NEW INSIGHTS IN PREDICTION OF OVARIAN HYPERSTIMULATION SYNDROME

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SUMMARY - Ovarian hyperstimulation syndrome is the most dangerous complication following the administration of gonadotropins. There is no preventive and pharmacological intervention that can fully prevent development of this syndrome. The best strategy to reduce the incidence of the condition is to identify the patients at risk before ovarian stimulation and to recognize potential predictors. A history of ovarian hyperstimulation is an important risk factor for recurrence of the syndrome. The risk of the syndrome is evident with elevated gonadotropin dosages and with the use of gonadotropin releasing hormone agonists. Human chorionic gonadotropin is the main risk factor. The combination of pretreatment diagnosis of polycystic ovary disease and estradiol of 4500 pg/mL gives higher prediction rates for the risk factor. Serum concentration of inhibin is not a reliable predictor of the syndrome. Recent evaluation of antimüllerian hormone as a reliable predictor candidate, vascular endothelial growth factor with cadherin as indicators of vascular permeability, and detection of mutations in the follicular stimulating hormone receptor as predictors of severity offer new insights in the prognosis of the syndrome. Identification of these prognostic markers in patients at risk would be very useful for prevention of the syndrome prior to the appearance of symptoms.

Key words: *Ovarian hyperstimulation syndrome; Ovulation induction – side effects; Risk factors; Predictive value of tests*

Introduction

Ovarian hyperstimulation syndrome (OHSS) is the most serious and potentially lethal complication of controlled ovarian hyperstimulation (COH) in the treatment of infertility[1]. It is a typically iatrogenic complication of ovulation induction associated with the use of exogenous gonadotropins and aggressive COH or occasionally with clomiphene citrate, occurring during the luteal phase or early pregnancy. However, some forms of OHSS invariably reported during pregnancy may be extremely rarely associated with a spontaneous ovulatory cycle, usually in case of multiple gestations, hydatid mole, hypothyroidism, polycystic ovary syndrome (PCOS), and follicle-stimulating hormone receptor (FSHr) mutations[2].

The incidence of OHSS has not changed over years, and it might not change until the pathogenesis is completely understood. Severe forms of OHSS arise in 0.5%-5% of *in vitro* fertilization (IVF) cycles. A critical condition develops with massive ascites or pleural effusion, dyspnea, hemoconcentration and oliguria[3]. The principal pathology is an increase in capillary permeability of the ovaries and mesothelial surfaces with extravasation of protein-rich fluid into the third space, which in turn causes hypovolemia, reduced organ perfusion and the risk of thromboembolism. The manifestations of OHSS are believed to be the result of increased capillary permeability and range from mild abdominal discomfort to severe, life-threatening illness[4].

The pathogenesis of OHSS is a complex process, which still remains unclear. It was assumed that cer-

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tain ovarian biosynthetic components produced in excess during the induction of ovulation initiate the cascade of events that result in the syndrome. In recent years, several studies indicate that human chorionic gonadotropin (hCG), either exogenous or endogenous (e.g., pregnancy derived), is the main factor that triggers OHSS. It seems to be the pivotal stimulus of the syndrome in a susceptible woman because elimination of hCG will prevent the full-blown picture of the syndrome[5,6]. Using an *in vivo* murine model to induce OHSS, it was clearly demonstrated that vascular endothelial growth factor (VEGF) and VEGF-2 receptors are produced in human granulosa-lutein cells and that VEGF acts through its receptors to increase vascular permeability in response to hCG. VEGF is the main responsible mediator because of the prominent role in the pathologic increase of vascular permeability. In addition, hCG and VEGF individually produce a significant increase in VE-cadherin release, which is involved in the loosening of endothelial intercellular junctions. VE-cadherin is a soluble cell adhesion molecule, which may play a key role in the pathophysiology and progression of vascular hyperpermeability[6-8].

Currently, the condition of OHSS is incompletely understood and its pathogenesis remains complex. There is no pharmacological intervention that fully prevents development of the syndrome and no completely curative therapy. Withholding hCG and cycle cancellation was the most commonly used method of preventing OHSS, but at the expense of losing the cycle, with large psychological and financial burdens imposed onto the patient[9]. Coasting with cessation of gonadotropins has been widely adopted to reduce OHSS, however, prolonged coasting has a drawback of a reduced pregnancy rate[10]. In the first report, early unilateral follicular aspiration applied in patients at risk of OHSS 12 h after hCG administration was followed by regular oocyte retrieval 36 h later. The method of post-hCG aspiration in one ovary has been described as a simple and effective method that prevents the development of OHSS[11]. However, in a prospective randomized study comparing unilateral ovarian aspiration with coasting, neither method completely prevented the occurrence of severe OHSS[12]. Prophylactic albumin could be helpful in preventing it in high risk patients. However, it does not eliminate severe OHSS completely[9]. Cryopreservation of all embryos for postponement of transfer can prevent the occurrence of late OHSS from pregnancy. In high risk patients, mild ovarian stimulation with the gonadotropin-releasing hormone (GnRh) antagonist protocol may prevent OHSS[9,13]. The vast majority of patients with severe OHSS had their condition successfully managed as outpatients with the use of aggressive transvaginal paracentesis[14]. It was recently found that dopamine or dopamine receptor 2 agonists transact inhibition of VEGF-2 receptors dependent vascular permeability through its endothelial cell receptors[6].

OHSS continues to be among the most serious complications of ovulation induction with exogenous gonadotropins. All physicians who prescribe medications with the potential to cause OHSS require knowledge of the pathophysiological mechanisms of the disease and experience with ovulation induction therapy, prevention strategies, staging and treatment[1,15]. As in the prevention of any disease, it should be emphasized that the possibility of primary prevention depends on two main requirements, i.e. the etiology of the disease that must be known, while causal and predisposing factors should be identified. It must be feasible to avoid or manipulate such factors as part of prevention. At present, the greatest clinical challenge is to correctly predict patients at a high risk of OHSS, and how to treat them to prevent the complication. The best strategy and the key to prevent OHSS or to reduce its incidence to minimum is to identify patients at risk before ovarian stimulation and to recognize some prognostic markers that may be beneficial in predicting OHSS development.

Risk Factors

History of OHSS

Those patients with PCOS who developed OHSS in a previous cycle are prone to develop the condition in any subsequent cycle. In future cycles, extreme caution should be taken and it is suggested that the lowest possible dose of FSH be given as a starting point[16]. In addition, patients should be closely monitored using ultrasound and serial estradiol (E2) measurements as a preventive measure in patients at risk of developing OHSS. The use of recombinant FSH (rFSH) in a low-dose protocol was effective in achieving a 20% pregnancy rate without OHSS[17].

Age

It has been reported in most studies that women suffering from OHSS were significantly younger than those who did not. A plausible explanation is that the ovaries of younger women are more responsive to gonadotropins because they possess a higher density of gonadotropin receptors or a larger number of follicles that are able to respond to gonadotropins[15,18].

Body mass index (BMI)

Only one group with 54 OHSS cycles has described positive correlation between lean body mass and OHSS[19]. However, others failed to find correlation between either body mass index (BMI) or body weight and propensity of OHSS[15,18]. BMI does not appear to be a useful marker of an increased risk of OHSS.

Allergy

The pathophysiological changes that occur in the ovaries during OHSS closely resemble an overactive inflammatory response with participation of immunomodulatory cytokines. It has been hypothesized that differences in the immune sensitivity of patients may be a predictive sign of OHSS. In a prospective study recording 18 severe OHSS cases, a significant increase was observed in the prevalence of allergies (50% *versus* 21% in the control group)[18]. However, this observation should be studied through biological assessment in a larger cohort.

PCOS

It is well established that PCOS is more frequent in patients with OHSS and appears to be the major predisposing factor in a large number of studies. Women with PCOS appear to have greater sensitivity to gonadotropins and this effect may be secondary to the increased recruitment of follicles of varying maturational phases owing to pathologic endogenous gonadotropin and steroid hormone responses to exogenous stimulation[9,15,20]. Increased ovarian volume together with increased number of antral follicles and the „necklace“ or „ring of pearls“ appearance of the ovaries should alert the clinician to a higher sensitivity to gonadotropins. In addition, significant correlation was found between the baseline number of follicles and the number of oocytes retrieved in 101 patients who underwent IVF[21]. The levels of inhibin B are high in PCOS patients and the expression pattern of inhibin in the ovary suggests that inhibin has roles in the regulation of both steroidogenesis and growth during follicle recruitment[22]. It was demonstrated that hyperinsulinemic PCOS patients are exposed to a greater risk than normoinsulinemic patients are. The mechanism may be related to that as insulin acts as a survival factor for early stage follicles and this would allow for more follicles to mature into a luteinizing hormone (LH) and hCG-responsive state[23]. An increased expression of VEGF may be related to the increased vascularity within the hyperthecal stroma of women with PCOS, and this may be responsible for their higher risk of OHSS[24]. Therefore, it is important to diagnose PCOS before ovarian stimulation is initiated, as these patients are more likely do develop severe OHSS. There is evidence that severe OHSS is preventable in patients with PCOS when ovarian stimulation is achieved with a chronic low-dose gonadotropin protocol, compared with a conventional regimen[20].

Antimüllerian hormone (AMH)

The traditional determinants for OHSS prior to gonadotropin stimulation appear to include only the subject's age, lean habitus and signs of PCOS (both hormonal and ultrasonographic characteristics). Accurate prediction of OHSS in an individual IVF treatment cycle, however, remains a difficult task. Serum levels of AMH have been reported recently to be closely related to the ovarian response or ovarian reserve during IVF cycles[25]. The serum level of AMH would appear to better reflect the level of ovarian aging than other known markers of ovarian reserve, such as basal serum FSH level, inhibin B and antral follicle count. In a recently reported study, all patients with cancelled IVF cycles due to poor response to COS were in the group with the lowest serum AMH level, whereas those with cancelled cycles due to a high risk of OHSS had serum levels in the highest quartile[26]. Based on this evidence, AMH may be a useful marker to predict OHSS for IVF cycles in addition to being an appropriate marker of ovarian reserve. Furthermore, in women with PCOS, serum AMH level appeared to be strongly elevated and to be associated

significantly with ultrasonographic features of PCOS, such as the presence of multiple small follicles in the ovaries. The inverse relationship between AMH and E2 levels suggests that AMH may modulate ovarian E2 synthesis and have a role in the disordered folliculogenesis characteristic of PCOS[27]. The AMH level has been reported to affect the initial recruitment of primordial follicles and the cyclic recruitment of FSH dependent follicles (follicular sensitivity to FSH). Serum level of AMH may precisely reflect the number of small to intermediate follicles and they correlate strongly with the number of small antral follicles present (diameter <12 mm)[28]. A recent retrospective study showed that the mean follicular phase AMH level was 3.62 ng/mL and was about 6-fold higher in patients who subsequently developed OHSS than in non-hyperstimulated ones[29]. Moreover, these results were later confirmed in a cohort of 262 IVF cycles investigated prospectively, and the mean serum AMH level of 5.02 ng/mL has been reported in OHSS patients. The basal serum AMH level is reported to be a reliable marker of ovarian response to ovulation induction and a significant predictor of OHSS, better than age or BMI. Currently, it could be utilized effectively as a prognostic marker to predict OHSS and thus to direct the selection of mild COH protocols[30].

Stimulation protocols

There is no doubt that the incidence of OHSS is related to the stimulation regimen used. The risk of OHSS is particularly evident when COH for IVF procedure is performed with elevated gonadotropin dosages[31]. It is advisable to use a low starting dose of 150 IU for all patients at the possible risk of OHSS, irrespective of their age. The low-dose, step-up protocol and the step-down protocol are associated with a low risk of OHSS. A much higher incidence of OHSS has been observed when using urinary gonadotropins than with purified FSH in clomiphene-resistant PCOS[32]. The use of gonadotropin releasing hormone (GnRh) agonists, especially of a long protocol, increases the incidence of OHSS, maybe because of the stimulation of a large cohort of follicles associated with the abolition of the spontaneous luteinization process[1,9,15]. hCG is currently used as a standard method for triggering oocyte maturation, but it is the main factor that increases the risk of OHSS. Therefore, it has been suggested that a lower dose of urinary hCG (e.g., 5000 *vs.* standard 10,000 IU dosage) be used for ovulation induction in the presence of risk factors of OHSS[1]. Alternatively, a GnRh agonist or recombinant LH might be used to promote final oocyte maturation and induce ovulation[33]. Regardless of whether hCG or its alternatives are administered at midcycle, the use of progesterone for luteal phase support rather than supplemental doses of hCG may further reduce the risk of OHSS[34].

Response to ovulation stimulation

Although the mean E2 levels are almost always significantly higher following COH and hCG in patients who develop OHSS compared with controls, the relevance of E2 levels has been challenged because severe OHSS has been observed in patients with very low E2 levels of 475 and 29 pg/mL[30,35]. The threshold of E2 peak level above which there is a considerably higher risk of OHSS, varies widely among different investigators and most of the studies selected E2 of 3000 pg/mL as a safe value for hCG administration. Monitoring E2 was found to be effective in reducing the incidence of OHSS. It is suggested that the association of a high E2 level with OHSS is a mere marker of granulosa cell activity. Although E2 alone is not a sufficiently predictive factor, there is a general opinion that E2 assay is an important marker to detect the majority of patients at risk of OHSS[36].

The growing follicular count is correlated with the OHSS status, since the high number of growing follicles is a prerequisite for OHSS development. The risk of OHSS was found to be often related to the large number or size of pre-ovulatory follicles on the day of hCG administration and to the number of collected oocytes (90% of follicles seen)[18]. As individual markers, each of these factors together with E2 peak value and the presence of PCOS show a suboptimal sensitivity to predict OHSS development. However, the combination of pretreatment diagnosis of PCOS along with a threshold of more than 15-18 follicles >15 mm in size and E2 of 4500 pg/mL gives higher prediction rates for the risk of developing OHSS[37,38].

It was observed previously that basal levels of inhibin B on day 3 and day 5 positively correlated with the expected ovarian response and IVF outcome[39]. However, analyzing serum and follicular levels of in-

hibin A and inhibin B following regular COH at the time of oocyte pickup, it was found that both serum inhibin A and inhibin B were elevated at OHSS onset, but that only inhibin A was elevated significantly. Moreover, serum concentrations of inhibin A and inhibin B strongly correlated with the growing follicular count. Considering these observations, it was concluded that serum concentration of inhibin is not a very reliable predictor of OHSS[40].

VEGF is the most important mediator of hCG-dependent increased ovarian angiogenesis. The expression of VEGF and VEGF-2 receptors increases during ovarian stimulation with gonadotropins and with the administration of hCG the expression of each rises to maximum. The expression of VEGF/VEGF-2 mRNAs correlates with stimulation of new blood vessel development, but also induces vascular hyperpermeability, with both peaking 48 h following hCG[6]. Recent observations suggest that increased vascular permeability may be mediated through adhesion molecules such as VE-cadherin, a component of the adherence junction strand and the endothelial barrier. It was reported that women with severe OHSS had significantly higher levels of VE-cadherin than patients without OHSS. Serum VE-cadherin levels decreased with clinical improvement; however, they did not reach normal values in the resolution phase. Serum VE-cadherin levels were more closely chronologically correlated with corpus luteum function than with biological and clinical aspects of severe OHSS. VE-cadherin may be involved in the pathogenesis of severe OHSS and may possibly serve as an indicator of corpus luteum function after COH, which indirectly reflects the risk of OHSS development[7,41].

Several gene variations in the FSHr gene have been identified in the very rare cases of spontaneous OHSS. There are only few published data on gene variations in sterility and iatrogenic OHSS. In most cases, activation of the FSHr gene causes ovarian hyper-responsiveness to circulating FSH or even cross-responsiveness of FSHr to hCG or thyroid-stimulating hormone (TSH), leading to predisposition to OHSS. However, mutations in the FSHr could be inactivated by reducing the FSHr function up to a total block, resulting in amenorrhea, infertility and primary ovarian failure. Polymorphisms of FSHr have been investigated and to date 744 single nucleotide polymorphisms have been identified in the FSHr gene, of which only eight are located in the coding region, exons, with the rest being intronic. Interestingly, a significant enrichment in the allele N680 was observed as the severity of OHSS increased. It was demonstrated that identification of the polymorphism of FSHr, Ser680Asn, in the FSHr gene could not identify patients that would develop OHSS, but could predict the severity of symptoms among iatrogenic OHSS patients[41-43].

Conclusion

Until the multifactorial etiopathogenesis of OHSS is completely understood, absolute prevention will not be possible. At present, treatment of the acute phase of OHSS merely relies on an empirical and symptomatic approach. More appropriate methods would require better understanding of the underlying pathophysiological mechanisms to promote an etiologic therapeutic approach. It seems reasonable that identification of risk factors and potential prognostic markers in patients at a high risk of OHSS could be very useful in prevention of complications prior to ovulation induction. As previously described, PCOS, elevated gonadotropin and HCG dosages, GnRh agonists and combination of increased E2 peak levels with larger number of follicle represent important risk factors of threatening OHSS. Moreover, recent evaluation of AMH as a reliable predictor candidate and the potential roles of VEGF, VE-cadherin and FSHr mutations as prognostic markers represent new insights in the prognosis of OHSS. The presence of these risk factors and predictors need to alert all clinicians to be prepared to recognize and to prevent the condition, enabling the use of low-dose protocols with gonadotropins and hCG dose tapering or its alternatives, before the appearance of signs of severe OHSS.

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Sažetak

NOVI UVIDI U PREDSKAZIVANJU OVARIJSKOG HIPERSTIMULACIJSKOG SINDROMA

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Ovarijski stimulacijski sindrom je najopasnija komplikacija nakon primjene gonadotropina. Ne postoji nijedna preventivna ni farmakološka intervencija koja u potpunosti sprječava pojavu ovoga sindroma. Najbolja strategija koja smanjuje pojavnost takvog stanja je identifikacija rizičnih bolesnica prije stimulacije ovulacije te prepoznavanje mogućih predznaka bolesti. Anamnestički podatak o ranijoj hiperstimulaciji jajnika predstavlja važan rizični čimbenik za ponovno javljanje sindroma. Rizičnost za nastanak sindroma je očita pri korištenju gonadotropina u većim dozama, kao i kod primjene agonista gonadotropnog otpuštajućeg hormona. Humani korionski gonadotropin je glavni rizični čimbenik. Kombinacija prethodno utvrđene dijagnoze policističnih ovarija te koncentracija estradiola iznad 4500 pg/mL omogućuju bolje predskazivanje čimbenika rizičnosti. Koncentracija inhibina u serumu nije pouzdana u predikciji sindroma. Nedavne spoznaje o antimilerovom hormonu kao pouzdanom kandidatu u predskazivanju sindroma, vaskularnom faktoru rasta s kaderinom kao pokazateljima vaskularne propusnosti te otkriće mutacija receptora folikularno stimulirajućeg hormona koji ukazuju na težinu bolesti predstavljaju nove uvide u prognozi ovoga sindroma. Prepoznavanje ovih prognostičkih biljega u rizičnoj skupini bolesnica bilo bi vrlo korisno u prevenciji sindroma prije pojave simptoma bolesti.

Ključne riječi: *Sindrom hiperstimulacije jajnika; Indukcija ovulacije – nuspojave; Čimbenici rizika; Prediktivna vrijednost testova*