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OVARIAN HYPERSTIMULATION SYNDROME. THE NEW APPROACHES FOR DIAGNOSIS, TREATMENT AND PREVENTION

Summary. *Ovarian hyperstimulation syndrome (OHSS) is the most serious consequence of induction of ovulation, as part of assisted conception techniques. Although the ultimate physiologic mechanism of OHSS is not yet known, there are well-known risk factors that must be considered during the administration of medications to treat infertility. The clinical course of OHSS may involve, according to its severity and the occurrence of pregnancy, electrolytic imbalance, neurohormonal and hemodynamic changes, pulmonary manifestations, liver dysfunction, hypoglobulinaemia, febrile morbidity, thromboembolic phenomena, neurological manifestations and adnexal torsion. Specific approaches such as paracentesis, pleural puncture, surgical approach of OHSS and specific medication during OHSS were evaluated sporadically. More adequate treatment methods would require a better understanding of the underlying pathophysiological mechanisms, to promote an etiopathogenic therapeutic approach. The following review aims to examine the available evidence to guide best practice in diagnosis, treatment and preventing ovarian hyperstimulation syndrome.*
Key words: *ovarian hyperstimulation syndrome, in vitro fertilization, human chorionic gonadotrophin, anti-müllerian hormone, cabergoline, relcovaptan, GnRH agonists, cryopreservation.*

Ovarian hyperstimulation syndrome (OHSS) is encountered in practice as an iatrogenic complication of controlled ovarian stimulation (COS). COS is aimed at producing multiple ovarian follicles during assisted conception cycles in hope of increasing the number of oocytes available for collection. OHSS, however, is characterised by an exaggerated response to this process [ASRM., 2008]. OHSS was first described in 1943, and the first fatal cases were documented in 1951. As many as 33% of IVF cycles have been reported to be associated with mild forms of OHSS. While these are often described as not being clinically significant, the severity of OHSS can worsen over time and even initially mild presentations should be kept under review. More severe OHSS has been reported in 3,1-8,0% of IVF cycles. This calculation lends important perspective on the potential impact of this condition. Notably, mortality is rare but several cases have been reported. The incidence of OHSS is increased in young women, women with polycystic ovaries and in cycles where conception occurs, particularly multiple pregnancies [Nastri et al., 2015].

The precise cause of OHSS is currently unknown and is the subject of controversy, however, ovarian response is directly correlated with risk of OHSS. Typically, OHSS is a phenomenon which is associated with gonadotrophin use during COS. There are instances, however, where OHSS has been documented to arise spontaneously either in conjunction with clomiphene or with gonadotrophin releasing hormone use [Tan, Mathur, 2013]. Increased estradiol levels occurring in such a scenario are important, but are unlikely to be high enough to cause OHSS; nevertheless, in the presence of human chorionic gonadotropin (hCG), high estradiol levels may increase the expression of cystic fibrosis transmembrane conductance regulator leading to a massive shift in body fluids through epithelial ion channels. There is also evidence of an increased secretion of inflammatory mediators, vascular endothelial growth factor (VEGF) and activation of the renin-angiotensin system in women with OHSS. VEGF seems to play a key role in the pathophysiology of OHSS, with a probable mechanism of action dependent on hCG, acting on cell-to-cell adhesion complexes in the endothelium, particularly claudin [Papanikolaou et al., 2010]. VEGF concentration has also been shown to be increased in the follicular fluid, but not in the blood, of women who undergo final oocyte maturation triggering with hCG, compared to maturation triggering with a gonadotropin-releasing hormone (GnRH) agonist. The first objective of the present review was to identify, appraise and summarize the predictive accuracy of tests aimed at identifying women who develop an exaggerated response to COS and/or who develop OHSS during ART. The second, and equally important, objective was to identify and estimate the effect of interventions aimed at reducing the risk of a high ovarian response during COS and/or the occurrence of OHSS [Nastri et al., 2015].

This review *aims* to examine the pathophysiology of OHSS and the evidence behind the various methods employed by clinicians to prevent its occurrence.

A literature search was carried out on the following electronic databases (until April 2015): MEDLINE, EMBASE, PubMed database, and the Cochrane central register of controlled trials. Only articles in English were taken into consideration and abstracts were excluded. A combination of text words or Medical Subject Headings (MeSH) terms were subsequently utilized to generate a list of citations: ("OHSS" OR "ovarian hyperstimulation syndrome") AND ("diagnosis, treatment, prevention"). Articles and their references were then examined in order to identify other potential studies which could provide perspective for the following review.

Systematic reviews, meta-analyses, and randomized controlled trials (RCTs) were then preferentially selected over other forms of data where feasible in order to formulate the following review and recommendations.
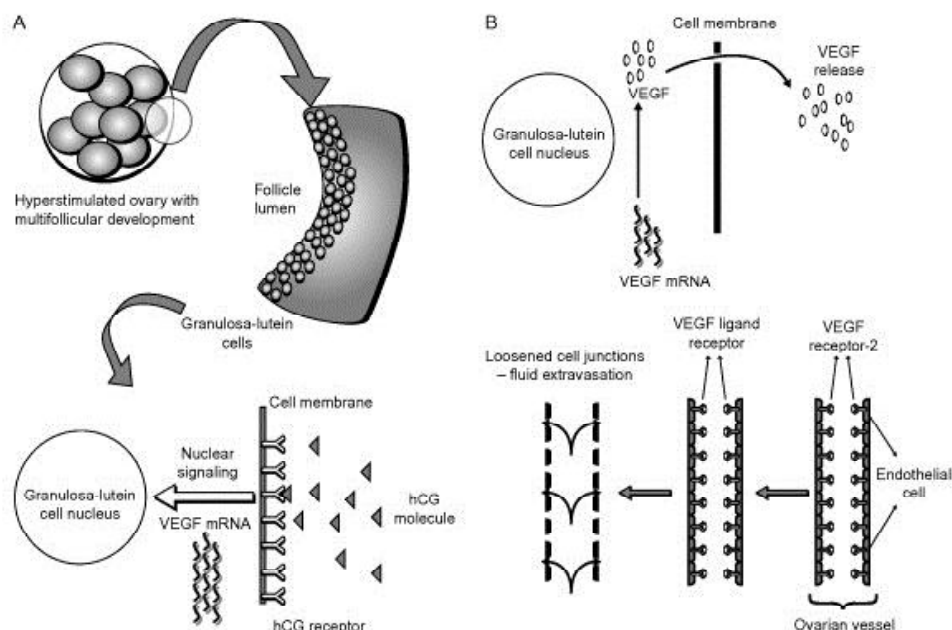
OHSS is an exaggerated response to COS characterized

by the shift of protein-rich fluid from the intravascular space to the third space, mainly the abdominal cavity that occurs when the ovaries become enlarged due to follicular stimulation [Delvinge, Rozenberg, 2002]. This shift in fluid is due to increased vascular permeability in response to stimulation with human chorionic gonadotropin (hCG). Prostaglandins, inhibin, the renin-angiotensin-aldosterone system and inflammatory mediators have all been implicated in the aetiology of OHSS, however, vascular endothelial growth factor (VEGF) has been identified as the major mediator (Figure 1). The expression of VEGF and VEGF receptor 2 (VEGFR-2) mRNA increases significantly in response to hCG, and peak levels

Fig.1. The pathogenesis of OHSS. Human chorionic gonadotropin (hCG) stimulates a high number of granulosa-lutein cells leading to the increased production of vascular endothelial growth factor (VEGF) mRNA (Figure 1A); VEGF receptor-2 (VEGFR-2) mRNA production in the granulosa-lutein and endothelial cells is also increased in response to hCG. High amounts of VEGF are produced and released from the granulosa-lutein cells and bind to VEGFR-2 on the endothelial cell membranes. Downstream signaling augments vascular permeability (Figure 1B). Adapted from Tollan, et al., 1990.

coincide with maximum vascular permeability. The clinical manifestations of OHSS reflect the extent of the shift of fluid into the third space and the resulting hemoconcentration due to intravascular volume depletion. Symptoms range from mild abdominal distention due to enlarged ovaries alone or with an accompanying fluid shift into the abdomen, to renal failure and death as a result of hemoconcentration and reduced perfusion of organs such as the kidneys, heart and brain.

We found seven different classifications based on the severity of OHSS (Tab. 1). Although many of the studies were published decades ago, they are still valid and might be useful in clinical practice [Nastri et al., 2015].

Seven studies were included, the number of participants in each ranging from 107 to 256. The incidence of moderate/severe OHSS in these studies was 3.8% (95% CI, 2.3-5.6%). All studies were considered to be at low risk of bias and concerns regarding applicability, according to QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies-2).

Hormonal markers are also increasingly being utilized in predicting ovarian response to stimulation. Anti-Müllerian Hormone (AMH) in particular is a marker which shows much promise. Gnoth et al., in their prospective study of 316 women, have demonstrated that AMH [AMH$\leq$0,18pmol/L (1,26 ng/mL)] can identify normal responders ($\geq$4 oocytes retrieved) to COS with a success rate of 98% [Broer et al., 2011]. This predictive capacity extends to identifying women

at risk of developing OHSS as well. Using receiver operating characteristics (ROC) curves, Lee et al. have identified a high pretreatment basal AMH concentration [AMH >0,47 pmol/L (3,36 ng/mL)] as a useful predictor of developing OHSS (sensitivity 90,5%, specificity 81,3%). Moreover, AMH performed better than weight, age, or ovarian response markers in identifying these women. Given its low inter- and intracycle variability, AMH has the potential to become an excellent predictive tool should issues surrounding its validity be completely resolved [Dewailly et al., 2014].

Absolute serum oestradiol (E2) concentrations, however, have performed poorly in identifying women at risk of developing OHSS. This can mostly be attested to the marked heterogeneity in studies with regard to the threshold E2 levels used to define high risk women [Aboulghar, Mansour, 2003].

Ultrasonographic markers, such as the antral follicle count (AFC), are also another facet worthy of mention in the prediction of OHSS. Available evidence suggests that the AFC is equally predictive of excessive response to COS and OHSS as the basal serum AMH. Jayaprakasan et al., in their prospective study of 1012 subjects, noted an AFC$\geq$24 to be correlated with an increased risk of moderate to severe OHSS in comparison to an AFC<24 (8.6% versus 2.2%). These findings are mirrored by Delvigne and Rozenberg who cite an increased risk of OHSS with an AFC (2-8 mm) $\geq$12. There are, however, variances amongst the studies regarding the definition of what constitutes antral follicles on ultrasound

Table 1. Classification of ovarian hyperstimulation syndrome (OHSS) by severity and time of onset, as determined previously in 15 studies included in the meta-analysis.

Severity:	Mild	Moderate	Sever
Rabau (1967)	Grade 1: Estrogen >150 μg/24 h and pregnanediol>10 mg/24 h Grade 2: Grade 1+enlarged ovaries and possibly palpable cysts	Grade 3: Grade 2+confirmed palpable cysts and distended abdomen Grade 4: Grade 3+vomiting and possibly diarrhea	Grade 5: Grade 4+ascites and possibly hydrothorax Grade 6: Grade 5+changes in blood volume, viscosity and coagulation tim
WHO (1973)	Grade 1: Variable ovarian enlargement sometimes associated with small cysts; urinary estrogen levels>150 μg/24 h and pregnanediol excretion titers>10 mg/24 h	Grade 2: Additional symptoms of a variable nature: abdominal distension, nausea, vomiting and diarrhea	Grade 3: Large ovarian cysts, ascites and sometimes hydrothorax; hemoconcentration with increased blood viscosity and coagulation abnormalities may appear
Schenker (1978)	Grade 1: Estrogen >150 μg/24 h and pregnanediol>10 mg/24 h Grade 2: Grade 1+enlarged ovaries, sometimes small cysts	Grade 3: Grade 2+abdominal distension Grade 4: Grade 3+nausea, vomiting and/or diarrhea	Grade 5: Grade 4+large ovarian cysts, ascites and/or hydrothorax Grade 6: Marked hemoconcentration +increased blood viscosity and possibly coagulation abnormalities
Schwartz (1981)	Lower abdominal discomfort; ovaries slightly enlarged, but no larger than 5x5 cm, and no marked weight gain.	Ovaries enlarged up to 10x10 cm; some ascites and weight gain of up to 100 lbs	Ovaries extremely enlarged and easily palpated abdominally; ascites, pleural effusion, oliguria, hemoconcentration, hypotension, azotemia and electrolyte imbalance occur; increased blood coagulability and weight gain of more than 10 lbs are common
Golan (1989)	Grade 1: Abdominal distension and discomfort Grade 2: Grade 1+nausea, vomiting and/or diarrhea, enlarged ovaries 5-12 cm.	Grade 3: Grade 2+US evidence of ascites	Grade 4: Grade 3+clinical evidence of ascites and/or hydrothorax and breathing difficulties Grade 5: Grade 4+hemoconcentration, increased blood viscosity, coagulation abnormality and diminished renal perfusion
Navot (1992)			Severe OHSS: variable enlarged ovary; massive ascites, hydrothorax; Hct>45%; WBC>15 000; oliguria; creatinine 1.0-1.5 mg/dL; creatinine clearance>50 mL/min; liver dysfunction; anasarca Critical OHSS: variable enlarged ovary; tense ascites, hydrothorax; Hct>55%; WBC>25 000; oliguria; creatinine>1.6; creatinine clearance<50 mL/min; renal failure; thromboembolic phenomena; acute respiratory distress syndrome
Risk (1999)		Discomfort, pain, nausea, distension, US evidence of ascites and enlarged ovaries, normal hematological and biological profiles.	Grade A: Dyspnea, oliguria, nausea, vomiting, diarrhea, abdominal pain, clinical evidence of ascites, marked distension of abdomen or hydrothorax, US showing large ovaries and marked ascites, normal biochemical profile Grade B: Grade A+massive tension ascites, markedly enlarged ovaries, severe dyspnea and marked oliguria, increased Hct, elevated serum creatinine and liver dysfunction Grade C: Complications such as respiratory distress syndrome, renal shut-down or venous thrombosis.

which limits their applicability [Delvinge, Rozenberg, 2002].

Body mass index was found to be a moderately useful test, though with lower accuracy compared to the aforementioned tests, but it, also, was only evaluated in one small study. During COS, OHSS may be predicted successfully by three markers of high ovarian response: estradiol levels, medium/large follicle count on the day of hCG administration and the number of oocytes retrieved subsequent to follicle aspiration. These three tests were evaluated by more than one study, and accounted for a relatively high number of participants. The estimate on vascular endothelial growth factor (VEGF) was too imprecise to reach any conclusion regarding its applicability [Nastri et al., 2015].

Eight studies evaluated high ovarian response, which was defined as more than 15-20 oocytes retrieved. We identified eight studies encompassing 34 databases; the number of participants in each study ranged from 110 to 4650. One study was an individual patient meta-analysis that included databases from five other identified studies, accordingly these five studies were removed from the analysis to avoid duplication of the participant count. Another study was reported by four articles and information from all of them was used in this review. This study was deemed to be at high risk of applicability bias because extremely strict inclusion/exclusion criteria were adopted. All other studies were considered as being at low risk of bias according to QUADAS-2 [Nastri et al., 2015].

The calculated estimates of interventions to reduce the occurrence of OHSS and its precision, the interpretation of the observed effect, the assessed heterogeneity, the number of studies and participants included and the overall quality of evidence was described considering all evaluated interventions and comparisons.

The mechanisms underlying the potential effect of intravenous fluids on OHSS is unknown, however, some theories have been suggested. One theory attributes a beneficial effect of the binding properties of albumin in neutralizing vascular permeability mediators that could be responsible for the onset of OHSS. Another theory is that intravenous fluids, such as albumin and hydroxyethyl starch (HES), promote a rapid increase in intravascular volume, which could maintain the volume in the event of capillary leakage, thus avoiding hypovolemia and hemoconcentration. This theory is, however, somewhat inconsistent, as two-thirds of the infused albumin is rapidly distributed across the capillary membrane, even when permeability is normal, thus increasing the albumin concentration in extracellular fluid. Similarly, 16% of the infused HES shifts to the extravascular space soon after administration. HES is a plasma expander that has been mooted as an alternative to albumin as it is nonbiological and therefore negates the above-mentioned risks associated with albumin use. The evidence behind its benefit is certainly more robust as well. The Cochrane Review by Youssef et al. noted that there was a statistically significant decrease in severe OHSS (OR 0,12; 95% CI 0,04-0,40) with HES use without any effect on pregnancy rates (OR 1,20; 95% CI 0,49-2,95). There is also a systematic review on the topic51, the authors of which included eight of the 10 studies evaluated in the present review. They also observed a decrease in rates of OHSS with a small decrease in rates of clinical pregnancy [Venetis et al., 2011].

The GnRH antagonist competes with the natural GnRH for its receptor, causing a fast and reversible suppression of gonadotropin release, and constitutes an alternative for the prevention of premature luteinizing hormone (LH) surges during COS. The introduction of a GnRH antagonist in COS enables the use of shorter protocols with reduced amounts of gonadotropin. We identified 28 studies that compared the effect of using a GnRH antagonist with long GnRH agonist protocols in women undergoing ART. In 12 studies, the antagonist was used in daily doses, beginning on a fixed day of COS; in one study a single dose of long-lasting antagonist was used; in 14 studies the antagonist was used in daily doses beginning on a flexible day depending on the size of the leading follicle. Although the stimulation protocols differed between the studies, the heterogeneity found was not substantial and the estimates could be pooled together. We observed moderate-quality evidence showing that antagonist protocols are associated with a lower risk of OHSS and that they are unlikely to have a clinically relevant impact on clinical pregnancy rate [Nastri et al., 2015].

Aspirin inhibits a cyclo-oxygenase enzyme in platelets, preventing the synthesis of thromboxane, thus having been tested as an intervention to improve pregnancy rates in ART. Two studies evaluating the effect of administering 100 mg/day aspirin during COS reported OHSS. The average rate of OHSS in the control groups was 6%. Both reported rates of OHSS incidence and clinical pregnancy. They described very low-quality evidence for the benefit of aspirin compared with no intervention with regard to rates of OHSS and found no effect on clinical pregnancy. Considering these two studies, along with the other 15 studies that evaluated the effect of aspirin on clinical pregnancy, pooled for two published systematic reviews, we observed high-quality evidence that aspirin does not reduce rates of clinical pregnancy [Nastri et al., 2015].

We identified 11 studies that utilized dopamine agonists for the prevention of OHSS. Cabergoline is a dopamine antagonist which prevents the excessive increase in VEGF mediated vascular permeability encountered with OHSS through its antiangiogenic properties [Venetis et al., 2011]. Tang et al. in their Cochrane Review of 230 women in 2 RCTs found cabergoline to be effective in significantly reducing the incidence of moderate OHSS (OR 0,38; 95% CI 0,19-0,78) with no significant effect on clinical pregnancy rate and miscarriage rates. This protective effect, however, did not extend to severe OHSS, possibly due to the number of studies available for comparison [Tang et al., 2012]. A recent systemic review by Leitao at el. on the issue, which took 7 RCTs into consideration, has further established its efficacy in preventing the occurrence of moderate and severe OHSS (RR 0,38; 95% CI 0,29-0,51) as well as without a negative impact on clinical pregnancy or oocytes retrieved. Therefore, the use of cabergoline is recommended and it is suggested that treatment be commenced on the day of hCG trigger at a dose of 0,5 mg for 8 days [Kasum et al., 2014].

Amongst the novel therapies being investigated for the prevention of OHSS, the vasopressin V1a receptor antagonist, relcovaptan, has been studied for its ability to inhibit VEGF by modulating vasoconstriction and vascular smooth muscle proliferation. Relcovaptan, in the hyperstimulated rat model, has shown lower concentrations of VEGF-A in the peritoneal fluid and lesser ovarian weight gain significant decreases in the number of corpora lutea in contrast to control groups. Further research in this area remains rather promising and may broaden the management protocols which clinicians have for OHSS in the near future [Cenksoy et al., 2014].

"Coasting" is defined as the withholding of ovarian stimulation drugs for a few days, waiting for a time when it would be safer to trigger the final maturation with hCG. Coasting is a commonly used first line secondary prevention strategy by clinicians [Delvinge, Rozenberg, 2002]. Question marks remain however about the evidence behind the procedure. D'Angelo et al., in their Cochrane Review, identified 4 RCTs which highlighted that there was no difference in the incidence of moderate and severe OHSS (OR 0,53, 95% CI 0,44-1,08) with coasting. In addition, a lower number of oocytes were retrieved from the coasting group which prompted them to recommend that there was no benefit of coasting in comparison to other interventions [SOGC-CFAS, 2011]. An earlier meta-analysis also came to the conclusion that coasting may decrease the risk of OHSS in high risk women but does not completely prevent it. Coasting, however, seems to have no effect on live birth rates and clinical pregnancy rates [Nastri et al., 2015].

Aspiration of the follicles from one ovary before this final maturation has been proposed as an intervention to decrease the risk of OHSS. Follicle aspiration is believed to cause intrafollicular hemorrhage and a decline in some ovarian substances, such as estradiol, progesterone and hCGThree studies evaluated unilateral follicular aspiration before final oocyte maturation: one compared this with standard care, one with coasting and one with albumin 50 g. In two studies, complete aspiration of one ovary was performed before hCG was administered, and in one study, aspiration was performed 10-12 h after administration of hCG. All three studies reported cases of OHSS but only two reported rates of clinical pregnancy, however, the estimates were too imprecise for any conclusion to be drawn [Nastri et al., 2015].

One strategy to decrease hCG exposure would be to limit the use of hCG to the trigger dose only, avoiding extended exposure to the natural hCG from pregnancy, which could prolong and worsen an otherwise brief OHSS. In 'freeze all' following oocyte retrieval, all oocytes/embryos are cryopreserved and, afterwards, transferred in a non-stimulated cycle. A Cochrane Review only identified 2 RCTs for analysis and came to the conclusion that there was insufficient evidence to support routine cryopreservation [Nastri et al., 2015]. Recent evidence however strongly supports the use of a GnRHa trigger followed by cryopreservation as being the most effective method in preventing OHSS, best illustrated by Devroey and colleagues through their OHSS-Free Clinic.

OHSS-related complications could theoretically be eliminated if hCG was not used, and very few cases of OHSS without the use of hCG for final maturation have been reported. In order to completely avoid OHSS, cycle cancellation before final follicular maturation with hCG is a simple and safe alternative. It is, however, associated with significant emotional and financial burdens for the couple. Other options would be to replace hCG with GnRH agonists therefore reducing the hCG dose. There is consensus on the fact that reducing the duration of gonadotrophin exposure reduces the risk of OHSS. One way this is achieved is through "mild" stimulation protocols which delay the administration of FSH till the mid or late follicular phase. However, the addition of GnRH antagonists for late cycle suppression of gonadotrophin release has resulted in improved clinical outcomes, a lower risk of OHSS, and multiple pregnancies and made it cost effective as well. On a side note, the pooled data of 3 RCTs have shown mild stimulation to be less effective than conventional "long" regimens in terms of the pregnancy rates per cycle (15% versus 29%) [Mathur, Sumaya, 2008].

Ketoconazole inhibits key steroidogenic enzymes of the p450 family. In the ovary, it acts in the theca and granulosa cells, leading to reduced estradiol production, and high estradiol levels are correlated with an increased risk of OHSS. Two studies were included, one of which evaluated the use of ketoconazole 50 mg/day starting on Day 4 of stimulation until hCG administration compared with no drug, and the other compared ketoconazole 50 mg every other day, from

Day 1 to the last day of administration of human menopausal gonadotropin (hMG) compared with placebo. Both reported rates of OHSS and clinical pregnancy, the average rate of OHSS in the control groups was 17,3%. The estimates of the effect on both OHSS and clinical pregnancy were too imprecise for any conclusions to be drawn [Nastri et al., 2015].

PCOS may be associated with some hormonal changes, such as hyperandrogenism and hyperinsulinemia, and anovulation. The granulosa cells' intracellular metabolism of glucose, dependent on insulin, is impaired in women with anovulatory PCOS while their LH-dependent glucose metabolism is normal. Metformin is a biguanide that enhances insulin sensitivity not only in the liver but also peripherally, in target tissues. One of these target tissues is the granulosa cells in the ovaries. Metformin changes the insulin-dependent metabolism of glucose in granulosa cells, and decreases ovarian sensitivity to FSH, possibly ameliorating the response to COS. Metformin is theorized to exert its influence in preventing OHSS by inhibiting the secretion of vasoactive molecules, such as VEGF, during OI and thereby modulates vascular permeability. In the recent Cochrane Review by Tso et al., based upon 8 RCTs with 798 women, it was noted that there was a lower risk of OHSS with metformin use (OR 0,29; 95% CI 0,18-0,49). It was also of note that metformin reduced the risk of OHSS by 63% and increased the clinical pregnancy rate (OR 1,52; 95% CI 1,07-2,15) without an effect on live birth rates [Tso et al., 2014]. These findings were consistent with an earlier systemic review by Palombo et al., which described a significantly lower OHSS rate with metformin administration too (0,27; 95% CI 0,16-0,46). Based on the studies, a daily dose between 1000 and 2000 mg at least 2 months prior to COS is recommended for the purpose of preventing OHSS [Nastri et al., 2015].

Extensive ovarian stimulation may take several weeks, cause discomfort and increase the risk of adverse symptoms. OHSS is dependent on the degree of ovarian stimulation and is expected to be more frequent as more follicles are stimulated. Moreover, there is concern regarding the abnormal luteal-phase endocrinology and its impact on embryo genetics and endometrial receptivity. Stimulation protocols that include daily FSH doses of less than 150 IU are considered to be milder than the traditional protocols and are expected to cause fewer adverse events, including OHSS. Eight studies evaluated milder ovarian stimulation compared to the long-agonist protocol. They all reported OHSS and clinical pregnancy rates; the average rate of OHSS in the control groups was 4,6%. We observed moderate-quality evidence that mild stimulation reduces OHSS without producing a clinically relevant difference in clinical pregnancy rate [Nastri et al., 2015].

Aromatase Inhibitors (AIs), such as letrozole, function by downregulating oestrogen production through inhibition of cytochrome P450 enzymes. This causes an increase in pituitary secretion of FSH which promotes folliculogenesis. In addition, the central negative feedback mechanisms still remain intact, which leads to the theory that it may reduce

the incidence of OHSS during ovulation induction (OI). A recent Cochrane Review by Franik et al., however, failed to show any difference in OHSS rates through utilization of AIs in contrast to other methods of OI. As such, AIs are not routinely recommended [Franik et al., 2014].

This meta-analysis combined data from studies that differed in the baseline OHSS risks as well as in nuances in the interventions or predictive tests analyzed. Before starting COS, the assessment of either AFC or AMH levels allows prediction of the risk of facing a high ovarian response to COS. Other baseline parameters, such as age, FSH and inhibin-B levels, have lower predictive accuracy. At this point, COS might be planned according to the assessed risk. The use of a GnRH antagonist protocol (with either standard or, preferably, mild stimulation) is beneficial to high-risk women as it markedly decreases the incidence of OHSS without affecting clinical pregnancy. Another option is the use of aspirin throughout COS until the pregnancy test is performed, as it possibly reduces the risk of OHSS without interfering with reproductive outcome; increased bleeding during oocyte retrieval due to aspirin is not an issue [Nastri et al., 2015]. However, there is one point to consider before deciding to use this intervention: aspirin is unlikely to reduce the occurrence of a high response to ovarian stimulation, and some patients/clinicians will probably consider using additional strategies in such a situation.

On the day of hCG administration, the risk of OHSS may be predicted by serum estradiol levels and a medium/large follicle count. In the case of a high-risk situation, administration of cabergoline or another dopamine agonist may be initiated, as they markedly decrease the incidence of OHSS without affecting clinical pregnancy. If an imminent risk of OHSS is identified, a possible alternative is to use an agonist for the final maturation, as it strongly reduces OHSS risk. There is, however, concern regarding a possible negative effect on clinical pregnancy, and the freezing of all oocytes/embryos for later transfer would constitute a conservative approach. The other interventions identified that seem to be beneficial, but for which the evidence is still of very low quality, are: albumin or other plasma volume expander, coasting, metformin for PCOS women and intravenous calcium gluconate. Some studies also evaluated early unilateral follicular aspiration, the use of lower doses of hCG for the final maturation and luteal support after agonist triggering, glucocorticoids following oocyte retrieval, ketoconazole, increased progesterone for luteal support and laparoscopic ovarian drilling; however the estimates of effect are imprecise and no conclusions may be drawn. There are useful predictive tools and several preventive interventions aimed at reducing the incidence of OHSS. Having a good understanding of these tools and interventions is of crucial importance for planning the treatment of, and, ultimately, eliminating the occurrence of, OHSS, while maintaining high pregnancy rates.

Conclusion and prospects for future research in this direction

1. OHSS is a complication associated with COS which clinicians have no complete way of preventing at present.

2. Through the various prevention strategies reviewed in this paper, there are avenues by which its incidence can be greatly reduced.

3. This begins with the identification of the "high risk" woman through to the woman who is "at risk" and subsequently initiating the appropriate therapies.

The further research initiatives should be directed in a bid to strengthen the preexisting evidence base for available therapies and to develop novel techniques to aid in the prevention of OHSS. Continued research will further our understanding of the pathophysiology of OHSS and may advance our ability to predict and prevent this potentially serious illness.

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Булавенко О.В., Коньков Д.Г., Буртяк Н.Г.
СИНДРОМ ГИПЕРСТИМУЛЯЦИИ ЯИЧНИКОВ. НОВЫЕ ПОДХОДЫ ДЛЯ ДИАГНОСТИКИ, ЛЕЧЕНИЯ И ПРОФИЛАКТИКИ
Резюме. *Синдром гиперстимуляции яичников (СГЯ) является наиболее серьезным последствием индукции овуляции, при вспомогательных репродуктивных технологиях. Хотя механизм СГЯ пока не известен, существуют факторы риска, которые должны быть рассмотрены во время назначения препаратов для лечения бесплодия. Клинические симптомы СГЯ могут включать, в соответствии с его тяжестью и вероятности беременности - дисбаланс электролитов, нейрогормональные и гемодинамические нарушения, легочные проявления, дисфункция печени, гипоглобулинемия, лихорадка, тромбоэмболическую и неврологическую симптоматику и болевой синдром. Современный менеджмент при СГЯ, как пункции плевральной пункции, хирургическое вмешательство и назначение конкретных препаратов был оценен спорадически. Более адекватные методы лечения требуют лучшего понимания основных патофизиологических механизмов, чтобы проводить этиопатогенетическую терапию. Данный обзор направлен на изучение имеющихся доказательств, для лучшей клинической практике в диагностике, лечении и профилактики синдрома гиперстимуляции яичников.*
Ключевые слова: *синдром гиперстимуляции яичников, оплодотворение, хорионический гонадотропин человека, антимюллеров гормон, каберголин, агонисты ГнРГ, криоконсервация.*

Булавенко О.В., Коньков Д.Г., Буртяк Н.Г.
СИНДРОМ ГІПЕРСТИМУЛЯЦІЇ ЯЄЧНИКІВ. НОВІ ПІДХОДИ ДО ДІАГНОСТИКИ, ЛІКУВАННЯ ТА ПРОФІЛАКТИКИ
Резюме. *Синдром гіперстимуляції яєчників (СГЯ) є найбільш серйозним наслідком індукції овуляції при допоміжних репродуктивних технологіях. Хоча механізм СГЯ доки не відомий, існують фактори ризику, які повинні бути розглянуті під час призначення препаратів для лікування незпліддя. Клінічні симптоми СГЯ можуть включати, згідно з його важкістю та вагітності - дисбаланс електролітів, нейрогормональні та гемодинамічні порушення, легеневі прояви, дисфункція печінки, гіпоглобулінемія, лихоманка, тромбоемболічну та неврологічну симптоматику і больовий синдром. Сучасний менеджмент при СГЯ, як пункції плевральної порожнини, хірургічне втручання і призначення конкретних препаратів був оцінений спорадично. Більш адекватні методи лікування потребують кращого розуміння основних патофізіологічних механізмів, щоб проводити етіопатогенетичну терапію. Даний огляд спрямований на вивчення наявних доказів, для кращої клінічної практики у діагностиці, лікуванні і профілактики синдрому гіперстимуляції яєчників.*
Ключові слова: *синдром гіперстимуляції яєчників, запліднення, хоріонічний гонадотропін людини, антимюлерів гормон, каберголін, агоністи ГнРГ, кріоконсервація.*

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НОВІ ДАНІ ПРО ЛЮДСЬКИЙ ВІРОМ ТА ВПЛИВ МІКРОБІОТИ НА ЙОГО ФУНКЦІОНУВАННЯ

Резюме. *В оглядовій статті зібранні останні наукові матеріали, які стосуються персистенції вірусів в кишківнику людини. Охарактеризовано роль вірусно-бактеріальних асоціацій в нормі та при патології. На основі аналізу літературних даних зроблено висновок, що шлунково-кишковий тракт є середовищем для однієї з найскладніших мікробних екосистем, який вимагає значно глибшого вивчення його складу, ролі в фізіологічних процесах і динаміки змін при дії навколишнього середовища.*
Ключові слова: *віром, мікробіота, бактеріофаги, інфекційність, асоціації, нормальна мікрофлора, кишкові інфекції.*