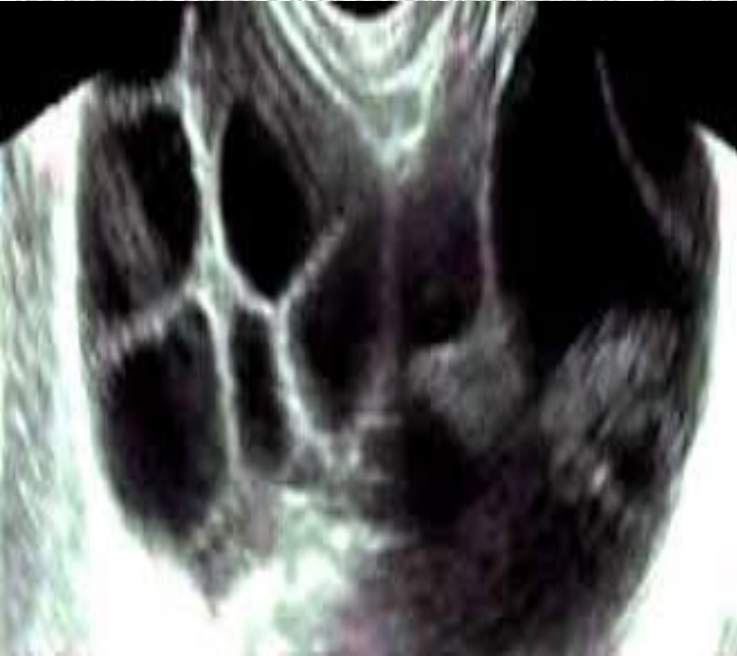




# How do we assess OHSS by ultrasound. - what are the high risk markers

Jointly Organized by The PCOS Society (India) & The Androgen Excess & PCOS Society (International) | Dates: June 16 - 18, 2017 | Bengaluru

**Dr BINA VASAN, MD, MSc ( Rep..Medicine, U.k.)**  
**DIRECTOR,,MANIPAL FERTILITY**



# Outline of the presentation

- Ovarian hyperstimulation syndrome (OHSS)
- Risk Factors for OHSS
- Prediction I Before stimulation
- Prediction II During ovarian stimulation
- Summary

# Ovarian hyperstimulation syndrome (OHSS)

- Ovarian hyperstimulation syndrome (OHSS) is an uncommon but serious complication associated with controlled ovarian stimulation during assisted reproductive technology (ART).
- Moderate-to-severe OHSS occurs in approximately 1%-5% of cycles
- OHSS is characterized by cystic enlargement of the ovaries and transudation of fluid and proteins from the intravascular compartment into the third space due to increased capillary permeability.

Fertil Steril 2016;106:1634-47

# Risk Factors for OHSS



## Primary Risk Factors

- Young age
- Low body weight
- PCOS, or isolated PCOS characteristics because of increased number of recruitable follicles
- H/O previous OHSS or increased response to gonadotropin therapy.

## Secondary Risk Factors

- Factors which become apparent during stimulation include:
- Absolute levels of E2 > 3,000 pg/ml or rate of increase of serum E2
- Follicular size and number ( $\geq 20$ ) on both ovaries
- Number of oocytes collected.

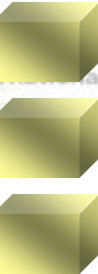


# Need for Prediction of OHSS



- Develop ovarian stimulation routines that are associated with a per se decreased risk of OHSS

- Also need measures of OHSS prevention for individual patients, which are safe and efficacious, and can therefore be liberally utilized



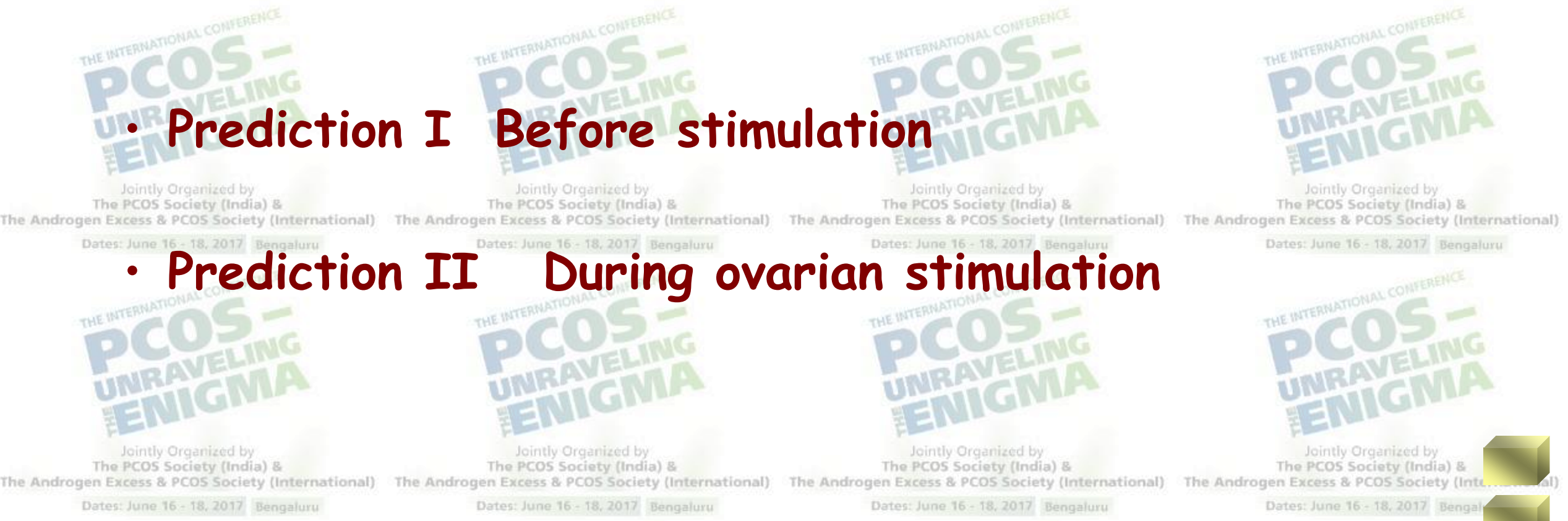


# *Prediction of OHSS*



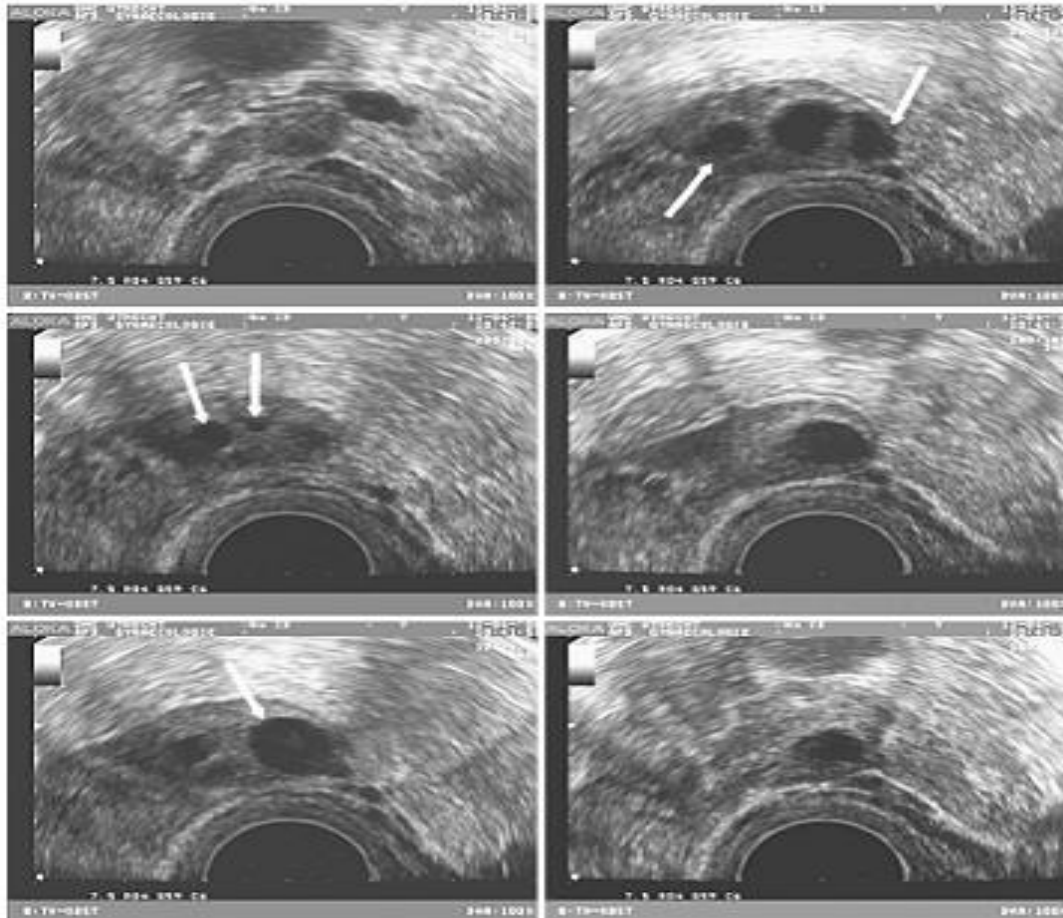
• Prediction I Before stimulation

• Prediction II During ovarian stimulation



# Antral follicle count (AFC)

Serial transvaginal ultrasound images, depicting a scout sweep to delineate the contours of the ovary, prior to measurement and counting of antral follicles (structures to be identified as antral follicles are indicated by white arrows). Images produced by van Disseldorp, UMC Utrecht, the Netherlands.



- AFC is the sum of antral follicles in both ovaries, as observed with transvaginal ultrasonography during the early follicular phase. Antral follicles : defined as measuring 2-10mm in mean diameter in the greatest two-dimensional plane

# Prediction of OHSS at different antral follicle count thresholds in a prospective cohort of 1,012 women

A total of 1,012 consecutive subjects of all ages undergoing their first cycle of assisted reproductive technique

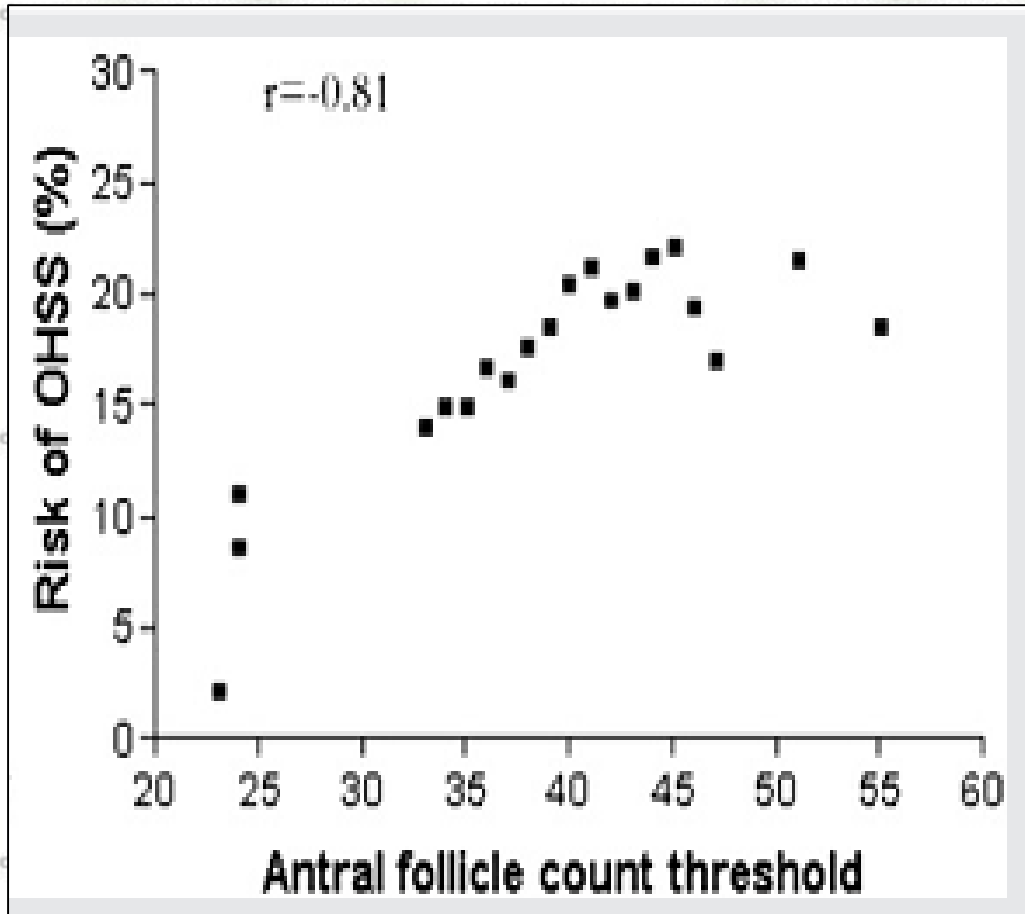
- The risk of moderate or severe OHSS is 2.2% with AFC of < 24, the risk increases to 8.6% at AFC of  $\geq 24$ .

The risk of OHSS increases further to 11% if there are signs and symptoms of polycystic ovary syndrome.

Fertil Steril 2012;98:657-63.



# Prediction of OHSS at different antral follicle count thresholds in a prospective cohort of 1,012 women

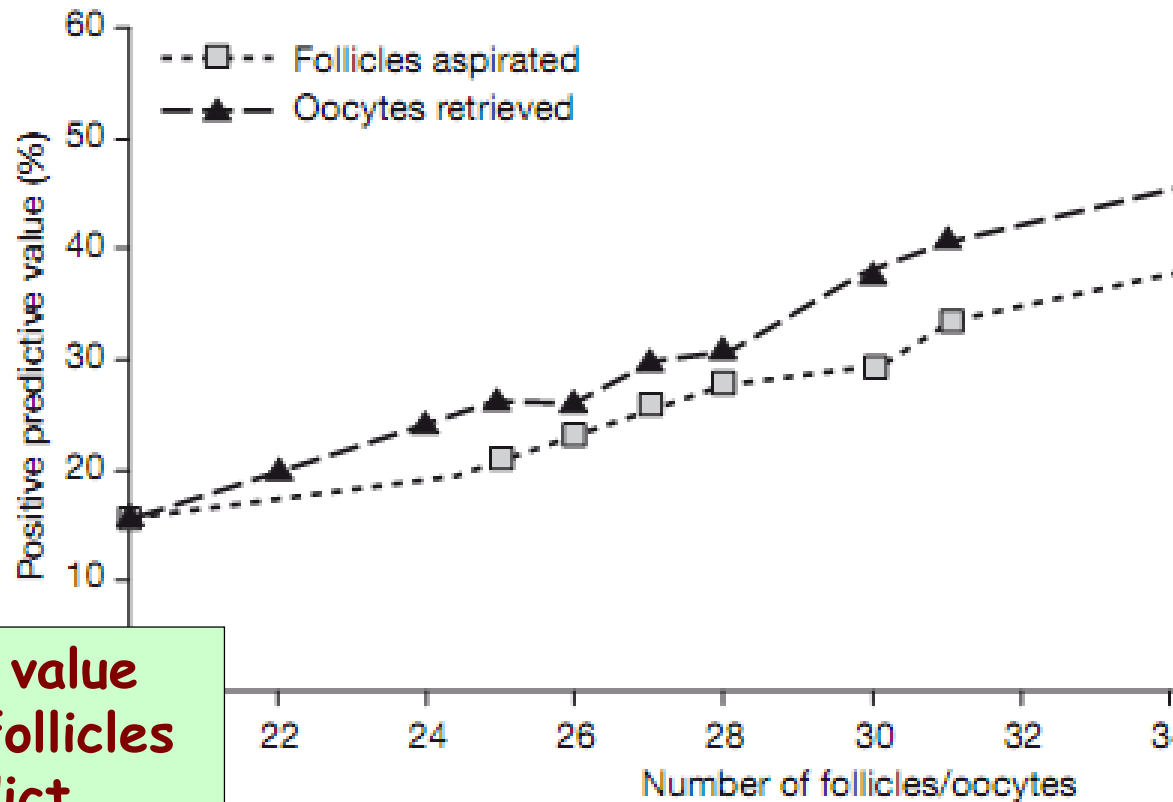


- The risk of OHSS increased in a linear fashion from 8.4% to approximately 21% as the AFC threshold increased from 24 or more.
- The risk of OHSS continued to rise in a linear fashion to an AFC of 41 or more but then plateaued

# Ovarian volume and antral follicle count for the prediction of low and hyper responders with in vitro fertilization

- AFC performs well as a test for ovarian response being superior or at least similar to complex expensive and time consuming endocrine tests
- Total volume of the ovaries detected by transvaginal ultrasound is correlated with the outcome parameters but not better than the count of antral follicles. Its performance was slightly to moderately less than that of AFC, both for poor and high response.

# Optimal follicle and oocyte numbers for cryopreservation of all embryos in IVF cycles at risk of OHSS



A retrospective study of 2253 cycles identified a threshold of 24 or more retrieved oocytes to recommend a freeze-all cycle, a strategy in which a fresh transfer is avoided to allow the ovaries to return to a normal state before attempting pregnancy in order to prevent OHSS

Positive predictive value using numbers of follicles or oocytes to predict early-onset ovarian hyperstimulation syndrome among women with 20 or more oocytes retrieved.

# Can quantitative three-dimensional power Doppler angiography be used to predict ovarian hyperstimulation syndrome?

- 118 subjects undergoing IVF had a three-dimensional (3D) TVS in early follicular phase of menstrual cycle preceding IVF treatment.
- 18 of them developed moderate or severe OHSS and 100 subjects had normal ovarian response.
- AFC, ovarian volume, and ovarian vascularity (vascularization index (VI), flow index (FI) and vascularization flow index (VFI)) were compared between OHSS and control groups.
- The study demonstrated that women developing OHSS during IVF do not demonstrate an increased ovarian blood flow as measured by 3D ultrasound but do have a significantly higher antral follicle count, which is the only significant predictor of OHSS.



# Doppler in PCOS to predict OHSS

- The use of Doppler to assess ovarian stromal flow in women with PCO may have a useful predictive role for the future development of OHSS.
- Patients with PCO who have a high ovarian stromal flow are more likely to be at risk of ovarian hyperstimulation during treatment.





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# Prediction of OHSS During stimulation

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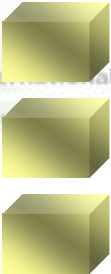
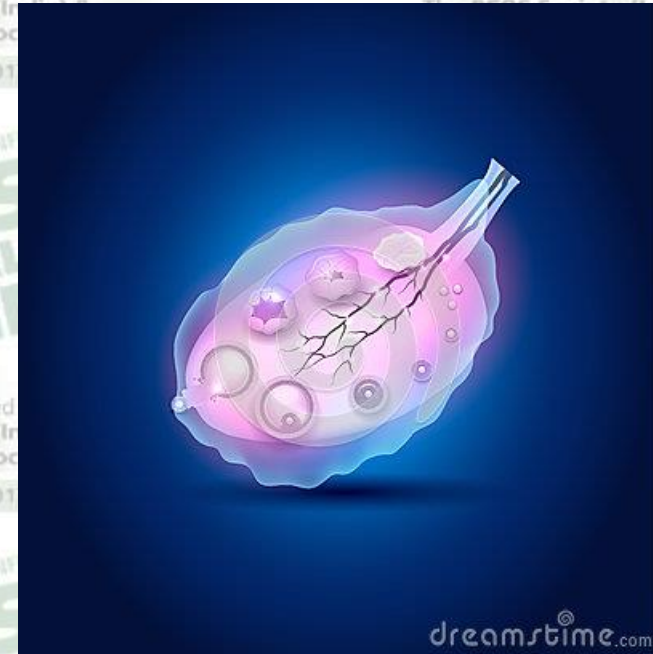
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# *The number of follicles on the day of HCG administration -indicator for the occurrence of severe OHSS*

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- The number of follicles on the day of HCG administration appears to be a better prognostic indicator for the occurrence of severe OHSS than the estradiol values (87% of the severe cases had  $\geq 14$  or follicles of a diameter  $> 11$ mm, whereas only 50% of them had an estradiol value  $3000$  ng/l).

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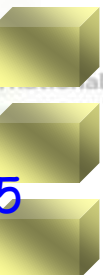
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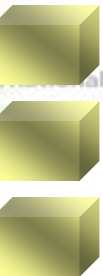
# Ovarian hyperstimulation syndrome: prediction by number and size of preovulatory ovarian follicles

- 65 infertile patients treated with hMG for ovulation induction and human chorionic gonadotropin (hCG), 5A specific preovulatory follicular configuration characterizes mild and severe hyperstimulation.

• Mild OHS was characterized by the presence of eight to nine follicles, 68.7% of which were of intermediate size (9 to 15 mm).

- In moderate to severe OHS 95% of the preovulatory follicles were < 16 mm, most of them (54.7%) < 9 mm in diameter.

• It can be concluded that This is important information before heG administration and emphasizes the value of ovarian ultrasonography in predicting OHS.

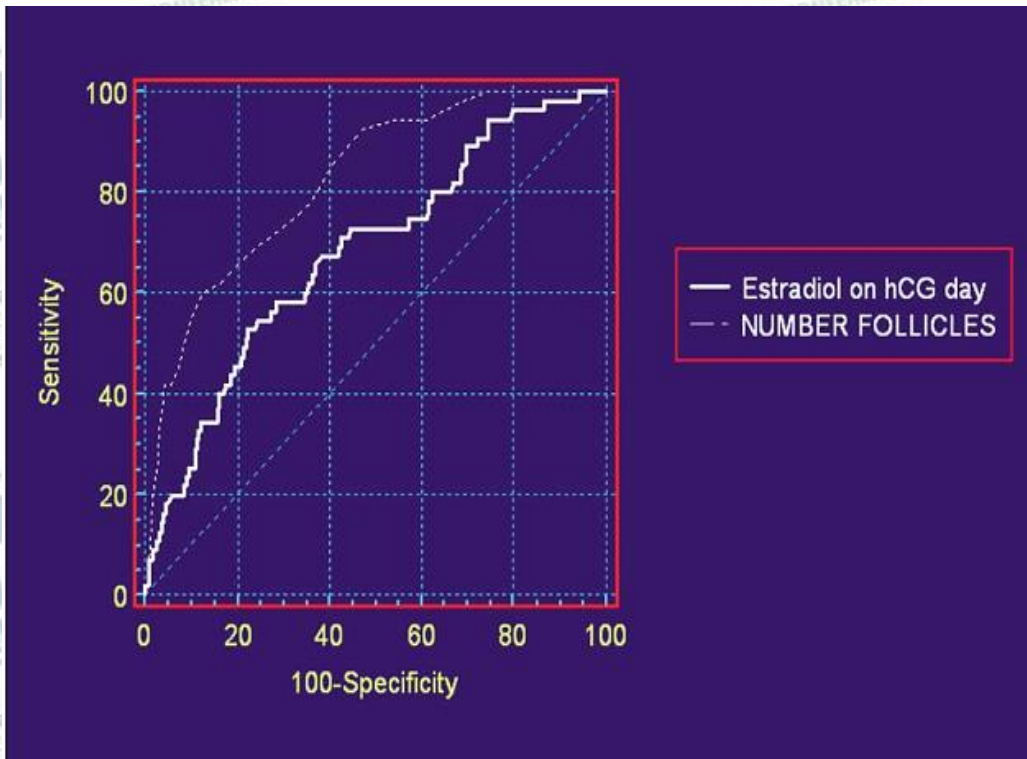






# Number of follicles VS E2 concentrations for the purpose of prediction of OHSS

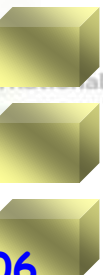
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1801 patients who underwent 2,524 cycles.



Analysis for several E2 concentrations and number of follicles with a diameter of > 11 mm

- predictive value of the optimal threshold of > 13 follicles (85.5% sensitivity; 69% specificity) was statistically significantly superior to the optimal threshold of 2,560 ng/L for E2 concentrations (53% sensitivity, 77% specificity) in identifying patients at risk for OHSS.

- a threshold of > 18 follicles and/or E2 of > 5,000 ng/L yields a 83% sensitivity rate with a specificity as high as 84% for the severe OHSS cases.





# Number of follicles VS E2 concentrations for the purpose of prediction of OHSS

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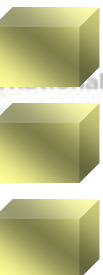
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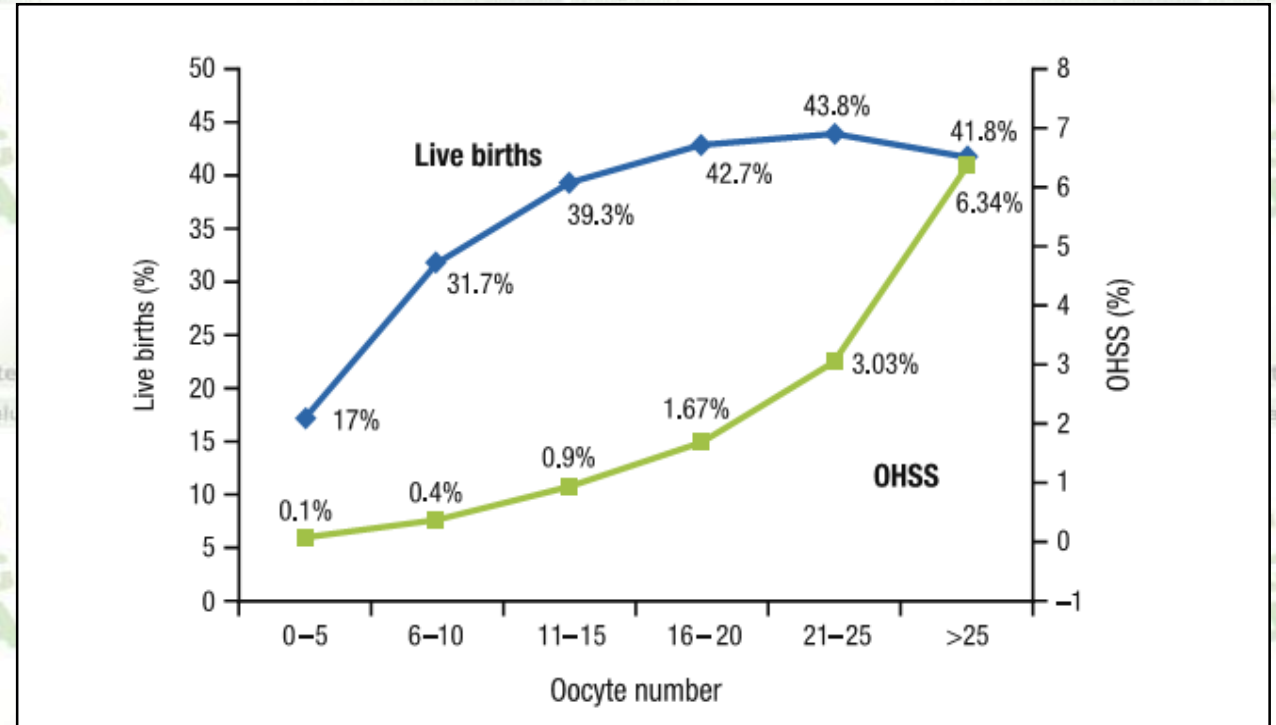
Clinically significant OHSS still remains a limitation of multifollicular ovarian stimulation for IVF even with the use of GnRH antagonist protocols.

The number of follicles can discriminate the patients who are at risk for developing OHSS, whereas E2 concentrations are less reliable for the purpose of prediction



# Oocyte number as a predictor for ovarian hyperstimulation syndrome and live birth; an analysis of 256,381 in vitro fertilization cycles

SART data from 2008-2010, the incidence of OHSS was 0.37% in fresh cycles with six to 10 oocytes and 1.67% in fresh cycles with 16-20 oocytes



Rates of live birth and ovarian hyperstimulation syndrome with increasing oocyte yield Based on Society for Assisted Reproductive Technology (SART) data from 2008-2010

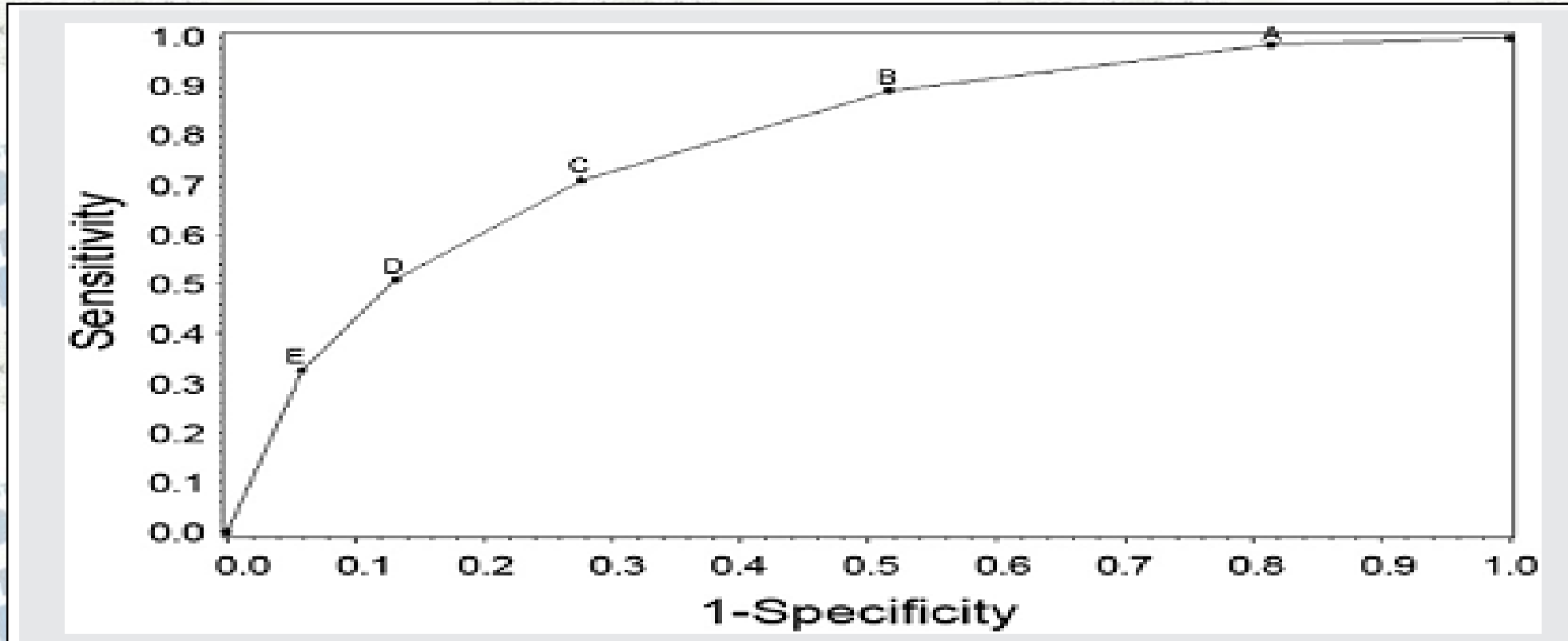
**The risk for ovarian hyperstimulation syndrome significantly increases and live birth rates plateau in patients with >15 oocytes retrieved: an analysis of 256,381 fresh, autologous ivf cycles.**

**TABLE 1. Rates of CP, LB, OHSS per oocyte group**

	0-5	6-10	11-15 <sup>1</sup>	16-20	21-25	>25
n (%)	47,080 (18.25)	75,741 (29.36)	61,471 (23.83)	37,178 (14.41)	18,906 (7.33)	16,005 (6.20)
Clinical Pregnancy %	27.4	42.0	49.8	53.2	55.3	56.1
Live Birth %	17.0	31.7	39.3	42.7	43.8	41.8
OHSS %	0.09	0.37	0.93	1.67	3.03	6.34

**Retrieval of >15 oocytes significantly increases the risk of OHSS with minimal gain in LB rate.**

# ROC for retrieved oocyte number as a predictor of ovarian hyperstimulation syndrome.

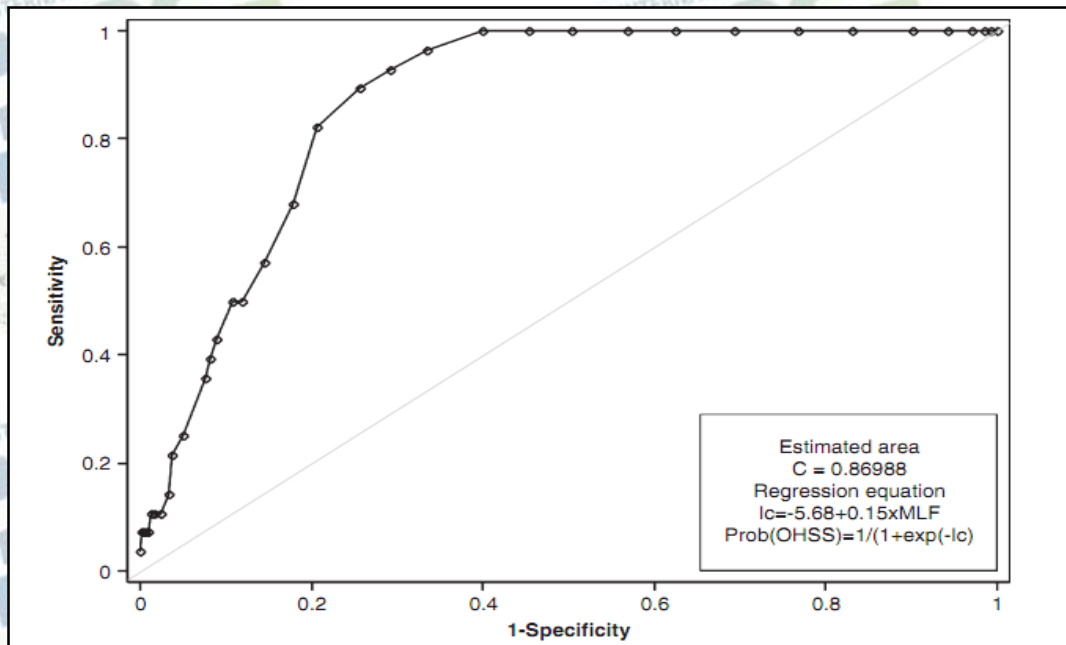


Oocyte number thresholds: A: 5; B: 10; C: 15; D: 20; E: 25.

Fertil Steril 2014;101: 967-73.

# OHSS prediction before hcg administration

624 ICSI patients. Observational clinical data were compared. Patients who developed OHSS were compared with patients who did not develop OHSS. Twenty-eight patients developed OHSS considered as severe



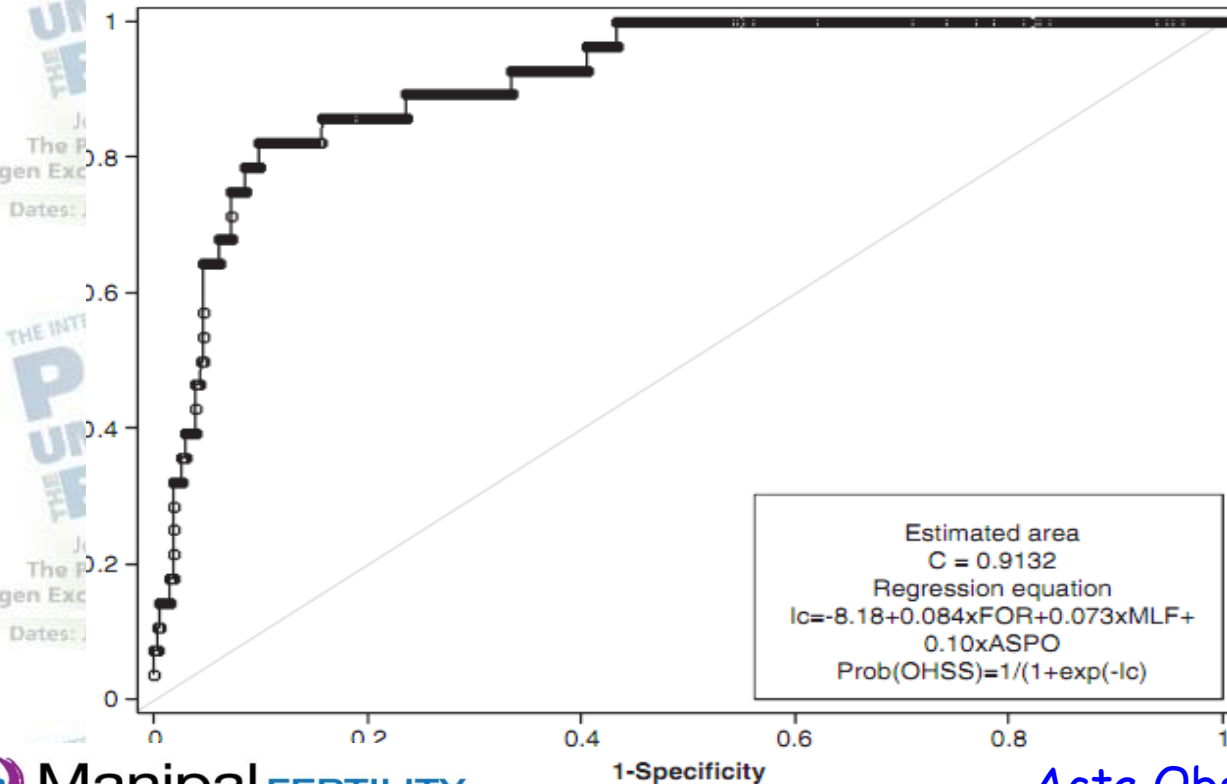
The only independent predictor of OHSS before the ovulatory dose of hCG was total number of medium/large-sized follicles before hCG. A corresponding ROC found a sensitivity of 82.1% and specificity of 79.4%

ROC curve for the predicted probabilities of OHSS requiring hospitalization, including variables until administration of hCG with number of MLF as predictor

# OHSS prediction after oocyte aspiration

624 ICSI patients. Observational clinical data were compared. Patients who developed OHSS were compared with patients who did not develop OHSS. Twenty-eight patients developed OHSS considered as sever.

After oocyte aspiration, the variables number of follicles at oocyte aspiration, number of aspirated oocytes and total number of medium/large-sized follicles before hCG were predictive of OHSS. Women with a high risk of OHSS requiring hospitalization could be identified with reasonable high sensitivity and specificity by a combination of these predictors.



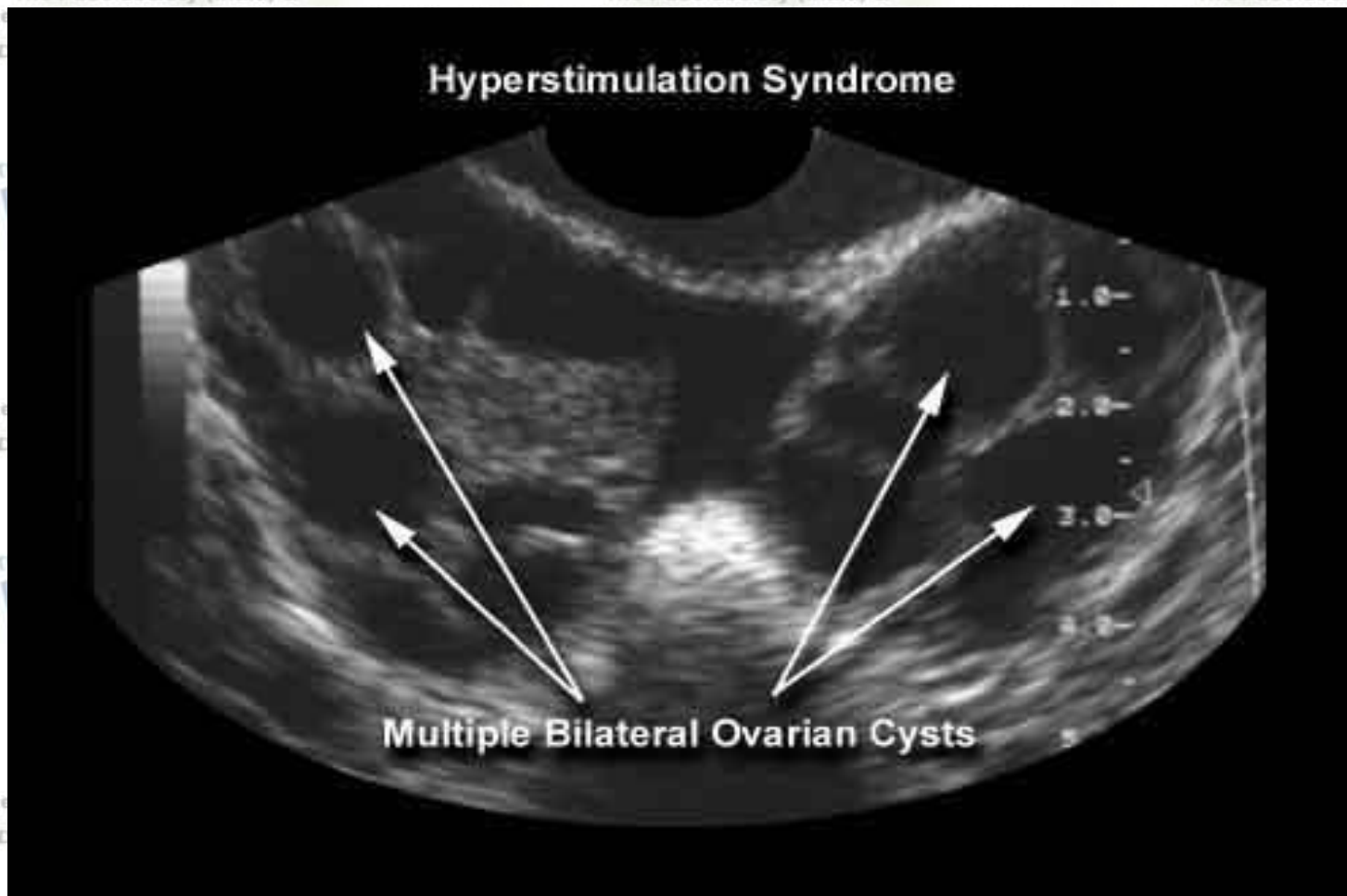
# Classification of OHSS symptoms.

OHSS stage	Clinical feature	Laboratory feature
Mild	Abdominal distension/discomfort Mild nausea/vomiting Mild dyspnea Diarrhea Enlarged ovaries	No important alterations
Moderate	Mild features Ultrasonographic evidence of ascites	Hemoconcentration (Hct >41%) Elevated WBC (>15,000 mL)
Severe	Mild and moderate features Clinical evidence of ascites Hydrothorax Severe dyspnea Oliguria/anuria Intractable nausea/vomiting  Low blood/central venous pressure Pleural effusion Rapid weight gain (>1 kg in 24 h) Syncope Severe abdominal pain Venous thrombosis	Severe hemoconcentration (Hct >55%) WBC >25,000 mL CrCl <50 mL/min Cr >1.6 mg/dL Na+ <135 mEq/L K+ >5 mEq/L Elevated liver enzymes
Critical	Anuria/acute renal failure Arrhythmia Thromboembolism Pericardial effusion Massive hydrothorax Arterial thrombosis Adult respiratory distress syndrome Sepsis	Worsening of findings

Note: Hct = hematocrit; WBC = white blood cell; CrCl = creatinine clearance; Cr = creatinine; Na+ = sodium; K+ = potassium.



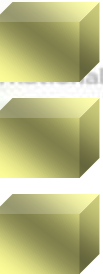
# Ovarian hyperstimulation syndrome.



Multiple large anechoic cysts are visualized in both ovaries in this image.



# Ultrasound of moderate OHSS with ascites.





# Ultrasound of ascites in the cul-de-sac with severe OHSS

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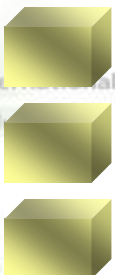


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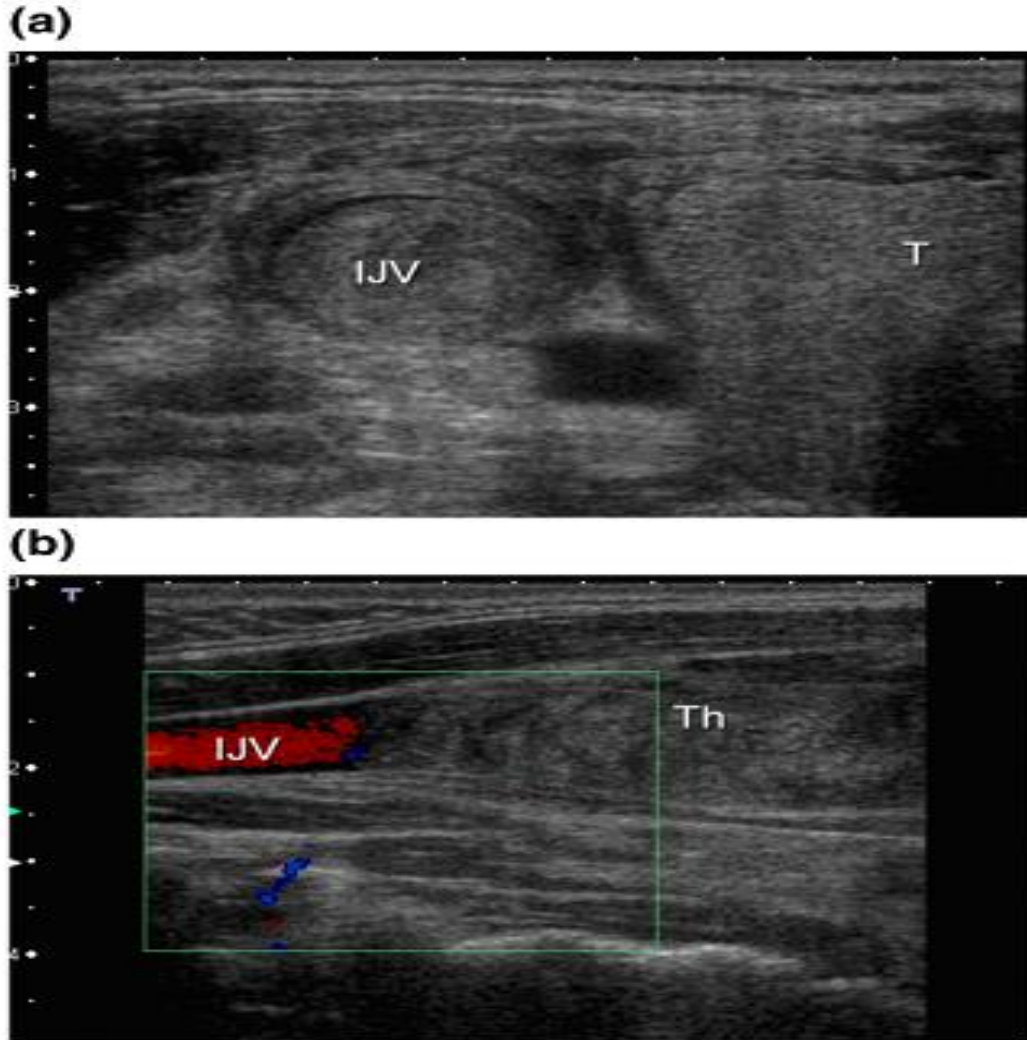
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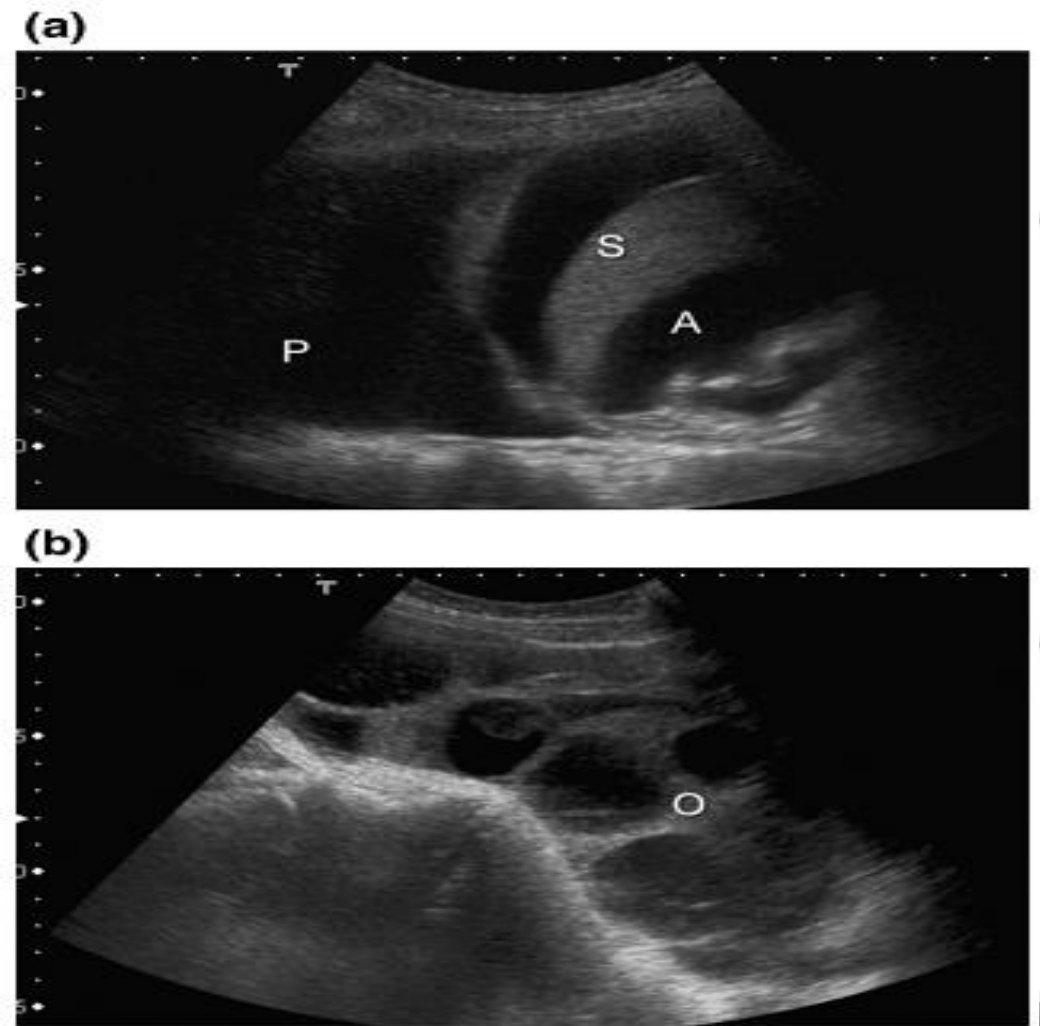
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# Internal jugular vein thrombosis and ohss

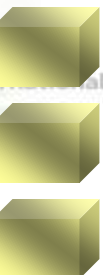
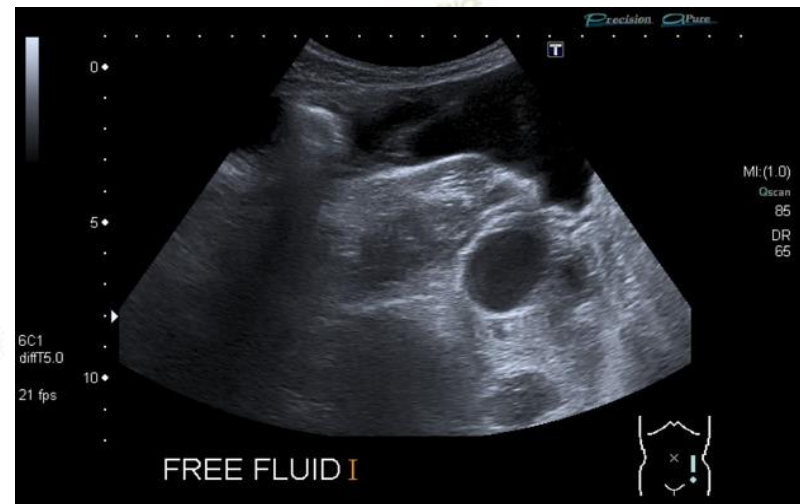
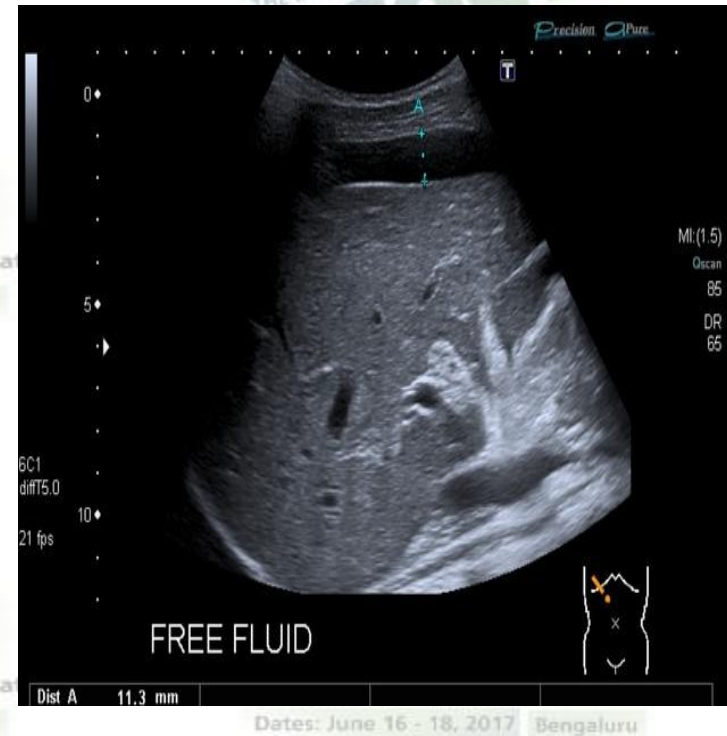
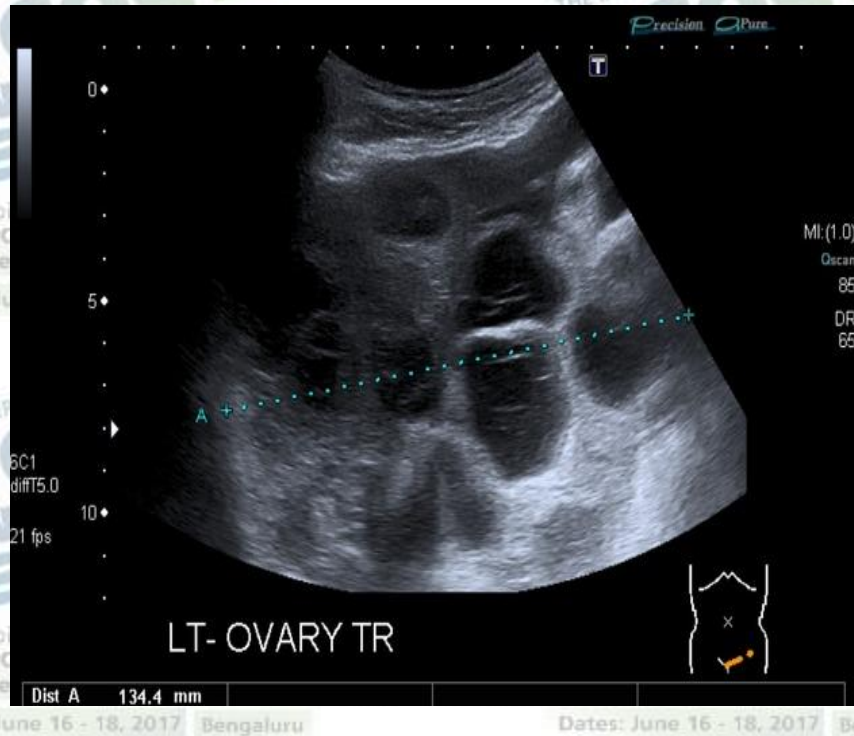
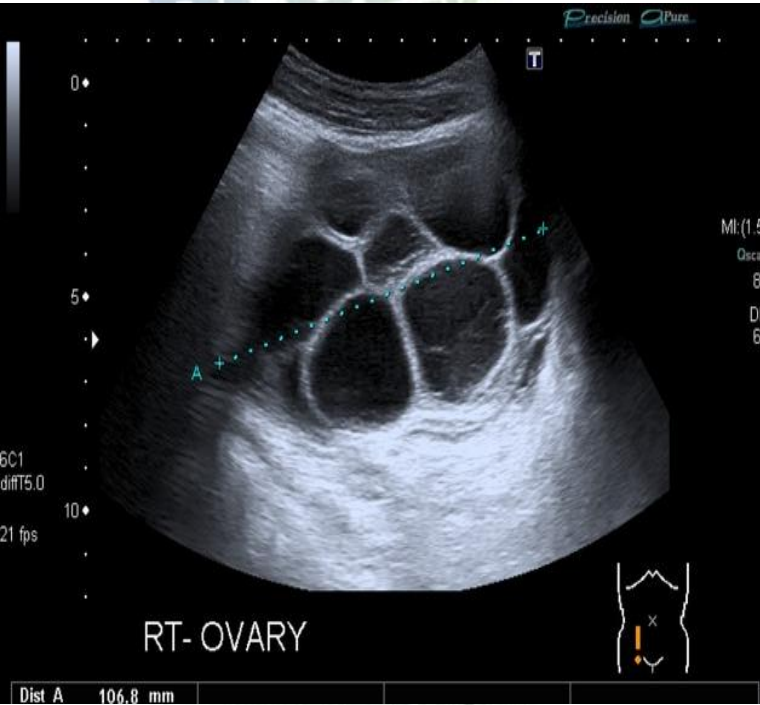


**Figure 1** A: Ultrasound image in transverse plane at the level of the thyroid (T). The right internal jugular vein (IJV) is enlarged containing echogenic thrombus. B: Longitudinal ultrasound image showing flow above the level of thrombus (Th) on colour Doppler. Internal jugular vein (IJV). [In colour online.]



**Figure 2** A: Longitudinal ultrasound image of the left upper quadrant of the abdomen showing moderate pleural effusion (P) and ascites (A) surrounding the spleen (S). B: Longitudinal ultrasound image of the pelvis showing a markedly enlarged right ovary (O).

# Severe OHSS





# hyper - responders

• For the younger individual, careful assessment and identification of the "high-responder" should guide the clinician in choosing the optimal, gentlest stimulation, thus avoiding or diminishing the risk of OHSS

Hyperstimulated ovary after gonadotropin therapy

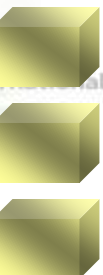


## OPINION

### Can we eliminate severe ovarian hyperstimulation syndrome?

Raoul Orvieto

- The syndrome almost always presents either 3-7 days after hCG administration in susceptible patients (early onset) or during early pregnancy, 12-17 days after hCG administration (late onset).
- Early OHSS can to some extent be predicted by pre-ovulatory indices of ovarian response, in time to institute preventive measures such as cancellation (Hancock et al., 1970).
- Late OHSS does not relate strongly to pre-ovulatory ovarian response, making it difficult for clinicians to identify the cycles in which it is likely to occur



# Elimination of ovarian hyperstimulation syndrome

- If the combined GnRH antagonist/agonist or the tailored COS protocols yield  $\geq 20$  oocytes, or  $\geq 10$  embryos develop, the patient should be followed for 5 days after oocyte retrieval for signs of early OHSS (ultrasonographic signs of ascites, Hct levels for the degree of haemoconcentration).
- If signs develop, embryo transfer should be withheld and all resulting embryos cryopreserved. This will limit early OHSS, if it appears, to a milder and shorter form.
- If it does not appear, the transfer of one blastocyst will decrease the risk of multiple pregnancy to almost zero, thereby eliminating the risk of late OHSS.



# Prevention and treatment of moderate and severe ovarian hyperstimulation syndrome: a guideline

Practice Committee of the American Society for Reproductive Medicine  
American Society for Reproductive Medicine, Birmingham, Alabama

While cut points require validation, AMH values  $>3.4$  ng/mL, AFC  $>24$ , development of  $\geq 25$  follicles, estradiol values  $>3,500$  pg/mL, or  $\geq 24$  oocytes retrieved are particularly associated with an increased risk of OHSS

# Summary

The number of follicles on the day of HCG administration appears to be a better prognostic indicator for the occurrence of severe OHSS than the estradiol values

AFC >24, development of  $\geq 25$  follicles, or > 24 oocytes retrieved are particularly associated with an increased risk of OHSS.

For patients with 19 follicles or more  $\geq 11$  mm on the day of hCG, measures to prevent the development of OHSS should be considered.

SUMMARY



# Summary

If the combined GnRH antagonist/agonist or the tailored COS protocols yield  $\geq 20$  oocytes, or  $\geq 10$  embryos develop, the patient should be followed for 5 days after oocyte retrieval for signs of early OHSS (ultrasonographic signs of ascites, Hct levels for the degree of haemoconcentration).

If signs develop, embryo transfer should be withheld and all resulting embryos cryopreserved. This will limit early OHSS, if it appears, to a milder and shorter form.



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