A clinical symptom complex that can occur in some women undergoing assisted reproductive technologies and that could result in pregnancy complications.

**Diagnosis**
- Female

**About Ovarian hyperstimulation syndrome**

Ovarian hyperstimulation syndrome (OHSS) is a clinical symptom complex that can occur in some women who take fertility medication to stimulate egg growth, and in other women in very rare cases.

OHSS is characterized as mild, moderate, or severe, based on signs, symptoms, and laboratory findings:

- **mild** - enlarged ovaries (5–12 cm) and additional accumulation of ascites (abnormal accumulation of fluid within the abdomen) with mild abdominal distension, abdominal pain, nausea, and diarrhea
- **severe** - enlarged ovary (largest diameter greater than 12 cm), presence of numerous ovarian cysts, ascites (abnormal accumulation of fluid within the abdomen) and, sometimes, pleural and/or pericardial effusion
- **critical** (Pic. 1) - enlarged ovary, tense ascites with hydrothorax (excess fluid around the lung) and pericardial effusion, hematocrit (number of red blood cells in the blood) > 55%, white cell count (WBC) > 25,000, oligoanuria (less than 100 ml of urine is produced per day), renal failure, thromboembolic phenomena (the blocking of a blood vessel by a particle that has broken away from a blood clot at its site of formation), and acute respiratory distress syndrome (ARDS)

OHSS is common, occurring in mild forms in 33% of in vitro fertilization (IVF) cycles and in moderate or severe forms in 3% to 8% of IVF cycles. Although it can occur in all age groups, it is less common in women over the age of 39 years. Severe OHSS can be a life-threatening complication. The prognosis is usually worse in patients who get pregnant and have this syndrome.

There is currently no consensus on the exact cause of OHSS. Human chorionic gonadotrophin (hCG) exposure, however, is thought to be a critical mediator of the syndrome, since OHSS is particularly associated with injection of a hormone called human chorionic gonadotropin (hCG) which is used for inducing final oocyte maturation and/or triggering oocyte release. Ovarian blood vessels react abnormally to HCG and begin to leak fluid. This fluid swells the ovaries, and sometimes large amounts move into the abdomen. The risk is further increased by multiple doses of hCG after ovulation and if the procedure results in pregnancy.

This disease imposes a heavy physical, psychological and economical burden on patients as a consequence of hospitalization, fear of infertility or miscarriage, and absenteeism.
**Associated diseases**

**Polycystic ovarian syndrome**

Polycystic ovarian syndrome (PCOS) is an endocrine disorder that is diagnosed by anovulation, hyperandrogenism, and the polycystic ovary morphology. PCOS is one of the main predispositions for ovarian hyperstimulation syndrome (OHSS). The aim of fertility treatment in women with subfertility and PCOS is to safely induce mono-follicular ovulation resulting in the birth of a singleton child.

**Complications**

The complications of OHSS depend on the severity of the condition although a misdiagnosis and mistreatment can potentially become fatal. Complications from mild cases are usually self-limiting. In the more severe forms, fluid shifts can lead to dehydration resulting in acute kidney injury, multiple organ failure, and adult respiratory distress syndrome. Dehydration also increases the risk of thromboembolic phenomena and this occurs in 0.7% to 10% of OHSS patients. Thromboembolic disease is therefore an important condition to rule out in any potential patient who has had assisted reproductive technologies (ART).

OHSS may be complicated by ovarian torsion, ovarian rupture, thrombophlebitis (a blood clot blocks one or more of veins of leg near the surface) and renal insufficiency (a medical condition of impaired kidney function in which the kidneys fail to adequately filter metabolic wastes from the blood). Symptoms generally resolve in 1 to 2 weeks, but will be more severe and persist longer if pregnancy occurs. This is due to human chorionic gonadotropin (hCG) from the pregnancy acting on the corpus luteum (a temporary endocrine structure in female ovaries that is involved in the production of relatively high levels of progesterone) in the ovaries in sustaining the pregnancy before the placenta has fully developed. Typically, even in severe OHSS with a developing pregnancy, the duration does not exceed the first trimester.

**Risk factors**

The following factors increase the risk independently for the development of OHSS:

- young age
- low body mass index (BMI)
- polycystic ovarian syndrome (PCOS)
- allergic history
- high antral follicle count
- high doses of gonadotropins
- high or rapidly rising estradiol levels
- large numbers of large and medium-sized follicles
- large numbers of oocytes retrieved
- high or repeated doses of hCG
- pregnancy
- prior OHSS

Ovarian hyperstimulation syndrome in spontaneous pregnancy is an extremely rare event. Under certain circumstances such as twin pregnancies, the possibility of its existence may be higher because of higher HCG concentrations during the early pregnancy.

**Impact on fertility**

Ovarian hyperstimulation syndrome is almost always presents either after human chorionic gonadotropin (hCG) administration or during early pregnancy. Various inflammatory cytokines (a
broad and loose category of small proteins that are important in cell signaling), including vascular endothelial growth factor, have been implicated in the pathophysiology of several late pregnancy complications, including preterm labor, pregnancy induced hypertension or preeclampsia (a disorder of pregnancy characterized by high blood pressure and a large amount of protein in the urine) and intra-uterine growth restriction (poor growth of a fetus while in the mother’s womb during pregnancy).

Gynecologic findings include enlarged ovaries (Pic. 2) which may torse or rupture. Finally, electrolyte findings classically include hyponatremia (low sodium in blood secondary to increased antidiuretic hormone due to decreased intravascular volume) and hyperkalemia (high potassium in blood secondary to the renal sodium/potassium pump alterations).

Future fertility can be threatened in cases of severe complications such as ovarian torsion or ovarian rupture. In cases when the ovary is necrotic (the premature death of cells in living tissue) due to cessation of blood supply, this ovary needs to be removed.

In very rare occasions, this complication is bilateral (on both sides). This leads to infertility and women needs to undergo an egg donation.

**Prevention**

As the old adage goes, prevention is better than cure. As it stands, there is no perfect strategy which completely eliminates OHSS. There are factors however which could be taken into consideration in order to reduce its incidence. Being aware of the risk factors for OHSS will allow clinicians to preempt its occurrence and thereby reduce its incidence during ovulation induction with gonadotrophins.

**Primary prevention**

In women who are identified as being at a high risk of OHSS, treatment regimens need to be modified in view of curtailing an overexcessive ovarian response.

**Targeting Unifollicular Ovulation**

As previously highlighted, women with PCOS are at an increased risk for OHSS. Since 4–8% of women worldwide have the syndrome, this is a major subpopulation towards whom primary prevention should be directed. The goal of therapy therefore in this subgroup of women is to induce unifollicular ovulation through ovulation induction (OI) and thereby prevent progression to OHSS.

**Individualizing IVF Treatment Regimens**

There is increasing evidence to suggest that individualized controlled ovarian stimulation (iCOS) can reduce OHSS and associated cycle cancellations. As it stands, however, iCOS shows a lot of promise in curtailting OHSS through tailored COS regimens and seems to be the initial steps towards an ART of the near future.

**Avoiding hCG for Luteal Phase Support (LPS)**

During COS, endogenous LH concentrations are markedly lower due to the negative feedback caused by the high progesterone (P4) concentrations maintained by the multiple corpora lutea. This results in a shortened luteal phase and poor endometrial receptivity resulting in reduced implantation and pregnancy rates. As such luteal phase support is imperative to improve these parameters.
Considering Alternatives for Triggering Ovulation

The agent of choice for triggering ovulation should be picked based on the risk of the woman for developing OHSS. No agent, however, completely eliminates the risk of OHSS.

**Secondary prevention**

**Cycle cancellation**

IVF cycle cancellation with withholding of hCG trigger is the most effective preventative technique, but is emotionally and financially stressful for all involved. Cycle cancellation is generally reserved for patients with a history of severe OHSS in a prior cycle and in cases of total loss of control of the cycle.

**Coasting**

Coasting involves temporarily stopping gonadotropin administration and postponing the hCG trigger until the estradiol (E2) level is lower. It is a good alternative that can be used to avoid cycle cancellation in extremely high responders to ovulation induction, who have high risk of developing severe OHSS. Even if OHSS develops after coasting, both incidence and severity will be diminished. However, prolonged coasting has a drawback of a reduced pregnancy rate.

**Decreasing the dose of hCG trigger**

Although theoretically it makes sense to reduce the dose of hCG, there is little data to support this practice and studies are either limited by small sample size or not powered to detect a difference.

**Agonist trigger**

Using an agonist medication to trigger ovulation has been proposed as another strategy to prevent OHSS. Agonist trigger can only be used in the setting of an antagonist protocol.

**Cryopreservation of all embryos**

Elective transfer of a single zona-free day 5 embryo and freezing of the supernumerary embryos or cryopreservation of all embryos for postponement of transfer can prevent the occurrence of late OHSS from pregnancy. However, it does not prevent early OHSS development due to exogenous hCG administration. As with all methods, it may reduce but not eliminate OHSS.

**Intravenous albumin at the time of oocyte retrieval**

Albumin is a low molecular weight plasma compound with a major impact on oncotic pressure. Human albumin has been used on the day of hCG administration in high-risk women to prevent OHSS.

**Non-steroidal anti-inflammatory administration**

Low-dose aspirin therapy (100 mg daily, beginning on the first day of ovarian stimulation) was shown to be effective in preventing OHSS among high risk women in a recent studies.

**Dopamine agonist**

The most recently suggested strategy to prevent the development of OHSS is the use of dopamine
agonists such as Cabergoline.

**In vitro maturation of oocytes (IVM)**

The safest way to prevent OHSS would be by not stimulating the ovaries. During an IVM cycle, immature oocytes are retrieved from barely stimulated or completely unstimulated ovaries. The oocytes are matured in defined culture media for 24–48 h and then fertilized by in vitro fertilization or intracytoplasmatic sperm injection. The embryo transfer is performed as usual; normally two embryos are transferred in two or three days after fertilization. The lack of ovarian stimulation during IVM cycles brings many benefits, including the following: reduction in medication cost, no risk for OHSS, and a reduction in the total number of patient visits for clinical and laboratory evaluations. Although good results have been reported by some clinics, IVM has not yet become a mainstream fertility treatment. The most important reasons are: technical difficulties for retrieving immature oocytes from unstimulated ovaries and to cultivate them, lower chance of a live birth per treatment compared with conventional in vitro fertilization, the report of higher rates of meiotic spindle and chromosome abnormalities from immature human oocytes.

### Symptoms

The symptoms of mild OHSS include abdominal distention, ovaries up to 12 cm in diameter, nausea, vomiting, and diarrhea. 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 (Pic. 3) 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. Indeed, as the severity of OHSS increases, so does the number of organs affected.

### Therapies

#### Self therapy

Oral fluid intake should be maintained at no less than 1 L per day. Women should be encouraged to drink to thirst, rather than to excess. Strenuous exercise and sexual intercourse should be avoided. Strict bed rest is unwarranted and may increase risk of thromboembolism (the blockage of a blood vessel by a thrombus carried through the bloodstream from its site of formation). Discomfort may be relieved with acetaminophen or opiate medications if severe. Nonsteroidal anti-inflammatory agents (NSAIDs) are not recommended because they may compromise renal function in patients with OHSS.

#### Conventional medicine

There is no treatment that specifically targets the cause yet. Therefore, the interventions of experts are mainly aimed at relief from symptoms and in severe cases life support cases.

Patients with mild manifestation of OHSS do not require any specific treatment. Mild OHSS and moderate OHSS can be treated symptomatically and patients monitored on an outpatient basis, for example, by tracking weight gain, which is one of the first signs of fluid retention.

Severe OHSS, on the other hand, must be regarded as a potentially fatal complication that requires immediate treatment to maintain circulatory volume and restore electrolyte balance using intravenous fluids. However, this often leads to increased ascitic fluid
Pharmacotherapy

Medication is used not only to prevent OHSS, but it could also be used to reduce the symptoms. The condition spontaneously falls within 2-3 weeks.

Surgical therapy

Paracentesis

Aggressive outpatient management of patients with moderate-to-severe OHSS using early paracentesis (aspiration of the ascitic fluid) has been shown to effectively reduce the need for hospitalization. In addition to preventing hospitalization, paracentesis rapidly relieves symptoms, with patients experiencing improvements in urine output, renal function and hematocrit levels as early as 24 hours following the procedure.

Both abdominal and transvaginal routes for paracentesis have been shown to be effective.

Furthermore, early outpatient paracentesis for moderate-to-severe OHSS is more cost effective than traditional conservative inpatient therapy.

Assisted reproduction

There has been a rapid increase in the number of couples receiving treatment for infertility with assisted reproductive technology (ART) in recent years. While there is robust evidence supporting the efficacy and safety of ART, it is important to be aware of the risks, the most serious of which is ovarian hyperstimulation syndrome (OHSS).

Ideally, ART practitioners seek a balance between optimum ovarian stimulation and successful treatment outcome with minimal rate of severe OHSS or multiple pregnancies. Individualization of treatment according to the specific risk factor and the specific response in the current cycle with the option of freezing (cryopreservation) of all embryos, or replacement of only a single embryo, has the potential of reducing the risk and the severity of the syndrome in susceptible cases. Moreover, while withholding the ovulation-inducing trigger of hCG, or replacing hCG with GnRH agonist (GnRHa) to trigger ovulation, may eliminate severe early OHSS, these methods are associated with decrease reproductive outcome.

Controlled ovarian hyperstimulation (COH) which combines GnRH antagonist co-treatment and GnRHa trigger has recently become a common tool aiming to eliminate severe early OHSS and to support the concept of an OHSS-free clinic. However, due to the reported significantly reduced clinical pregnancy and increased first trimester pregnancy loss, efforts have been made to improve reproductive outcome, by manipulating the luteal phase. While discussing the recent developments in GnRHa trigger, Kol and Humaidan presented 3 optional strategies aiming to improve outcome: freeze-all policy; fresh transfer and intensive luteal support; and fresh transfer and low-dose HCG supplementation.

Freeze-all policy is offered in extreme cases in an attempt to ensure OHSS risk-free and maintain a reasonable cumulative pregnancy rate. However, despite the recent improvement in live birth rates after replacement of frozen-thawed vitrified oocytes/embryos, it should be emphasized, that in most centers, there is still a gap in live birth rates between fresh and frozen/thawed cycles (in favour of fresh cycle).
Vaginal ultrasonography in the coronal plane in mild ovarian hyperstimulation syndrome (hence the enlarged ovary).

Vaginal ultrasonography in the sagittal plane in mild ovarian hyperstimulation syndrome. 35-year-old woman with mild ovarian hyperstimulation syndrome.

Egg donation
Process by which a woman donates eggs for purposes of assisted reproduction or biomedical research.
Learn more at: www.fertilitypedia.org/edu/therapies/egg-donation

ICSI
A micromanipulative fertilization technique in which a single sperm is injected directly into an egg.
Learn more at: www.fertilitypedia.org/edu/therapies/icsi

Sperm donation
The procedure in which a man (sperm donor) provides his sperm for fertility treatment.
Learn more at: www.fertilitypedia.org/edu/therapies/sperm-donation

Standard IVF
A process in which an egg is fertilised by sperm outside the body: in vitro. Own or donated gametes may be used.
Learn more at: www.fertilitypedia.org/edu/therapies/standard-ivf
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