Contemporary approach in OHSS treatment

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TAJEV 2014

OHSS
HOW COMMON IS IT?

Human Reproduction Vol.20, No.12 pp. 3293–3300, 2005 doi:10.1093/humrep/dei253
Advance Access publication August 26, 2005.

Complications of IVF and ovulation induction

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- Finland registry: 9,175 IVF cycles
- Severe OHSS:
  - → **1.4%** per cycle
  - → 2.3% per patient (mean 3.3 cycles/pt)

OHSS
HOW COMMON IS IT?

~ 300,000 IVF (Europe 2003)

~ 130,000 IVF (USA 2005)

→ 430, 000 IVF cycles reported

→ **6,020 severe OHSS patients from IVF**

Table I. Classification of OHSS*. OHSS may be early onset (within 9 days of hCG trigger) or late onset (after 9 days from hCG trigger), with severity as indicated below.

Mild OHSS
Abdominal bloating
Mild abdominal pain
Ovarian size usually < 8 cm**
Moderate OHSS
Moderate abdominal pain
Nausea $\pm$ vomiting
Ultrasound evidence of ascites
Ovarian size usually $8-12$ cm**
Severe OHSS
Clinical ascites (occasionally hydrothorax)
Oliguria
Haemoconcentration haematocrit $> 45\%$
Hypoproteinaemia
Ovarian size usually > 12 cm**
Critical OHSS
Tense ascites or large hydrothorax
Haematocrit $> 55\%$
WCC $> 25{,}000$/ml
Oligo/anuria
Thromboembolism
Adult respiratory distress syndrome (ARDS)

*Mathur et al. (2005); see also: http://www.rcog.org.uk for full explanation.

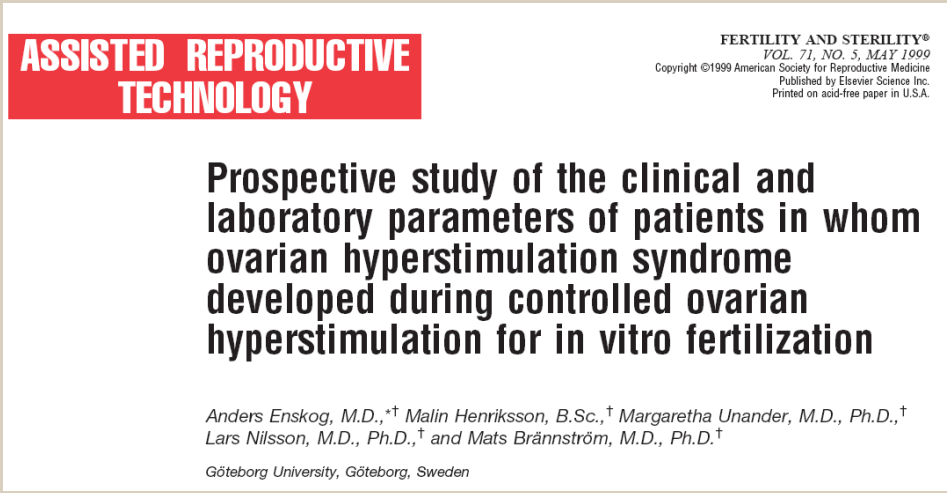
**Ovarian size may not correlate with severity of OHSS in cases of assisted reproduction because of the effect of follicular aspiration.

Outline

- ✓ Risk factors
- ✓ Prevention
- ✓ Management

OHSS RISK FACTORS

1. Young age
2. Low BMI
3. PCOS
4. Allergic history
5. High TAFC
6. High doses of gonadotropins
7. High or rapidly rising E2 levels
8. Large number of large & medium-size follicles
9. Large numbers of eggs retrieved
10. High or repeated doses of hCG
11. Pregnancy
12. Previous OHSS



ASSISTED REPRODUCTIVE TECHNOLOGY

FERTILITY AND STERILITY®
VOL. 71, NO. 5, MAY 1999

Published by Elsevier Science Inc.
Printed on acid-free paper in U.S.A.

Prospective study of the clinical and laboratory parameters of patients in whom ovarian hyperstimulation syndrome developed during controlled ovarian hyperstimulation for in vitro fertilization

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Estradiol	Estradiol level is a reliable predictor of OHSS during ART [5]
	OHSS can occur despite low estradiol levels [10]
	High estradiol concentrations are not sufficient to induce OHSS [6]
	Currently considered a mere marker of granulose activity [11]
hCG	Fundamental for triggering OHSS
	hCG alone is not sufficient to induce OHSS [4]
Interleukins	Some interleukins are associated with OHSS, and elevated concentrations are associated with increased vascular permeability, hemoconcentration, elevated plasma estradiol concentration, and inhibition of hepatic albumin production [12]
Renin-angiotensin system	There is a direct correlation between plasma renin activity and the severity of OHSS [13]
	All hypovolemic conditions are associated with a secondary reactive hyperaldosteronism via renin-angiotensin cascade activation [17]
	Renin-angiotensin system activation is probably the effect and not the cause of OHSS
VEGF	VEGF expression is associated with OHSS increased vascular permeability [18]
	VEGF levels are elevated during ovarian stimulation with exogenous FSH, which is enhanced after hCG administration [19, 20]

OHSS RISK FACTORS
E2 levels are over-rated predictors of OHSS

Incidence and prediction of ovarian hyperstimulation syndrome in women undergoing gonadotropin-releasing hormone antagonist in vitro fertilization cycles

Evangelos G. Papanikolaou, M.D., Ph.D., Cristina Pozzobon, M.D., Efstratios M. Kolibianakis, M.D., Ph.D., Michel Camus, M.D., Herman Tournaye, M.D., Ph.D., Human M. Fatemi, M.D., Andre Van Steirteghem, M.D., Ph.D., and Paul Devroey, M.D., Ph.D.

Centre for Reproductive Medicine, University Hospital, Dutch-Speaking Brussels Free University, Brussels, Belgium

- A cut-off of 3,000 pg/ml will miss 2/3 of severe OHSS
- Number of follicles ≥ 12 mm better pred. than E2
- E2 ≥ 5,000 and ≥18 foll best predictor of OHSS
  - 83% SENSITIVITY
  - 84% SPECIFICITY

Papanikolaou EG et al (2006) Fert Steril

Which patients become high risk for OHSS during HMG therapy?

1.Those with high serum estradiol concentrations

When to measure E2? Is there a cut-off value?

- Day 3-5:Poor sensitivity and high False Pos Rate

Hendrics et al 2004

- Day 9: E2 >800pg/ml
- Day of HCG: E2>3000pg/ml

Delvigne et al (1997);Navot et al (1998)

Estradiol concentration on day of HCG and risk for OHSS

Asch et al (1991)

- E2<3500pg/ml ---------- 0%
- 3500pg/ml < E2< 5999pg/ml--- 1.5%
- E2 > 6000pg/ml---------- 38%

Sensitivity:83% Specificity 99%

Levy et al (1996);Shimon et al (2001);

- OHSS with E2 <500pg/ml !!!
  which means 1…2…3…

Estradiol concentration on the day of HCG and risk for OHSS

…1. There is a large overlap in E2 concentrations between women who develop and women who do not develop OHSS

…2. E2 concentration is inadequate as the only predictive factor

…3.Is found at highest concentrations >6000pg/ml when it becomes very predictive of OHSS

Which patients become high risk for OHSS during HMG therapy?

2. Those who have large number of follicles on the day of HCG

>14 follicles of 11mm.(Papanikolaou et al2006)

>11 follicles of 10mm.(Lee et al 2008)

3. Those who have large number of oocytes retrieved

>30 OOR	14% severe OHSS(Morris et al 1995)
<20	0% severe OHSS (Asch et al 1991)
<20 OOR< 30	1.4% severe OHSS
>30 OOR	23% severe OHSS

The role of VEGF in OHSS

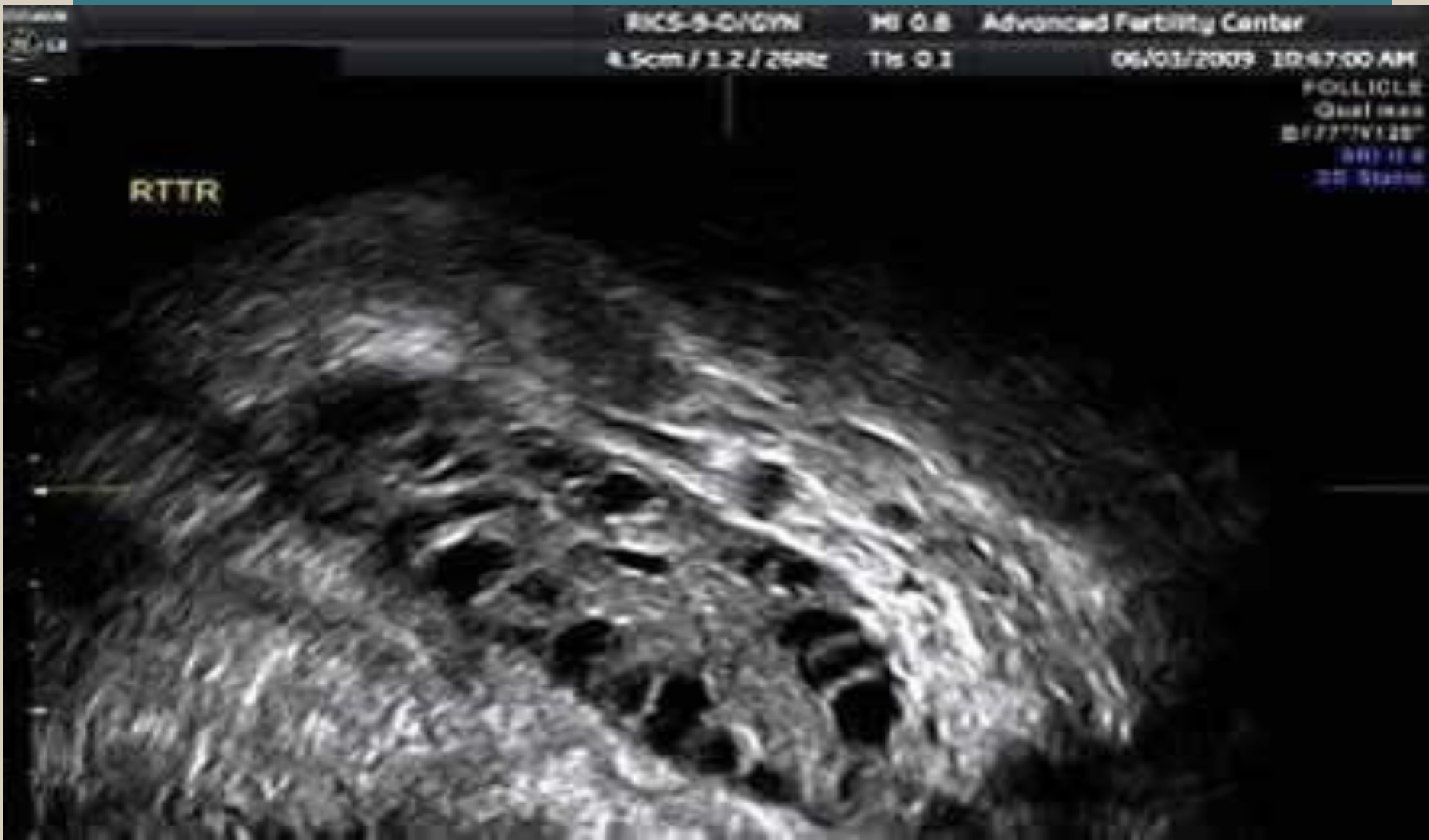
- OHSS is a dramatic complication of OI
- VEGF mRNA is expressed by granulosa & theca cells
- Ovarian VEGF levels correlate with the dose of gonadotrophins administered
- Excess of bioactive VEGF in FF increases OHSS risk
- VEGF expression is dependent on LH
- There is an association between hCG & OHSS
- VEGF is increased by hCG in a dose-& time-dependent fashion

Rizk B et al,HR Update.1997;(3):255-66

Neulen J et al,Hum Reprod,2001;16(4):621-6

Gomez et al Bio Repro 2003

PCO - high risk for OHSS



OHSS -AMH

- >1.26 ng/ml normoresponder
- >3,36 ng/ml OHSS risk
- >7 ng/ml OHSS risk very high

OHSS PREVENTION STRATEGIES CAREFUL CLINICAL APPROACH

BEFORE STIMULATION

1.Use protocols with low dose HMG

2.Use protocols that reduce the duration of exposure to HMG

3.GnRH Antagonists

4.Insulin Sensitizers

5.IVM of Oocytes

DURING STIMULATION

1.Low D HCG to trigger Ov/tion
2.GnRHa to trigger Ov/tion
3.Recombinant human LH
4.Coasting
5.Cycle cancellation
6.Cryopreservation of embryos
7. IV Albumin
8.Hydroxyethyl starch
9.Glucocorticoids
10. DOPAMINE AGONISTS

PREVENTION OHSS

A. Cancel Cycle -withhold hCG trigger
B. Coasting
C. Decrease dose of hCG trigger
D. Agonist trigger
E. Cryopreservation of embryos
F. IV albumin at time of egg retrieval
G. Paracentesis

OHSS-PREVENTION STRATEGIES

Non-IVF cycles

- **Recommended Stimulation Protocols with Low Dose HMG**

1. Low dose step-up protocol

   75IU FSH--37.5IU

   (Homburg and Howels 1999)

1. Step-down protocol

   150IU FSH – 75IU

   (Macklon and Fauser 2000)

OHSS-PREVENTION STRATEGIES

In IVF cycles

- **Recommended Stimulation Protocols with Low Dose HMG**

1. Limited Ovarian Stimulation (LOS) protocol-PCO
2. HMG stimulation until the leading follicle reached 12mm prior to HCG *(El-Sheikh et al 2001)*
3. Low starting dose of 150IU FSH for all patients at high risk for OHSS *(Homburg and Insler 2002)*
4. FSH from day5+GnRHant when follicles >/=14 *(Hobmann et al 2003)*

PREVENTION OHSS

A. **Cancel Cycle -withhold hCG trigger**
B. Coasting
C. Decrease dose of hCG trigger
D. Agonist trigger
E. Cryopreservation of embryos
F. IV albumin at time of egg retrieval
G. Paracentesis

PREVENTION OHSS
Cancel Cycle – withhold hCG trigger

- **IVF:** Most effective preventative technique, BUT emotionally & financially stressful
- Reserved for prior severe OHSS and total loss of control of the cycle

PREVENTION OHSS

A. Cancel Cycle -withhold hCG trigger
B. Coasting
C. Decrease dose of hCG trigger
D. Agonist trigger
E. Cryopreservation of embryos
F. IV albumin at time of egg retrieval
G. Paracentesis

PREVENTION OHSS
Coasting

CONCEPT: Stopping gonadotropin and postponing hCG trigger until E2 level is lower.

Mechanism

- Lower gonadotropin stimulation → decreased LH receptors → decreased luteinization → ↓ VEGF
- Lower gonadotropin stimulation may increase rate of granulosa cell apoptosis, especially of smaller follicles
- Coasting lowers concentration of follicular fluid VEGF[1]

[1] Tozer AJ et al: *Human Reprod (2004)*

PREVENTION OHSS
Coasting

What does the literature tell us:

- Unable to determine true effectiveness of coasting since no RCT
- Indications for coasting variable amongst studies
- Target E2 level quite variable (typically about 3,000 pg/ml)
- Coasting does not totally prevent OHSS: 16% of patients still had ascites and 2.5% required hospitalizations[1]
- Coasting for > 4 days results in lower pregnancy/implantation rates[2,3]

[1] Delvigne A, Rozenberg S: *Human Reprod (2002)*

[2] Levinsohn-Tavor O, et al: *Human Reprod (2003)*

[3] Mansour R, et al O et al: *Human Reprod (2005)*

PREVENTION OHSS

A. Cancel Cycle -withhold hCG trigger
B. Coasting
C. Decrease dose of hCG trigger
D. Agonist trigger
E. Cryopreservation of embryos
F. IV albumin at time of egg retrieval
G. Paracentesis

PREVENTION OHSS
Decrease dose of hCG

Reducing the dose of human chorionic gonadotropin in high responders does not affect the outcomes of in vitro fertilization

David W. Schmidt, M.D., Donald B. Maier, M.D., John C. Nulsen, M.D., and Claudio A. Benadiva, M.D.

The Center for Advanced Reproductive Services, Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology and Infertility, University of Connecticut Health Center, Farmington, Connecticut

TABLE 2

Incidence of OHSS according to dose hCG.

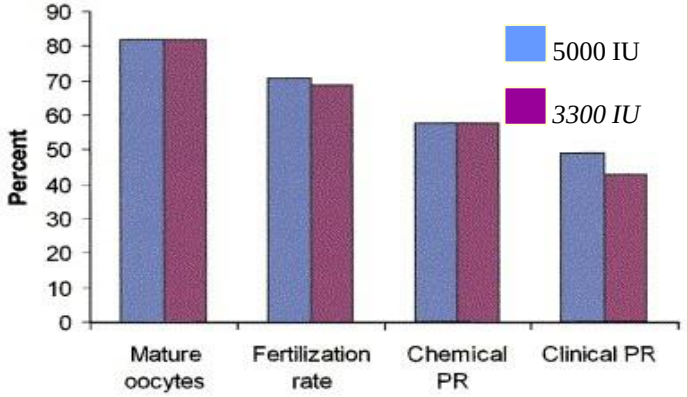
OHSS	5,000 IU	3,300 IU	*P* value[a]
Total	10.6% (5/47)	21.3% (10/47)	.357
Mild	8.5% (4/47)	6.3% (3/47)	.978
Moderate	2.1% (1/47)	10.6% (5/47)	.207
Severe	0% (0/47)	4.2% (2/47)	.495

[a] Not significant.

Schmidt. Reduced hCG dose in high responders. Fertil Steril 2004.

<u>Retrospective</u> review of high responders
- 94 IVF cycles
- If E_2 2,500-4,000 pg/ml → 5,000 IU hCG
  E_2 > 4,000 pg/ml → 3,300 IU hCG

RESULTS
- **<u>No</u> difference in OHSS** but note excellent maturation with as low as 3,300 IU hCG



PREVENTION OHSS
Decrease dose of hCG

Triggering final oocyte maturation using different doses of human chorionic gonadotropin: a randomized pilot study in patients with polycystic ovary syndrome treated with gonadotropin-releasing hormone antagonists and recombinant follicle-stimulating hormone

Efstratios M. Kolibianakis, M.D., Ph.D., Evangelos G. Papanikolaou, M.D., Ph.D., Herman Tournaye, M.D., Ph.D., Michel Camus, M.D., Andre C. Van Steirteghem, M.D., Ph.D., and Paul Devroey, M.D., Ph.D.

Centre for Reproductive Medicine, Vrije Universiteit Brussel, Brussels, Belgium

SAME DEAL…….

Although it theoretically makes sense to reduce the dose of hCG, there is little data to support.

Studies are small/not powered to detect a difference.

Trigger	**10,000 IU**	**5,000 IU**	**2,500 IU**
N	28	26	26
Preg	26.9% 7/26	30.8% 8/26	34.8% 8/23
Severe OHSS	**1/26**	**1/26**	**0/26**

Kolibianakis EM et al (2007) Fert Steril

Vol 14. No 6. 2007 682-685 Reproductive BioMedicine Online; www.rbmonline.com/Article/2843 on web 24 April 2007

Article

Low-dose HCG is useful in preventing OHSS in high-risk women without adversely affecting the outcome of IVF cycles

Abstract

(Nargund G 2007)

Severe ovarian hyperstimulation syndrome (OHSS) is a rare but potentially fatal condition associated with conventional IVF treatment. It is found predominantly in women with polycystic ovaries who have an exaggerated response to exogenous FSH, leading to a large number of follicles and an overproduction of vascular endothelial growth factor with resultant excessive increases in vascular permeability. There is evidence to suggest that OHSS is also linked to the use of human chorionic gonadotrophin (HCG) to induce ovulation. Therefore while HCG is essential for corpus luteum function, high amounts of HCG can lead to OHSS in high responders. In a pilot study, infertile patients at high risk of developing OHSS were given half the current minimum dose of HCG (i.e. 2500 IU). No woman developed moderate or severe OHSS; 13 women (61.9%) conceived and there were three twin pregnancies. In women at high risk of OHSS, a low dose of HCG appears to prevent the development of OHSS without compromising success rates.

PREVENTION OHSS

A. Cancel Cycle -withhold hCG trigger
B. Coasting
C. Decrease dose of hCG trigger
D. Agonist trigger
E. Cryopreservation of embryos
F. IV albumin at time of egg retrieval
G. Paracentesis

PREVENTION OHSS
Agonist trigger

- Reserved for antagonist protocol
- Agonist (Triptorelin 0.2 mg, Lupreulide 1 mg) trigger
- First described by Itskovitz-Eldor J et al (Hum Reprod 2000) to treat 8 patients at risk for OHSS

- So, what's the data……..

PREVENTION OHSS
Agonist trigger

Human Reproduction Update, Vol.12, No.2 pp. 159–168, 2006 doi:10.1093/humupd/dmi045
Advance Access publication October 27, 2005

GnRH agonist for triggering final oocyte maturation in the GnRH antagonist ovarian hyperstimulation protocol: a systematic review and meta-analysis

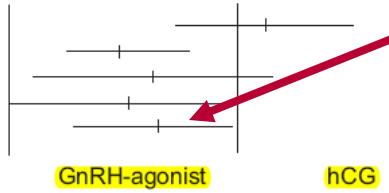
G.Griesinger[1,3], K.Diedrich[1], P.Devroey[2] and E.M.Kolibianakis[2]

[1]Department of Obstetrics and Gynecology, University Clinic of Schleswig-Holstein, Campus Luebeck, Luebeck, Germany and [2]Centre of Reproductive Medicine, Dutch Speaking, Brussels Free University, Brussels, Belgium

[3]To whom correspondence should be addressed at: Ratzeburger Allee 160, 23538 Luebeck.
E-mail: georg.griesinger@frauenklinik.uni-luebeck.de

Pregnancy rate per randomised patient

Citation	EffectName	GnRH-agonist	hCG	NTotal
Fauser, 2002	PR	6 / 32	2 / 15	47
Humaidan, 2005	PR	3 / 55	24 / 67	122
Kolibianakis, 2005	PR (centre 2)	1 / 34	5 / 30	64
Kolibianakis, 2005	PR (centre 1)	1 / 18	10 / 24	42
Combined (4)		11 / 139	41 / 136	275



- 23 papers published
- Only 3/23 meet criteria for meta-analysis (RCT)

Agonist versus hCG Trigger

- No diff in no. oocytes, fert rate, or embryo score
- No OHSS either gp

BUT

? Lower preg rate with agonist trigger

(? Lut support issue)

Human Reproduction Vol.20, No.9 pp. 2421–2425, 2005
Advance Access publication May 12, 2005
doi:10.1093/humrep/dei074

Comparison of GnRH agonists and antagonists in assisted reproduction cycles of patients at high risk of ovarian hyperstimulation syndrome

G.Ragni[1,4], W.Vegetti[1], A.Riccaboni[1], B.Engl[2], C.Brigante[3] and P.G.Crosignani[1]

fer) were obtained. CONCLUSIONS: Although this study presents some limitations owing to the use of historical controls, our data show a favourable effect of GnRH antagonists in reducing the incidence of OHSS and the number of assisted fertilization cycles cancelled because of the risk of OHSS in high responder patients. As a consequence, GnRH antagonist plus gonadotrophin administration could also increase the percentage of oocyte

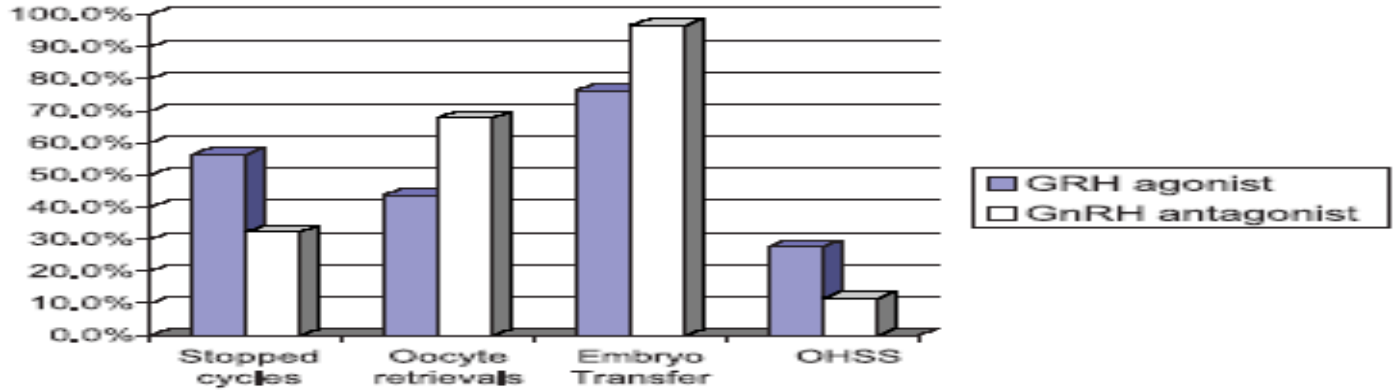


Figure 1. Comparison of stopped cycles, oocyte retrieval, embryo transfer and incidence of OHSS between the two treatment cycles (filled bars, GnRH agonist; empty bars, GnRH antagonist). Values are expressed in percentages; differences were statistically significant for stopped cycles and oocyte retrieval (both $P < 0.001$), embryo transfer ($P < 0.003$) and OHSS ($P < 0.006$).

PREVENTION OHSS

A. Cancel Cycle -withhold hCG trigger
B. Coasting
C. Decrease dose of hCG trigger
D. Agonist trigger
E. Cryopreservation of embryos
F. IV albumin at time of egg retrieval
G. Paracentesis

PREVENTION OHSS
Cryopreservation of all embryos

OHSS is more common and severe with pregnancy due to hCG-induced ovarian stim.

THE DATA

- ✓ Cochrane review found insufficient evidence
  Amso NN, D'Angelo (2002) Hum Reprod
- ✓ As with all methods, it may reduce but not eliminate OHSS
  Queenan Jr JT (1997) Hum Reprod
- ✓ Cryo = Coasting *Benavida C et al. (1997) F&S*
- ✓ Cryo = IVF albumin *Shaker A (1996) F&S*

PREVENTION OHSS

A. Cancel Cycle -withhold hCG trigger
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C. Decrease dose of hCG trigger
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F. IV albumin at time of egg retrieval
G. Paracentesis

PREVENTION OHSS
IV Albumin prophylaxis

Intravenous albumin does not prevent moderate-severe ovarian hyperstimulation syndrome in high-risk IVF patients: a randomized controlled study

José Bellver[1], Elkin A.Muñoz, Agustín Ballesteros, Sérgio Reis Soares, Ernesto Bosch, Carlos Simón, Antonio Pellicer and José Remohí

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Human Reprod (2003) 18: 2283-2288

Largest/best RCT (976 patients)

- Patients at high risk OHSS (20 eggs)
- 40 g albumin at VOR versus nothing x 30 minutes

CONCLUSIONS

- **No benefit** of albumin
- Risks (prions, virus/CJD

Table IV. Comparison of clinical evolution of albumin and control groups in severe ovarian hyperstimulation syndrome (OHSS) cases (n = 46)

Parameter	Albumin group (n = 23)	Control group (n = 23)	P
Paracentesis (n)	21	20	NS
No. of paracenteses per patient	1.3 (0.8)	1.9 (1.8)	NS
Hospital admission (n)	7	5	NS
Complications (n)	3[a]	2[b]	NS
Days from oocyte retrieval to beginning of OHSS	4.4 (4.0)	4.5 (3.3)	NS
Duration of OHSS (days)	8.4 (5.8)	10 (6.9)	NS

Values are mean (SD) unless otherwise indicated.
[a]Two adult respiratory distress syndromes and one pleural effusion.
[b]One thromboembolic event and one cerebrovascular accident.

Dopamine Agonist Cabergoline Reduces Hemoconcentration and Ascites in Hyperstimulated Women Undergoing Assisted Reproduction

The Journal of Clinical Endocrinology & Metabolism 92(8):2931–2937

doi: 10.1210/jc.2007-0409

PREVENTION OHSS

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G. Paracentesis

Outpatient paracentesis

Smith LP, Hacker MR, Alper MM. Fertil Steril (In Press)

STUDY RESULTS

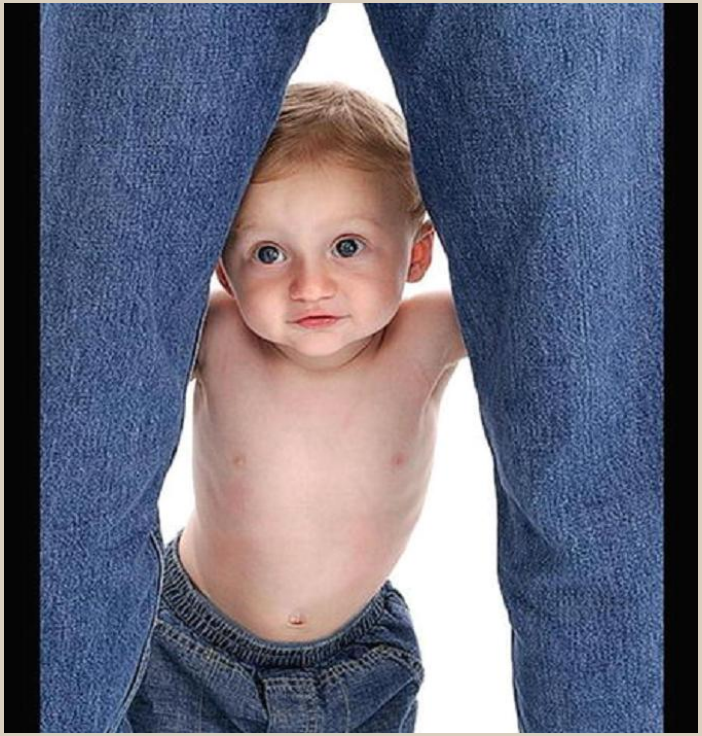
- 146 outpatient paracentesis (96 patients)
  - 50 pts (52%) → Only one paracentesis
  - 35 pts (36%) → paracentesis #2
  - 8 pts (8%) → paracentesis #3
  - 3 pts (3%) → paracentesis #4
  - 1 pt (1%) → paracentesis #5
- Volume of fluid removed
  - Mean: 2,155 ml
  - Range: 500-4,500 ml

Prevention of OHSS

1. Coast when E2 levels very high or too many medium range follicles
2. Always give standard dose of hCG (Ovidrel®) - Never cancel cycle irrespective of E2
3. No IV albumin prophylaxis
4. Cryo-all if patient is symptomatic on day of ET
5. Aggressive **outpatient vaginal paracentesis** for moderate-severe symptoms.

SUMMARY
Prevention of OHSS

- **No** universally agreed upon best method to prevent OHSS
  - **Coasting** the most common method used, followed by **cryopreservation** of embryos
  - Consider outpatient paracentesis early!
- Data limited in RCT for all preventative measures
  - Difficult to prove on method superior due to **low incidence** of severe OHSS



Summary points

- ✓ Risk factors
- ✓ Prevention
- ✓ Clinical features
- ✓ Outpatient Management

1. OHSS is a potentially life threatening complication
2. Estradiol levels alone not highly predictive
3. Beware of risk factors
4. The only method to completely prevent OHSS is cycle cancellation.
5. No good data on best method to prevent OHSS (due to ↓ incidence)
6. Not totally preventable although coasting and freezing embryos are most commonly used.
7. Outpatient paracentesis prevents hospitalizations.

OHSS PREVENTION STRATEGIES SUMMARY

Effective

- Low dose HMG
- GnRH ant
- Metformin (PCO)
- IVM
- Low dose HCG
- GnRHag to trigger ovulation
- Coasting
- HES
- Dopamine agonists

Not Effective/Doubtful

- Recombinant LH
- IV Albumin
- Cryopreservation

Dr. Lukas D. Klentzeris

Thank you for your patience…