Preventing ovarian hyperstimulation syndrome: guidance for the clinician

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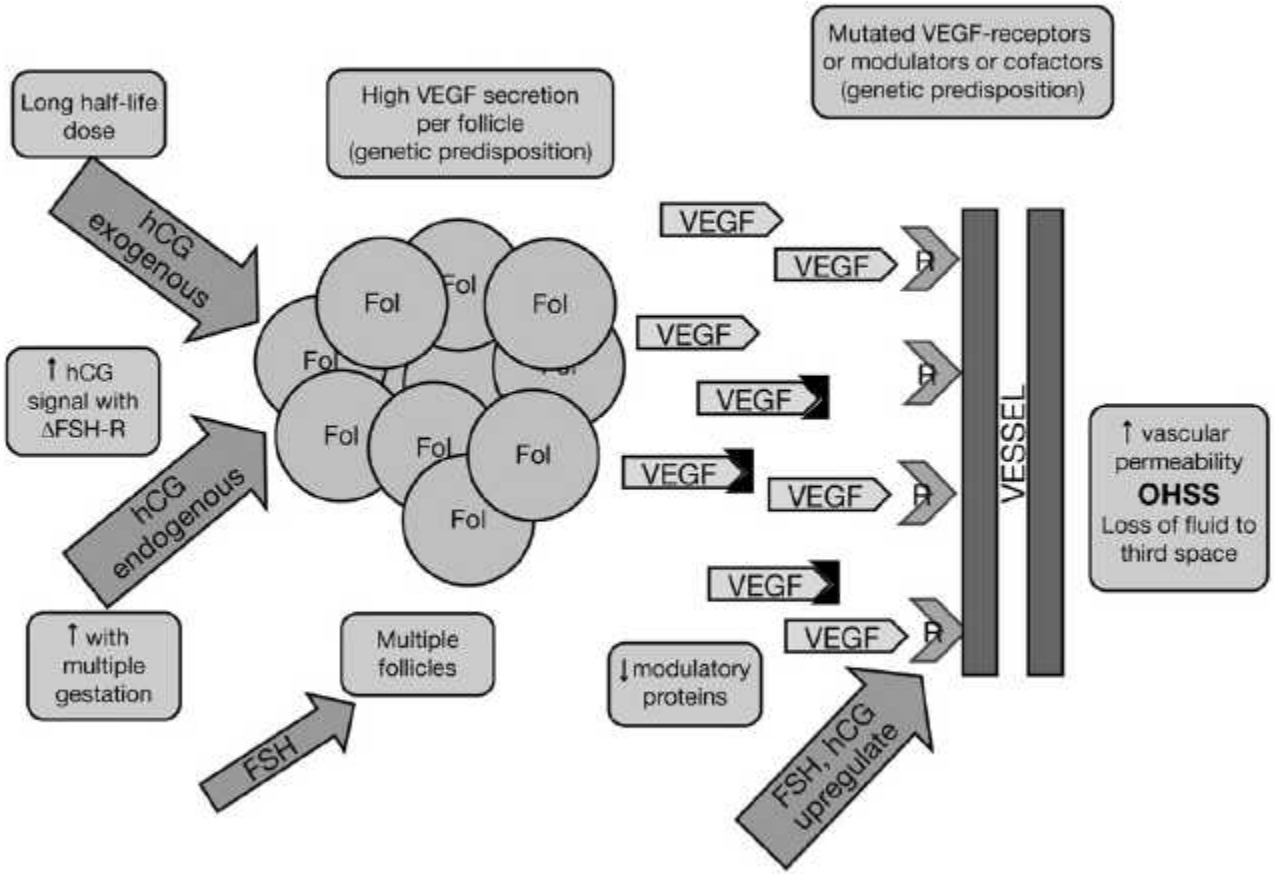
OHSS

(all ovarian stimulation protocol result in some degree of hyperstimulation)

- ***iatrogenic complication*** of ovulation induction (OI) and ovarian stimulation for ART
  - Cystic enlargement of ovaries and rapid fluid shift from intravascular compartment to 3rd space
  - Life-threatening in severe form → hospitalization rate of 1.9%
  - hCG (exogenous or endogenous) as triggering factor, mediated via VEGF

FIGURE 1

The pathogenesis of OHSS.



Humaidan. Prevention strategies for OHSS. Fertil Steril 2010.

- Current guidelines for prevention do not encompass the most recent advances in the literature.
- To review the most recent evidence supporting different OHSS reduction strategies:
  - **Pubmed**, published in the last 5 years
  - Key words: ‘‘controlled ovarian stimulation’’, ‘‘controlled ovarian hyperstimulation,’’ , ‘‘ovarian hyperstimulation syndrome’’, ‘‘OHSS’’, ‘‘prevention’’, ‘‘chorionic gonadotropin’’, ‘‘hCG’’, ‘‘GnRH agonist’’, ‘‘GnRH antagonist’’, ‘‘coasting’’, ‘‘cryopreservation’’

Classification

(clinically)

	Early OHSS	Late OHSS
onset	≦ 9 days after oocyte retrieval	> 10 days
reason	Correlate to ovarian response to exogenous hCG stimulation	1. Correlate to endogenous hCG produced by implanting embryo 2. Administration of hCG for luteal phase support (LPS)

OHSS severity classification

(by TVS + lab)

TABLE 1

Proposed new clinical grading system for OHSS.

	Mild	Moderate	Severe
Objective criteria			
Fluid in Douglas pouch	✓	✓	✓
Fluid around uterus (major pelvis)		✓	✓
Fluid around intestinal loops			✓
Hematocrit >45%		✓[a]	✓
White blood cells >15,000/mm^3		±[a]	✓
Low urine output <600 mL/24 h		±[a]	✓
Creatinine >1.5 mg/dL		±[a]	±
Elevated transaminases		±[a]	±
Clotting disorder			±[c]
Pleural effusion			±[c]
Subjective criteria			
Abdominal distention	✓	✓	✓
Pelvic discomfort	✓	✓	✓
Breathing disorder	±[b]	±[b]	✓
Acute pain	±[b]	±[b]	±[b]
Nausea/vomiting	±	±	±
Ovarian enlargement	✓	✓	✓
Pregnancy occurrence	±	±	✓

Note: The ± sign means may or may not be present.
[a] If two of these are present, consider hospitalization.
[b] If present, consider hospitalization.
[c] If present, consider intensive care.

Life threatening severe OHSS:

- hepatorenal failure
- acute respiratory distress
- hemorrhage from ov rupture
- thromboembolism

Rapid weight gain (> 1kg/day)

presentation and management

- mild OHSS is relatively common in stimulated cycles
- Ovarian enlargement on TVS is a key indicator of severity after OI.
  - less indicative in IVF as follicle aspiration (→ ov ↓)
- Most can be managed on an outpatient basis:
  - oral analgesics and antiemetics
  - patient education
  - careful monitoring daily: PE, sono, BW, Hct, e-, Cr

- In nonconception cycles: mild or moderate OHSS likely to **resolve spontaneously** after menstruation
- **Pregnant**: ↑ endogenous hCG → ↑ risk of severe OHSS
  - Hospitalization
  - IV fluid
  - Ascites puncture
  - Prophylactic measures to prevent thromboembolism

Predicting OHSS:
identifying the at-risk patient

- Change of ovarian stimulation regimen / other preventative measures

- *Primary risk factor* ***(patient related)***
- *Secondary risk factor* ***(ovarian response related)***

Primary risk factors (1)

- **AMH**
  - expressed in granulosa cells from preantral and small antral follicles → ovarian reserve
  - more accurate predictor of normal ovarian response than age, FSH, or inhibin-B alone or in combination
  - All cycle cancellations due to OHSS risk were in pts with highest AMH quartile → as OHSS predictor

    Hum Reprod 2007;22:766–71
  - better predictor of OHSS than age and BMI
  - Cut-off value: 3.36 ng/mL (sensitivity: 90.5%; specificity: 81.3%) → *international standard needed*

Primary risk factors (2)

High basal AMH	Cut-off level of 3.36 ng/mL has a sensitivity of 90.5% and specificity of 80% in predicting OHSS (8)	Can be assessed on any day of the menstrual cycle (37)	Regression analysis has proven that receiver operating characteristic curve is superior to age, number of follicles (8)
High AFC	AFC >14 may predict hyperresponse (48)		Interobserver variability
Age	<33 y (8)		Inferior compared with AMH
Previous OHSS	Moderate or severe cases especially when hospitalization required	History	
PCOS/isolated PCOS characteristics	≥12 antral follicles 2–8 mm in diameter is predictive (46) "necklace" sign high # of follicle recruited	Yes	10%–12% incidence of moderate or severe OHSS in PCOS population compared with 0%–3% in women with normal ovaries

- AFC (antral follicle count)
  - Alone and in combination for predicting ovarian response comparable
  - >14 may predict hyperresponse (sensitivity: 82%; specificity: 89%)

Secondary risk factors

ovarian response parameters

1. Absolute level or rate of increase of serum E2
2. Follicle size and #: >14 follicles of 11 mm; > 11 follicles of 10 mm
3. VEGF: conflicting result → no applicable
4. ↑ inhibin-B: potential candidate, may prime the follicle to overresponse to hCG (mechanism ?)

- None to be independently predictive of OHSS, combination ? ? 1+2 ??

Preventing OHSS: better than cure

- Complete prevention is still not possible !!
- Early identification of risk factors and careful monitoring → ↓ incidence
- **Primary prevention**: stimulation protocol personalized after assessment of primary risk factors to classify pts as poor, normal or high responders
- **Secondary prevention**: based on ovarian response to involve withdrawal, delay, or modification of protocol to avert OHSS

Primary prevention

1. Reducing exposure to gonadotropins
   a. Reducing dose (IUI cycles) – low-dose gonadotropin protocol in PCOS
   - ***Aim***: to facilitate a single dominant follicle rather than multiple follicles

- **low-dose step-up protocol**:
  - starting FSH (75 IU) for 14 days, followed by small ↑ at interval ≧ 7 days until follicle development initiated, dose continued until ovulation triggering
  - higher rate of monofollicular development, fewer cycle cancelled owing to hyperstimulation, lower incidence of OHSS and multiple pregnancy

b. Reducing duration of FSH exposure (IVF/ICSI cycles)

- ***FSH tx duration? no consensus*** → ∵ wide variation in individual response
- ***When to stop gonadotropin therapy and trigger final oocyte maturation?***
- ***Wheather FSH should be given on the day of hCG administration?***

- Prospective RCT in 413 IVF pts cotreated with GnRH antagonist
  - Delaying triggering and continuing FSH had a negative impact on pregnancy rates
  - Once primary follicle reach the criteria for triggering, additional FSH is not necessary and may be detrimental to outcome (possibly due to negative impact on ***endometrial receptivity***)

Hum Reprod 1999;14:1457–60

- **mild stimulation protocol**:
  - administration of FSH delayed until mid to late follicular phase
  - early attempts at natural cycle or minimal stimulation protocols resulted in high cancellation rate owing to **premature luteinization** → + GnRH antagonist for late-cycle suppression of pituitary gonadotropin release → improved outcome

Normo-responder (404 pts, 769 cycles)	Mild stimulation protocol with single ET (444) 1. offer benefits 2. further RCTs	Long agonist protocol with double ET (325)
intervention	FSH from D5 and GnRH antagonist cotreatment when at least one follicle ≧ 14 mm	As traditional protocol
OHSS	6 (1.4%)	12 (3.7%)
Cumulative live birth rate	43.4%	44.7%
Multiple pregnancy rate	0.5%	13.1%
	cost reduction	

Hum Reprod 2006;21:344–51

1. GnRH antagonist protocol
   - GnRH agonist led to ↑ incidence of OHSS: pretreatment blockade of endogenous gonadotropin needs increased dose of FSH for ovarian stimulation
   - Rapid competitive blockage of pituitary GnRH receptor → administrated before expected rise in endogenous LH, usually at follicle size 12-14 mm
   - Lack of suppression of natural endogenous FSH during early follicular phase → reduced FSH dose for ovarian stimulation

- GnRH antagonist superior to GnRHa in OHSS rate.

Cochrane Database Syst Rev 2006;(3):CD001750

Hum Reprod Update 2006;12:651–71

- Advantages:
  - Lack of flare effect
  - No accompanying menopausal-like symptoms
  - No refractory period
  - ↓ ovarian cyst formation
  - Shorter treatment cycle
  - ↓ FSH consumption

- GnRH antagonist vs. GnRHa in clinical pregnancy and live birth rate → conflicting
  - Clinical pregnancy rate lower with antagonists.

    Cochrane Database Syst Rev 2006;(3):CD001750
  - No difference.

    Hum Reprod Update 2006;12:651–71

- Further studies indicated.
- **GnRH antagonist regimen** should be considered in normal and predicted high responders.

1. Avoidance of hCG for LPS

- **Luteal phase impairment**: negative feedback of supraphysiological (E2 and P) after hyperstimulation → low endogenous LH → reduced implantation and ↑ pregnancy loss
- **Luteal phase support**: **P ± E2**
  - hCG: shown to have benefit in agonist cycle but ↑ risk of OHSS
  - **Progesterone**: halve OHSS risk, similar benefit

Cochrane Database Syst Rev 2004;(3): CD004830

Fertil Steril 2008;91:1012–7

  - intranasal GnRHa

Human Reprod 2005;20: 1798–804.

1. In vitro maturation
   - Offer great potential for OHSS prevention
   - Not widely used due to ↓ live birth rate
   - Clinical outcomes improved in recent years

1. Insulin-sensitizing agents
   - Insulin resistance with hyperinsulinemia thought to play a role in PCOS
   - **Metformin**: *cheap, effective insulin-sensitizing agent with good safety profile*
     - Meta-analysis (8 RCTs): metformin use during OI or IVF with PCOS → no benefit in clinical outcome but *had positive effect on OHSS* (5)

Secondary prevention

1. Coasting: withholding further gonadotropin stimulation and delaying hCG until E2 plateau or ↓
   - Coasting does not eliminate OHSS but may reduce incidence and severity

     Hum Reprod Update 2002;8:291–6
   - As 1st line intervention for reducing risk and severity of OHSS in over response pts

     Hum Reprod 2001;16:2491–5
   - **insufficient evidence**

1. Reduced dose of hCG:
   - Cornell low dose protocol: hCG dosage according to serum E2 on the day of hCG administration
     - E2: 2000-3000 pg/ml → hCG 3300-5000 IU
     - E2 >3000 pg/ml → coasting until E2 below 3000 pg/ml
   - Similar pregnancy outcome but ↓ in early OHSS and severe OHSS

     Fertil Steril 2006;86(Suppl 2):S182–3 (P-138)
   - Potentially increase cycle cancellation rate
   - No strong evidence

1. Cryopreservation of all embryos:
   - after oocyte pickup (OPU) → cryopreservation of embryo → thawed and reimplantation when hormone level not elevated
   - Early OHSS associated with hCG administration still occur but late or severe form can be avoided
   - Disadvantage: success rate of frozen/thawed embryo lower than fresh embryos
   - Evidence conflicting !!
     - Retrospective or observational study

1. Cycle cancellation:
   - Only guaranteed method for preventing early OHSS
   - Physicians reluctant to use in IVF → financial burden of tx and pts' psychological distress

1. Alternative agents for triggering ovulation:

- ✓ long half life of hCG → ↑ OHSS
- ✓ risk similar for rhCG

a. GnRHa

- Continued GnRHa → receptor down regulation and desensitization
- A bolus of GnRHa in gonadotropin only or antagonist cycle → surge (flare) of FSH and LH → mimic natural midcycle surge of gonadotropin and stimulating ovulation and final oocyte maturation
- BUT gonadotropin level reduced !!!

a. GnRHa

- 4/13(30.8%) triggered with hCG develop moderate or severe OHSS; 0/15 (0) triggered with GnRHa

  Hum Reprod 2006;21:1260–5

- 10/32(31.3%) in hCG group had OHSS; none in GnRHa arm
- hCG compared with GnRHa: risk of OHSS (3.79X), moderate/severe OHSS (1.35X)

  Fertil Steril 2008;89:84–91

- poor reproductive outcome → luteal phase insufficiency (too low circulating endogenous LH)

a. GnRHa

- + a small bolus of LH (1500 IU hCG) after GnRHa triggering
- RCT: GnRHa + hCG 1500 IU (35 hrs after triggering) vs. hCG 10000 IU → no difference in live-birth rate
- Retrieval of more mature oocytes (4%) in GnRHa group → beneficial effect of midcycle FSH surge on oocyte maturity
- 1/3 of pts with >14 follicles of 11 mm → but no OHSS seen in GnRHa triggering group

a. GnRHa

- Additional LPS is important !!!!
  - no consensus form
- In oocyte donation cycle: GnRHa triggering widely adopted as LPS disregarded
  - 2077 donor cycle: 13/1031 pts with moderate or severe OHSS in hCG group but no case in GnRHa group
- GnRHa triggering ovulation is a very promising approach for high-risk pts in conjunction with GnRH antagonist-stimulated cycles
  - Optimal LPS required

a. Recombinant LH

- More closely mimic LH surge than hCG
- Reduce pregnancy rate, poor cost/benefit ratio

1. Other strategies:

a. GnRH antagonist salvage

- Administration to pts with elevated E2 at risk of developing OHSS may provide interrupting development or progression of condition

a. Albumin and hydroxyethyl starch (HES)

- Albumin: ***evidence not strong***

1. major plasma-binding protein, bind to vasoactive agents responsible for OHSS and facilitate their removal
2. ↑ plasma osmotic pressure → maintain intravascular volume

- HES: cheaper, safer, as 1st line management

1. Other strategies:

a. Dopamin agonists:

- Cabergoline: owning both 1 ° and 2 ° prevention (act at VEGF receptor)
- Effective in reducing but not eliminating OHSS

a. Glucocorticoids

- Have inhibitory effect on VEGF gene expression
- Inhibiting vasodilation and preventing ↑ vascular permeability
- Undesirable side effect

1. Nonrecommended strategies:
    a. Follicular aspiration
        - limiting OHSS mediator production
        - cost, patient discomfort, invasive procedure

    a. Aromatase inhibitors
        - Aromatase catalyzes rate-limiting step in production of estrogen
        - ↓ excessive E2

Limitation

- Retrospective, uncontrolled, small studies
  - Relative rarity of OHSS, very large sample size required to identify meaningful change
  - Potential seriousness → unethical for RCTs

Take home message

- OHSS is a preventable condition
- Evidence-based strategies enable to reduce the incidence and severity of OHSS
- Improved understanding of OHSS pathogenesis and more accurate predictive test should facilitate more individualized IVF protocol to produce optimal ovarian response and minimize occurrence of OHSS.

Current clinical guidelines and summary of the most recent evidence for OHSS prevention strategies.

OHSS prevention strategy	Findings based on current evidence	Level of evidence
Decreasing exposure to gonadotropins	Chronic low dose (OI); limited ovarian stimulation (OI); mild stimulation protocol (IVF); no FSH on day of hCG	1b, 2a, 2b, 4
GnRH antagonist	Decreases risk of severe OHSS, reduces incidence of OHSS hospital admissions, reduces the need for secondary interventions such as coasting or cycle cancellation	1a
Reduced dose hCG for triggering ovulation	Appears to reduce risk of severe OHSS but large RCTs needed	2a
Avoiding hCG for LPS	Approximately half the risk of OHSS with P for LPS vs. hCG	1a
IVM	Promising, but no data on OHSS prevention available	—
Insulin-sensitizing agents	Reduces risk of OHSS in women with PCOS undergoing OI or IVF; may reduce risk of moderate/severe OHSS in normal responders	1a, 2a
Cycle cancellation	Almost eliminates risk of OHSS; in nonsuppressed cycles, ovulation may still occur and ensuing pregnancy could lead to the development of late OHSS	4
Coasting	Appears to reduce, but not eliminate, the incidence of severe OHSS in high-risk patients compared with expected values; no placebo-controlled RCTs; optimal criteria and protocols remain to be determined	1a
Alternative agents for triggering ovulation:		
GnRHa	Very significant reductions in incidence of OHSS in high-risk patients compared with hCG	1b
Recombinant human LH	Appears to be effective in reducing the incidence of OHSS, but associated with poor outcomes and high costs; not commercially available	1b
Cryopreservation of all embryos	Insufficient evidence available	1a
Antagonist salvage	Appears to halt the development of severe OHSS; as effective as coasting	1b
Albumin	Does not appear to be effective	1a
Hydroxyethyl starch	Appears to reduce the risk of moderate and severe OHSS	1b
Follicular aspiration	Results are variable and negative drawbacks of this approach not trivial; cannot recommend	1a
Aromatase inhibitors	No literature on the effects of aromatase inhibitors on incidence or severity of OHSS	—
Dopamine agonists	Superior to placebo at reducing incidence of OHSS in high-risk patients but does not eliminate the risk	1b
Glucocorticoids	Conflicting results; may be effective when used at an early stage of ovarian stimulation	2a

THANK YOU !