Gynaecol Perinatol 2004;13(2):62–68

Klinika za ženske bolesti i porode Medicinskog fakulteta Sveučilišta u Zagrebu i KBC-a

OVARIAN HYPERSTIMULATION SYNDROME

SINDROM HIPERSTIMULACIJE JAJNIKA

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Review

Key words: ovarian hyperstimulation syndrome, ovaries, stimulation

Summary. In the article all the basic characteristics, clinical significance, risk factors, pathogenesis, prevention and treatment modalities of ovarian hyperstimulation syndrome were described. In the introduction all the main characteristics, classifications and incidence of the syndrome were noted. The best known risk and predictive factors that characterize the patients at risk with their significance include polycystic ovarian disease, multiple and immature follicles, young age (<35 years), lean habitus, high serum estradiol (>3000 pg/ml), hypothyroidism, hyperprolactinemia, oligomenorrhea, anovulatory infertility, stimulation protocols with gonadotrophin releasing hormone agonists, and human chorionic gonadotrophin for the induction of ovulation and luteal support were reported. To understand modern etiologic aspects and pathophysiologic mechanisms in the development of the syndrome the underlying causes of all relevant vasoactive substances were described. In the prophylaxis of the syndrome all significant and judicious methods and procedures which could prevent the appearance of symptoms were reported. Modern strategies for the treatment of OHSS which include macromolecular plasma expanders with its usefulness and controversies, diuretics, paracentesis, anticoagulants and surgery, that could reduce the complications and long-term sequels were described.

Pregled

Ključne riječi: sindrom hiperstimulacije jajnika, jajnici, stimulacija

Sažetak. U članku su opisane temeljne karakteristike, rizični faktori, patogeneza, prevencija i liječenje sindroma hiperstimulacije jajnika. U uvodu članka istaknut je patološki supstrat, klinički značaj bolesti i komplikacije koje mogu vitalno ugroziti zdravlje bolesnica. Učestalost i klinička slika sindroma hiperstimulacije klasificirana je prema težini i brojnosti postojećih simptoma, lokalnom nalazu, poremećajima u krvnoj slici, pojavi ascitesa i općem stanju, na tri stupnja bolesti: blagi, srednji i teški. U poglavlju o rizičnim faktorima istaknute su skupine bolesnica koje treba uočiti prije profilakse i liječenja bolesti, od kojih su najvažniji sindrom policističnih jajnika, multipli i nezreli folikuli, mlađa životna dob (<35 godina), astenični habitus, povišena razina estradiola u krvi (>3000 pg/ml), hipotireoza, hiperprolaktinemija, oligomenoreja, anovulacijska neplodnost, stimulacijski protokoli s agonistima gonadotropnih oslobađajućih hormona te egzogeni ili endogeni (rana trudnoća) humani korionski gonadotropin. U poglavlju o patofiziologiji koja još nije potpuno razjašnjena, navedeni su, prema najnovijim spoznajama, značaj citokina i mehanizmi njihova djelovanja u nastanku bolesti. Istaknuta je ključna uloga prevencije u olakšavanju ili sprečavanju sindroma hiperstimulacije primjenom raznih metoda, od kojih se navode prestanak ili prolazno odustajanje od stimulacije u tom ciklusu, smanjivanje doze humanog korionskog gonadotropina te primjena rekombinantnog luteinizirajućeg hormona ili agonista gonadotropnog oslobađajućeg hormona za indukciju ovulacije, antidota ili inhibitora citokina, kortikosteroida, metformina te aspiracije folikula. U liječenju bolesti potvrđena je vrijednost plazma ekspandera albumina, premda su kasnija istraživanja relativizirala njegovu djelotvornost, učinivši ju prijepornom, upitnom ili čak štetnom. U terapijskom pristupu nadalje su istaknuti važnost, opravdanost te indikacije za primjenu diuretika, antikoagulancija, paracentezu i kirurškog liječenja.

Introduction

Ovarian hyperstimulation syndrome (OHSS) is the most serious complication of ovulation induction. This iatrogenic condition severely impacts the patient's health, leading to morbidity and even mortality. The syndrome is characterized by ovarian enlargement and vascular hyperpermeability which accompanies fluid shifts from intravascular to extravascular space, including formation of ascites, hypotension, hemoconcentration, electrolyte disturbances, abdominal distension and discomfort, liver and kidney dysfunctions, hydrothorax, and even thromboembolic phenomena.[1–4]

The oldest OHSS classification scheme consisted of six levels (Rabau 1967),[5] which was later modified (Schenker 1978)[6] into three categories: mild, moderate, and severe, each with two grades of severity, A and B. The newest and widely accepted classification scheme emphasises clinical signs of the syndrome (Golan 1989),[7] which is also divided into three categories: mild, moderate, and severe. Mild grade of the syndrome is characterized with high estradiol (E2) serum levels, mild abdominal distension, large ovaries up to 12 cm in diameter, nausea, vomiting, and diarrhea. Moderate level of OHSS include mild signs with clinical evidence of ascites and hydrothorax. Severe OHSS is further aggravated by hemoconcentration, coagulation and electrolyte disorders, oliguria/anuria, renal failure, hypovolemic shock, and ovarian enlargement above 12 cm.[1,3,7] Classically, the incidence of OHSS has been reported to vary from 8–23% in mild, 0.5–7%, in moderate, 0.8–10% in its severe form, respectively.[3]

Risk factors

Patients at risk of developing OHSS should be identified prior to preventive medicine and treatment because of risk factors or clinical predictors. The best known risk factor for OHSS is polycystic ovarian disease (PCOD), and a luteinizing hormone (LH) and follicle stimulating hormone (FSH) ratio higher than two is a valuable predictive tool. A novel ultrasonic risk factor, »the necklace« sign of the ovaries, is characterized by the presence of multiple small, immature, and intermediate, early, antral follicles 2 to 8 mm in diameter that are arranged as a string or palisade around the periphery of the ovary with abundant stroma in the deeper ovarian structures. This was described by several authors during the early follicular phase and eventually linked to OHSS. Although frequent in patients with a PCOD-like picture, this sign may appear in an individual with normal 25 to 35 day cycles.[1,8,9]

Similarly, OHSS correlates positively with luteal supplementation with human chorionic gonadotrophin (HCG) and conceptual cycles and is almost exclusively related to either exogenous or endogenous HCG stimulation.[5,6]

Other risk factors that are widely accepted include young age (<35 years), lean (asthenic) habitus, high serum E2 levels, hypothyroidism, hyperprolactinemia, oligomenorrheic and anovulatory infertility.[1,10] However, others have failed to find a correlation between either body mass index or body weight with propensity for OHSS.[11]

Peak levels of E2 are significantly higher in in vitro fertilization (IVF) cycles complicated by OHSS than in the control cycles. It has been suggested that the rate of serum E2 rise is more important than the absolute levels, with very rapid rises reflecting hypersensitivity of the ovary to stimulation. It was anticipated that it would be possible to define a peak limit of serum E2, above which the risk of OHSS would be so high that the treatment cycle should be abandoned, thereby avoiding OHSS. Although a marked interinstitutional variability of E2 levels exist and there is a lack of agreement as to the upper limit of E2, many authors consider that a significant risk of developing OHSS is increased once the concentration of 3000 pg/mL is reached, with different investigators quoting values from 1500 pg/mL to greater than 6000 pg/mL.[12,13] Asch et al.[14] described a 38% risk of severe OHSS in IVF cycles with peak E2 concentration exceeding 6000 pg/mL on the day of HCG administration and reported a good correlation between the number of follicles on ultrasound scan and the number of oocytes retrieved, and observed a 23% risk of severe OHSS if more than 30 oocytes were obtained. Morris et al.[17] found that the same criterion, using the same E2 assay, predicted only 8.8% risk of severe OHSS. The levels of E2 alone do not provide a clinically useful guide to the risk of OHSS, both because of the considerable overlap with normal cycles and the variation in assay results between laboratories. If no single factor can predict OHSS it might be hoped that a combination of features would be more successful.[1,12–17]

In addition to the epidemiologic, hormonal, and ultrasonic criteria, various stimulation protocols may offer relative protection of increased risk. OHSS may develop after ovulation induction with exogenous gonadotrophins or Clomiphene citrate (CC) followed by HCG which is required for triggering of ovulation. Luteinization, therefore, appears to be a prerequisite for the development of OHSS.[18] The sensitivity of the ovary to gonadotrophic stimulation and the magnitude of the ovarian response to gonadotrophins appear to be important determinants of the probability of developing OHSS, especially of »early« clinical form which appear 3–7 days after the ovulatory dose of HCG, whereas, »late« form of OHSS is more likely to be severe and appears 12–17 days following HCG and depends on the occurrence of pregnancy.[12,14,18] Women who develop OHSS, especially with low body mass index and PCOD, require significantly lower doses of human menopausal gonadotrophins (HMG) for stimulation and have a lower ratio of HMG dose duration of stimulation than the matched controls. There is no evidence that the use of purified FSH for ovarian stimulation alters the risk of OHSS. Studies comparing HMG and FSH for controlled ovarian stimulation do not indicate that one is better than the other with regard to the risk of OHSS. Several investigators have described the use of purified FSH in low doses by a step-up or incremental regimen in previously hyper-responsive patients[1,12,20,21] The routine use of gonadotrophin releasing hormone agonists (GnRH-a) for controlled ovarian stimulation has introduced an additional, though paradoxical, risk factor. A number of mechanisms have been described to account for this including the initial »flare-up,« a direct effect of GnRH-a on the ovarian stroma, and inhibition of premature luteinisation. GnRH agonists, by allowing us to prolong the stimulatory phase, abolish the body's protective mechanism of early luteinization, resulting in higher E2 values and a larger number of follicles selected. Thus, in contrast to patients with hypogonadotrophic hypogonadism, »medical hypophysectomy« induced GnRh-a confers increased risk rather than protection. Thus, the use of GnRH-a may be blocking a self-protecting mechanism (spontaneous LH surge with luteinization) that will check any further stimulation. In addition, the use of pituitary down-regulation requires that ovulation be induced by HCG, with probably higher risks of OHSS than the use of endogenous LH for ovulation.[21,22]

Pathogenesis

Because the intensity of the OHSS is related to the degree of ovarian response to ovulation induction therapy, OHSS is probably an exaggeration of normal ovarian physiology.[3] In understanding pathophysiology of OHSS it is essential to the rational development of strategies for preventing and treating it. The underlying cause of OHSS is not clearly known, but a vasoactive ovarian factor is likely to be involved. It is now generally accepted that this factor is liberated by the corpora lutea into the bloodstream where it is dispersed and exerts its effects. A vasoactive substance secreted by the ovaries under HCG

stimulation plays a key role in triggering the syndrome. Several substances have been proposed as the intermediary responsible for the increase in capillary permeability. Physiologically, this increase in capillary permeability results from a contraction of endothelial cells which leads to gap formation in between adjacent cells that allows a form of capillary transport and leads to third spacing. A number of studies have suggested several vasoactive substances and various pathophysiologic mechanisms, but a distinction should however be made between primary processes and compensatory mechanisms that are secondarily activated in the course of OHSS. The candidate mediators are cytokines (including allergenes-cytokines-histamine as a system), vascular endothelial growth factor (VEGF), angiogenin, the kinin kallikrein system, selectins, von Willebrand factors, prolactin, prostaglandins and the ovarian prorenin-renin-angiotensin system. The main conclusion is that OHSS is the result of disturbance of the basic inflammation – like normal ovulation process, and has its main feature of capillary leakage and transmission to other compartments.[24–26]

Because several cytokines, IL-2, IL-8, and especially IL-6, tumor necrosing factor alpha (TNF-alpha) mediate increases in vascular permeability and suppression of hepatic albumin production, that indicate its potential utility as OHSS markers. It was noticed that the serum concentrations of cytokines declined in parallel with the improvement of clinical conditions and resolution of OHSS which may be useful in the evaluation of severity of the syndrome. Because follicular fluid IL-6 concentrations at the time of oocyte retrieval and serum IL-8 concentrations at the time of embryo transfer were significantly higher in OHSS, that may serve as early predictors for this syndrome.[27,28]

In addition to inducing angiogenesis of endothelial cells in dominant follicle and corpus luteum of a natural cycle, which is more pronounced during ovarian stimulation, VEGF is regarded as the major capillary permeability factor in OHSS ascites, because 70% of the capillary permeability activity was neutralized by recombinant VEGF antiserum.[3,29,30] It was found that IVF patients suffering from OHSS had follicular, plasma and ascitic VEGF levels which were significantly higher and correlated to the clinical picture. Although HCG which binds to microvascular endothelial cells as a primary target plays a key role in the up-regulation and acute release of VEGF in OHSS, the addition of potent synthetic progesterone antagonist RU-486 reduces the extension of OHSS, which demonstrates that progesterone is in part implicated in the development of the sydrome.[31–33] It was noticed that the increased levels of VEGF under the action of gonadotrophins, act through an overexpressed VEGF receptor-2, that may be responsible for the accumulation of ascitic fluid.[34,35] Because VEGF levels are elevated in all the patients with hyperstimulated ovaries there is no signicant difference between those who develop OHSS and those who do not, and therefore plasma VEGF levels are poorly predictive of subsequent OHSS.[36] Because the patients with developed OHSS had significantly more free or unbound VEGF and lower follicular fluid and plasma levels of the binding protein, that offers a hypothesis of intermediate relationship which determines the patient who will be prone to OHSS.[37,38]

Many investigators have highlighted the role of the ovarian renin-angiotensin system and other endogenous vasoconstrictor systems in the evolution of systemic manifestations OHSS leading to the consideration of angiotensin converting enzyme (ACE) inhibitor to prevent or modify the course of OHSS.[39,40] However, it was shown that the primary importance in the pathogenesis of OHSS belongs to peripheral arterial vasodilatation suggesting that the activation of the renin-angiotensin system seen in OHSS might represent a secondary homeostatic response, rather than a primary pathogenic mechanism of the syndrome. Inhibition of angiotensin synthesis may not, therefore, be the key to preventing the actual occurrence of the syndrome, but may modify its course once established.[41,42]

Prevention

Key to the prevention of OHSS is a proper identification of the population at risk. Various methods for prophylaxis of OHSS or diminishing its severity have been suggested. Approximately two-thirds of the physicians preferred to apply some preventive measures while others selected only one preventive method.[1,3,16,25,26]

The oldest and the most effective has been to abandon the cycle. However, only 11% physicians would consider cancelling it because of high costs and tremendous hopes fostered by the couple. No relationship was found between the case-scenario description and the decision to cancel the cycle, although there was a relationship with the peak E2 concentration chart. However, even in the most severe case, for which a peak E2 level of 6590 pg/mL was rapidly reached, only a fifth of the physicians would consider cancelling that cycle. Furthermore, some physicians commented spontaneously that in their country only a limited number of IVF treatments are reinbursed by social security or insurance plans, whether the trials are completed or not. One may feel that it is neither ethically acceptable to have these factors influence the decision to proceed to a potentially dangerous procedure.[26]

Among different preventive measures, coasting clearly represents the most popular choice which is a preferred technique for about 60% physicians. The advantage of this technique is that the cycle is not abandoned i.e. induction of ovulation is stopped and HCG is witheld until serum E2 level decreases to »a safer zone«. In addition, coasting can be carried out in all countries, which is not the case for cryopreservation and the use of recombinant LH (r-LH). Some of the main retrospective studies presented encouraging results after coasting i.e. that the chances of pregnancy remain unaffected. However, others regarded coasting as effective as i.v. albumin in preventing OHSS in high risk patients but with inferior pregnancy rates. In addition, the longer the interval between discontinuing gonadotrophin administration and the administration of HCG, the lower the conception rate is likely to be.[12,13,43,44]

The ovulatory doses of HCG vary between centres from 1000 IU to 25 000 IU. The customary, average dose of ovulatory HCG is 10 000 IU. Higher doses of HCG (10 000 IU or more) are associated with a higher incidence of OHSS, but using a reduced dose of HCG (5000 IU) would exert a shorter period of stimulation and alleviate the symptoms of the syndrome. However, doses of HCG less than 5000 IU are associated with lower conception rates. The optimum dose of HCG is, therefore, a compromise between efficacy and comparative safety. Native LH differs significantly from HCG in significantly shorter half-life and binding to ovarian receptors with lower affinity and for a shorter duration than HCG. These characteristics would sugest that an endogenous LH surge produces less sustained luteotrophic stimulation and is less reliable to be followed by OHSS than exogenously administered HCG.[16,25,45,46]

Theoretically, a variety of hormonal and pharmacological compounds can be used as substitutes for the mid-cycle LH surge. Because the use of GnRh-a to effect pituitary down-regulation prior to initiation ovarian stimulation is associated with an increased risk of developing OHSS, the administration of r-LH derived from genetically engineered cells, instead of HCG, has been described as a possible preventive measure for OHSS and an effective alternative to HCG. The pharmacokinetics and bioactivity of rLH appear to be similar to those of native LH, possibly making it less likely than HCG to cause OHSS. However, only 13% physicians advocated the administration of rLH instead of HCG. This low percentage is probably due to the fact that in many countries rLH is not commercialized, as was commented by several respondents.[47] The risk for OHSS may be also reduced by using subcutaneous or nasal administration of GnRh-a that is acceptable as an effective alternative in place of HCG to induce preovulatory LH surge, which unfortunatelly could be used only in the cycle where down regulation has not been affected with GnRh-a. The relatively short life – life 3 to 5 hours of GnRh-a may conceivably eliminate the risk of OHSS in non-conception cycles. The main disadvantage in this regimen is that it is not applicable with GnRh-a suppression, which are the most prevalent treatment schedules currently used. Alternativelly, in patients who have been pre-treated with GnRh antagonists during ovarian stimulation, the pituitary gonadotrophins retain their sensitivity to GnRh-a to induce ovulation, enabling the resulting endogenous LH surge, which is probably less likely to be associated with OHSS than the use of HCG.[21–23,25,43,48]

It has been suggested that follicullar aspiration after HCG triggering, but before oocyte retrieval, protects against severe OHSS by causing intrafollicular hemorrhage, leading to a decline in the ovarian production of substances responsible for its occurrence in high risk patients of OHSS.[49] Few physicians (9%) chose to proceed to two follicular aspirations during the same IVF cycle, a method which has been previously published. By using early follicular aspiration more oocytes were retrieved, however the method of follicular aspiration followed by oocyte retrieval was not selected by all physicians because it was considered to be to invasive.[1,25,49,50]

Cryopreservation avoids the risk of pregnancy and of endogenous production of HCG, a well-known promoting factor of severe OHSS. Withholding of embryo transfer and its replacement at a later date as an elective cryopreservation of all embryos, a decline in the severity of OHSS has been found, but without totally eliminating it. By using cryopreservation the reduction of the risk of OHSS was estimated to be similar to that obtained by coasting and that of albumin administration. It is possible that cryopreservation was less often selected because of its negative psychological impact and the prevailing opinion that the chances for pregnancy are reduced when thawed embryos rather than fresh ones are transferred. However, very favorable implantation rates in a series of cases with cryopreserved embryos for OHSS prevention were obtained, although one should note that cryopreservation is not available in all countries.[47,51,52] Alternatively, instead of cryopreservation a novel approach of prolonging the evaluation time for up to 5 and 6 days after the oocyte retrieval and transferring of a single zona free embryo (blastocyste) offers for patients at risk for developing OHSS.[53]

It is consistently well-known that HCG could exacerbate OHSS and there is a significantly higher incidence of the syndrome if ovulation was triggered with HCG. Severe OHSS is very rare in the absence of luteal support with HCG, either exogenous or pregnancy-derived. Therefore, if luteal HCG is withheld and luteal support bypassed and substituted with progesterone, OHSS will be largely prevented. It is not clear whether HCG or progesterone provides the better pregnancy rates, and meta-analysis of all IVF luteal support regimens found no significant difference between the two options. In contrast, when cycles using GnRh-a were analyzed separately, luteal support with HCG was associated with a significantly higher pregnancy rate. Given the likelihood that luteal HCG can induce or worsen OHSS, it would therefore seem prudent to avoid its use in cycles deemed to be at risk for this complication.[1,25,54]

The existence of several substances with inhibiting effects on VEGF offers a new modality of preventing vascular permeability in patients with OHSS.[33,55] Administration of corticosteroids (methylprednisolone) used by some failed to demonstrate any beneficial effect on preventing OHSS.[56] Conversely, the others demonstrated that corticosteroids appear to reduce the risk for OHSS thus helping to avoid hospitalization, reducing cycle cancellations, and improving the cost-effectiveness of IVF cycles.[57] Metformin appears to reduce the risk for OHSS during gonadotrophin stimulation in women with PCOS by lowering intraovarian androgen levels and E2 blood concentrations.[58] Although pentoxyphyline was found to inhibit TNF-alpha synthesis, it did not prevent ascites formation, despite the observation in decrease in ovarian weight and number of ovulations in OHSS.[59]

In the cycle of ovulation induction where OHSS seems likely, conversion to IVF and aspiration of all the follicles

has been advised, however later persisted a 15% incidence of severe OHSS.[1,3,25,26]

Treatment

The treatment of OHSS is conservative and bed rest with symptomatic relief are usually sufficient for mild and moderate stages. In *mild* cases, symptoms subside usually within a few days, while in *moderate* cases, symptoms can require up to three weeks to subside especially when pregnancy occurs. *Severe* OHSS can be life-threatening and patients therefore should be hospitalized and monitored closely. Patients are put on bed rest, daily body weight and fluid balance monitoring are necessary; hematocrit, coagulation, and kidney functions, serum electrolyte and albumin studies are obtained daily, as well as ultrasound scan of the pelvis and chest; oxygen saturation measurements (using an oxymeter while breathing air, and if less than 85% using blood gases) should be performed if dyspnea is notified; and pelvic examination should be avoided because of fragility of the enlarged ovaries, and ovarian surgery is relatively contraindicated.[1,3,15,16,25]

Hypovolemia and hemoconcentration need immediate corrections. When necessary, intravenous crystaloid infusion or macromolecular plasma expanders (human albumin or hydroxyethyl) administered around the time of oocyte retrieval were first suggested as measures in the prevention and treatment of severe OHSS in high risk women to maintain central venous pressure. Albumin was generally considered as a safe product that acts by inactivating and binding the ovarian vasoactive factors which contribute to the development of OHSS, with a half-life up to 19 days. The role of albumin is also to maintain plasma oncotic pressure by drawing fluid from the third space into the vascular compartment, and preventing the ensuing effects of hypovolemia, ascites, and hemoconcentration, representing the volume expander of choice.[3,24,25,43,51,59,60] However, more recent, prospective, randomized, placebo-controlled double blind studies were controversial because they could not confirm this beneficial effect. Paradoxycally, it was concluded that albumin is ineffective and even dangerous because of well-documented serious risks, which include exacerbation of the syndrome, and therefore this form of treatment should not be included in the regimen of OHSS prevention and treatment.[3,61–64]

Diuretics, although highly controversial, do have a role in the treatment of OHSS, and should be administered with caution since the fluids in the abdominal and thoracic cavity are not responsive, and even the further intravascular depletion can cause hypotension, shock and thrombosis. Therefore, diuretics should be administered following pre-treatment with albumin when hemodilution has been achieved.[1,3,7,16,23]

Paracentesis constitutes the single most important treatment modality in life-threatening OHSS not controlled by medical therapy. It is usually immediatelly accompanied with dramatic improvement in clinical symptoms and almost instantaneous diuresis. The indications for paracentesis include the need for symptomatic relief, a tense ascites, oliguria, rising creatine and creatinine clearance, and hemoconcentration unresponsive to medical therapy. Ultrasound transvaginal guidance is obligatory, and up to 4 litres of ascitic fluid may be removed by slow drainage.[1,3,23] The best correlation with the severity of OHSS is an elevated hematocrit, which directly reflects an intravascular volume depletion and blood viscosity.

In cases of impeding thromboembolic phenomena heparin is indicated, whereas cauterization or laser vaporization, abdominal surgery and therapeutic termination of pregnancy are reserved in a life-threatening situations when all other measures have failed.[1,3,63–65]

Despite many years of clinical experience, pathophysiology is still poorly understood and there is no reliable test to predict who of the patients at risk will subsequently develop OHSS. Additional and properly conducted studies with larger number of patients are required in order to determine the best method and strategy for the prevention and treatment of OHSS.

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Paper received: 18. 12. 2003.; *accepted:* 3. 02. 2004.

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