OVARIAN HYPERSTIMULATON SYNDROME: AN UPDATE FOR PREDICTION, PREVENTION AND TREATMENT

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SUMMARY

Ovarian hyperstimulation syndrome (OHSS) is a life-treating and iatrogenic complication of assisted reproductive technologies. In order to exclude the probability of OHSS, women with high risk should be identified and proper controlled ovarian hyperstimulation protocol should be assigned. However, the improvement of approaches and strategies that also maintain high pregnancy rates are as important as preventing OHSS for both patients and the physicians. Otherwise, it is hard to introduce to the aforementioned protocol to the daily practice. In the current review, we aimed to summarize established risk factors which could be useful in order to identify high risk women. The procedures for prevention that has the least deleterious effect on pregnancy rates and treatment would be also discussed.

Key words: *assisted reproductive technologies, mortality, pregnancy, ovarian hyperstimulation syndrome*

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OVARİAN HİPERSTİMÜLASYON SENDROMU: ÖNGÖRME, ÖNLEME VE TEDAVİSİNE GÜNCEL BAKIŞ

ÖZET

Ovarian hiperstimülasyon sendromu (OHSS) yardımcı üreme tekniklerinin hayatı tehdit eden iyatrojenik bir komplikasyonudur. Önlenebilmesi için risk altındaki hastaların ayırt edilebilmesi ve bu hastalarda etkinliği kanıtlanmış kontrollü ovarian hiperstimülasyon protokollerinin seçilmesi riski belirgin olarak azaltacaktır. OHSS riskini azaltırken gebelik oranlarından ödün vermeyecek yöntem ve stratejilerin seçilmesi ise hem doktor hem de hasta açısından OHSS'nin önlenmesi kadar önemlidir. Aksi halde o yöntemin klinik pratikte uygulama alanı bulması mümkün olmamaktadır. Bu derlemede OHSS açısından riskli hastaların başarılı bir şekilde ayırt edilebilmesi için kullanılabilir ve güncel risk faktörleri anlatılacaktır. Ayrıca OHSS açısından riskli kadınlarda gebelik oranlarını en az etkileyecek korunma stratejileri ve tedavisi de güncel araştırmalar ışığında tartışılacaktır.

Anahtar kelimeler: *gebelik, mortalite, ovarian hiperstimülasyon sendromu, yardımcı üreme teknikleri*

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INTRODUCTION

Ovarian hyperstimulation syndrome (OHSS) is an iatrogenic complication caused by exogenous hCG for triggering in assisted reproductive techniques (ART) cycles or endogenous secretion from placenta during the pregnancy. Although it has been accepted to be self limited in the majority of cases, hospitalization can be required in 2% of all in vitro fertilization (IVF) cycles[1]. The overall death rate for OHSS is estimated to be 3/100.000[1]. Although this rate sounds to be low enough, one should consider that 600.000 cycles are undertaken annually in European and US based IVF centers. That suggests there will be 6 to 7 death will arise in every year among otherwise healthy women seeking just for fertility.

Although OHSS mostly appears during ART cycles, it might be encountered in non-IVF cycles during hyperstimulation. To give the definitions, **"early OHSS"** is the type that occurs in the following 9 days after oocyte retrieval and caused by exogenous hCG for triggering. **"Late OHSS"** is the one that occurs after 10 days from egg collection and generates from endogenous hCG arising from the placenta.

High ovarian response in IVF cycles do not cause only OHSS and related life-threatening risks, but might also deteriorate implantation rates by increasing sex steroid levels to supraphysiological levels[2,3]. There are clinical studies proposing that high ovarian response might negatively affect oocyte and embryo quality[4]. Therefore, management of OHSS seems to be highly crucial both for health risks and IVF outcome. In this review, we aimed to identify different ways to diagnose risk factors and proper management to prevent OHSS.

PREDICTION OF OHSS AND RELATED RISK FACTORS

The major step to prevent OHSS is to determine high-risk patients and assign patient based treatment strategies. For this reason, risks factors should be distinguished in detail. In this manner, the risk factors can be classified as primary and secondary risk factors. Primary risk factors are the characteristic properties of the patient herself that reflect high probability of OHSS. Secondary factors can be defined as findings appearing during controlled ovarian hyper stimulation (COH) which warrants high risk of hyperresponse.

Primary Risk Factors

One of the primary risk factors is young age. OHSS occurs more frequently in young population than elderly women[5,6]. Reasons might be diminished ovarian follicular reserve and growth hormone levels in older women. However, while the risk of thromboembolic event increases, the success rate of pregnancy decreases in that population[6]. Besides age, body mass index (BMI) is also a risk factor for OHSS[5-7]. Young women with low BMI have higher risk of OHSS when compared with younger women. Previous history of OHSS is also a significant risk factor[8].

The presence of polycystic ovarian syndrome (PCOS) is a well-known risk factor related with hyperresponse. In a systemic review by Tummon et al[9], which includes eight cohort and two case control studies[9], patient with PCOS had noted to have 7 fold higher risk of OHSS than women without (OR: 6.8%95CI: 4.9-9.6). Not only in women carrying PCOS but also in cases having high number of antral follicle count (AFC), a high risk can be noticed. Nevertheless, in 2007 with 110 cycles, Kwee et al[10] reported that if there was more than 14 AFC in bilateral ovaries, the sensitivity and specificity of having OHSS is %81 and %89, respectively (Figure 1A). There are similar results for another marker of ovarian reserve: anti-mullerian hormone (AMH). In a cohort study with 262 IVF cycles[11], patient`s age, body mass index, serum estradiol (E2) level, retrieved number of oocytes and basal AMH levels were analyzed. By this study, when threshold level is taken as 3.36ng/ml, OHSS could be predicted with 91% sensitivity and 81% specificity. Of note, Broer SL et al[12] reported that the validity of AMH and AFC in means of prediction of OHSS was comparable. Therefore, both AMH and AFC are useful to define the risk level.

Besides biochemical and phenotypic properties, genetic differences are also risk factors for OHSS[13]. As generally known, ovarian response in controlled ovarian stimulation is arranged with multiple genetic factors which are naturally candidates for over response than expected[13]. To recall, follicular stimulation hormone (FSH) receptor signal, estrogen

biosynthesis, folate metabolism and folliculogenesis regulatory genes are part of the cascade and can be evaluated in that manner. To cite an example, with the presence of BMP15 allele gene which is important in folliculogenesis, OHSS seems to be 2.7 times frequently observed than women who are lack of[14]. That finding might explain why some women are complicated with OHSS while others have no problem with the same dose under similar ovarian reserve and female age.

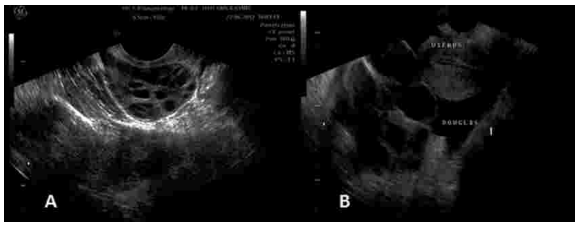

Figure A: *The imaging of an ovary that includes many antral follicles. B: The visualization of a severe OHSS. The large ovaries and accumulation of ascites in the rectouterine space is significant.*

Secondary Risk Factors

As discussed before, secondary risk factors are the variables that appear during controlled hyper stimulation. The mostly known is high estradiol level during COH or at the day of hCG administration. In several studies[6,15], average estradiol levels are noticed to be high in patients with OHSS. However, for a successful prediction of OHSS, the level of estradiol should be extremely high. To give an example, on the day of hCG administration, whereas OHSS risk is only 1.5% if the estradiol level is between 3500-5999 pg/ml, that rapidly increases to 38% when E2 is ≥6000 pg/ml [16]. Of note, estradiol levels are less reliable in GnRH antagonist cycles and there is significant overlap between values reflecting risk of OHSS or not. Another secondary risk factor for OHSS is number of follicles on the day of hCG. Papanikolaou et al[15] reported that with the presence of eighteen or more ≥ 11mm follicles in bilateral ovaries, the presence of severe OHSS was predicted with a sensitivity of 83% and specificity of 69%. The number of retrieved oocytes might also be speculated in this manner. However, unless ≥30 oocytes are not collected, the risk of OHSS is generally quiet low[17]. The main problem of secondary risk factors is their low validity of prediction without reaching high thresholds.

Recently, vascular endothelial growth factor (VEGF) has been addressed due to its potential role in the pathogenesis of the syndrome. VEGF has two main effects. First, it is a potent stimulant for neovascularization; and secondly, it increases the permeability of the vascular wall partly by increasing the synthesis of nitric oxide[18]. In addition to that, by breaking the integrity of cellular actin fibrils down, it relaxes tight intercellular junctions[19]. Of interest, the role for the prediction of OHSS with VEGF is inconclusive, even though it can be detected both in plasma and follicular fluid. However, in a recent study by Pietrowskiet et al[20], it was pointed out that when high plasma free VEGF-A and low plasma soluble VEGF-R2 levels were revealed OHSS became more severe[20].

PREVENTION

There are two types of prevention modalities for OHSS. ***Primary prevention*** methods define the policy to determine primary risk factors of the patient initially and then assigning the best treatment and protocol of COH that carries the lowest risk. ***Secondary prevention*** defines the strategy that tries to abandon the risk of OHSS when secondary risk factors became apparent during COH.

Primary Prevention

When a patient has primary risk factors for OHSS, the most implemented choice of strategy is to decrease the dose of FSH that will be initially prescribed. However, at least for a subgroup of patients, lower dose of FSH might reveal insufficient follicle response or long time of COH until triggering. In this manner, individualizing the FSH dose according to the characteristics of the patient fail to demonstrate a conclusive result. In a study by Popovic-Todovic et al[21], starting FSH dose was personalized by AFC, ovarian volume, Doppler scores, female age and habitus of smoking and compared with conventional protocol. However, the authors could not reveal any difference regarding the rate of hyperresponse. In 2009, a non-controlled trial tested the individualization of the FSH with the mathematical model including basal FSH level, BMI, female age and AFC. However, they experienced 7 cases of severe OHSS among 113

women, when the dose of FSH was given according to the mathematical model[22]. In a recent retrospective study[23], starting FSH dose was tailored solely according to the AMH level and compared with historical controls that had been treated with conventional manner. The authors reported less number of cycle cancellation due to the risk of OHSS (6.9% vs 2.3%; p: 0.004). Therefore, tailoring the lowest dose of FSH that will bring optimum number of oocyte without increasing the risk of OHSS might be encouraging, even though current status hardens its application. However, strong variables such as AMH should be discovered that might be applied to mathematical models.

Another primary prevention method might be using minimal or mild protocols. In mild protocols, generally GnRH antagonists are selected and 100-150 IU FSH are initiated at the Day 5 of the menstrual cycle. The primary purpose is to obtain less than 10 oocytes. In 3 prospective randomized studies which compare with conventional cycles[24-26], at the end of first year, the cumulative pregnancy rates were similar (43.4% vs. 44.7%) but OHSS rates were less than half (1.4% vs. 3.7%; p: 0.04). Of note, for providing same cumulative pregnancy rates, the mean required number of cycles was 2.3 vs 1.8 in mild and conventional protocols, respectively. That fact suggests that, in mild group, 1 fresh and 1 frozen-thawed cycle has similar pregnancy rates with single fresh cycle in conventional IVF. In minimal stimulation, the purpose is to obtain 5 or less oocytes, and there are several protocols related with it in literature. Clomiphene citrate and exogenous FSH can be given in several different combinations. In 43.000 minimal cycles, there were no OHSS; but the live pregnancy rates were around 10%[27]. The barrier that blocks the utilization of minimal and mild protocols in clinical practice seems to be lower pregnancy rate per cycle.

There have been several debates on GnRH agonists and antagonists for a decade. In a recent meta-analysis performed by Al-Inany et al including 29 studies and 5417 patients[28], OHSS risk was 50% less in the antagonist arm than agonist group (OR: 0.50%95CI: 0.37-0.66). The live birth rates were similar. In this manner, in high-risk patients, assigning antagonist protocol instead of agonist will yield 50% less risk of OHSS. In addition, in antagonist protocols, GnRH agonists might be selected for triggering instead of hCG which further decreases the risk of the complication with a better safety profile.

Another strategy to lower the risk of OHSS is to use insulin sensitization agents. In a meta-analysis including 5 studies, by using metformin, risk significantly decreases (OR: 0.21 %95CI: 0.11-0.41) without deteriorating pregnancy rates[29]. In a unique RCT investigating the risk of OHSS as the primary outcome among patients with PCOS[30], when compared with controls, prescribing 1500mg/day metformin beginning from the 21st of the previous cycle until the day of hCG significantly decreases the risk of OHSS (30% vs. 8.3%; p:0.003). However, when the results are identified in detail mild OHSS cases decreased significantly but frequency of severe cases was not affected.

Another primary prevention method is the in vitro maturation technique. By picking up oocytes without giving FSH, the probability of OHSS is almost zero; however pregnancy rates are currently far from conventional IVF[31]. Although it is not frequent nowadays, continuing hCG injections for luteal support after embryo transfer also increases the risk of OHSS clearly. In this manner, using progesterone instead of hCG decreases OHSS rates significantly[6].

Secondary Prevention

Once OHSS risk appears clearly during COH, there are still some strategies that can be applied to decrease the risk of complication. Although some of these applications are supported with randomized controlled studies, some, which are used frequently, has not sufficient scientific support. One of the typical policy is “coasting”. In this method, gonadotropin injections are stopped till the estradiol levels decrease to an acceptable level. Although there is no clear estradiol level for applying hCG with confidence, it is generally applied when E2 level is between 2000-5500 pg/mL in most of the related trials[32]. In this manner, some authors offer to look out for the safest zone according to their own center outcome.

In a meta-analysis[32] including 3 RCT`s evaluating efficiency of coasting in IVF cycles, there were no difference in the rate of mild or severe OHSS among intervention and control groups (OR: 0.53 %95CI: 0.23-1.23). However, if the included 3 studies are speculated in detail, to compose control groups, one

has undertaken patients who had unilateral follicular aspiration[33]. and one has retrieved patients who took GnRH agonists for COH[34]. In this meta-analysis only one study has created a control group including patients who were not performed coasting. This study is an abstract from an annual meeting and currently has not been published as a full paper yet[35]. Therefore, efficiency of coasting method is currently debatable.

Other than coasting, another common approach is decreasing the dose of hCG. However, there is no sufficient clinical proof for this strategy. When the given dose was adapted according to the estradiol level on the day of hCG (estradiol ≥ 11.000 pmol/ml, do coasting; 7000-11.000 pmol/ml do 3300-4000 IU hCG; 4000-7000 pmol/ml do 5000 IU hCG, <4000 pmol/ml do 10.000 IU hCG) OHSS risk decreased significantly when compared with giving full dose of hCG[36]. However, this study reflects a retrospective data and results should be claimed with cautious. Actually, the only RCT about this topic was published in 2007 by Kolibianakis et al[37]. According to this study, by applying 5.000 or 10.000 IU hCG to PCOS patients, similar number of oocytes were collected and the risk of OHSS were quite similar. It is worthy to note that there were no differences between urinary or recombinant hCG regarding the risk of hyper response according to a meta-analysis[38].

Another approach to abandon risk of late OHSS is freezing all oocytes or embryos and cancelling the embryo transfer. However, if the ovulation is triggered with hCG, early OHSS risk still continues. For this reason, studies that evaluate the role of alternative medications instead of hCG for triggering will be highly valuable. In a recent retrospective study[39], in the first arm, the cases of coasting had been retrieved within the long agonist protocol. In the second arm, GnRH triggered antagonist cycles had been recruited in which all the oocytes were frozen. A few months later, ICSI was performed with thawed oocytes and embryo transfer was performed. The surprising thing is, the pregnancy rate was lower in the coasting group (29.5% vs. 50%) and severe OHSS frequency was higher (19.2% vs. 0). Indeed, in cycles that were triggered with GnRH agonists (2mg decapaptil or 4mg leuprolid acetate) early OHSS frequency was extremely low; but to reveal similar pregnancy rates as in fresh cycles, studies that are seeking for optimal luteal support are highly warranted.

Dopamine agonists are also frequently used agents for the prevention of OHSS. In animal studies, the decreased activation of VEGF receptor 2 with dopamine agonists is noticed[40]. In a meta-analysis related with the topic[41] including 5 RCTs, the authors concluded that cabergolin decreased the risk of OHSS by almost 60% (OR: 0.41 %95CI: 0.25-0.66). When examined in detail, there was no clear decrease in severe form of OHSS frequency (OR: 0.50 %95CI: 0.20-1.26) but clear benefit was noted in the rate of moderate OHSS (OR: 0.38 %95CI: 0.22-0.68). Although various type of administration are described for using dopamine agonists in the literature, the most quoted way of utilization is 0.5mg/day beginning from the day of hCG for 8 days.

The interventions during oocyte retrieval are also worth to discuss. The most applied technique is infusion of albumin or HES (hydroxyletil starch) during the procedure. In 8 RCTs for albumin (OR: 0.67 %95CI: 0.45-0.99) and 3 RCTs for HES (OR: 0.12 %95CI: 0.04-0.40) decreased the risk of OHSS significantly when compared with controls[42]. However, in the same meta-analysis, adverse effects and cost were less in HES than albumin. The most proposed method is giving 1000cc of 6% HES in 2 hours, but beginning one hour after the oocyte retrieval. Except the strategy that was mentioned above, applying glucocorticoid[16] and follicle aspiration[33] are the methods that have no effect on the risk of OHSS.

In conclusion, unless the cycle is canceled, it is very though to rule out the risk of OHSS totally and saving pregnancy rates at this time. In this manner, a protocol by Devroey et al is recommended as follows: assigning antagonist cycle in high risk women, triggering with GnRH agonist, freezing all oocytes/embryos and performing thawed cycle. By this way, theoretical risk of OHSS might be extremely low, even though still might be encountered. However, the success rate of frozen-thawed cycles in the IVF center is crucial to maintain such a protocol.

TREATMENT

Before evaluating the strategies to treat OHSS, it is worthy to recall the importance of prevention once more. Although it is a self-limiting process, mortality and morbidity might occur due to metabolic disturbance, thromboembolic events and long duration of hospitalization. Expectant management and metabolic support is sufficient for most of the patients. Surgery (oophorectomy and cystectomy) has no role in the treatment with the exceptions of ovarian torsion, rupture and internal bleeding.

As a general recommendation, because the rupture risk of follicles increases, sexual intercourse and heavy physical activity should be limited in all cases of OHSS.

In mild hyperstimulation, treatment is generally conservative. Only weight gain should be followed up and in case of abdominal discomfort or difficulty in respiration, patient should be advised for applying to the hospital. Generally this condition resolves by two weeks, but it can progress to moderate or severe OHSS in some cases. Rapid weight gain, and exacerbated nausea and vomiting are important symptoms for the progression of the syndrome that patient should be cautious with.

In moderate OHSS, to prevent from hemoconcentration, sufficient fluid replacement should be provided. In addition, ultrasonography should be performed to follow the severity of the syndrome. According to the policy of the health provider, patients might be hospitalized or followed as outpatient. Fluid intake and urine output should be monitored and if there is weight gain more than 1 kg in 24 hours, patient should be followed up more carefully. In addition to mild OHSS group, hematocrit values and renal function should be closely monitored.

Patients with severe OHSS should be hospitalized. Severe OHSS could be seen in 2% of all IVF cycles (Figure 1B). Full blood count and electrolyte of the patient should be closely monitored. Liver function tests and protrombine time can be checked at least in the initial exam. Weight gain, urine output and abdominal circumference should be followed up daily. In necessary cases, thorax x-ray or ultrasonography should be performed to rule out pleural effusion. Especially for patients with hemoconcetration, intravenous saline infusion up to 2000 ml should be considered. The primary aim is to decrease the hematocrit under 38%. After this point, infusion might be adjusted according to oral intake and urine output. In severe cases, monitoring could be performed with central venous catheter. Except saline infusion, efficiency of albumin in the treatment is unknown. Indomethacin that decreases the vascular permeability by decreasing the cytokine synthesis could be also applied. Dopamine infusion could be restricted to patients with low urine output in spite of adequate fluid infusion.

Because of intravascular volume that has already decreased, diuretics have limited usage in the treatment of OHSS. However, diuretics can be used cautiously with the aid of central venous pressure monitoring if the desired urine output is not achieved by the adequate fluid resuscitation[43]. When excess ascites or pleural effusion occurs, parasynthesis or thorasynthesis can be performed. Especially, patients who had weight gain ≥15kg in 5-10 days after hCG, this procedure could be highly required. However, to prevent bleeding because of ovarian injury, procedure should be performed carefully with the guide of ultrasonography. Following the procedure of parasynthesis, the related symptoms, kidney functions and hemoconcentration generally improve. Alternative strategy might be infusing the fluid of ascites after microfiltration. Thromboembolic complications can be within the arterial or venous system. Especially patients with high hematocrits, anticoagulation treatment and elastic compressive stockings should be applied.

Tablo I: *Risk factors and prevention methods for OHSS*

Primary risk factors	Secondary risk factors	Primary prevention	Secondary prevention
Antral follicle count	Estradiol level	GnRH antagonist protocols	Triggering alternative to hCG
Anti-mullerian hormone	Follicle/oocyte count	Metformin	Dopamine agonists
		Mild/minimal stimulation	Cryopreservation
		In vitro maturation	HES/albumin

During the improvement of severe cases, rapid diuresis occurs and continues up to 2-3 weeks. In this stage, the clinician must be aware of electrolyte imbalance.

RESULT

OHSS is an iatrogenic complication that cannot be totally ruled out. With this manner, defining high-risk patients (Table 1) and determining most suitable protocol decreases the risk significantly. However, in spite of primary prevention methods, if the risk becomes evident during COH, triggering with GnRH agonist instead of hCG might eradicate most of the cases. Such an approach requires an antagonist cycle and freezing all the oocytes/embryos after triggering; because the pregnancy rate is generally low when fresh ET is performed. Conservative treatment, metabolic support and close observation should be done in patients experiencing OHSS in spite of preventive strategies.

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