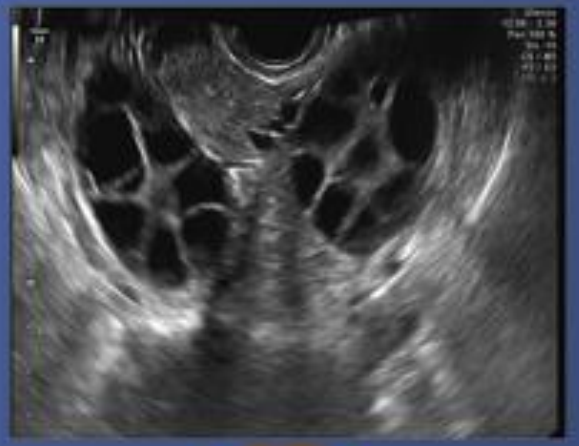
In the name of God, the Beneficent, the Merciful

OHSS



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Background

Ovarian hyperstimulation syndrome (OHSS) is the most serious complication of controlled ovarian hyperstimulation (COH) for assisted reproduction technologies (ART). It occurs when the ovaries are hyperstimulated and enlarged due to fertility treatments (or rarely, mutations in the follicle-stimulating hormone [FSH] receptor), resulting in the shift of serum from the intravascular space to the third space, mainly to the abdominal cavity. In its severe form,OHSS is a life-threatening condition because it can cause venous or arterial thromboembolic events, including stroke and loss of perfusion of an extremity.

OHSS is an <u>iatrogenic complication</u> of <u>ovarian induction</u> during in-vitro fertilization treatment.

3% to 6%

Factors Implicated in the Past in Pathogenesis of OHSS

Gonadotropins

High serum estradiol levels

ovary

Multiple follicles

Oocyte retrieval

hCG

Angiogenesis

Release vasoactive factors(VEGF,IL-6,IL-8,etc.)

Multiple corpora luteal

Pregnancy

Luteal hCG

Increased capillary permeability

Liver/Renal impairment

Decreased organ perfusion

Capillary leaking "Third spacing "

Increased abdominal pressure

Thromboembolic events

Hemoconcentration

Hypovolemia

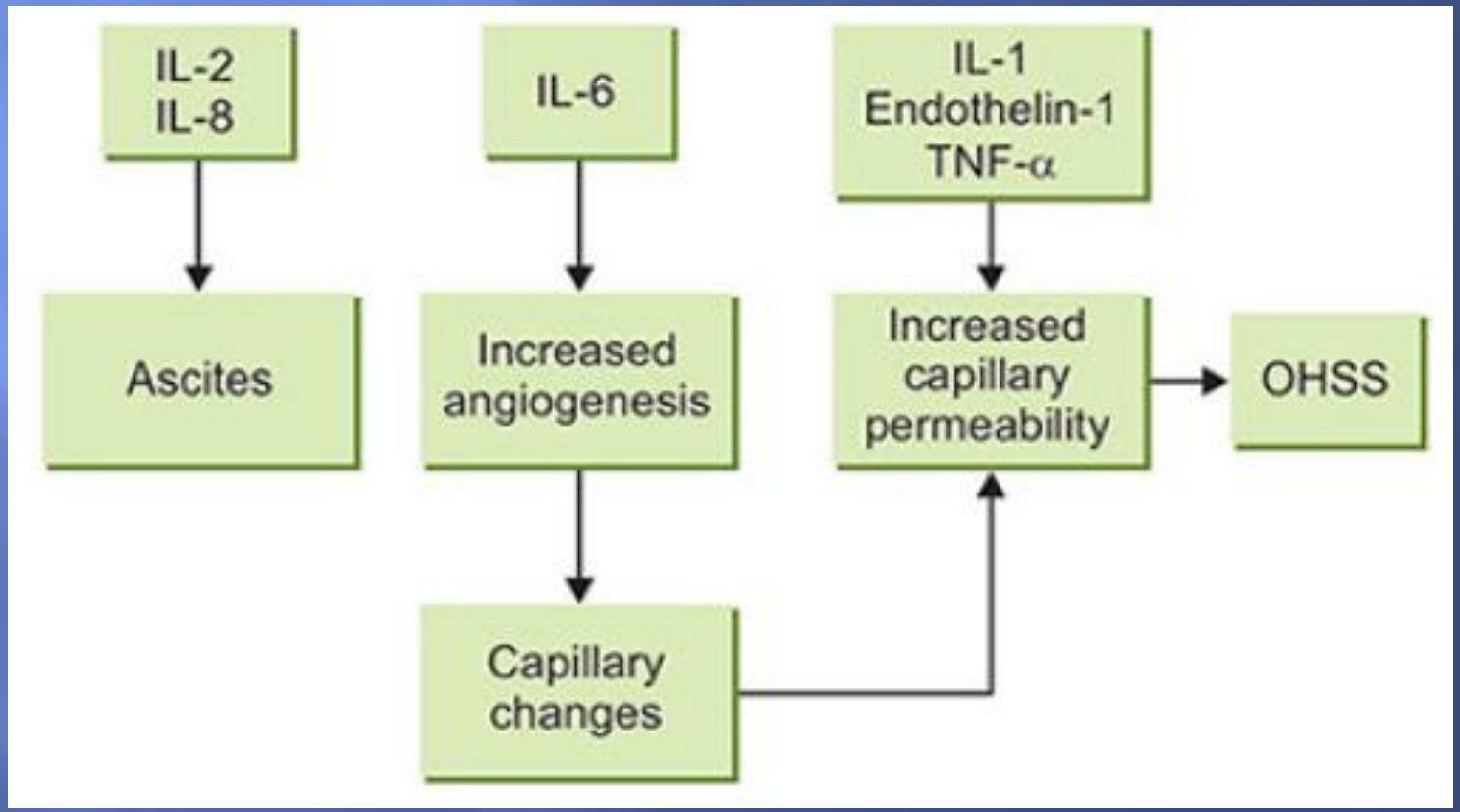
Tissue edema

Ascites/ Hydrothorax

Compartment syndrome

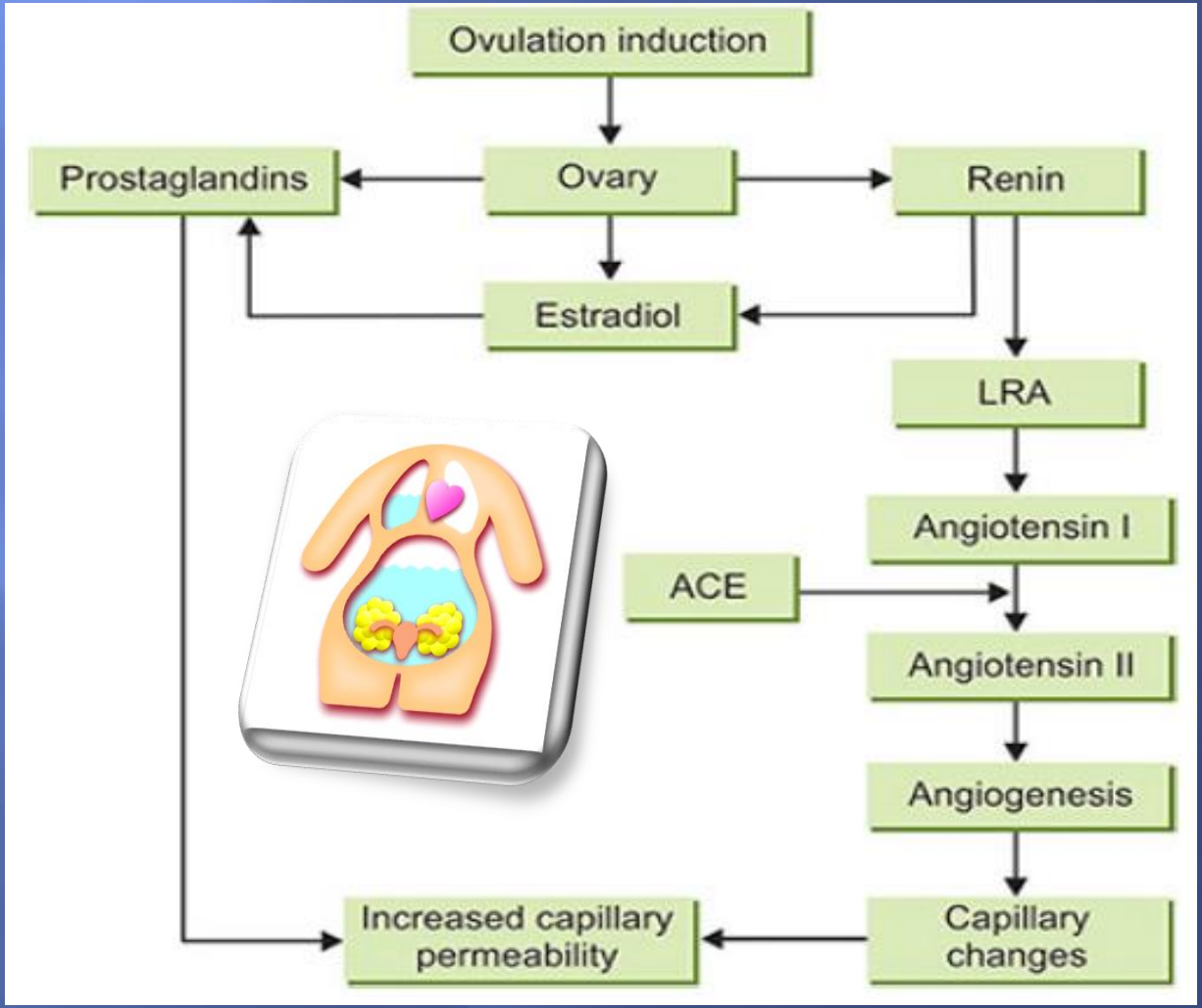
Role of cytokines and other factors in ovarian hyperstimulation syndrome

Pathophysiology



Role of angiotensin-renin system and prostaglandins in the pathogenesis of OHSS

Pathophysiology



Pathophysiology

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

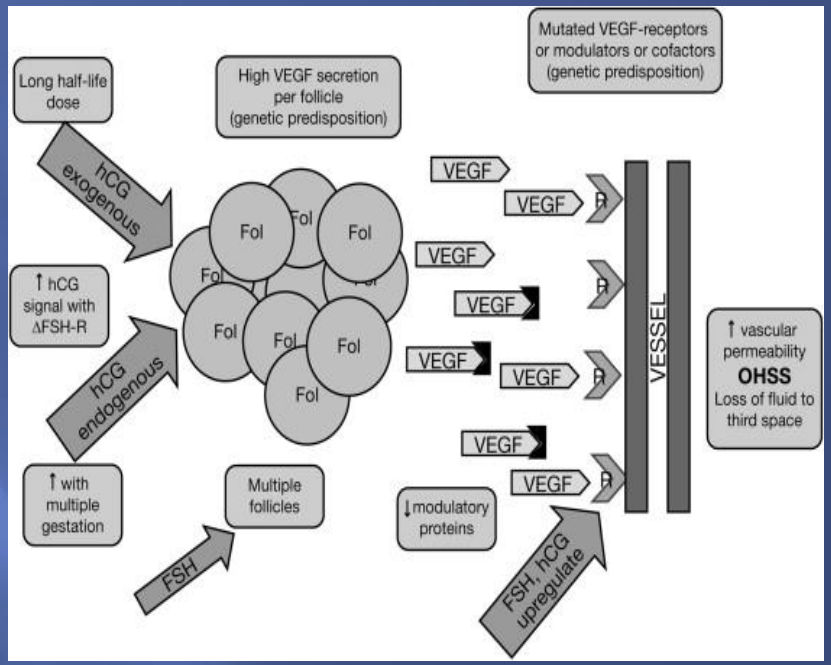
This shift in fluid is due to increased vascular permeability in response to stimulation with human chorionic gonadotropin (**hCG**).

Pathophysiology

HCG and OHSS

It is well known that the development of severe OHSS is dependent on either exogenous administration of HCG or endogenous pregnancy-derived HCG stimulation.

HCG is administered during ovarian stimulation both to trigger ovulation and for luteal support.



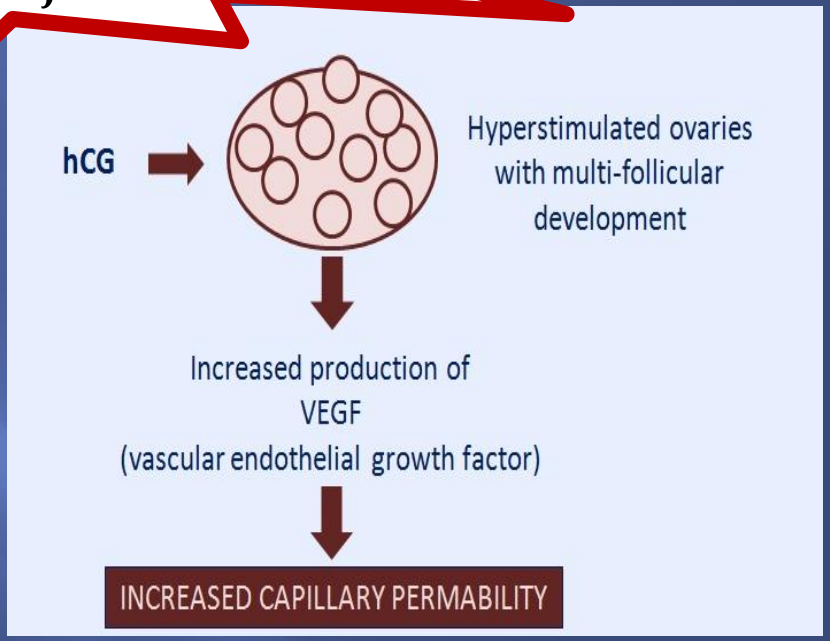
It is also established that, by withholding HCG when oestrogen concentrations are too high, severe OHSS may be prevented.

But failure to ovulate and conceive may also occur.

Pathogenesis of OHSS

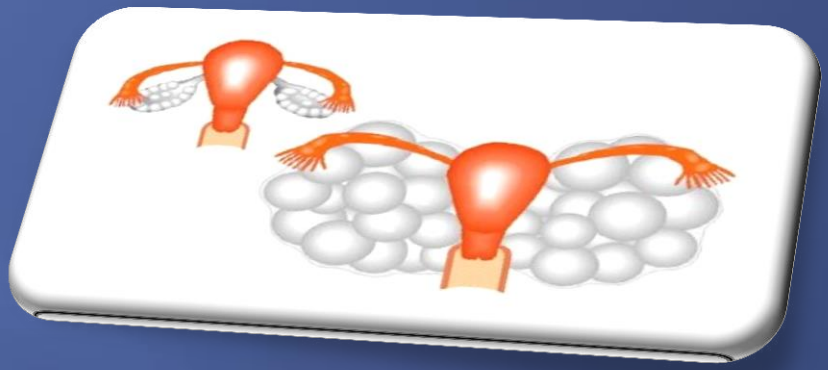
Vascular endothelial growth factor (VEGF) has been identified as the major mediator

Vascular endothelial growth factor is a vasoactive glycoprotein (cytokine) which stimulates endothelial cell proliferation, cell permeability, and angiogenesis.



VEGF mRNA has been found to be expressed in granulosa cell culture. The expression of VEGF and VEGF receptor 2 (VEGFR-2) mRNA increases significantly in response to hCG.

Risk factors



- Young age
- Polycystic ovarian syndrome
- High or repeated doses of hCG, Pregnancy
- Previous OHSS
- Low body weight
- High follicle count
- Elevated serum estradiol

Basal AMH

In some cases, OHSS affects women who have no risk factors at all.

Risk factors for OHSS

Risk factors present at baseline: Before gonadotropin administration
Previous OHSS
PCOS
Potential markers:
▪ Basal serum anti-müllerian hormone >3.3 ng/mL
▪ Antral follicle count >8
Single nucleotide polymorphisms (SNPs) in genes involved in follicular growth (*BMP15*)

Risk factors for OHSS

Risk factors related to ovarian response
Multiple follicles >20 follicles larger than 10 mm
High or rapidly rising serum estradiol concentration (>3500 pg/mL [12,850 pmol/L] in COH)
High number of oocytes retrieved
hCG given for luteal phase supplementation
Elevated serum/follicular fluid VEGF levels
Pregnancy (increase in endogenous hCG)

OHSS can be "early" or "late" based on the source of hCG.

Early OHSS

Early OHSS is usually mild to moderate and manifests 4-7 days after the administration of exogenous hCG to induce oocyte maturation.

Late OHSS

Late OHSS is usually severe and occurs more than 10 days after hCG treatment.
Occurs when ART results in pregnancy and is the consequence of an increase in endogenous hCG levels following conception.

Classification on the basis of disease onset

	Early OHSS	*Late OHSS*
hCG	**Exogenous**	**Endogenous**
Time of onset	**3–7 days after hCG trigger**	**>10 days after hCG trigger**
Occurrence	**Occurs in a stimulated cycle**	**Occurs in setting of a pregnancy**
Associated with	**Higher peak E2 levels, greater gonadotropin doses**	**Singleton or multiple pregnancy**

Clinical symptoms

Clinical Symptoms

- Clinical manifestations reflect the extent of fluid shift into the third space
- Clinical spectrum ranges from:

- ✓ Abdominal bloating (commonest)
- ✓ Nausea & vomiting
- ✓ Weight gain
- ✓ Dyspnea
- ✓ Oliguria & Anuria
- ✓ Venous thrombosis
- ✓ Thrombo-embolism & Arrythmias
- ✓ ARDS (adult respiratory distress syndrome)
- ✓ Sepsis
- ✓ Death

Lethargy

Peripheral edema

Classification of OHSS: Clinical and biochemical features

	Clinical features	Biochemical features
Mild	▪ Abdominal distention/discomfort ▪ Mild nausea/vomiting ▪ Diarrhea ▪ Enlarged ovaries	▪ No clinically important laboratory findings
Moderate	▪ Presence of mild features plus: • Ultrasonographic evidence of ascites	▪ Elevated Hct (>41%) ▪ Elevated WBC (>15,000/microL) ▪ Hypoproteinemia

Classification of OHSS: Clinical and biochemical features

	Clinical features	Biochemical features
Severe	▪ Presence of mild and moderate features plus: • Clinical evidence of ascites (can be tense ascites) • Severe abdominal pain • Intractable nausea and vomiting • Rapid weight gain (>1 kg in 24 hours) • Pleural effusion • Severe dyspnea • Oliguria/anuria • Low blood/central venous pressure • Syncope • Venous thrombosis	▪ Hemoconcentration (Hct >55%) ▪ WBC >25,000/microL ▪ Serum creatinine >1.6 mg/dL ▪ Creatinine clearance <50 mL/min ▪ Hyponatremia (Na^+ <135 mEq/L) ▪ Hyperkalemia (K^+ >5 mEq/L) ▪ Elevated liver enzymes

Classification of OHSS: Clinical and biochemical features

Critical	▪ Presence of severe features plus: • Anuria/acute renal failure • Arrhythmia • Pericardial effusion • Massive hydrothorax • Thromboembolism • Arterial thrombosis • ARDS • Sepsis	▪ Worsening of biochemical findings seen with severe OHSS

Abdominal pain, nausea, and vomiting

Enlargement of the ovaries causes abdominal pain, nausea, and vomiting. The enlargement is sometimes as much as 25 cm.

Acute abdominal pain

Acute abdominal pain may be due to ovarian torsion, intraperitoneal hemorrhage, or rupture of cysts secondary to enlarged ovaries with fragile walls.

Ascites and tense distention

Another consequence of ovarian hyperstimulation syndrome (OHSS) is discomfort resulting **from increased intra-abdominal pressure** due to ascites. **Ascites** and **tense abdominal distention** occur because of extravasation and increased leakage of protein-rich fluid from the intravascular space into the abdominal cavity, owing to an osmolar differential.
In addition, leakage of fluid from large follicles, increased capillary permeability (due to the release of vasoactive substances), or rupture of follicles can all contribute to ascites

Localized or generalized peritonitis

is caused by peritoneal irritation secondary to blood from ruptured cysts, protein-rich fluid, and inflammatory mediators.

Hypotension and/or hypovolemia

Follicular fluid and **perifollicular blood** containing large amounts of vascular endothelial growth factor (VEGF), which is thought to **increase** vascular permeability, escape into the peritoneal cavity.
Blood vessels within and outside the ovary become functionally impaired, resulting in the leakage of fluid through those vessels and a massive fluid shift from **the intravascular** to the **extravascular compartment**.
This process results in **intravascular hypovolemia** with the concomitant development of **edema**, **ascites**, **hydrothorax**, and/or **hydropericardium**.
Hypotension and/or hypovolemia are also **caused** by compression of the **inferior vena cava** because of enlarged cysts or ascites.
As a result, **venous return decrease**.
Eventual outcomes are **reduced cardiac output and hypotension**.

Dyspnea

Pulmonary function may be compromised as enlarged ovaries and ascites restrict diaphragmatic movement.

Other possible causes of dyspnea are the relatively rare manifestations of OHSS, such as pleural effusion, pulmonary edema, atelectasis, pulmonary embolism, acute respiratory distress syndrome (ARDS), and pericardial effusion.

Hypercoagulable state

A hypercoagulable state is likely due to **hemoconcentration** and **hypovolemia** resulting from fluid shift.

It is also related to increased **estrogen** levels.

Patients have an **increased risk** of developing deep venous thromboses and pulmonary embolisms.

Electrolyte imbalance

Electrolyte imbalance occurs due to the extravasation of fluid and resultant renal dysfunction resulting from decreased perfusion.
Increased reabsorption of **sodium** and **water** occurs in the proximal tubule, leading to **oliguria** and **low urinary sodium excretion**.
The exchange of **hydrogen** and **potassium** for sodium in the distal tubule is **reduced**.
As a result, hydrogen and potassium ions **accumulate** and cause hyperkalemia and a tendency to develop acidosis.

Acute renal failure

Hypovolemia in OHSS leads to hemoconcentration and creates a hypercoagulable state.
Microthrombi form in tubules, leading to **decreased renal perfusion** and **acute renal failure may result**

DIAGNOSIS

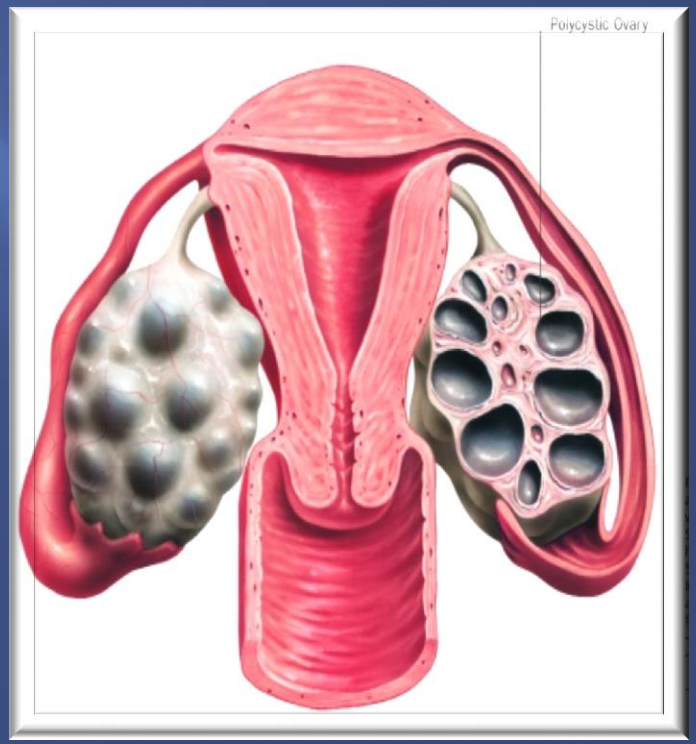
Classic symptoms of moderate to severe OHSS include a sensation of bloating, abdominal pain, rapid weight gain, and decreased urine output. Alternative diagnoses such as pelvic infection, intra abdominal hemorrhage, ectopic pregnancy, appendicitis, and complications of ovarian cysts such as torsion or hemorrhage must be kept in mind.

Physical examination

Physical findings of OHSS include right or left **lower quadrant pain** below the umbilicus, as well as edema.

Of note, abdominal palpation must be performed gently to avoid the possibility of rupturing a large cyst.

Pelvic examination should be deferred in favor of ultrasonography of the pelvis



Prevention

Remember that women at risk are those with high levels of estrogen and many follicles at the assumed time of ovulation. Patients with polycystic ovarian syndrome should be closely monitored as well.

OHSS prevention have included the following strategies:

Cancelling ovulation induction

Ovarian hyperstimulation syndrome (OHSS) is a self-limiting disease of the luteal phase. **Without** luteinizing hormone (LH) or its imitator, hCG, ovulation or the luteal phase **does not occur**. **Avoidance of hCG** during ovarian stimulation offers an opportunity to prevent OHSS in high-risk patients.

Prevention

hCG induces the production of VEGF, the primary mediator of OHSS

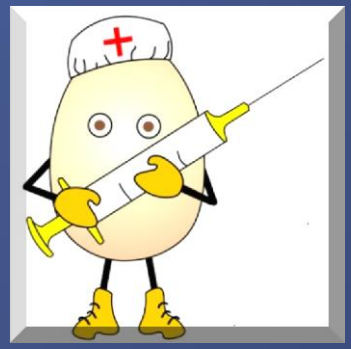
However, this course of action is costly and psychologically demanding for the participants.

Individualizing the hCG trigger dose

Decreasing the standard dose of hCG administered to trigger oocyte maturation (10000 IU) might prevent OHSS.
Doses of hCG as low as **3300 IU** have been shown to effectively trigger oocyte maturation in ART without adversely affecting cycle outcome.

Doses of hCG as low as **2500 IU** have been shown to be effective in patients with PCOS.

Prevention



Choice of luteal phase support

luteal support with HCG should be excluded whenever oestradiol concentrations are 2500 pg/ml and the number of follicles exceeds 10.

When progesterone is administered as luteal support there is clinical evidence of a lower risk of OHSS **than** when HCG is used, and ovarian enlargement declines more rapidly.

Prevention

Coasting

Coasting involves **temporarily stopping** gonadotropin administration and postponing the hCG trigger **until** the estradiol level is lower.

The proposed mechanism of coasting is as follows:

lower gonadotropin stimulation leads to decreased LH receptors, leading to decreased luteinization, and subsequent decreased VEGF levels. Lower gonadotropin stimulation may also increase the rate of granulosa cell apoptosis, especially of smaller follicles.

Coasting lowers the level of follicular fluid VEGF, thereby Potentially preventing the development of OHSS

Prevention

Agonist medication

Using an **agonist** medication to **trigger ovulation**, instead of an **hCG** trigger, has been proposed as another strategy to prevent OHSS.

Agonist trigger can only be used in the setting of an antagonist protocol, and Leuprolide 0.5-1mg or Triptorelin 0.1- 0.2mg have been suggested.

Cryopreservation

Cryopreservation of oocyte and embryos in patients with OHSS or at risk for developing OHSS is a strategy which has been employed

Activity

intercourse is restricted in women with any grade of OHSS because of the **risk of rupturing a cyst**.
Patients should also avoid impact-type activities or strenuous exertion.

Albumin

The administration of IV albumin has been suggested as an alternate method to prophylax against the development of OHSS.

Cabergoline

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

The proposed mechanism is inhibition of phosphorylation of the VEGF receptor and preventing increased capillary permeability.

The dopamine agonist Cabergoline has been investigated in healthy egg donors At risk for OHSS (20 or more oocytes).

In the women who received Cabergoline, the **ascites volume** was statistically significantly **lower than** in those who received placebo.

The percentage of women who **developed moderate** OHSS was statistically significantly **lower** in those patients who **received Cabergoline**

Quinagolide

Quinagolide is a nonergot dopamine agonist drug

Prevention guidelines

The addition of **metformin** should be considered in patients with polycystic ovarian syndrome who are undergoing in vitro fertilization, because it may reduce the incidence of OHSS

Metformin pretreatment beginning four to five weeks before starting gonadotropin therapy for IVF reduced the risk of OHSS.

Elective **single-embryo transfer** is recommended in patients **at high risk for OHSS**

prevention of ovarian hyperstimulation syndrome

Pre-treatment	• Weight management
During stimulation	• Minimal/no stimulation cycles
	• Coasting
	• GnRH antagonist cycles
	• Cycle cancellation
Triggering ovulation	• HCG dose and type
	• GnRH antagonist/agonist as triggers
	• Recombinant LH
Oocyte retrieval	• Use of albumin
	• Elective cryopreservation of embryos
Luteal phase support	• Use of progesterone
Newer techniques	• Cabergoline

Treatment of OHSS

If iCOS is not applied and risk reduction strategies are unsuccessful, measures are required to minimize the effect of OHSS and prevent further morbidity

Mild OHSS, which due to the very nature of COS occurs in most patients, and moderate OHSS with no clinical evidence of ascites or enlarged ovaries are not associated with complications and as a result do not require specific treatment.

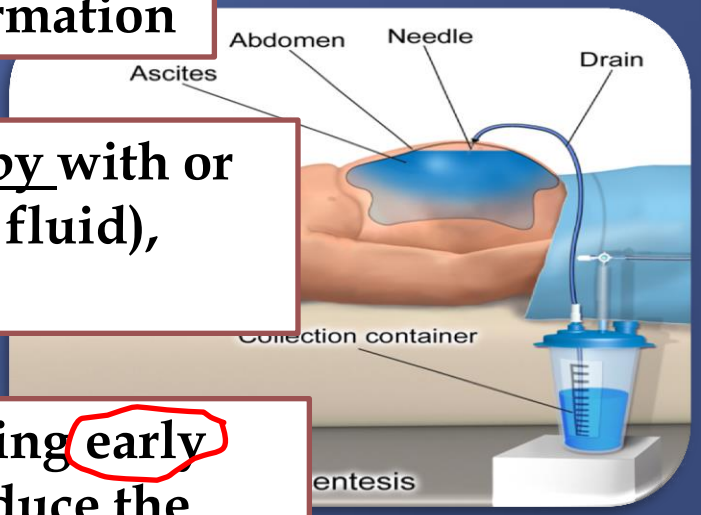
Mild OHSS and moderate OHSS can be treated symptomatically and patients monitored on an outpatient basis.

Severe OHSS must be regarded as a potentially fatal complication that requires immediate treatment to maintain circulatory volume and restore electrolyte balance using IV fluids

Ascitic

Treatment of OHSS

OHSS often leads to increased ascitic fluid formation



The treatment of OHSS, comprising IV therapy with or without paracentesis (aspiration of the ascitic fluid), involved prolonged hospitalization.

In patients with moderate-to-severe OHSS using early paracentesis has been shown to effectively reduce the need for hospitalization.

In patients with moderate OHSS, aggressive early paracentesis can prevent the progression of disease severity

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

Treatment of OHSS

Pain relief

Symptomatic relief of abdominal pain can be achieved with acetaminophen and if necessary oral or parenteral opiates.

Non-steroidal anti-inflammatory agents with **antiplatelet properties** should not be used because they may **interfere** with implantation and may also compromise renal function in women with severe OHSS.

Nausea and/or vomiting

Antiemetic agents considered to be safe in early pregnancy should be used to alleviate nausea and/or vomiting.

Treatment of OHSS

Monitoring

Admitted patients should be assessed by a physician at least once daily.

Weight and urine specific gravity should be recorded daily.

Vital signs, urine output, and fluid balance should also be recorded.

Urine output should be maintained at a minimum of 30 mL/hour.

Physical examination should assess hydration, cardiorespiratory status, degree of ascites and signs of thromboembolism.

Daily monitoring of hemoglobin, hematocrit, creatinine, electrolytes, and albumin is useful to document disease progress.

Treatment of OHSS

Prevention of thromboembolic complications

Hospitalized patients should be considered at risk of **thrombosis** secondary to hemoconcentration and immobilization.

Daily prophylactic doses of low-molecularweight heparin (heparin 5000 IU/12 hours) and use of thromboembolic deterrent stockings should be considered on admission and continued until discharge.

Treatment of OHSS

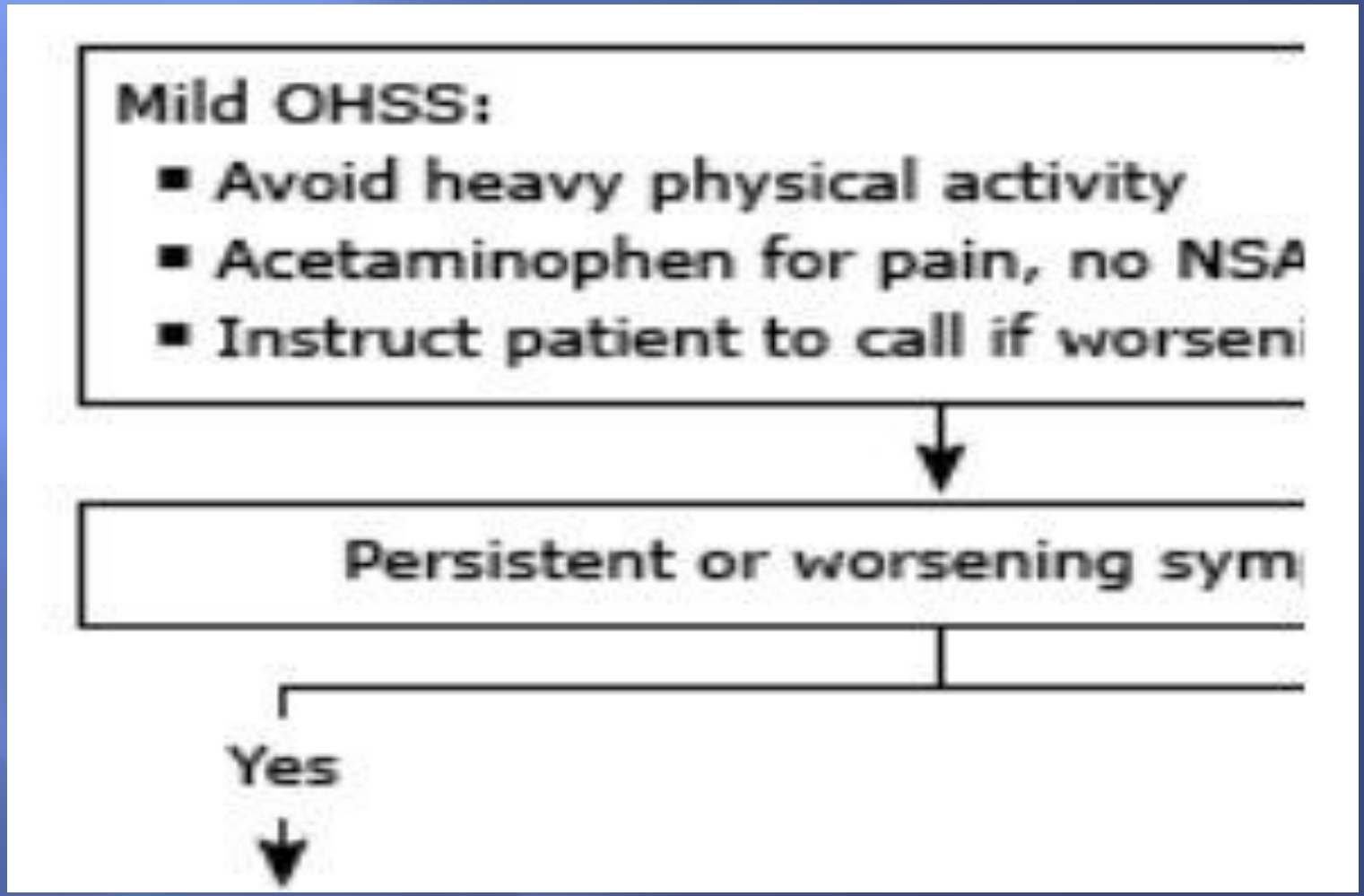
Management of Complications

Renal failure, thromboembolism, pericardial effusion and adult respiratory distress syndrome are potential **life-threatening complications** of OHSS. These conditions **should be diagnosed early** and managed by a multidisciplinary team possibly in an ICU setting.

Fluids and electrolytes

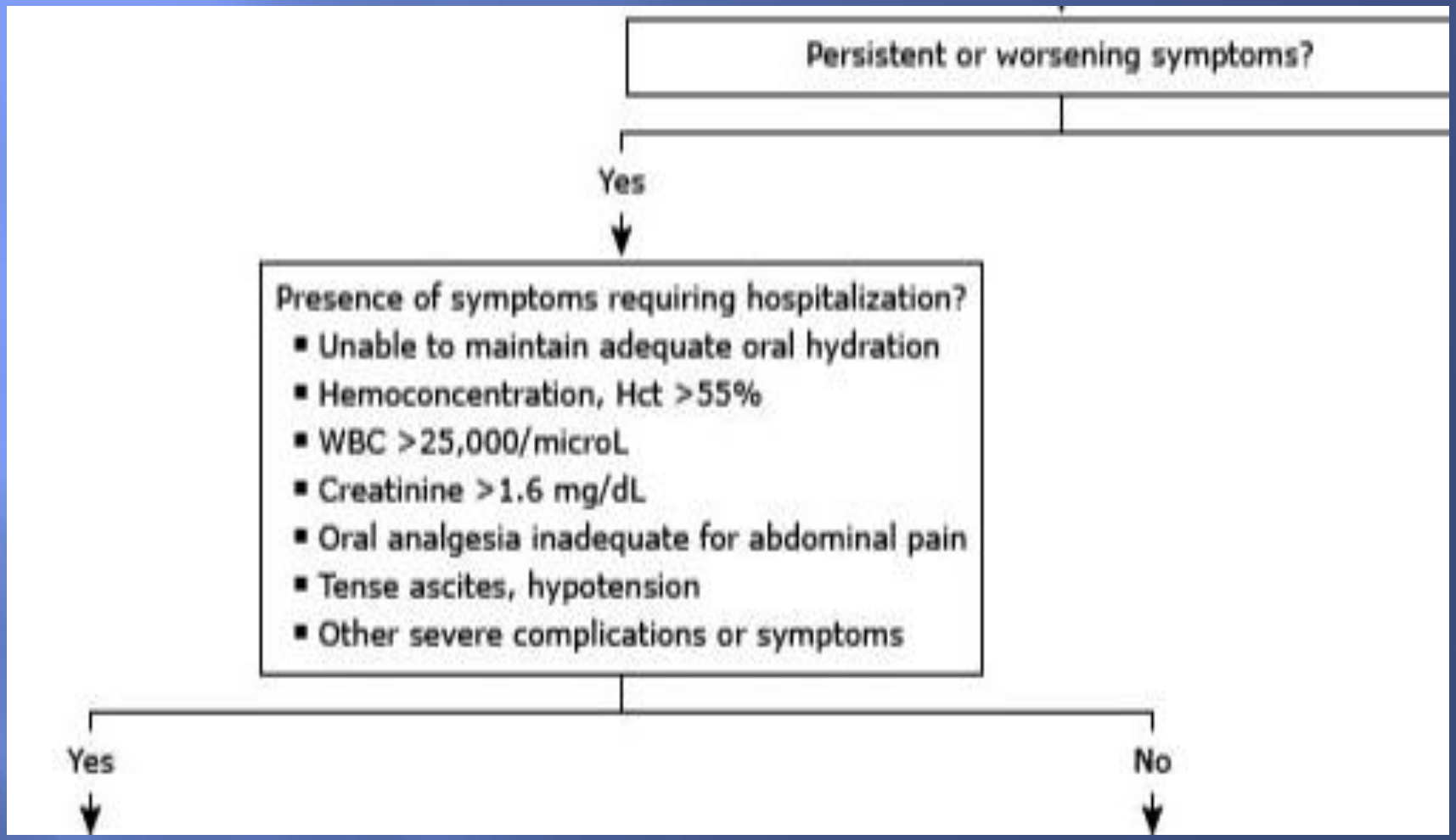
Women should drink according to their thirst. In addition, **IV hydration** with **a crystal loid solution** (100 to 150 mL/hr) should be instituted **until diuresis occurs.** If clinical and laboratory findings indicate persistent intravascular volume depletion despite aggressive IV fluid hydration, **IV albumin** (15 to 20 mL/hr of 25% albumin over 4 hours) should be initiated and repeated until hydration status improves.

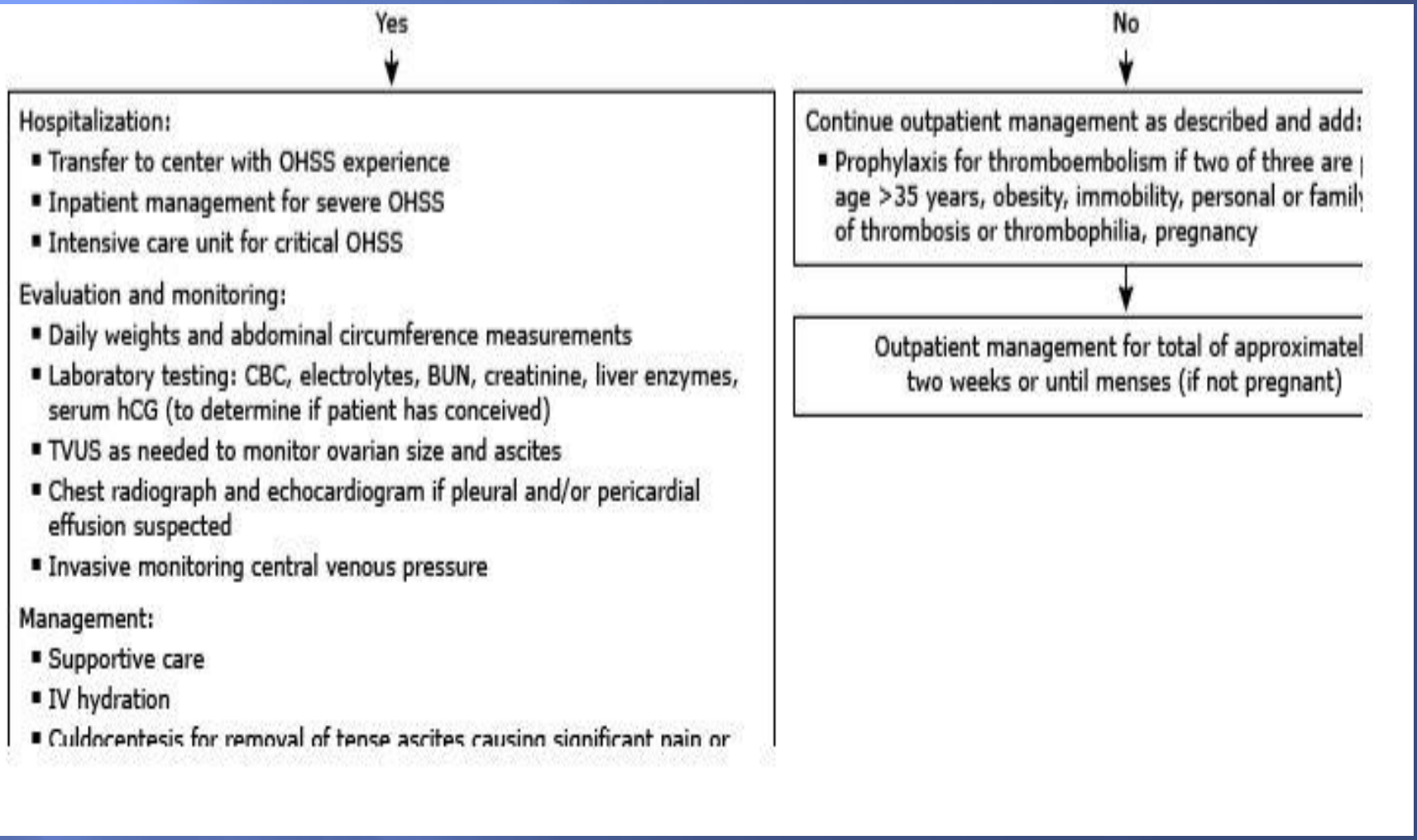
Management of ovarian hyperstimulation syndrome

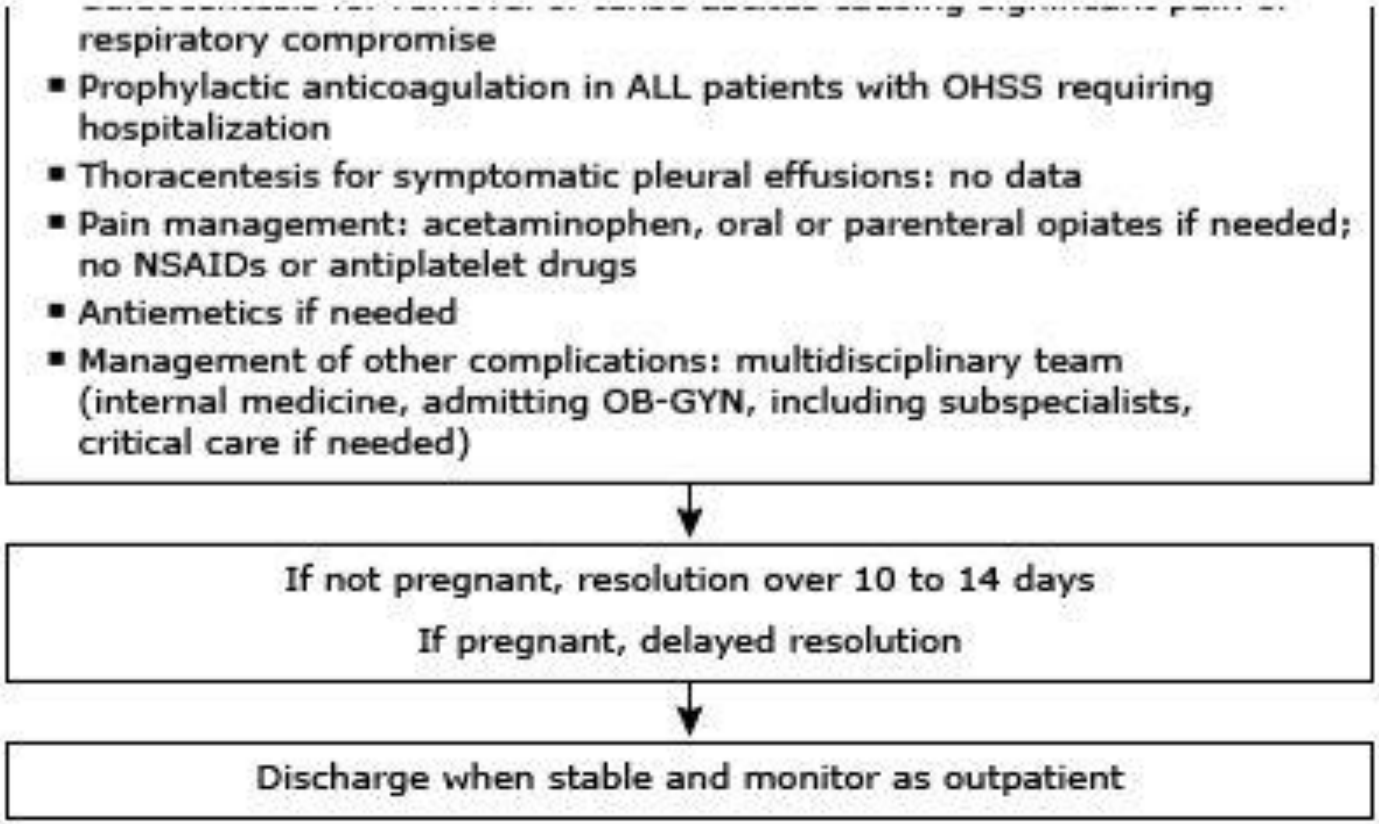


Moderate OHSS:

- Daily communication with patient:
  - Is patient able to maintain good hydration? (encourage 2 liters of fluids daily)
  - Get estimate of daily oral intake and urine output
  - Daily weight and abdominal girth measurements
  - Evaluate and report any symptoms of worsening
- Evaluation and treatment:
  - Ambulate, but avoid other physical activity, avoid sexual intercourse
  - Bed rest sometimes necessary
  - Baseline CBC, TVUS
  - If symptoms persist or worsen: physical examination, TVUS and CBC every 48 hours (or daily if worsening)
  - Culdocentesis to remove ascitic fluid as needed for symptomatic relief
  - For pain: acetaminophen, no NSAIDs; oral opiates rarely needed


Persistent or worsening symptoms?
Yes
Presence of symptoms requiring hospitalization?
Unable to maintain adequate oral hydration
Hemoconcentration, Hct >55%
WBC >25,000/microL
Creatinine >1.6 mg/dL
Oral analgesia inadequate for abdominal pain
Tense ascites, hypotension
Other severe complications or symptoms
Yes
No


Yes
No
Hospitalization:
Transfer to center with OHSS experience
Inpatient management for severe OHSS
Intensive care unit for critical OHSS
Evaluation and monitoring:
Daily weights and abdominal circumference measurements
Laboratory testing: CBC, electrolytes, BUN, creatinine, liver enzymes, serum hCG (to determine if patient has conceived)
TVUS as needed to monitor ovarian size and ascites
Chest radiograph and echocardiogram if pleural and/or pericardial effusion suspected
Invasive monitoring central venous pressure
Management:
Supportive care
IV hydration
Culdocentesis for removal of tense ascites causing significant pain or
Continue outpatient management as described and add:
Prophylaxis for thromboembolism if two of three are
age >35 years, obesity, immobility, personal or family
of thrombosis or thrombophilia, pregnancy
Outpatient management for total of approximatel
two weeks or until menses (if not pregnant)


respiratory compromise
Prophylactic anticoagulation in ALL patients with OHSS requiring hospitalization
Thoracentesis for symptomatic pleural effusions: no data
Pain management: acetaminophen, oral or parenteral opiates if needed; no NSAIDs or antiplatelet drugs
Antiemetics if needed
Management of other complications: multidisciplinary team (internal medicine, admitting OB-GYN, including subspecialists, critical care if needed)
If not pregnant, resolution over 10 to 14 days
If pregnant, delayed resolution
Discharge when stable and monitor as outpatient


Thanks for your attention. . . .