OVARIAN HYPERSTIMULATION SYNDROME
INTRODUCTION

- Ovarian hyperstimulation syndrome (OHSS) refers to a combination of ovarian enlargement due to multiple ovarian cysts and an acute fluid shift out of the intravascular space. The ovarian cysts are the result of multifollicular development. The most severe manifestations of the syndrome include massive ovarian enlargement from multiple cysts and, due to fluid movement out of the intravascular space, hemoconcentration and third-space accumulation of fluid; these changes may be complicated by renal failure, hypovolemic shock, thromboembolic episodes, acute respiratory distress syndrome, and death [1,2].
SPONTANEOUS VERSUS INDUCED OVULATION — In spontaneous ovulatory cycles, hypothalamic-pituitary-ovarian feedback mechanisms limit follicle recruitment to a small number of early antral follicles. Full development is generally restricted to a single leading follicle that will ovulate in response to the midcycle luteinizing hormone (LH) surge.

By comparison, ovulation induction involves administration of a pharmacological dose of exogenous gonadotropins, thereby overriding normal feedback mechanisms. This results in recruitment of a large number of antral follicles, several of which are sustained as leading follicles capable of either luteinization or ovulation. The monofollicular development that occurs in spontaneous cycles is extremely difficult to duplicate in stimulated cycles, even with meticulous ultrasound and serum estradiol monitoring.
ETIOLOGY

- **Exogenous gonadotropins** —

  Ovarian hyperstimulation occurs after luteinization of a large number of follicles. Such massive follicular luteinization is usually only observed in exogenous gonadotropin cycles following administration of **human chorionic gonadotropin** (hCG), or after administration of gonadotropin releasing hormone (GnRH) agonist; it rarely occurs in women treated with **clomiphene** citrate. The clinical symptoms usually appear five to ten days following the first dose of the ovulatory trigger (hCG, GnRH agonist).
Endogenous LH surge —

Mild ovarian hyperstimulation also rarely develops following an endogenous LH surge in a setting of spontaneous multifollicular development. This has been described in case reports, particularly in women with polycystic ovarian syndrome or hypothyroidism [3-5]. The rarity and mildness of OHSS in this situation is due to several factors:

- The number of intermediate follicles present at the beginning of the LH surge
- The duration and intensity of the LH surge
- Other factors, such as inhibin, insulin-like growth factor (IGF-1), and its binding proteins
FSH receptor mutations —

Severe, recurrent, spontaneous OHSS during pregnancy has been described in several reports. In these instances, the OHSS was due to a mutation in the serpentine region of the FSH receptor that resulted in a broadening of ligand specificity, thereby allowing stimulation by endogenous hCG \([3,6-8]\). The persistent stimulation of the FSH receptor during pregnancy resulted in excessive follicular recruitment and subsequent ovarian hyperstimulation.
PATHOGENESIS

— Development of massive ascites and hypovolemia due to increased capillary permeability are the cardinal clinical events in the pathogenesis of OHSS [9]. Hypovolemia results in hemoconcentration, decreased central venous pressure, low blood pressure, and tachycardia.
Role of vascular endothelial growth factor — The ovarian hyperstimulation syndrome appears to be due to increased capillary permeability triggered by excessive release of one or more vasoactive substances secreted during maturation and luteinization of multiple follicles. Vascular endothelial growth factor (VEGF) of follicular origin is the main, although possibly not the only, component responsible for development of OHSS. This peptide has two actions: it is a potent promoter of neovasculogenesis; and it may increase permeability of blood vessels walls (mediated by in part by nitric oxide), thereby disrupting functional integrity of the vascular bed [10-14]. VEGF levels correlate with both the presence and severity of OHSS [13].
The successive stages of OHSS are:

- Recruitment of a large number of small antral follicles into a functional cohort
- Sustained development of numerous large antral follicles until ovulation (or luteinization)
- Excessive production of VEGF by the developing large follicles
- Exaggerated perifollicular neovascularization with some of the new blood vessels exhibiting increased permeability
- Escape of follicular fluid and perifollicular blood containing large amounts of VEGF into the peritoneal cavity and its subsequent absorption into the general vascular bed
- Functional impairment of blood vessels.
- Massive fluid shift from the intravascular to the third compartment
- Intravascular hypovolemia, concomitant with development of edema, ascites, hydrothorax and/or hydropericardium.
- Impairment of cardiac, renal, pulmonary, and liver function
RENAL EFFECTS —

Severe hypovolemia is associated with decreased renal perfusion and increased reabsorption of sodium and water in the proximal tubule leading to oliguria and low urinary sodium excretion [20]. Exchange of hydrogen and potassium for sodium in the distal tubule is reduced, which can result in an accumulation of hydrogen and potassium ions, thereby causing hyperkalemia and a tendency to acidosis [9]. Additional factors leading to increased sodium retention in patients with OHSS include:

- Increased renin production
- Enhanced aldosterone secretion
- Elevated androgens
- Severe, persistent OHSS may finally lead to impaired function of vital organs such as kidneys, lung, liver, and the cardiovascular system
**RISK FACTORS**

- **RISK FACTORS** — Factors which should be considered include:
  - Young age and diagnosis
  - High serum estradiol concentrations immediately prior to human chorionic gonadotropin (hCG) administration
  - Transvaginal ultrasound examination findings (women with polycystic ovary morphology tend to have the most exuberant response to exogenous gonadotropins) [3].
Genetics — A number of mutations that are associated with OHSS, both spontaneous and iatrogenic have been identified. Most of these are in the FSH receptor.

ROLE OF TREATMENT REGIMENS — The incidence or severity of OHSS is also related to treatment schedule and to the dose of FSH and hCG. Administration of FSH according to an individually adjusted treatment regimen (with stepwise increasing or decreasing daily doses) is associated with a lower incidence of OHSS than with a fixed regimen. In addition, delayed administration of hCG ("coasting") appears to lower the risk of OHSS.
Gonadotropin dose — There are conflicting data on the importance of gonadotropin dose in the development of OHSS. In one report, gonadotropin doses correlated with OHSS severity as indicated by ovarian size and severity of ascites and pleural effusion [6].

It is possible that the variability of response is of greater significance than the variability of dosage, particularly in women of WHO group II, which includes those with polycystic ovary syndrome (PCOS).
Ovarian hyperstimulation is classified into three grades based upon the severity of symptoms, signs, and laboratory findings [1]. The cardinal event in the genesis of OHSS is ovarian enlargement, with ascites and hypovolemia resulting from an acute fluid shift out of the intravascular space.
Grade I ovarian hyperstimulation — Grade I (mild hyperstimulation) is characterized by bilateral ovarian enlargement with multiple follicular and corpus luteum cysts measuring up to 5 by 5 cm. Laboratory findings include a serum estradiol (E2) concentration greater than 1500 pg/mL (6000 pmol/L) and progesterone concentration greater than 30 ng/mL (115 nmol/L) in the early part of the luteal phase.
Grade II ovarian hyperstimulation — Grade II (moderate hyperstimulation) describes ovaries enlarged up to 12 by 12 cm, accompanied by abdominal discomfort and gastrointestinal symptoms (eg, nausea, vomiting, and diarrhea). A sudden increase in weight of more than 3 kg may be an early sign of moderate hyperstimulation.
Grade III ovarian hyperstimulation — Grade III (severe hyperstimulation) is defined by the presence of large ovarian cysts (more than 12 by 12 cm), ascites, and, in some patients, pleural and/or pericardial effusion, electrolyte imbalance (hyponatremia, hyperkalemia), hypovolemia, and hypovolemic shock [2-4]. Marked hemoconcentration, increased blood viscosity, and thromboembolic phenomena including disseminated intravascular coagulation occur in the most severe cases.

Spontaneous regression occurs over 10 to 14 days, but may take longer if implantation occurs.
INCIDENCE

— The incidences of moderate and severe ovarian hyperstimulation compiled from more than 11,300 ovulation induction cycles are 3.1 to 6 percent and 0.25 to 1.8 percent, respectively [1].
TREATMENT

- **TREATMENT** — The best treatment of OHSS is primary prevention. Preventing ovulation by withholding human chorionic gonadotropin (hCG) is an effective method of avoiding hyperstimulation in overstimulated ovaries. Alternatively, aspiration of follicles 36 hours after administration of the ovulatory dose of hCG may lower the risk of developing clinical hyperstimulation by reducing the mass of luteinized granulosa cells.

- OHSS is a self-limiting disease; thus, treatment should be symptomatic and conservative. Medical therapy suffices for most patients, with laparotomy reserved for catastrophic complications, such as ovarian torsion or rupture and internal haemorrhage. Women with severe symptoms often require intensive medical care. Vaginal intercourse is restricted in all grades of OHSS because of the risk of cyst rupture. Patients should also avoid impact-type activities or strenuous exertion.
Grade I hyperstimulation — Treatment is supportive, as needed. However, mild ovarian hyperstimulation can develop into moderate or severe disease, especially if conception ensues. Therefore, women with mild disease should be observed for enlarging abdominal girth, acute weight gain, and abdominal discomfort on an ambulatory basis for at least two weeks or until the appearance of menstrual bleeding.
Grade II hyperstimulation — Treatment of moderate hyperstimulation consists of observation, bed rest, provision of an adequate fluids, and sonographic monitoring of cyst size. Serum electrolytes, hematocrit, and creatinine should also be evaluated. Some physicians have outpatients keep track of their fluid intake and output; intake or output less than 1000 mL/day or a discrepancy in fluid balance greater than 1000 mL/day would be a cause for concern [2].

Initiation of resolution is apparent when the cysts become smaller on two consecutive ultrasound examinations and clinical symptoms recede. In contrast, early detection of progression to the severe form of the syndrome is marked by continuous weight gain (two pounds or more a day), increase in severity of existing symptoms, or the appearance of new symptoms, such as vomiting, diarrhea, and dyspnea.
Grade III hyperstimulation — Medical treatment of severe hyperstimulation is directed toward:

- Maintaining blood volume while correcting the disturbed fluid and electrolyte balance
- Relieving secondary complications of ascites and hydrothorax
- Preventing thromboembolic phenomena
- In addition to frequent monitoring of vital signs and intake/output, weight and abdominal girth should be checked daily.
Laboratory monitoring in women with grade 3 OHSS

- **Daily**
  - Leukocyte count, Hemoglobin and hematocrit
  - Electrolytes.

- **Once,**
  - repeat as indicated: Liver function tests, Prothrombin and partial thromboplastin time
  - Chest radiograph (if respiratory symptoms are present)
CONT.

- **Hypovolemia** — Hypovolemia is caused by extravasation of intravascular fluid ("third-spacing") and is associated with ascites, hemoconcentration, decreased central venous pressure, low blood pressure, and tachycardia. Decreased renal perfusion leads to increased reabsorption of sodium and water in the proximal tubule [15], resulting in oliguria and a low urinary sodium concentration.

- Fluid balance should be carefully monitored by net fluid flow (intake/output record), weight and girth measurements, and hematocrit examinations. A central venous pressure catheter may be required in women who are hemodynamically unstable.
In general, one to two liters of isotonic fluid is given to such women in the first hour to rapidly restore tissue perfusion. Further fluids optimally should be given while monitoring the central venous or pulmonary capillary wedge pressure. Fluid repletion should continue at the initial rapid rate as long as the cardiac filling pressures and the systemic blood pressure remain low.

Plasma expanders such as hemacell, dextran, human albumin (200 mL of 25 percent albumin over 4 hours), and plasma (500 to 1000 mL over 24 hours) supplemented with appropriate electrolytes should be administered early and repeated as needed. The effect of this treatment may be enhanced by the addition of oral indomethacin, which blocks prostaglandin synthesis and reduces capillary permeability. Hematocrit should be monitored every four hours; plasma expanders can be stopped when the hematocrit is less than 38 percent [2].
Diuretic agents are not recommended since fluid in the third space is not affected by these drugs. Furthermore, most diuretics act at the distal tubule with minimal effect on the proximal tubule [16]. Thus, the artificially induced diuresis may further diminish the intravascular volume, but may be unable to relieve ascites or hydrothorax. Renal failure may respond to a dopamine drip (0.18 mg/kg per hour) [17]. Oral docarpamine administration could be one of the options in the management of patients with OHSS requiring dopamine therapy [18].
**CONT.**

- **Ovarian enlargement** — Ovarian cysts associated with grade III OHSS are so large and brittle that surgical attempts at a palliative procedure usually result in oophorectomy. Therefore, surgery should be avoided unless there is torsion or cyst rupture with hemorrhage. Torsion is characterized by ovarian enlargement, abdominal pain, nausea, progressive leukocytosis, and anemia [19]. Treatment may require oophorectomy, although in many cases the ovary can be saved by unwinding at laparotomy or laparoscopy [20].
Ascites — The degree of ascites is reflected by the woman's weight gain: an initial gain of more than 3 kg following hCG administration should be considered a warning sign of developing OHSS and warrants close observation. Women with severe OHSS can gain as much as 15 to 20 kg over five to 10 days.

Increased intraabdominal pressure from ascites causes maternal discomfort, which may be severe, and also can have hemodynamic effects on the maternal circulation (eg, impede renal vein outflow) and can compromise pulmonary function resulting in hypoxia. Improvement in creatinine clearance, urine volume, and weight loss in women with severe OHSS treated with abdominal paracentesis has been described [21,22]. However, other authors have recommended that abdominal paracentesis for drainage of ascites not be performed because of the danger of intraperitoneal hemorrhage from inadvertent puncture of the large ovarian cysts [23].
Hydrothorax — Women with severe OHSS involving the lungs display an extraparenchymal restrictive type of pulmonary dysfunction due to intraabdominal or pleural fluid accumulation, which limits descent of the diaphragm and expansion of the lungs [28]. This causes uncoordinated lung ventilation and atelectasis leading to ventilation-perfusion mismatch and hypoxemia. Pulmonary infection, thromboembolism, or adult respiratory distress syndrome (ARDS) may further complicate the clinical picture. Clinical manifestations included dyspnea, tachypnea, moderate hypoxemia, increased alveolar-arterial oxygen difference, hypocarbia, respiratory alkalosis, and metabolic compensation.

Pleural effusions should be drained to relieve dyspnea. Paracentesis may also be useful in alleviating breathing difficulties in patients with ascites and hydrothorax [29].
- **Thromboemboli** — Thromboembolic events are the most serious, but rarest, complications of OHSS. Thromboses can occur in either the arterial (25 percent) or venous (75 percent) circulations \[30,31\] and may lead to permanent neurologic injury or death \[32\]. Prophylactic anticoagulation with heparin or low molecular weight heparin, antiembolism stockings, and or intermittent pneumatic compression boots should be considered to minimize the risk of venous thrombosis [2].

- The cause of these thromboembolic events is not fully established; however, it is probably related to hemoconcentration and hypercoagulation and associated with elevated estrogen concentrations. One study found high levels of factor V, platelets, fibrinogen, profibrinolysin, fibrinolytic inhibitors, and increased thromboplastin generation in women with OHSS [33]. All of these findings may be regarded as a result of hemoconcentration, and the majority of them are also a consequence of high estrogen levels.
Women with genetic thrombophilia (eg, antithrombin III deficiency, factor V Leiden mutation, protein C or S deficiency) are most prone to developing thromboembolic events in predisposing situations (eg, use of oral contraceptive pills, surgery). Some fertility clinics perform screening for thrombophilia before starting ovulation (superovulation) induction therapy since OHSS is a risk factor for thromboembolic disease. Some authors advise that high-risk patients should receive prophylaxis, such as low dose heparin therapy, prior to ovulation induction [34].
Thromboembolic complications of OHSS have been reported in the internal jugular, subclavian, axillary, and mesenteric vessels [28,35]. In one series of five cases of internal jugular vein thrombosis presenting at 7 to 10 weeks gestation after IVF, two occurred in women who had not had OHSS but had an underlying thrombophilia, while three occurred in women with severe OHSS and no underlying thrombophilia [36]. Cerebrovascular thrombosis typically presents as an ischemic infarct. Treatment is anticoagulation with heparin.
Resolution — After a period of several days, third space fluid begins to re-enter the intravascular space, hemoconcentration reverses, and natural diuresis ensues. The patient feels better and her appetite and ability to take oral fluids improve. Intravenous fluids are tapered as oral intake increases. Some physicians limit oral intake to 1000 mL/day at this time to facilitate diuresis and maintain euvolemia [2]. Complete resolution typically takes 10 to 14 days from the onset of initial symptoms.
Recommendations — All women undergoing ovarian stimulation with exogenous gonadotropins should be monitored with both serum estradiol measurements and transvaginal ultrasonography. Both are performed on the fifth day of treatment and every two to three days thereafter until hCG administration.

hCG may be given with a low risk of OHSS to women with estradiol levels less than 1500 pg/mL in the presence of no more than two follicles above 17 mm and less than four smaller follicles. The regimen may be altered in the following settings:
PREVENTION

- It has been recommended that hCG be withheld if the serum estradiol concentration is greater than 1500 pg/mL (>6,000 pmol/L) [19]. We generally adhere to this rule. In special cases, however, if there are not too many intermediate or large follicles on ultrasonography, we have given hCG when serum estradiol levels exceeded 1500 pg/mL (>6,000 pmol/L). This approach has usually not resulted in severe hyperstimulation.
hCG should be withheld if there are more than two follicles larger than 17 mm and more than four follicles <17 mm. In certain situations, the treatment cycle might be salvaged by inducing an LH surge with GnRH agonists.
hCG may be given and follicular reduction considered if the serum estradiol is above 1500 pg/mL (>6,000 pmol/L) in the presence of more than two large follicles but fewer than four smaller follicles [21].
OTHER PREVENTIVE STRATEGIES — In addition to withholding hCG in high risk cycles, the following treatment variants may be considered for reducing the incidence and/or severity of OHSS:

- Coasting [22-24]
- Transforming
- Replacing hCG with a GnRH agonist [25-27]
- Replacing hCG with recombinant LH [17]
- Performing follicular reduction [21]
- Intravenous albumin [28-33]
- Dopamine agonist administration [34,35]
‘Do not lose heart against the heaviest trials and never be in a state of grief, for you are bound to succeed if you are true in faith’

QURAN