
بسم الله الرحمن الرحيم

Prevention of OHSS: Modern Techniques

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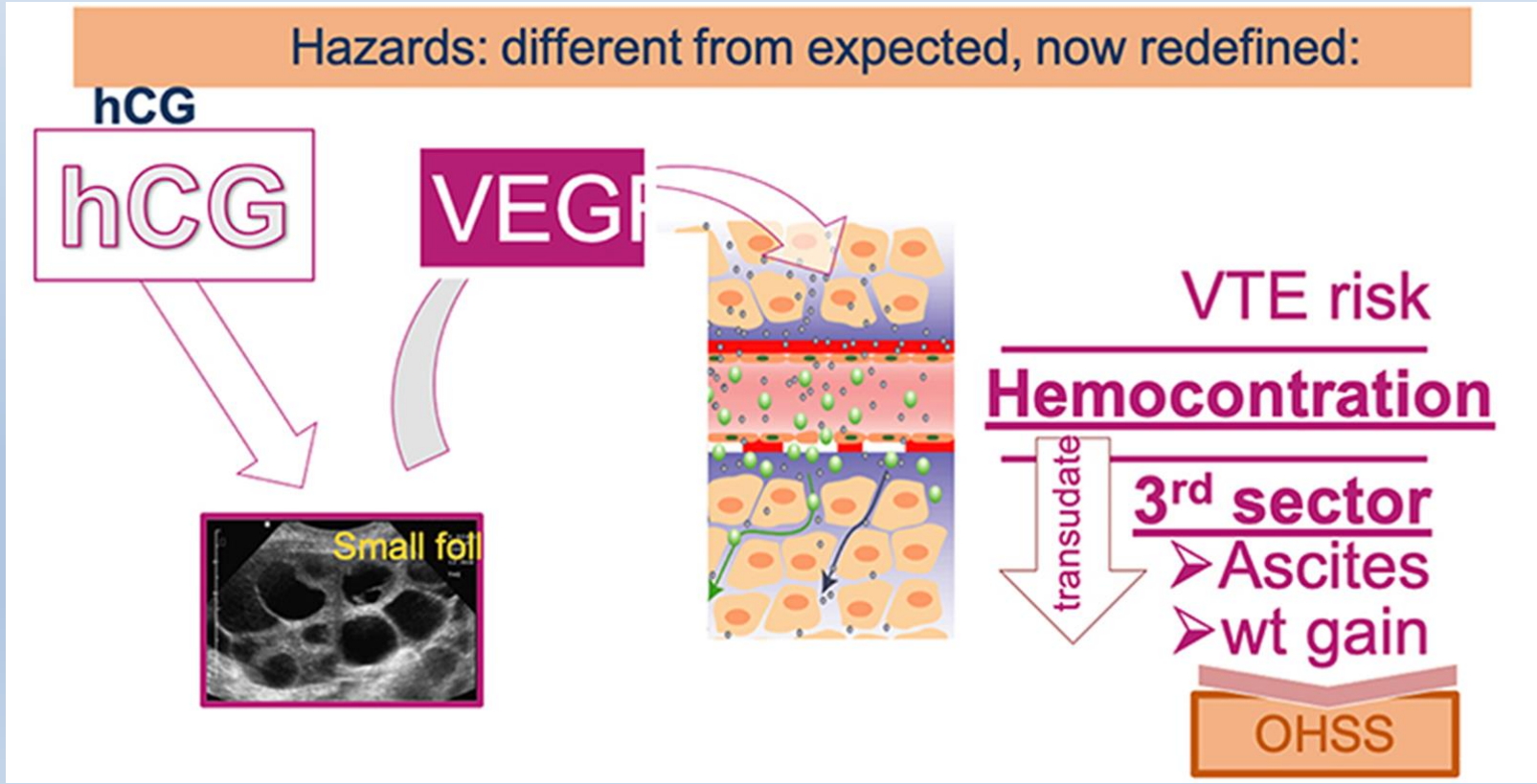
OHSS

- Define
- Systemic synd resulting from vasoactive products released by hyperstimulated ovaries.
- An iatrogenic complication of ovarian stimulation.
- Life threatening



Incidence and prediction of OHSS in women undergoing GnRH antagonist IVF cycles

- 2524 antagonist-based cycles (1801 patients)
- 53 patients (2%) were hospitalized because of OHSS
  - **Conclusions**: clinically significant OHSS is a limitation even in antagonist cycles

"There is more than ever an urgent need for alternative final oocyte maturation – triggering medication"

Incidence

- Mild: common, up to 33% of IVF
- Moderate: 5% (Delvigne, 2009).
- Mod to Severe: 3–8% of IVF cycles
- Cases requiring hospitalization: 2% (Papanikolaou et al., 2005).

▪Varies:

- 1.Treatments
- 2. Patient
- 3. Classification schemes

Predictions: Severe OHSS

"Severe OHSS will remain a complication of IVF cycles despite all attempts of prevention." R.G. Forman, 1999.

"…None of the strategies currently employed to avert severe OHSS …completely prevents the condition". P.E. Egbase, 2000.

Pathophysiology

- Inc cap permeability:
- leakage of fluid from vas compartment:

- 3rd space fluid accumulation

-IV dehydration.

❑RISK FACTORS

- The most important: PCOS & history of OHSS
- **❑Prior to an IVF cycle**

▪Young age (22 y), lean (BMI, 19 kg/m2), PCOS

▪History of:

High response during a previous COS Cycle cancellation related to high response
Development of moderate or severe OHSS

▪Basal investigations (NICE, 2013)

- Total AFC > 16
- AMH>3.5 ng/ml (25.0 pmol/l)
- FSH<4 IU/l

❑During IVF:

One of the following

- Peak E2 > 3000-4000 pg/mL,
- 20 follicles at least 10 mm, in addition to the leading follicles on the day of hCG
- Retrieval of >15 oocytes
- For GnRHan protocol:
- 18 follicles 11 mm on the day of hCG: 83% specificity in predicting severe OHSS

❑Types

Early onset	Late onset
Exogenous hCG administered for final oocyte maturation	**Endogenous hCG produced by implanting blastocyst**
3–7 days after hCG	12 -17 days after hCG
Predicted by high number of growing follicles and elevated E_2 levels	**Predicted by number of gestacional sacs (multiple pregnancy)**
Higher risk of preclinical miscarriage	**More likely to be severe**

❑Complications

- **Morbidity**
- 1.Thrombosis
- 2.Renal& liver dysfunction
- 3.ARDS
- 4.Psychological burden & their willingness to undergo further fertility tt (Verberg et al., 2008).
- 5.Pregnancy-related complications Miscarraige, PTL, PIH (Abramov et al., 1998; Courbiere et al., 2011).

❑Mortality

Three OHSS-related deaths (3:100,000), all had their embryos frozen

- Causes of mortality in OHSS

1.ARDS
2.Cerebral infarction
3.Hepatorenal failure

❑Prevention

- **I. Modified stimulation protocols**

1. HCG
   - a.HCG Withholding
   - b.Delaying HCG (Coasting or drifting)
   - c.Decrease HCG dose
2. HMG
   - a.Lower doses of gonadotrophins
   - b.Chronic low dose step up protocol
3. GnRHa to trigger ovulation
4. GnRHan rescue by replacing a GnRHa with a GnRHan

II. Modified techniques

1. Follicular aspiration before or after hCG
2. Cryopreservation of embryos
3- Selective oocyte retrieval in spontaneous conception cycles
4. Ovarian electrocautery

- **III. Adjuvant**

1. IV albumin
2. 6% Hydroxyethyl starch
3. Metformin
4. Dopamin agonist

Preventive strategies: intravenous albumin

- Intravenous (iv) colloid fluids … at the time of oocyte retrieval may be beneficial for women with a high risk of developing OHSS
- Borderline evidence of benefit with the routine use of human albumin in the prevention of OHSS (1660 patients)
- Good evidence to support the use of hydroxyethyl starch in the prevention of OHSS (487 patients)
- 1199 patients
- IV albumin does not appear to reduce the occurrence of severe OHSS

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human reproduction OPINION

An OHSS-Free Clinic by segmentation of IVF treatment

Paul Devroey*, Nikolaos P. Polyzos, and Christophe Blockeel

- We have to change totally the concept of IVF to obtain an OHSS Free Clinic

> "The concept of an OHSS-Free Clinic has become a reality. This approach should include pituitary down-regulation using a GnRH antagonist, ovulation triggering with a GnRH agonist and vitrification of oocytes or embryos"

> "…luteal phase supplementation with low-dose hCG has to be fine tuned."

❑**Proposed Protocol of Zero% OHSS:** 4 Steps

- GnRHan protocol instead of long protocol
- Ovulation Triggering with GnRHa
  instead of HCG trigger
- Vitrification of all oocytes and/ or embryos
- ET in frozen – thawed cycle

I. The use of the GnRHan protocol

- inhibition of the premature LH surge
- {an immediate action}: administered only when there is a need for suppressing the LH surge (Reissmann et al., 2000).

- Patient-friendly protocol (Lambalk et al., 2006).
  - Fewer injections
  - Short duration of stimulation
  - Absence of side effects caused by profound hypoestrogenaemia (Borm and Mannaerts, 2000; Fluker et al.,2001).

- No clinically significant difference in live birth rates between GnRHan and agonists (M A, Al-Inany et al., 2011).

- Significantly lower incidence of OHSS compared with GnRHa (Tarlatzis and Kolibianakis, 2007).

II. Ovulation triggering with GnRHa instead of HCG trigger

- GnRHan: significant reduction of severe OHSS, but cannot eliminate the syndrome

- HCG triggering:

✓gold standard {long half-life (30 H) with serum hCG detectable up to 14 days after the injection}: increased incidence of OHSS (Gonen et al., 1990).

✓Triggering with 5000 or 10 000 IU: effective ±severe OHSS (Kolibianakis et al., 2007).

- GnRHa triggering (triptorelin 0.2 mg)

✓breakthrough in the elimination of OHSS (Itskovitz et al., 1991; Shalev et al.,1994).

✓ Effective alternative to hCG (Segal and Casper, 1992).

✓Incidence of OHSS: 0% (Melo et al., 2009).

Disadvantages

- luteal phase defect (Segal and Casper, 1992).

- PR significantly decreased (Humaidan et al., 2005; Kolibianakis et al., 2006).

- {negative effect on: function of the corpus luteum function of the endometrium} (Humaidan et al., 2005, 2009).

- To correct the luteal phase and pregnancy rates Intensive luteal phase support (luteal phase rescues)

1. IM progesterone combined with E2 patches (Engmann et al., 2008; Diluigi et al., 2010).

2. 1500 units of hCG at oocyte retrieval (Humaidan et al., 2006, 2010).

Induction of preovulatory luteinizing hormone surge and prevention of ovarian hyperstimulation syndrome by gonadotropin-releasing hormone agonist.

"A bolus of GnRH-a is able to trigger an adequate midcycle LH/FSH surge…and may prevent the clinical manifestation of ovarian hyperstimulation syndrome"

Itskovitz et al, Fertil Steril. 1991 , 56:213-20.

Preventive strategies: coasting

- There was no evidence to suggest any benefit of withholding gonadotrophins (coasting) after ovulation in IVF for the prevention of OHSS

Embryo cryopreservation

- Safe alternative for patients at risk for OHSS.

- Similar CPR whether using elective cryopreservation of all embryos or fresh embryo transfer (Ferraretti et al., 1999; Aflatoonian et al., 2010; Surrey et al., 2010).

- Vitrification: an efficient method for patients at risk for OHSS (Selman et al., 2009).

Preventive strategies: cryopreservation

- There is not enough evidence to show whether using frozen embryos …can reduce OHSS in women who are at high risk

Conclusion

- The balance between the desire for pregnancy and the patients’ safety is a top priority.
- Mortality from OHSS: unacceptable.

Side benefits

- Agonist trigger: more MII oocytes compared with hCG trigger[1-4]

- Potential benefit of FSH surge:[5-9]
  - Promotes LH receptor formation in luteinizing granulosa cells
  - Promotes nuclear maturation (i.e. resumption of meiosis)
  - Promotes cumulus expansion

Conclusions

- ✓Mean LH concentrations and LH pulse amplitude are lower than those described for a natural cycle.
- ✓The process of luteolysis starts 48 hrs after oocyte retrieval.

Tannus et al, Gyn Endocrinol 33:741, 2017

❑The strategy to obtain an OHSS-Free Clinic is closely related to the segmentation concept.

- Segment A: Optimization of ovarian stimulation by GnRHa triggering in a GnRHan cycle
- Segment B: Optimization of embryology by oocyte and/or embryo vitrification
- Segment C: Optimization of endometrial implantation by embryo replacement in a receptive endometrium in a natural or artificial cycle.

Yesterday

- GnRHa
- HCG for triggering
- Fresh ET after progesterone in luteal phase
- Replacement in natural or artificial cycle
- OHSS: 2 %

Today

- GnRHan
- GnRHa triggering if at risk for OHSS
- ✓ Freeze all
- ✓ Fresh ET after progesterone and low dose hCG in luteal phase
- ✓ Replacement in natural or artificial cycle
- OHSS: 0 %


thank you!