

OHSS: prediction, prevention and treatment

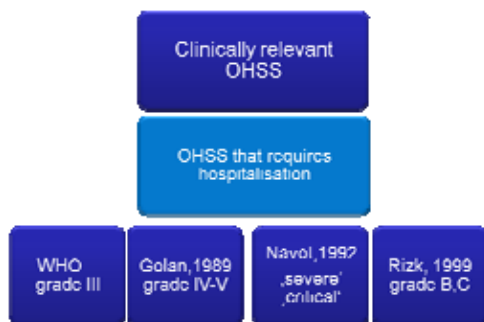
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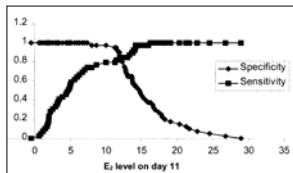
ESHRE campus workshop
Luebeck, 18 JAN 2008







Can we reliably predict OHSS?



Long GnRH-agonist protocol

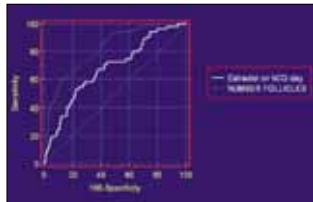
De Angelo et al., 2004

E2 = 3,354 pg/ml
Sens + Spec = 85%

GnRH-antagonist protocol

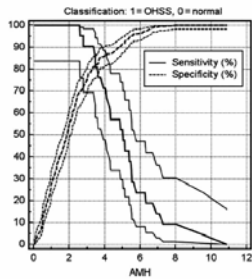
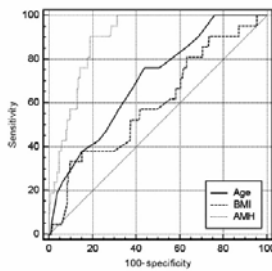
Papanicolaou et al., 2006

18 follicles >10 mm or E2 > 5,000 pg/l
Sens = 83%
Spec = 84%



**5/53 CASES OF SEVERE OHSS
STILL MISSED WITH THESE CRITERIA**

AMH



Long GnRH-agonist protocol, n = 262

Lee et al., 2008; Sensitivity 90.5%, Specificity 81.3%

No reliable test to identify all OHSS risk patients

→ develop ovarian stimulation routines that are associated with a *per se* decreased risk of OHSS

→ but still need measures of OHSS prevention for individual patients, which are safe and efficacious, and can therefore be liberally utilized

How to prevent OHSS?

OHSS incidence reduction efficacy

- Natural cycle IVF ✓ ?
- In vitro Maturation ✓ ?
- Cycle cancellation ✓ ---

GnRH-agonist vs. antagonist ovarian stimulation for IVF Hospital admission due to OHSS

Citation	Year	Antagonists	Agonists	0,01	1,00	100,00	Effect	PValue
Oliverines	2000	2 / 126	2 / 43				0,34	0,25
European	2000	4 / 486	6 / 244				0,33	0,07
Albano	2000	0 / 198	1 / 95				0,16	0,20
North American	2001	3 / 208	2 / 105				0,76	0,76
Middle East	2001	4 / 236	6 / 119				0,34	0,07
Lee	2005	3 / 41	2 / 20				0,73	0,72
Bahceci	2005	3 / 73	6 / 76				0,62	0,49
Badrawi	2005	2 / 50	2 / 50				1,00	1,00
Combined (9)		21 / 1418	26 / 751				0,47	0,01

Crude incidence of OHSS =
1.5%

A mild treatment strategy for in-vitro fertilisation: a randomised non-inferiority trial

	Mild treatment (n=444)	Standard treatment (n=325)	p
Duration of ovarian stimulation (days)	8.3 (2.7)	11.5 (3)	<0.0001*
Duration of injections (days)	8.5 (2.7)	25.3 (6.8)	<0.0001*
Total dose of follicle stimulating hormone (IU)	1361 (1259)	1822 (759)	<0.0001*
Cancellation of started cycle	80 (18.0%)	27 (8.3%)	<0.0001†
Number of oocytes per retrieval	6.9 (4.8)	3.5 (4.3)	<0.0001*
Number of embryos per retrieval	2.8 (2.7)	3.8 (2.9)	0.0002*
Number of cryopreserved embryos per fresh embryo transfer cycle	0.9 (1.8)	0.6 (1.4)	0.04*
Continuing pregnancy per started cycle (fresh embryos)	78 (17.6%)	53 (16.6%)	<0.0001†
Continuing pregnancy per started cycle (cryopreserved embryos)	6 (1.4%)	4 (1.2%)	0.8†
Term livebirth per started cycle (fresh embryos)	70 (15.8%)	78 (24.0%)	0.003†
Term livebirth per started cycle (cryopreserved embryos)	49 (11.1%)	3 (0.9%)	0.8†
Ovarian hyperstimulation syndrome	6 (1.4%)	12 (3.7%)	0.04†

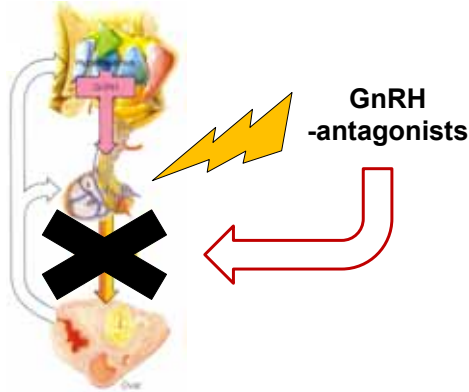
Values are mean (SD) or number (%). *Test for difference in frequency; †Test for difference in absolute risk for embryo transfer (SMA), miscarriage, and severe ovarian hyperstimulation syndrome.

Table 2: Cycle specific characteristics of IVF cycles finished within 1 year

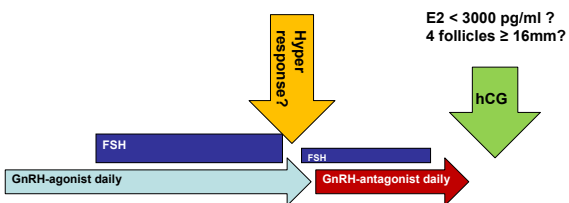
Incidence of OHSS =
1.4%

Heijnen et al., Lancet 2007; 369: 743-49

Novel concepts in OHSS prevention:



Novel concepts in Coasting



n= 85, coasting ~ 1.5 days
Ongoing pregnancy rate: ~ 60 %
Severe OHSS: 1.5 - 7.5 %

Gustafson et al., Hum Reprod 2006
Gustafson et al., Fertil Steril 2006

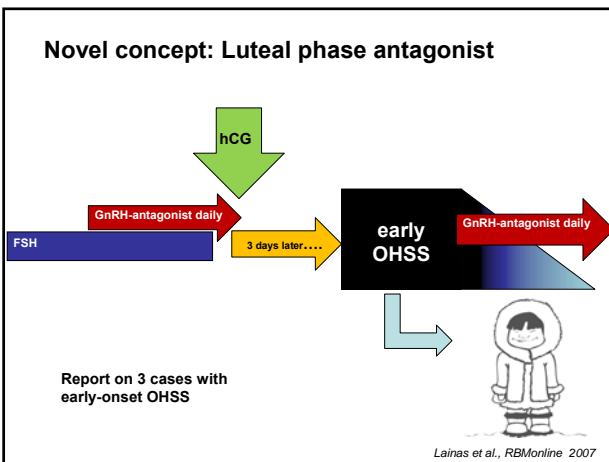
Novel concepts in Coasting

RCT: 192 patients

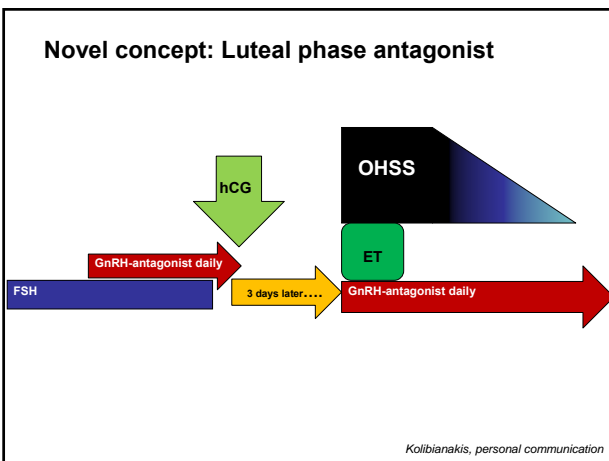
	Antagonist coasting	Conventional coasting
Days of coasting	1.74 ± 0.91	2.82 ± 0.97
No of oocytes	16.5 ± 7.6	14.06 ± 5.2
No of embryos	2.87 ± 1.2	2.21 ± 1.1
Clinical pregnancy (N.S.)	55.32%	47.92%
No OHSS in both study groups		

Aboulghar et al., RBMonline 2007

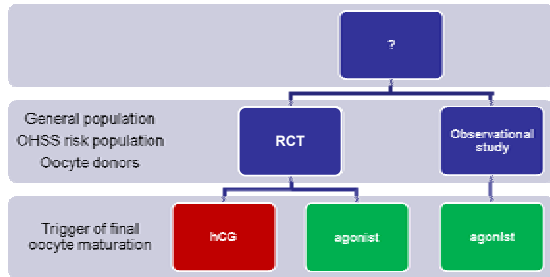
Novel concept: Luteal phase antagonist



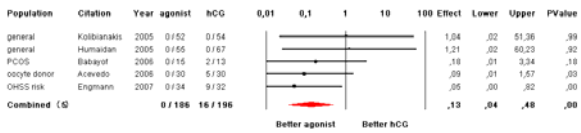
Novel concept: Luteal phase antagonist



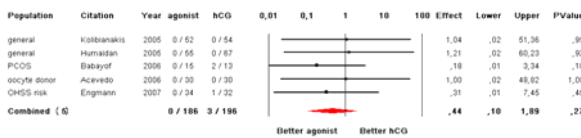
Does GnRH-agonist triggering prevent OHSS?



OHSS I-II: RR with 95% confidence intervals (heterogeneity p = 0.57)



OHSS III: RR with 95% confidence intervals (heterogeneity p = 0.90)

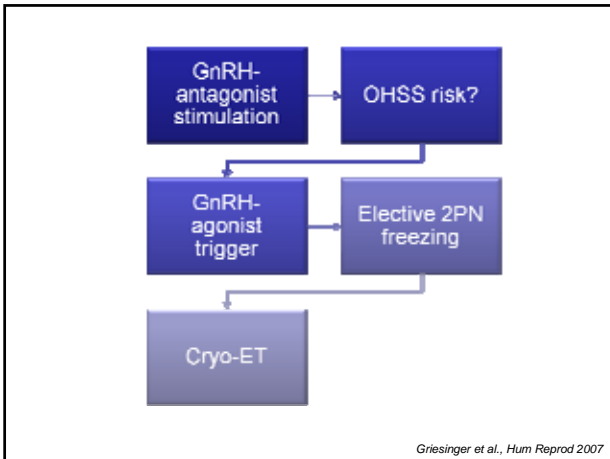


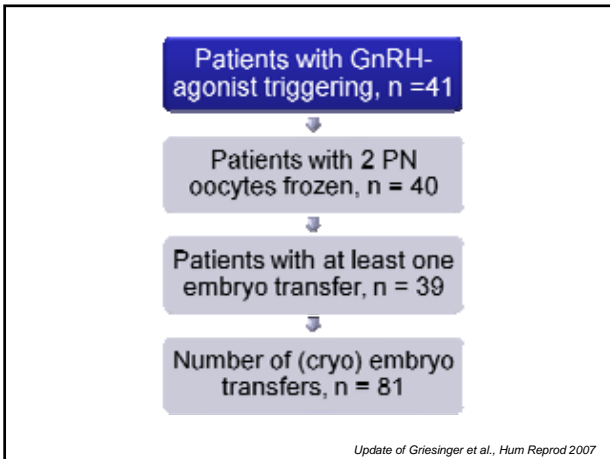
Update of: Griesinger et al., Hum Reprod update 2005

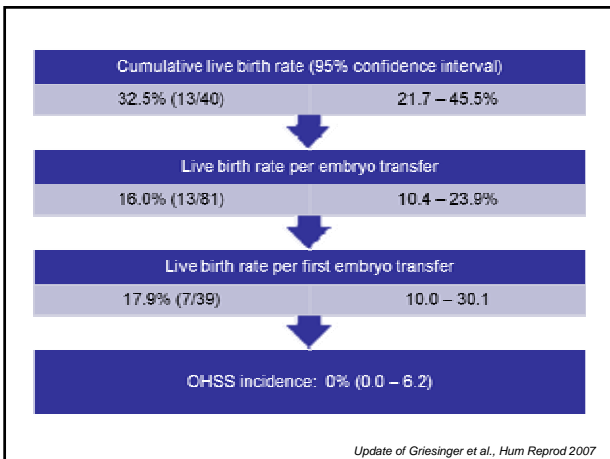
GnRH-agonist triggering in OHSS risk populations

Reference	Study type	n	OHSS
Full publications			
Alvarez-Blanco 2008	Observational, non-intervent	8	20 cases of severe OHSS
Chikara and Mochizuki 2005	Observational, non-intervent	6	20 OHSS including hospitalization
Reynolds 2006	Retrospective, case-control	23	20 cases of OHSS
Chikara 2004	Retrospective, cohort	22	20 cases of severe OHSS
Griesinger 2007 abstract	Retrospective, observational	20	20 cases of severe OHSS
Berman 2004	Retrospective, comparative	8	20 severe cases of OHSS (15 OHSS-IV) (nonfatal OHSS) requiring hospitalization
Alvarez 2006	Observational, non-intervent	27	20 cases of severe OHSS
Budnicki 2004	Retrospective, comparative	93	20 cases of severe OHSS
Chen 2007	Observational, non-intervent	81	20 severe cases of OHSS (1 OHSS-III) (nonfatal OHSS) requiring hospitalization
Chen 2007	Retrospective, cohort	25	20 severe cases of OHSS (1 OHSS-III) (nonfatal OHSS) requiring hospitalization
Reza 2007	Retrospective, cohort	93	20 severe cases
Engler 2007	Retrospective, cohort	50	20 OHSS requiring hospitalization
Alvarez 2006	Retrospective, comparative	61	20 cases
Engler 2007	Observational	63	15 OHSS-III (fatal OHSS) admitted to hospital with mild OHSS
Khalil 2006	Retrospective, comparative	27	20 severe cases
Bird 2005	Retrospective, comparative	547	20 cases of severe OHSS (severe OHSS)

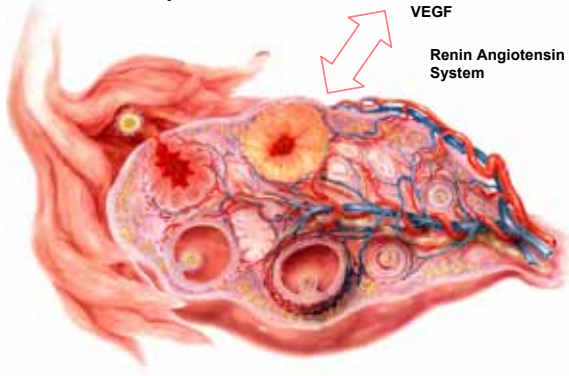
Update of: Griesinger et al., RBMonline 2006





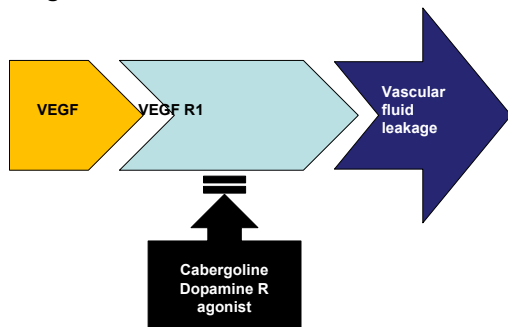


Novel concepts: treatment



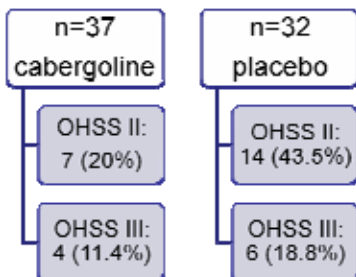
Novel concepts in treatment: Cabergolin

Background:



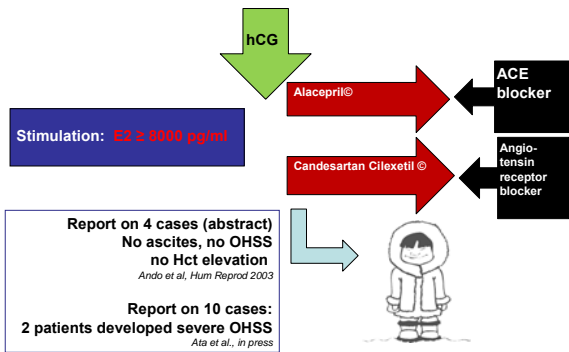
Alvarez et al, JCEM 2007

RCT: placebo-controlled
 Intervention: Cab 0.5 mg, day hCG → hCG+8
 Patients: oocyte donors
 Inclusion: > 20 oocytes retrieved

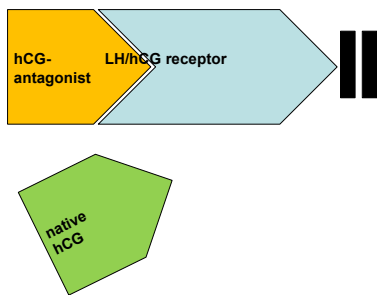


Alvarez et al, JCEM 2007 & Alvarez, Hum Reprod 2007

**Novel treatment concepts:
Renin-Angiotensin-system**



Novel treatment concepts: hCG antagonist



Vardhana et al., Fertil Steril (suppl)2006

hCG-antagonist



Competitive binding to LH receptor, but not stimulation (cAMP elevation)

- Reduced ovulation after PMSG stimulation
- Reduced vascular permeability

OHSS prevention

Agonist
trigger
± freezing

GnRH-
antagonist
coasting

Luteal
phase
antagonist
+freezing

OHSS treatment

Cabergoline

ACE
blocker
ATR
blocker

hCG
antagonist
