additional key component of prevention, particularly of late OHSS, which is associated with endogenous hCG from early pregnancy (42,49). This approach eliminates the luteotropic effect of pregnancy and significantly enhances the safety of the IVF procedure without adversely affecting cumulative live birth rates (42).

## PHARMACOLOGICAL PREVENTION

Dopamine agonists, particularly cabergoline, represent the only pharmacological strategy with a proven effect on the prevention of OHSS, supported by contemporary guidelines (46). Their mechanism of action is based on reducing VEGF-mediated vascular permeability by inhibiting VEGF receptor phosphorylation, without negatively affecting implantation or pregnancy outcomes (46). Routine use of cabergoline in cycles employing a GnRH agonist trigger remains a matter of debate, as available evidence does not indicate a significant additional benefit compared to the preventive strategy already implemented (46,48).

## THE CONCEPT OF THE "OHSS-FREE" CLINIC

The development of contemporary stimulation protocols, individualized strategies, and trigger modification has led to the concept of so-called "OHSS-free" reproductive medicine (49,51). This concept implies the use of antagonist protocols, GnRH agonist triggers, and a freeze-all strategy in patients at increased risk, thereby practically eliminating the possibility of developing severe and critical forms of the syndrome (49,50). Although complete eradication of OHSS is not yet absolutely achievable, the contemporary approach enables a significant reduction in the incidence of severe forms. It represents one of the greatest advances in safety in the history of assisted reproduction (50).

## STRATEGIES NOT ROUTINELY RECOMMENDED

Over the previous decades, numerous interventions have been investigated to reduce the risk of OHSS, including so-called "coasting," administration of intravenous albumin, hydroxyethyl starch, calcium, low-dose aspirin, metformin in unselected patients, and various modifications of luteal phase support (48,51-53). Although some studies suggested potential benefit of certain strategies, the results were often heterogeneous, methodologically limited, or without a clear effect on the incidence of moderate and severe forms of the syndrome (48,52).

Contemporary ESHRE recommendations therefore do not support their routine use in OHSS prevention, emphasizing that the greatest safety benefit has been achieved through appropriate patient selection, individualized stimulation protocols, the use of a GnRH agonist trigger, and the freeze-all strategy. At the same time, additional adjuvant measures have limited or insufficiently proven value (54,55).

## TREATMENT OF OVARIAN HYPERSTIMULATION SYNDROME

The therapeutic approach to OHSS depends on clinical severity. It is primarily supportive, with the goals of maintaining intravascular volume, preventing organ dysfunction, reducing thromboembolic risk, and identifying progression at an early stage. The main goals of treatment are maintenance of intravascular volume, prevention of organ dysfunction, and minimization of thromboembolic risk, with continuous clinical and laboratory monitoring (56, 57).

## MILD AND MODERATE FORMS

Mild OHSS is usually self-limiting and can be managed conservatively on an outpatient basis. Moderate OHSS

may also be managed outside the hospital in selected patients, but requires closer follow-up because of the risk of progression, particularly in the presence of increasing ascites, hemoconcentration, worsening abdominal distension, or reduced urine output (58). The therapeutic approach includes adequate oral rehydration, monitoring of body weight, abdominal circumference, and daily urine output, as well as periodic laboratory assessment of hematocrit and renal function. Analgesics and antiemetics are administered as needed, while nephrotoxic medications should be avoided.

It is essential to recognize early signs of progression to more severe forms, including rapid weight gain, reduced diuresis, and the onset of dyspnea, which require urgent re-evaluation and possible hospitalization (59).

## SEVERE AND CRITICAL FORMS

Severe and critical OHSS require hospital-based management, careful fluid balance assessment, close laboratory and clinical monitoring, and timely intervention in the presence of respiratory compromise, renal dysfunction, marked hemoconcentration, or significant third-space fluid accumulation (58). The central therapeutic challenge is the paradox of simultaneous intravascular hypovolemia and third-space fluid accumulation. Therefore, intravenous fluid replacement must be carefully titrated to restore perfusion without exacerbating ascites and pleural effusions. Continuous monitoring of fluid balance, hematocrit, electrolytes, and renal function underpins patient management.

Diuretics are not routinely recommended in the initial phase, as they may further worsen intravascular depletion if volume has not been adequately corrected (58,60). In patients with massive ascites, intra-abdominal hypertension, or respiratory compromise, therapeutic paracentesis may result in significant clinical improvement (57-59). Similarly, thoracentesis is indicated in cases of significant pleural effusion accompanied by dyspnea. These interventions have a symptomatic effect and help stabilize hemodynamics, but they do not alter the underlying VEGF-mediated mechanism of the disease (60).

## THROMBOEMBOLIC PROPHYLAXIS AND COMPLICATIONS

Due to hemoconcentration and a procoagulant state, the risk of venous thrombosis is significantly increased in severe forms of OHSS, particularly in the presence of pregnancy (58). Prophylactic administration of low-molecular-weight heparin is recommended in hospitalized patients with marked hemoconcentration, reduced mobility, or additional risk factors. In critical forms, acute renal failure, acute respiratory distress syndrome, and thromboembolic events may develop, requiring intensive monitoring and management in an intensive care unit (58-60).

## CONCLUSION

OHSS remains one of the most significant and potentially serious complications of assisted reproductive technologies (ART), despite substantial progress in understanding its pathophysiological mechanisms and clinical management. Although VEGF-mediated vascular permeability has been recognized as the central mechanism underlying syndrome development, complete etiological clarification has not yet been achieved, rendering the therapeutic approach primarily supportive. Over the past decade, a fundamental shift has occurred in the paradigm of OHSS management – from reactive treatment of complications to proactive prevention through individualized stimulation protocols. The contemporary approach, which includes precise risk stratification, the use of GnRH antagonist protocols, GnRH agonist trigger, and the "freeze-all" strategy, has significantly reduced the incidence of moderate and severe forms of the syndrome and constitutes the foundation of the concept of so-called "OHSS-free" reproductive medicine. Nevertheless, it is important to emphasize that OHSS may occur even in patients without apparent risk factors, and that clinical vigilance, early diagnosis, and timely intervention remain key to a safe IVF procedure. Further translational and clinical research is required to understand individual sensitivity to gonadotropin stimulation better, identify novel risk biomarkers, and develop targeted therapeutic strategies. Alongside prevention, early diagnosis and severity-based management remain essential for reducing morbidity and ensuring patient safety.

The ultimate goal of contemporary reproductive medicine is not only the optimization of reproductive outcomes, but also the achievement of maximal patient safety, through minimization and potential elimination of severe forms of ovarian hyperstimulation syndrome.

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# SINDROM OVARIJALNE HIPERSTIMULACIJE: SAVREMENI PRISTUP PATOFIZIOLOGIJI, STRATIFIKACIJI RIZIKA, PREVENCIJI I LEČENJU

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**Sažetak**

Sindrom ovarijalne hiperstimulacije (OHSS) predstavlja potencijalno ozbiljnu jatrogenu komplikaciju kontrolisane ovarijalne stimulacije u postupcima asistirane reprodukcije (ART). Uprkos značajnom napretku u savremenim stimulacionim protokolima i strategijama prevencije, OHSS i dalje ostaje važan klinički i bezbednosni izazov u savremenoj IVF praksi. Cilj ovog narativnog pregleda je da prikaže i kritički analizira savremena saznanja o patofiziologiji, faktorima rizika, kliničkoj prezentaciji, prevenciji i terapijskim pristupima ovom sindromu. Pregled literature obuhvatio je relevantne publikacije identifikovane u bazama PubMed/MEDLINE, Scopus i Web of Science, uključujući kliničke studije, kohortne analize, sistematske preglede i preporuke stručnih društava objavljene u periodu 2019–2026, uz selektivno uključivanje ranijih radova od značaja za razumevanje osnovnih mehanizama bolesti. Savremena saznanja ukazuju da je ključni patofiziološki mehanizam OHSS-a povećana vaskularna permeabilnost posredovana vaskularnim endotelijalnim faktorom rasta (VEGF), najčešće indukovana stimulacijom humanim horionskim gonadotropinom (hCG-om). Identifikacija pacijentkinja sa povećanim rizikom primenom biomarkera ovarijalne rezerve, individualizacija doze gonadotropina, primena GnRH antagonističkih protokola i GnRH agonist triggera, kao i strategija zamrzavanja svih embriona, značajno su doprineli smanjenju incidencije umerenih i teških oblika sindroma. Savremeni pristup OHSS-u zasniva se pre svega na prevenciji i personalizaciji stimulacionih protokola sa ciljem optimizacije reproduktivnih ishoda uz maksimalnu bezbednost pacijentkinja.

**Ključne reči:** sindrom ovarijalne hiperstimulacije, kontrolisana ovarijalna stimulacija, IVF, prevencija, VEGF, GnRH agonist trigger

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