Prevenció de la síndrome d'hiperestimulació ovàrica: prevenció terciària

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OHSS prevention strategies

- **Primary prevention: target large populations with aim at avoiding the development of a specific disease**

  Mild stimulation; GnRH antagonists

- **Secondary prevention: Early disease detection, thereby providing opportunities for interventions**

  Coasting; triggering ovulation with agonist; cryopreservation all embryos

- **Tertiary prevention : To reduce the negative impact of an already established disease reducing disease related complications**

  Luteal phase GnRH analogues; dopaminergic agents

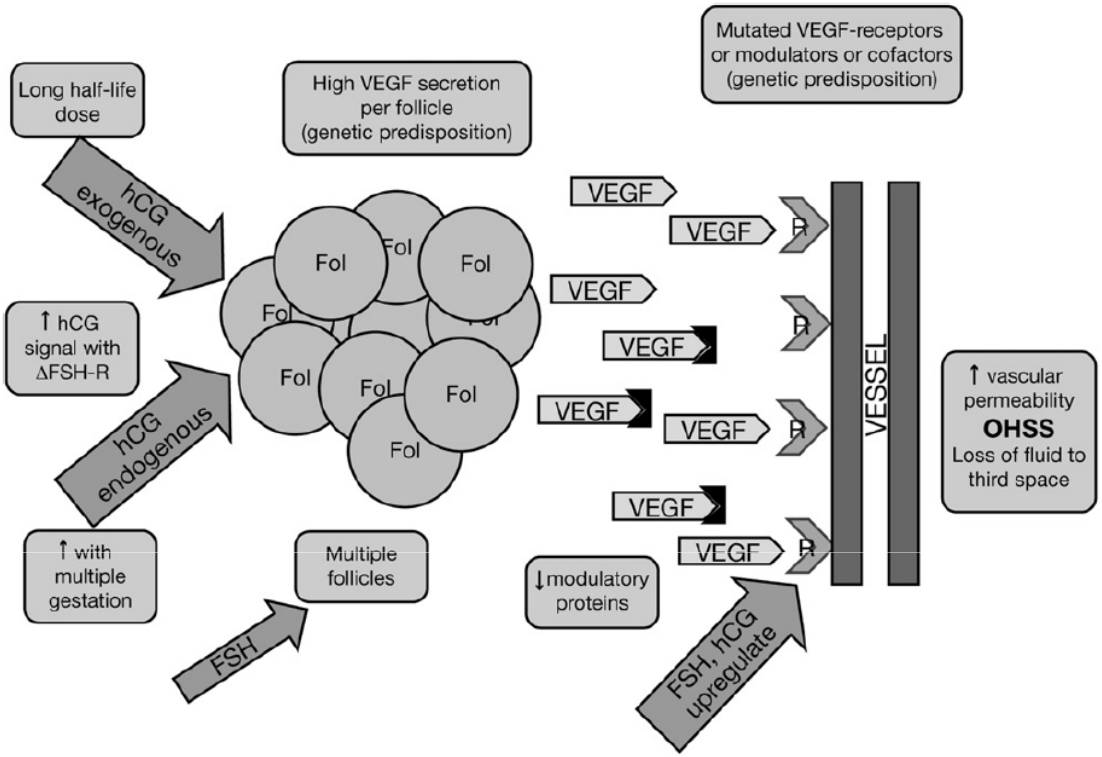
Antagonistes GnRH en fase lútea

Inhibidors de l'aromatasa

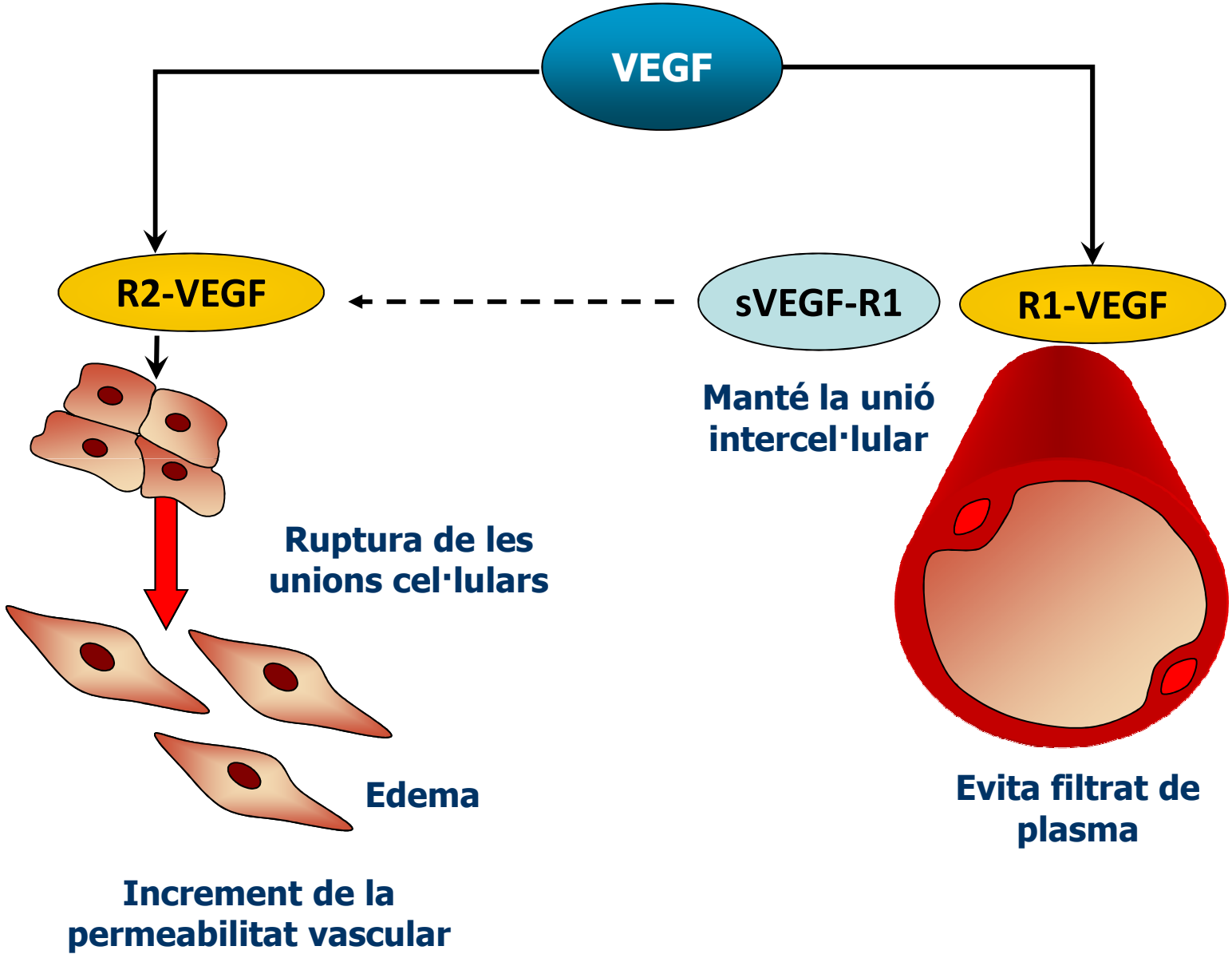
Agonistes de la dopamina

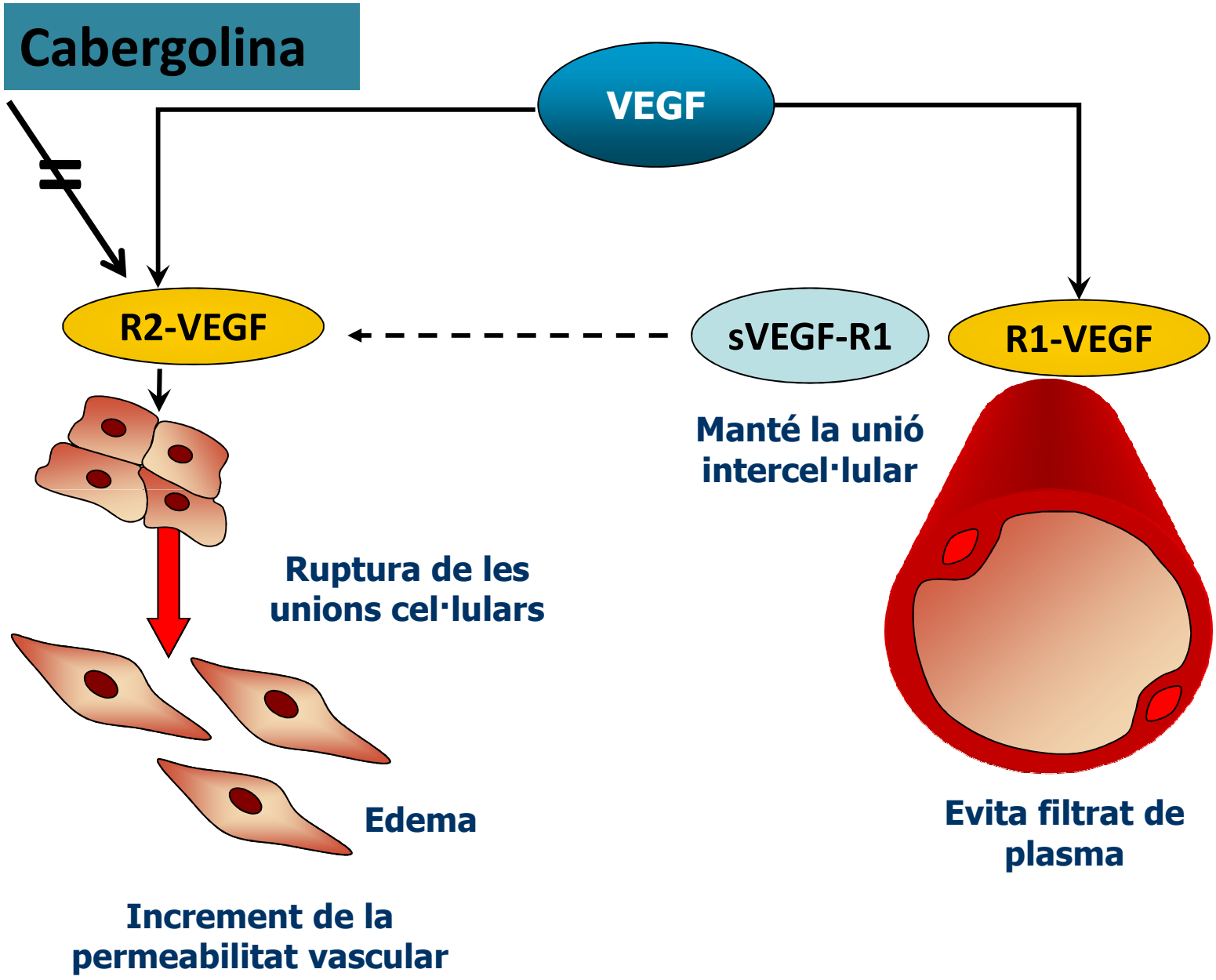
1. Agonistes de la dopamina

1. Agonistes de la dopamina: base fisiopatològica



- Teoria fisiopatològica: hCG indueix l'alliberament d'un mediador amb potents efectes sistèmics sobre el sistema vascular, responsable del desencadenament de la SHO
- L'administració d'hCG incrementa l'expressió de VEGF i VEGFR-2 en CG luteinitzades i cèl·lules endotelials del cos luti (Neulen et al., 1995)
- Les pacients amb SHO presenten una sobreexpressió de VEGF per part de les CG en resposta a hCG (Yamamoto et al., 1997): increment de la permeabilitat capil·lar


VEGF
R2-VEGF
sVEGF-R1
R1-VEGF
Manté la unió intercel·lular
Ruptura de les unions cel·lulars
Edema
Increment de la permeabilitat vascular
Evita filtrat de plasma


Cabergolina
VEGF
R2-VEGF
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Manté la unió intercel·lular
Ruptura de les unions cel·lulars
Edema
Increment de la permeabilitat vascular
Evita filtrat de plasma

1. Agonistes de la dopamina: primers estudis

Dopamine treatment for severe ovarian hyperstimulation syndrome

A.P. Ferraretti, L. Gianaroli, L. Diotallevi, C. Festi, A. Trounson

Hum Reprod 1992;7(2):180-3

Mc Clure N, Healy DL, Rogers PA, et al. Vascular endothelial growth factor as capillary permeability agent in ovarian hyper stimulation syndrome. Lancet 1994;344:235–6.

Lee A, Christenson LK, Stouffer PE, et al. Vascular endothelial growth factor levels in serum and follicular fluid of patients undergoing in vitro fertilization. Fertil Steril 1997;68:305–11.

Wang TH, Horng SG, Chang CL, et al. Human chorionic gonadotropin-induced ovarian hyperstimulation syndrome is associated with up-regulation of Vascular Endothelial Growth Factor. J Clin Endocrinol Metab 2002;87:3300–8.

Gomez R, Simon C, Remoti J, et al. Vascular endothelial growth factor receptor-2 activation induces vascular permeability in hyperstimulated rats and this effect is prevented by receptor blockade. Endocrinology 2002;143:4339–48.

Basu S, Nagy JA, Pal S, et al. The neurotransmitter dopamine inhibits angiogenesis induced by vascular permeability factor/vascular endothelial growth factor. Nat Med 2001;7:569–74.

Sarkar C, Chakroboty D, Mitra RB, et al. Dopamine in vivo inhibits VEGF-induced Phophotylation of VEGFR-2, MAPK and focal adhesion kinase in endothelial cell. Am J Physiol Heart Circ Physiol 2004;287:H1554–60.

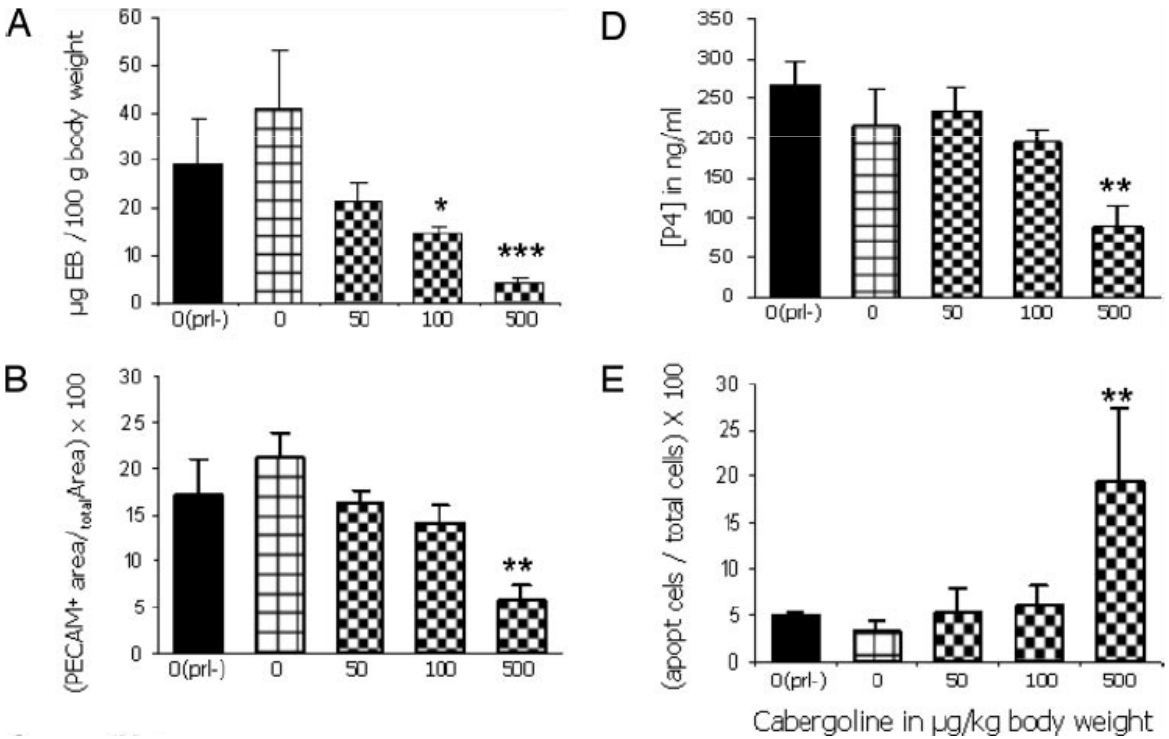
Cabergoline: a safe, easy, cheap, and effective drug for prevention/treatment of ovarian hyperstimulation syndrome?

M. Manno, F. Tomei, E. Marchesan, V. Adamo

Eur J Obstet Gynec Reprod Biol 2005;122:126-130

1. Agonistes de la dopamina: estudi de dosis en el model animal

Low-Dose Dopamine Agonist Administration Blocks Vascular Endothelial Growth Factor (VEGF)-Mediated Vascular Hyperpermeability without Altering VEGF Receptor 2-Dependent Luteal Angiogenesis in a Rat Ovarian Hyperstimulation Model



Gómez et al. Endocrinology, 2006

1. Agonistes de la dopamina: mecanisme d'acció

- **Administració d'un agonista de la dopamina a dosis baixes:** bloqueig de l'increment de la permeabilitat vascular sense alterar l'angiogènesi

- **Mecanisme d'acció:** bloqueig funcional del VEGFR-2 (defosforilació parcial de tirosina en la regió transmembrana)

1. Agonistes de la dopamina en donants d'ovòcits

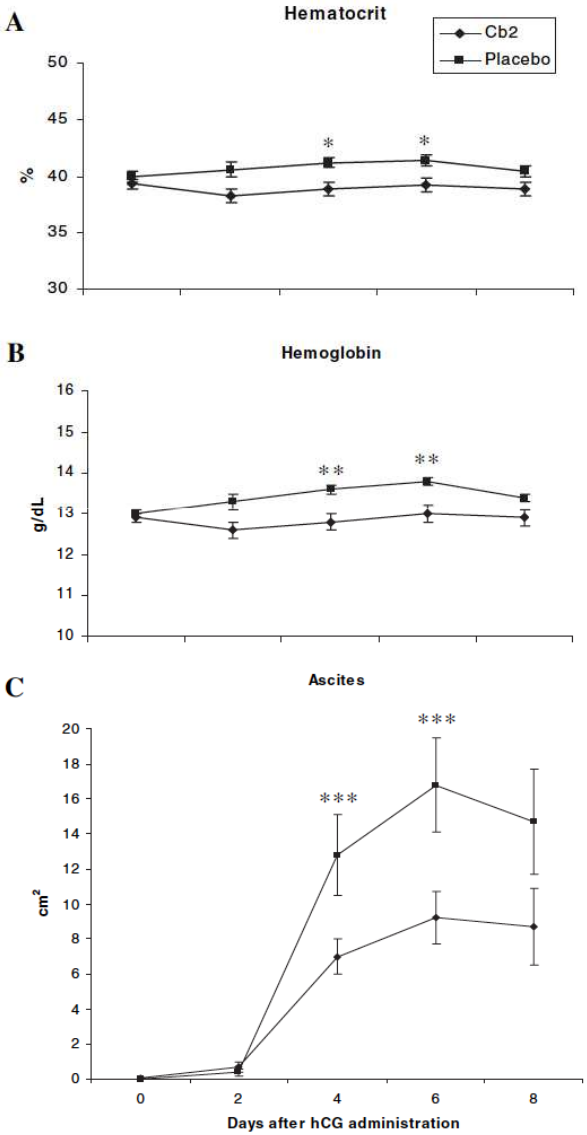


FIG. 4. Changes in hematocrit, hemoglobin, and ascites in Cb2- and placebo-treated patients during the study. *, $P < 0.01$; **, $P = 0.003$; ***, $P = 0.01$.

Cabergoline 0.5 mg/d (n= 35)
Placebo (n=32)

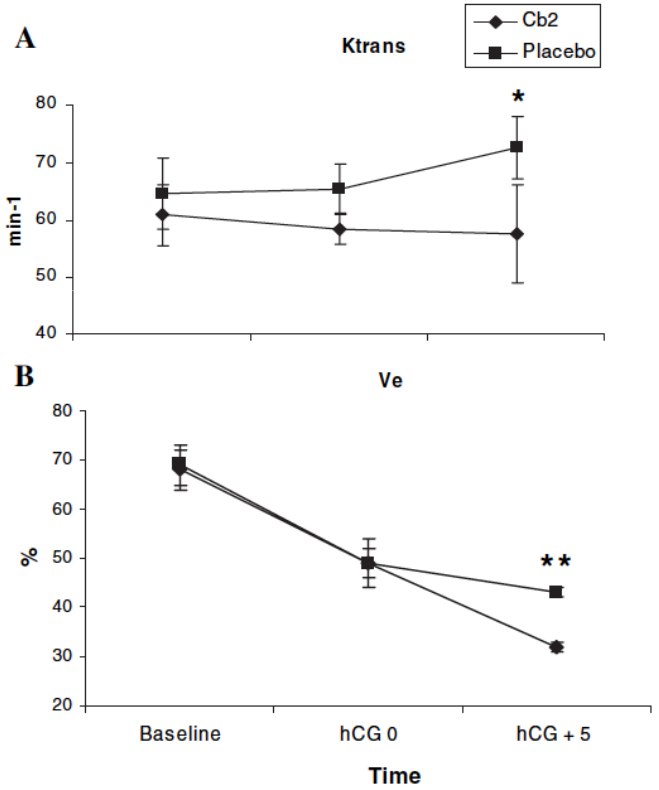


FIG. 5. Changes in pharmacodynamic parameters transfer constant rate (K^{trans}), a measure of vascular permeability, and the extravascular extracellular space (ve), which measures the volume of the leakage space. *, $P = 0.04$; **, $P = 0.001$.

Álvarez et al. JCEM, 2007

1. Agonistes de la dopamina en donants d'ovòcits

TABLE 1. Signs and symptoms of moderate and severe OHSS appearing in both groups

	Cb2 (n = 35)	Placebo (n = 32)	*P* value
Hemoconcentration[a]	2	5	NS
Renal dysfunction[b]	0	0	
Liver dysfunction[c]	2	2	NS
Thromboembolism	0	0	
Ascites > 9 cm^2 (%)	9 (25.7)	19 (59.4)	0.005
Moderate OHSS (%)	7 (20.0)	14 (43.8)	0.04
Severe OHSS (%)	4 (11.4)	6 (18.8)	NS

[a] Hematocrit greater than 45%.
[b] Creatinine greater than 1.2 mg/dl.
[c] AST or ALT greater than 40 U/ml.

Álvarez et al. JCEM, 2007

1. Agonistes de la dopamina: efectes sobre l'angiogenesi uterina

Implantation is apparently unaffected by the dopamine agonist Cabergoline when administered to prevent ovarian hyperstimulation syndrome in women undergoing assisted reproduction treatment: a pilot study

Women at risk of OHSS: cabergoline 0.5 mg/day for 8 days (from day of hCG)
Matched controls who were not at risk of developing OHSS

Table III. Assisted reproduction treatment outcome.

	Cb2 group ($n = 35$)	Control group ($n = 35$)	*P*-value
No. of oocytes[a]	28.2 ± 6.8	12.4 ± 5.9	0.0001
Fertilization rate	77.2 ± 13.0	83.4 ± 16.9	NS
No. of total embryos	15.5 ± 5.2	7.5 ± 3.9	0.0001
No. of total good quality embryos	4.9 ± 4.5	3.6 ± 2.6	NS
Good quality embryos rate	30.6 ± 26.8	48.9 ± 21.6	0.002
No. of embryos transferred	1.8 ± 0.4	1.8 ± 0.4	NS
Implantation rate	38.6 ± 38.5	41.4 ± 44.5	NS
Clinical pregnancy (%)	17 (48.6)	18 (51.4)	NS
Live birth per cycle (%)	14 (40.0)	14 (40.0)	NS
Twin pregnancy (%)	4 (11.4)	8 (22.8)	NS

[a]Values expressed as mean ± SD.

Álvarez et al. Hum Reprod, 2007

1. Agonistes de la dopamina: estudis randomitzats en pacients de risc

Cabergoline reduces the early onset of ovarian hyperstimulation syndrome: a prospective randomized study

Table 1. Results for 163 patients at high risk of OHSS after IVF and intracytoplasmic sperm injection treatment with and without the use of cabergoline.

	Group A (cabergoline) (n = 83)	*Group B (no medication) (n = 80)*
Age (years)	34.0 ± 4.6	33.6 ± 4.7
Weight (kg)	58.4 ± 6.6	58.6 ± 8.4
Height (cm)	1.67 ± 0.06	1.66 ± 0.03
BMI (kg/m^2)	21.1 ± 2.6	21.3 ± 2.9
Oestradiol (pg/ml)[a]	4931.6 ± 949.3	4948.7 ± 841.1
Positive β-HCG (*n*)	41 (49.4)	34 (42.5)
Clinical pregnancy (*n*)	33 (39.8)	32 (40.0)
Implantation (*n*)	60/271 (22.1)	49/258 (19.0)
Miscarriage (*n*)	1 (3.0)	3 (9.4)
Early OHSS cases (*n*)	0 (0.0)	12 (15.0)[b]
Late OHSS cases (*n*)	9 (10.8)	3 (3.8)
Total OHSS cases (*n*)	9 (10.8)	15 (18.8)

*Cabergoline 0.5 mg/day for 3 weeks

Carizza et al. Reprod Biomed Online, 2008

1. Agonistes de la dopamina: estudis randomitzats en pacients de risc

Cabergoline 0.25 mg/day for 8 days from the hCG day

Table 2
Clinical outcomes in cabergoline and control groups.

	Cabergoline (Group I) Mean ± SD	Control (Group II) Mean ± SD	RR (95% CI)	*P*-value*
OHSS incidence (*n*; %)	10 (10%)	21 (21%)	0.5 (0.29–0.83)	0.035
Severe OHSS (*n*; %)[b]	1 (1%)	3 (3%)	0.33 (0.03–3.19)	NS
Moderate OHSS (*n*; %)[b]	4 (4%)	11 (11%)	0.34 (0.10–1.10)	NS
Mild OHSS (*n*; %)[b]	5 (5%)	7 (7%)	0.70 (0.21–2.28)	NS
Early onset OHSS (*n*; %)[b]	0	8 (38%)	0.12 (0.01–1.86)	0.01
Late onset OHSS (*n*; %)[b]	10 (10%)	13 (13%)	0.74 (0.31–1.78)	NS
Hemoconcentration (*n*; %)[b]	8 (8.4%)	18 (18.75%)	0.44 (0.20–0.97)	0.03
Hospitalization (*n*; %)[b]	1(10%)	5 (23%)	0.42 (0.06–3.14)	NS
Ovarian volume (ml)[a]	129.3 ± 70	159.8 ± 56.6		<0.0001
Ascitic fluid (cm)[a]	4.6 ± 1.6	6.7 ± 1.7		<0.0001

* *P* value of ≤0.05 was considered statistically significant.
[a] Student *t*-test.
[b] Chi-square test.

Table 3
Ovarian stimulation and pregnancy outcomes in cabergoline and control groups.

	Cabergoline group (*n* = 100) Mean ± SD	Control group (*n* = 100) Mean ± SD	RR (95% CI)	*P*-value*
No. oocytes retrieved per woman randomized[a]	23.4 ± 2.7	24 ± 2.6		NS
No. MII oocytes per woman randomized[a]	16.4 ± 2.8	16.8 ± 2.7		NS
Fertilization rate (%)[b]	72%	74%		NS
Clinical pregnancy rate per woman randomized[b]	42 (42%)	41 (41%)	1.02 (0.74–1.42)	NS
Early miscarriage rate per woman randomized[b]	5 (5%)	5 (5%)	1.0 (0.30–0.35)	NS
Ongoing pregnancy rate per woman randomized[b]	37 (37%)	36 (36%)	0.90 (0.51–1.60)	NS
Live birth rate per woman randomized[b]	37 (37%)	36	1.27 (0.68–2.35)	NS

* *P* value of ≤0.05 was considered statistically significant.
[a] Student *t*-test.
[b] Chi-square test.

Shaltout et al. Eur J Obstet Gynecol Reprod Biol, 2012

1. Agonistes de la dopamina: metaanàlisis

Can dopamine agonists reduce the incidence and severity of OHSS in IVF/ICSI treatment cycles? A systematic review and meta-analysis

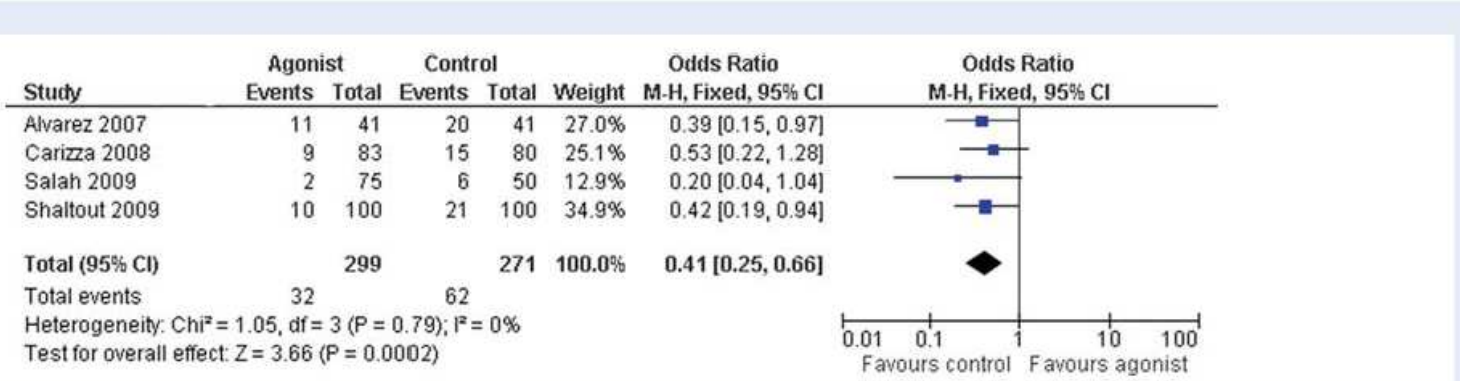


Figure 2 Forest plot of ORs and 95% CI of pooled trials comparing dopamine agonist to control for OHSS incidence per randomized woman.

Youssef et al. Hum Reprod Update, 2010

1. Agonistes de la dopamina: metaanàlisis

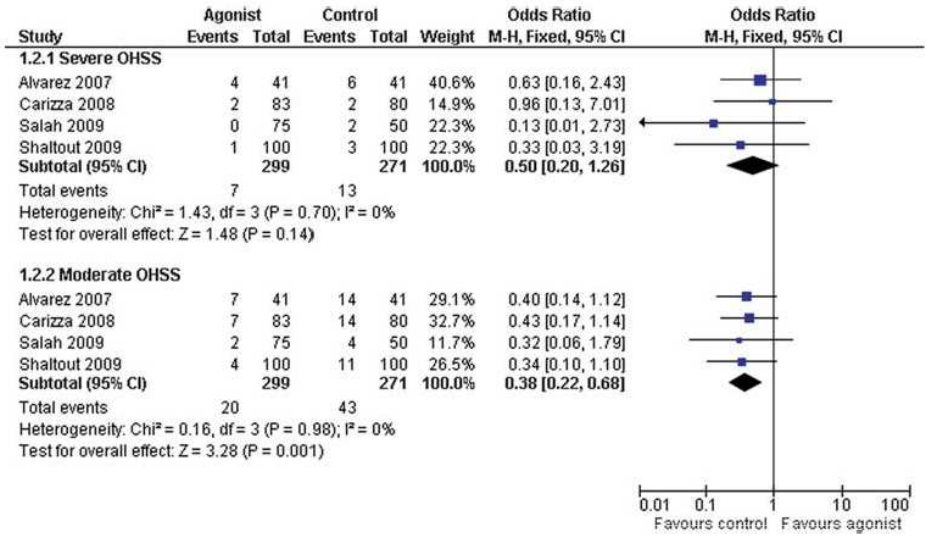


Figure 3 Forest plot of ORs and 95% CI of pooled trials comparing dopamine agonist to control according to the severity of OHSS per randomized woman.

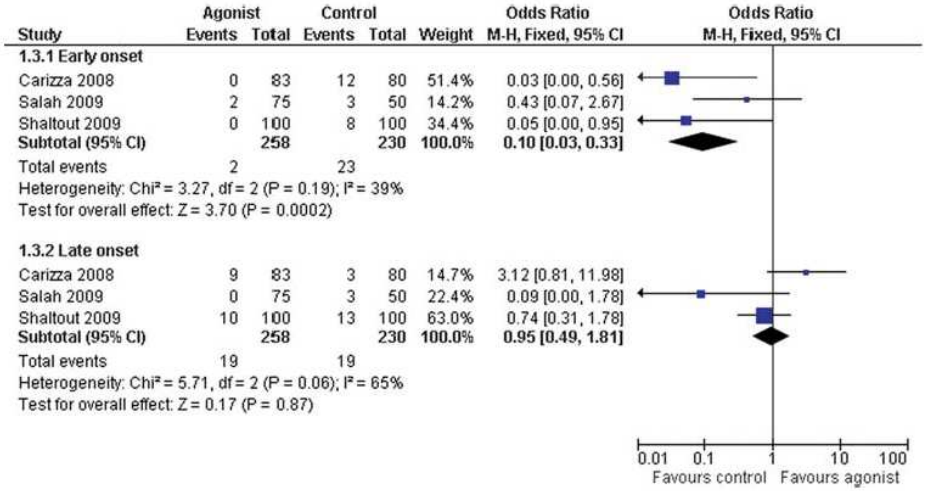


Figure 4 Forest plot of ORs and 95% CI of pooled trials comparing dopamine agonist to control according to the time of onset of OHSS per randomized women.

Youssef et al. Hum Reprod Update, 2010

1. Agonistes de la dopamina: metaanàlisis

Figure 3. Forest plot of comparison: 1 Cabergoline versus Control, outcome: 1.1 Incidence of OHSS.

Study or Subgroup	Cabergoline Events	Cabergoline Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Alvarez 2007	11	35	20	32	51.3%	0.28 [0.10, 0.76]
Carizza 2008	9	83	15	80	48.7%	0.53 [0.22, 1.28]
Total (95% CI)		**118**		**112**	**100.0%**	**0.40 [0.20, 0.77]**
Total events	20		35			

Heterogeneity: Chi² = 0.90, df = 1 (P = 0.34); I² = 0%
Test for overall effect: Z = 2.71 (P = 0.007)

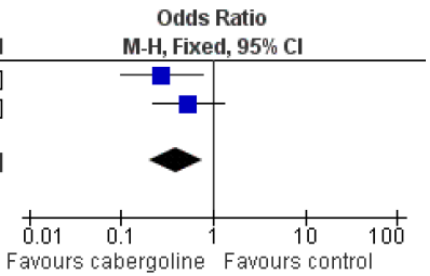


Figure 4. Forest plot of comparison: 1 Cabergoline versus Control, outcome: 1.1 Incidence of severe OHSS.

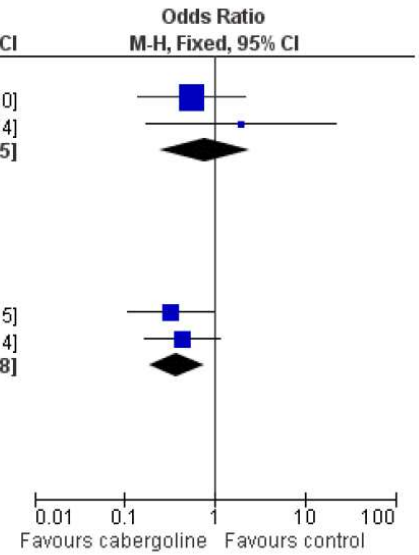
Study or Subgroup	Cabergoline Events	Cabergoline Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.2.1 Incidence of severe OHSS						
Alvarez 2007	4	35	6	32	84.8%	0.56 [0.14, 2.20]
Carizza 2008	2	83	1	80	15.2%	1.95 [0.17, 21.94]
Subtotal (95% CI)		**118**		**112**	**100.0%**	**0.77 [0.24, 2.45]**
Total events	6		7			

Heterogeneity: Chi² = 0.78, df = 1 (P = 0.38); I² = 0%
Test for overall effect: Z = 0.44 (P = 0.66)

1.2.2 Incidence of moderate OHSS						
Alvarez 2007	7	35	14	32	47.3%	0.32 [0.11, 0.95]
Carizza 2008	7	83	14	80	52.7%	0.43 [0.17, 1.14]
Subtotal (95% CI)		**118**		**112**	**100.0%**	**0.38 [0.19, 0.78]**
Total events	14		28			

Heterogeneity: Chi² = 0.17, df = 1 (P = 0.68); I² = 0%
Test for overall effect: Z = 2.62 (P = 0.009)

Test for subgroup differences: Chi² = 1.03, df = 1 (P = 0.31), I² = 2.7%



Tang et al, 2012

1. Agonistes de la dopamina: moment d'inici

Clinical outcome according to timing of cabergoline initiation for prevention of OHSS: a randomized controlled trial

Study group (n=100): cabergoline beginning on the hCG day
Control group (n=100): cabergoline beginning on the day of oocyte retrieval

Table 2 Clinical features and cycle outcomes.

	Control group (n = 100)	*Study group (n = 100)*
No. of oocytes retrieved	15.4 ± 3.3 (14.8–16.0)	16.0 ± 3.2 (15.4–16.6)
No. of MII oocytes	11.8 ± 4.6 (10.6–12.4)	11.6 ± 4.8 (10.5–12.3)
MII rate per oocytes retrieved	0.86 ± 0.16 (0.83–0.89)	0.85 ± 0.15 (0.82–0.88)
No. of 2PN	10.8 ± 4.6 (9.4–11.2)	10.3 ± 4.6 (9.4–11.2)
Fertilization rate per oocytes retrieved	0.79 ± 0.22 (0.75–0.85)	0.76 ± 0.20 (0.74–0.83)
No. of embryos transferred	2.03 ± 0.26 (1.98–2.08)	2.04 ± 0.28 (1.98–2.08)
Implantation rate per embryos transferred (*n*/total)	37 ± 12.3 (74/202)	34 ± 11.9 (69/203)
Clinical pregnancy rate	54 (54/100)	51 (51/100)
Ongoing pregnancy rate (≥12 weeks)	51	47
Patients with excess embryos for cryopreservation	67	66

Values are mean ± SD (95% confidence interval) or %, unless otherwise stated. There were no statistically significant differences between the two groups.
Control group = cabergoline treatment started on the day of oocyte retrieval; study group = cabergoline treatment started on the day of HCG administration.
MII = metaphase II; PN = pronuclei.

Seow et al. Reprod Biomed Online, 2013

1. Agonistes de la dopamina: quinagolida

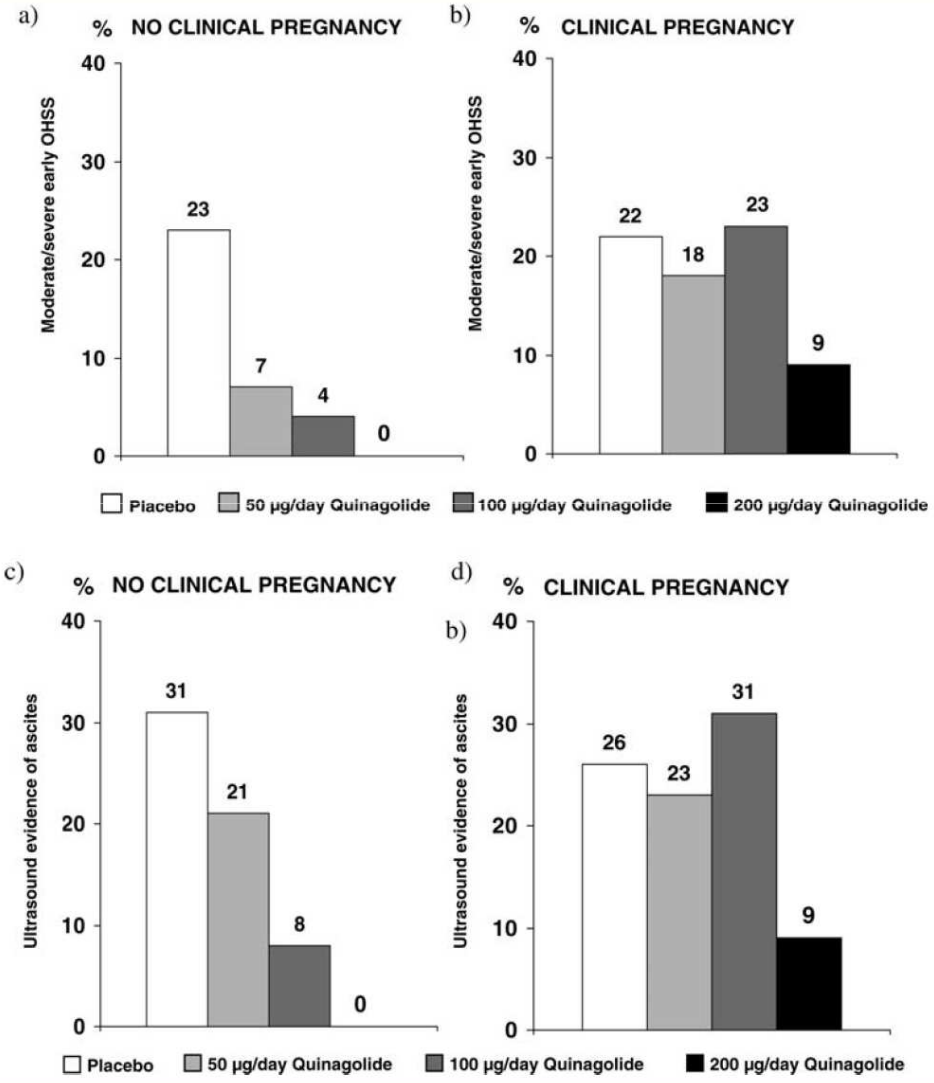


Figure 4 Moderate/severe early OHSS rate according to the patient's pregnancy status in the trial cycle; no clinical pregnancy (**a**) and clinical pregnancy (**b**); and percentage of patients with ultrasound evidence of ascites within the initial 9 days after hCG administration according to the patient's pregnancy status in the trial cycle; no clinical pregnancy (**c**) and clinical pregnancy (**d**).

Busso et al. Hum Reprod, 2010

1. Agonistes de la dopamina: quinagolida

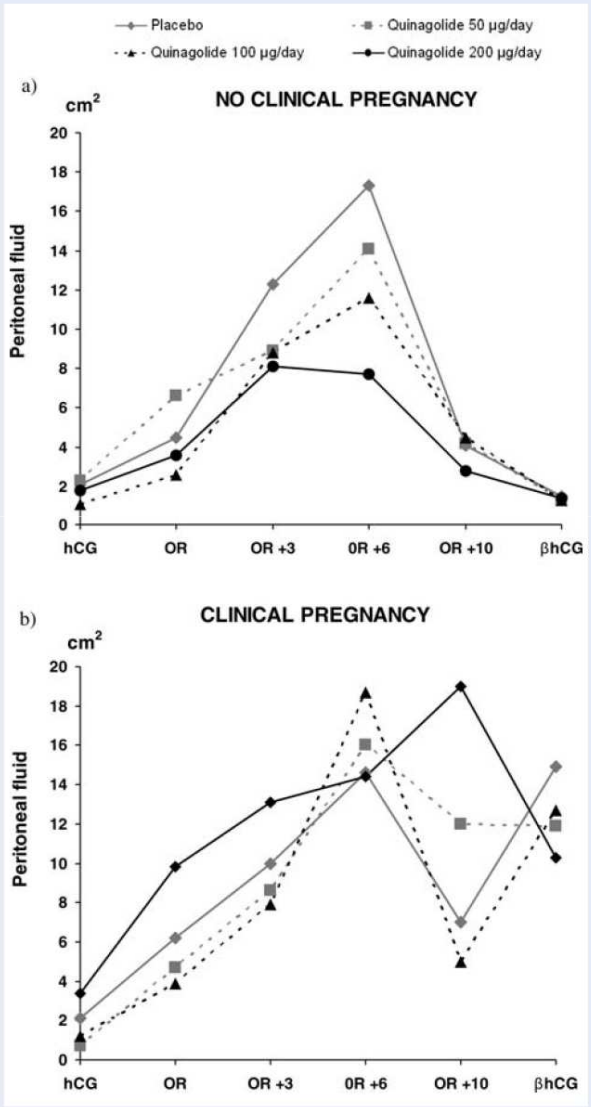


Figure 5 Mean peritoneal fluid (cm^2) according to the patient's pregnancy status in the trial cycle; no clinical pregnancy (**a**) and clinical pregnancy (**b**).

Table III Frequent adverse events.

	Placebo	Quinagolide		
		50 µg/day	100 µg/day	200 µg/day
Subjects randomized (ITT)	*n* = 53	*n* = 51	*n* = 52	*n* = 26
Nausea	25% (13)	35% (18)	50% (26)	69% (18)
Dizziness	15% (8)	41% (21)	52% (27)	42% (11)
Somnolence	13% (7)	25% (13)	33% (17)	42% (11)
Diarrhoea	13% (7)	12% (6)	13% (7)	12% (3)
Vomiting	8% (4)	24% (12)	71% (37)	69% (18)
Abdominal pain lower	8% (4)	8% (4)	8% (4)	4% (1)
Headache	6% (3)	10% (5)	10% (5)	12% (3)
Abdominal distension	6% (3)	0%	2% (1)	0%
Flatulence	4% (2)	8% (4)	2% (1)	4% (1)
Abdominal pain upper	4% (2)	6% (3)	0%	0%
Syncope	0%	2% (1)	8% (4)	12% (3)

ITT, intention-to-treat.

Busso et al. Hum Reprod, 2010

1. Agonistes de la dopamina: conclusions

- Administració d'un agonista de la dopamina a dosis baixes: bloqueig de l'increment de la permeabilitat vascular sense alterar l' angiogènesi. Mecanisme d'acció: bloqueig funcional del VEGFR-2 (inhibició de la fosforilació)
- No altera la implantació embrionària
- L'administració el dia hCG no sembla alterar la maduració final ovocitària
- Prevenció de la SHO moderada
- No prevenció de la SHO tardana (en presència de gestació)
- Fàrmac alternatiu: quinagolida

2. Inhibidors de l’aromatasa

2. Inhibidors de l'aromatasa

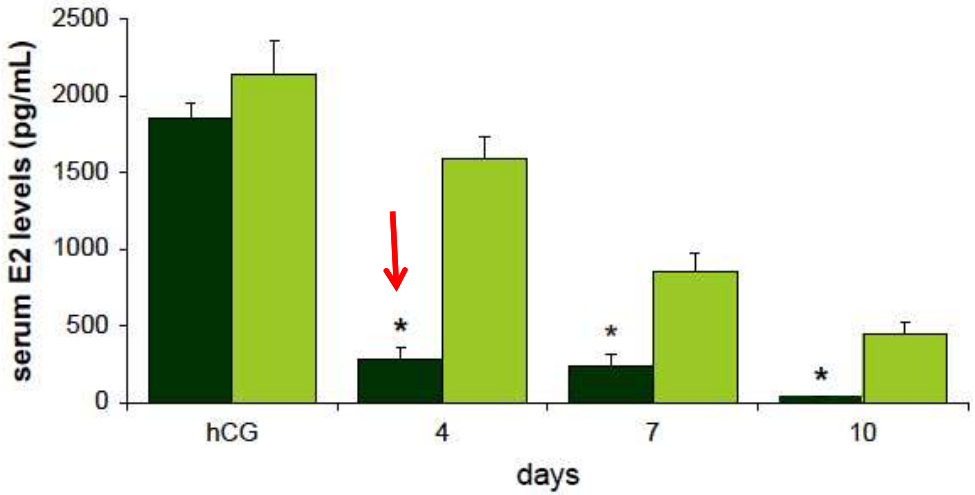
Table 1. Serum oestradiol concentration in the letrozole- and placebo-treated groups in the luteal phase of oocyte donation cycles.

Days after HCG administration	*Serum oestradiol concentration (pg/ml)* *Letrozole group*	*Placebo group*	*P-value*
1	4486 ± 502	2916 ± 730	NS
4	272 ± 65	749 ± 27	0.008
7	229 ± 69	1457 ± 152	0.005
10	31 ± 7	1308 ± 88	0.004

Values are mean ± SD. HCG = human chorionic gonadotrophin.

Letrozol 5mg/d
(de PF fins menstruació)

Fatemi et al. RBMO, 2008



Letrozole 2.5 mg /d

Placebo

Garcia-Velasco et al. Fertil Steril, 2009

3. Antagonistes GnRH en fase lútea

Antagonistes GnRH en fase lútea: mecanisme d'acció

- Efecte luteolític prominent (Friden i Nilsson, 2005): forma alternativa de minimitzar la producció excessiva de citoquines vasoacties dels cossos lutis, responsables dela instauració del SHO

- Reducció de l'expressió de VEGF i receptor de VEGF als ovaris de rates hiperestimulades (Taylor et al., 2004)

- Acció directa sobre l'ovari reduïnt l'expressió de factors angiogènics produïts localment, com VEGF (Asimakopoulos et al., 2006)

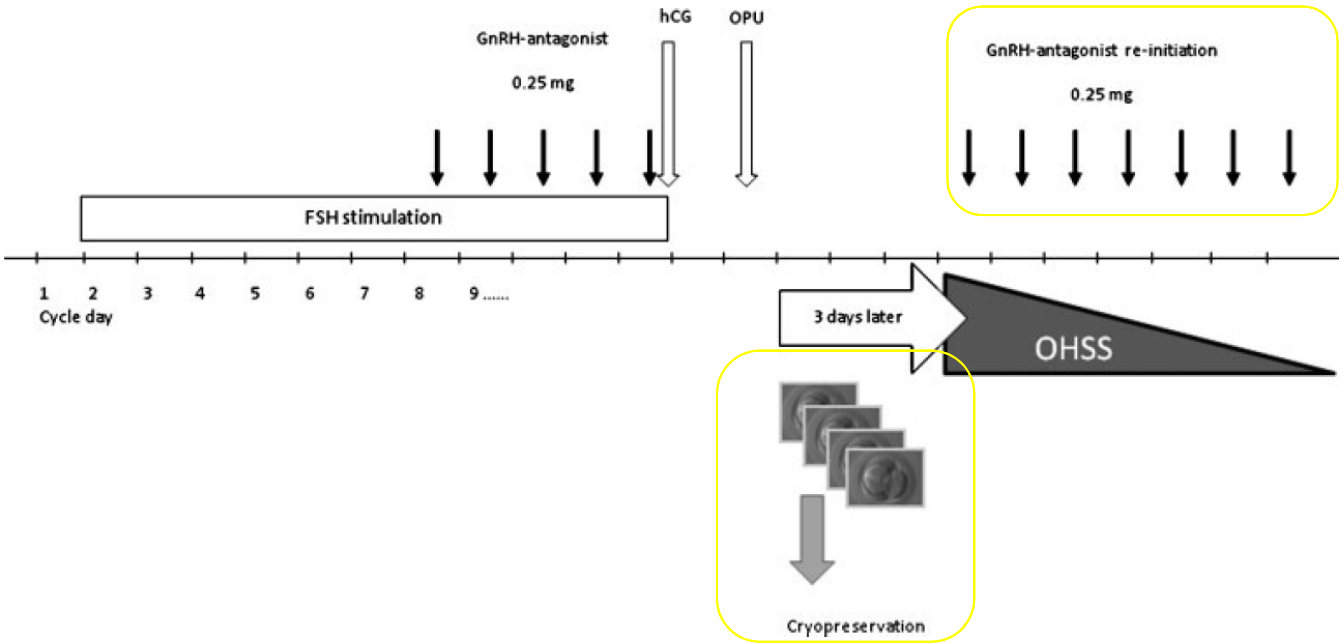
- **Efecte directe de l'antagonista sobre l'ovari**: receptors GnRH ovàrics (Minaretzis et al., 1995; Choi et al., 2006)

Antagonistes GnRH en fase lútea: reinici en cicle antagonistes

Management of severe early ovarian hyperstimulation syndrome by re-initiation of GnRH antagonist

3 pacients SOP
FIV amb pauta antagonistes GnRH
SHO severa 3 dies post-PF

	Patient 1	*Patient 2*	*Patient 3*
Height (m)	1.58	1.56	1.54
Weight (kg)	73	47	61
Age (years)	30	39	32
Oestradiol on HCG day (pg/ml)	2276	3402	3158
Number of COC collected	58	37	47
Number of MII oocytes	48	28	33
Number of 2PN zygotes	38	25	28
Method of fertilization	ICSI	ICSI	IVF
Fertilization rate (%)	65.52	67.57	59.57



Lainas et al. RBMO, 2007

Antagonistes GnRH en fase lútea: cicle agonistes

Management of severe OHSS using GnRH antagonist and blastocyst cryopreservation in PCOS patients treated with long protocol

3 pacients SOP
FIV amb pauta llarga (agonistes GnRH)
SHO severa 6 dies post-PF

Inici antagonistes GnRH durant 6 dies
CP embrionària (blastocists)

	Patient 1	*Patient 2*	*Patient 3*
Age	34	30	31
BMI (kg/m^2)	24.5	29.2	28.7
FSH (IU/l)	6.1	6	4.15
LH (IU/l)	6.1	11	5.9
Oestradiol (pg/ml)	31	19	54
Progesterone (ng/ml)	0.37	0.68	0.80
Years of infertility	4	5	6
Total dose of FSH (IU)	1300	2150	1700
Duration of stimulation (days)	11	13	12
Number of COC retrieved	36	48	31
Method of fertilization	IVF	ICSI	IVF
Number of fertilized oocytes (2PN)	24	38	27
Number of blastocysts frozen	12	17	14

Lainas et al. RBMO, 2009

Antagonistes GnRH en fase lútea: estudi prospectiu

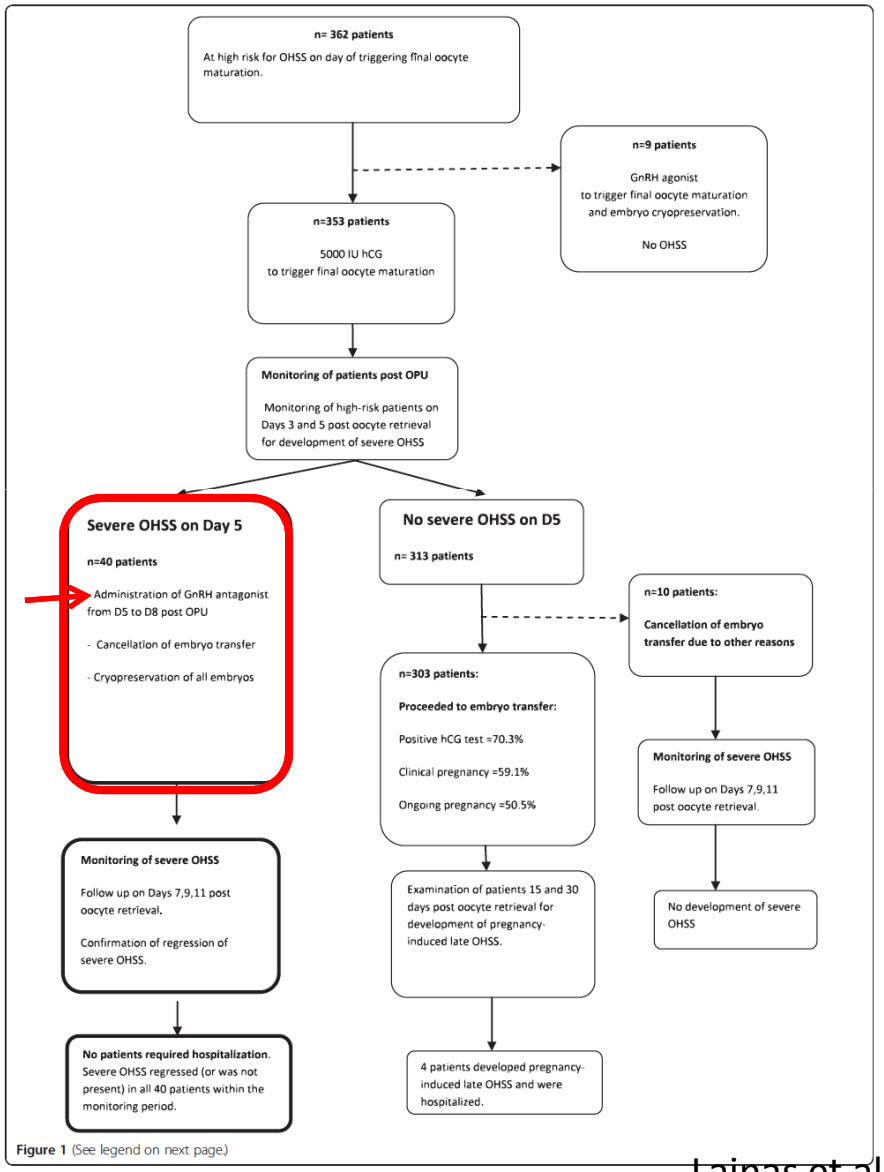


Figure 1 (See legend on next page.)

Lainas et al. Reprod Biol Endocrinol, 2012

Antagonistes GnRH en fase lútea: estudi prospectiu

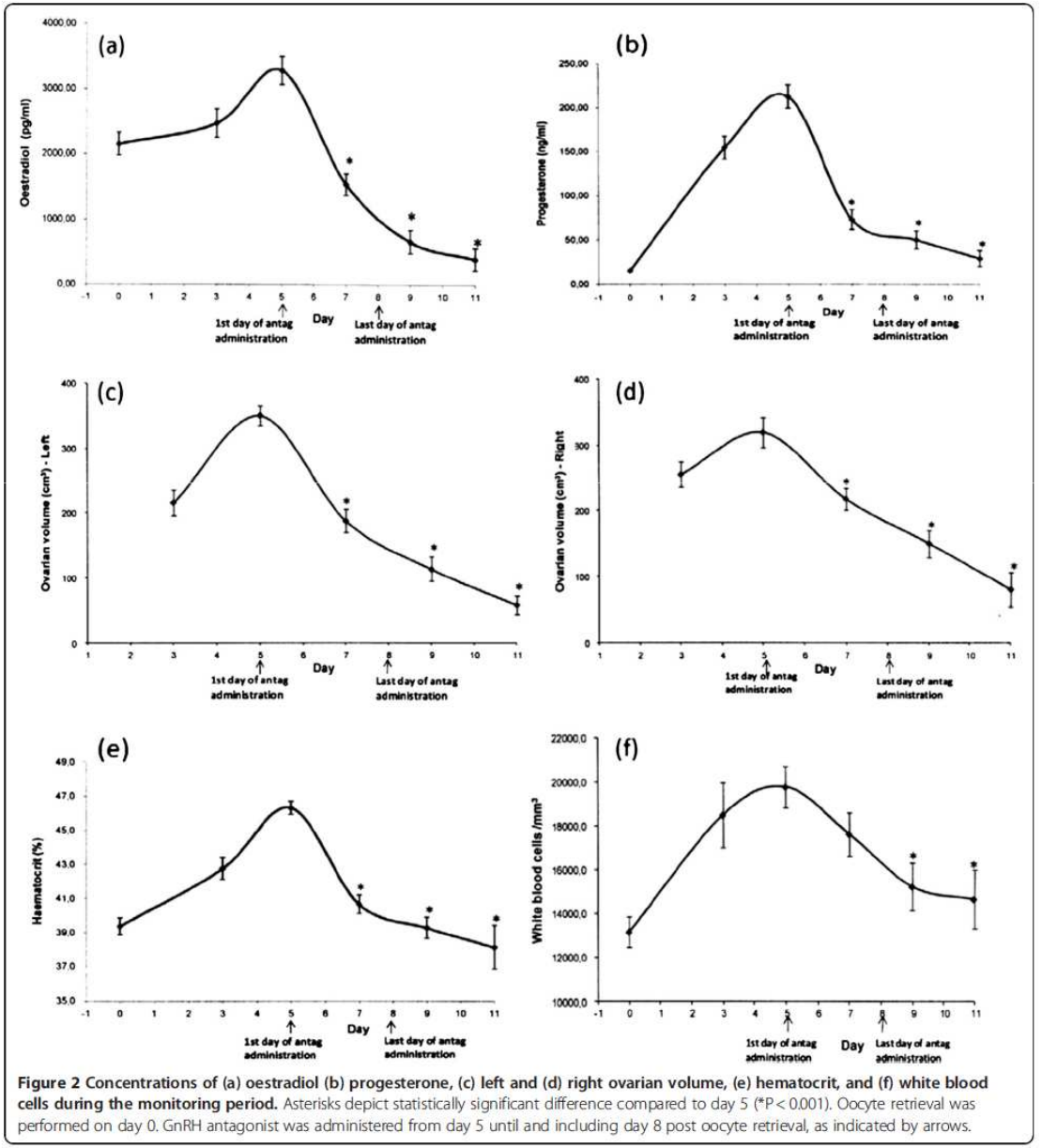
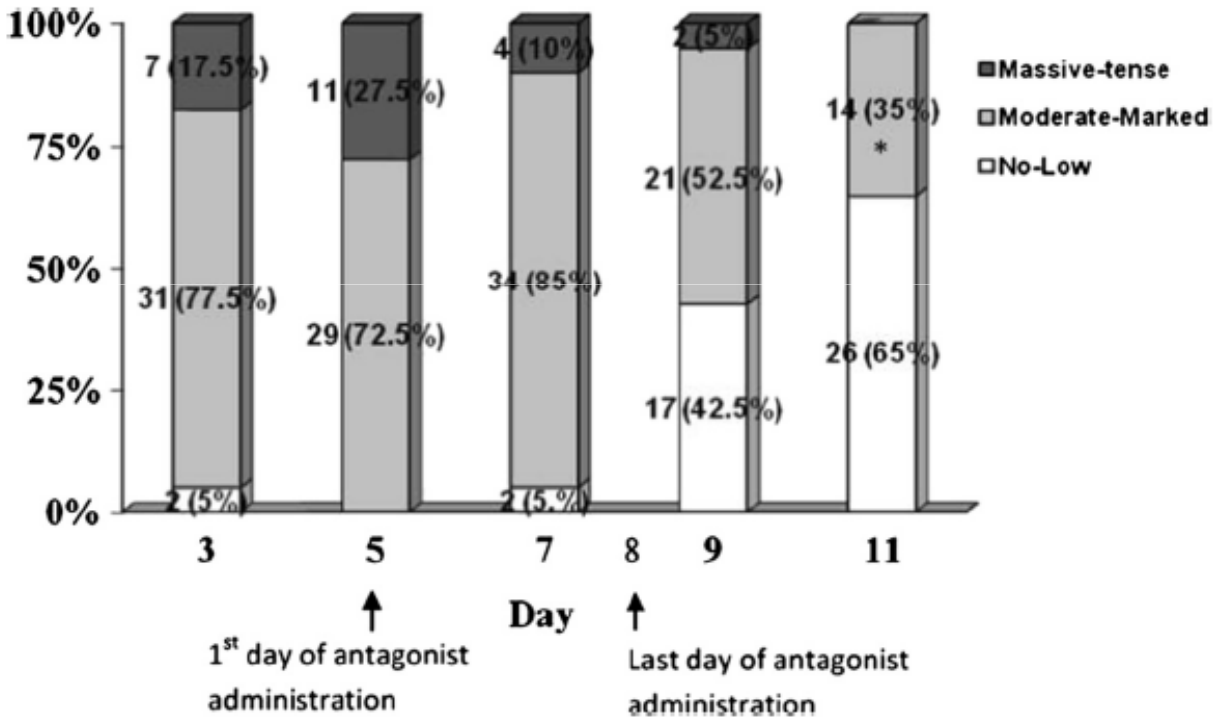


Figure 2 Concentrations of (a) oestradiol (b) progesterone, (c) left and (d) right ovarian volume, (e) hematocrit, and (f) white blood cells during the monitoring period. Asterisks depict statistically significant difference compared to day 5 (*P < 0.001). Oocyte retrieval was performed on day 0. GnRH antagonist was administered from day 5 until and including day 8 post oocyte retrieval, as indicated by arrows.

Antagonistes GnRH en fase lútea: estudi prospectiu



Antagonistes GnRH en fase lútea: transferència en fresc

Live births after management of severe OHSS by GnRH antagonist administration in the luteal phase

3 pacients SOP
SHO severa 6 dies post-PF

Transferència de 2 blastocists
Antagonistes GnRH 4 dies
(estradiol + progesterona)

Parameter	*Patient A*	*Patient B*	*Patient C*
Age (years)	32	29	26
BMI (kg/m^2)	25.7	18.4	25.5
FSH (IU/l)	3.9	5.4	4.7
LH (IU/l)	4.6	7.8	4.1
Oestradiol (pg/ml)	22	10	41
Progesterone (ng/ml)	0.32	0.56	0.43
Prolactin (ng/ml)	16.4	22	11.7
Cause of infertility	PCOS, unexplained	PCOS, endometriosis	PCOS, male factor
Protocol of stimulation	GnRH antagonist	GnRH agonist	GnRH agonist
Duration of stimulation (days)	9	11	13
Total dose of FSH (IU)	835	1350	2250
Oestradiol on day of HCG (pg/ml)	4800	4383	3713
Number of oocytes retrieved	47	41	20
Method of fertilization	IVF	IVF	ICSI
Number of fertilized (2PN) oocytes	28	15	10
Number of good quality embryos on day 3	20	12	8
Number of blastocysts transferred	2	2	2
Number of blastocysts frozen	14	5	3
Outcome	Live birth of 1 female	Live birth of 2 females	Biochemical pregnancy

Lainas et al. RBMO, 2009

EVALUATION OF GNRH AGONISTS AND ANTAGONISTS IN TERTIARY PREVENTION OF OHSS. CLINICAL, NEUROHORMONAL AND VASOACTIVE EFFECTS IN THE LUTEAL PHASE IN HIGH RISK PATIENTS

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Hospital Clinic. Institut d´Investigacions Biomédiques August Pi i Sunyer (IDIBAPS),
Faculty of Medicine- University of Barcelona

Design:
Prospective, randomized study

Patients:
High risk patients: > 20 follicles larger than 12 mm in diameter on hCG day and > 20 retrieved oocytes.
Cryopreservation of all embryos was decided as secundary prevention of OHSS

Interventions:
. Group A: Cetrorelix 0.25 mg/day for 7 days
. Group B: Triptorelin 0.1 mg /day for 7 days
. Group C: Supportive treatment (oral analgesics and oral hydratation)

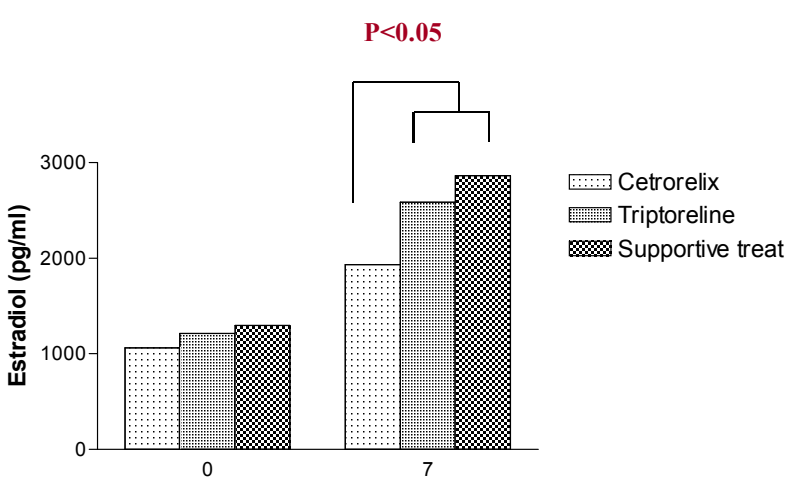
Study points:
. Day of oocyte retrieval (T0)
. Day 7 post-hCG (T7)

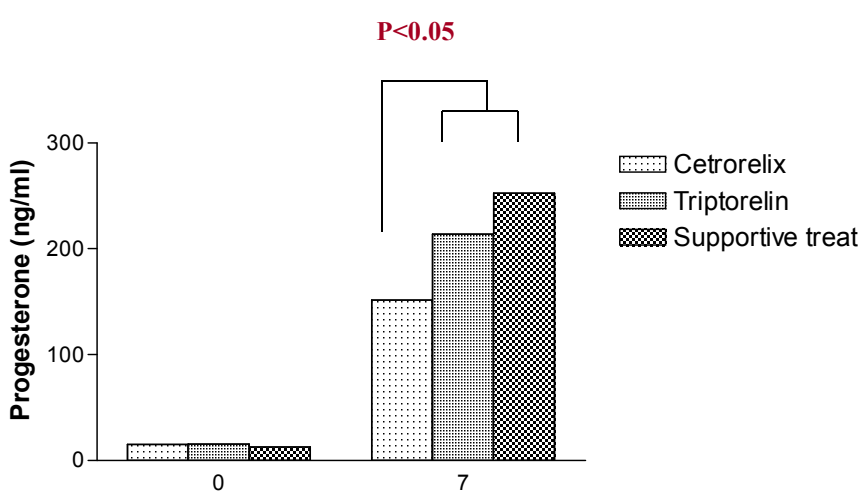
Results: Signs and symptoms of moderate and severe OHSS in the groups of study

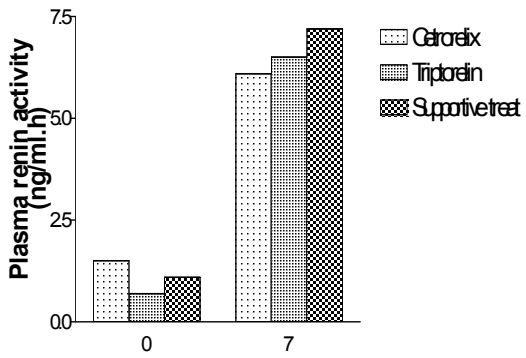
	Group A (n=19)	Group B (n=15)	Group C (n=15)	P
Hemoconcentration (n,%)[a]	2 (10.5)	-	1 (6.7)	NS
Renal dysfunction [b]	-	-	-	
Liver dysfunction (n,%)[c]	3 (15)	5 (33)	1 (6.7)	NS
Thromboembolism (n,%)	-	-	-	
Ascitis > 9 cm^2 (n,%)	13 (68.4)	11 (73.3)	11 (73.3)	NS
Moderate OHSS (n,%)	9 (47.4)	8 (57.1)	10 (71.4)	NS
Severe OHSS (n,%)	4 (21)	3 (21.4)	1(7.1)	NS

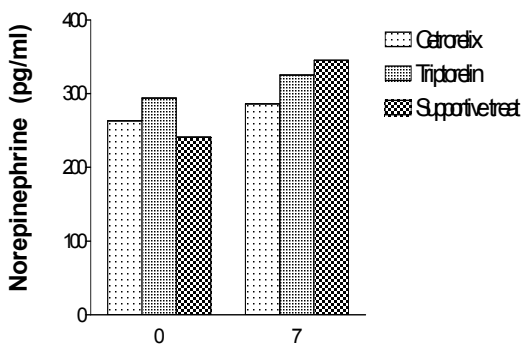
[a] Hematocrit > 45 %
[b] Creatinine > 1.2 mg/dl
[c] AST or ALT > 40 U/ml

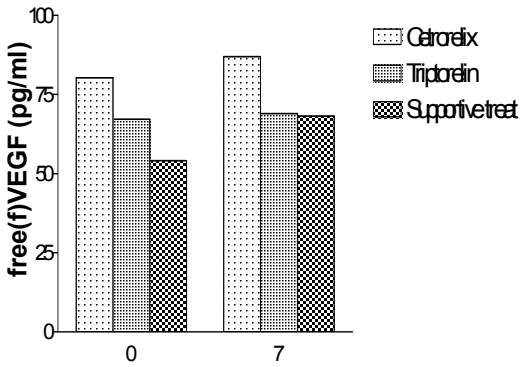
Results: Hormonal measurements at baseline and 7 days after hCG in the three groups of patients











CONCLUSIONS

✓ The use of GnRH analogues in the luteal phase of cycles at risk **does not decrease** the incidence of OHSS

✓ According to the results of our study antagonists exert a **luteolytic effect** greater than agonists, but no correlation with other hormonal and vasoactive parameters was observed in the luteal phase

✓ More studies are needed to study whether the luteolytic effect may be greater with **higher doses** of antagonists

Antagonistes GnRH en fase lútea: conclusions

→ Evidència limitada

- Estratègia per evitar la cancelació de la transferència embrionària en la majoria de pacients d'alt risc (88.7%)

- Regresió ràpida de SHO severa a moderada, millora de símptomes i de signes ecogràfics i de laboratori

- Produeixen major grau de luteolisi respecte agonistes GnRH

Administració en pacients de risc per a la prevenció de SHO???

Seguretat dels antagonistes GnRH en fase lútea en cicles amb transferència en fresc???

Conclusions globals

Agonistes dopamina:

- Mecanisme d'acció conegut. No alteració d'angiogènesi / implantació
- Prevenció de la SHO moderada i de la SHO precoç
- No prevenció de la SHO tardana

Inhibidors de l'aromatasa:

- Concepte pendent d'evaluar: prevenció de les complicacions derivades de l'hiperestrogenisme (fenòmens tromboembòlics / SHO) ???

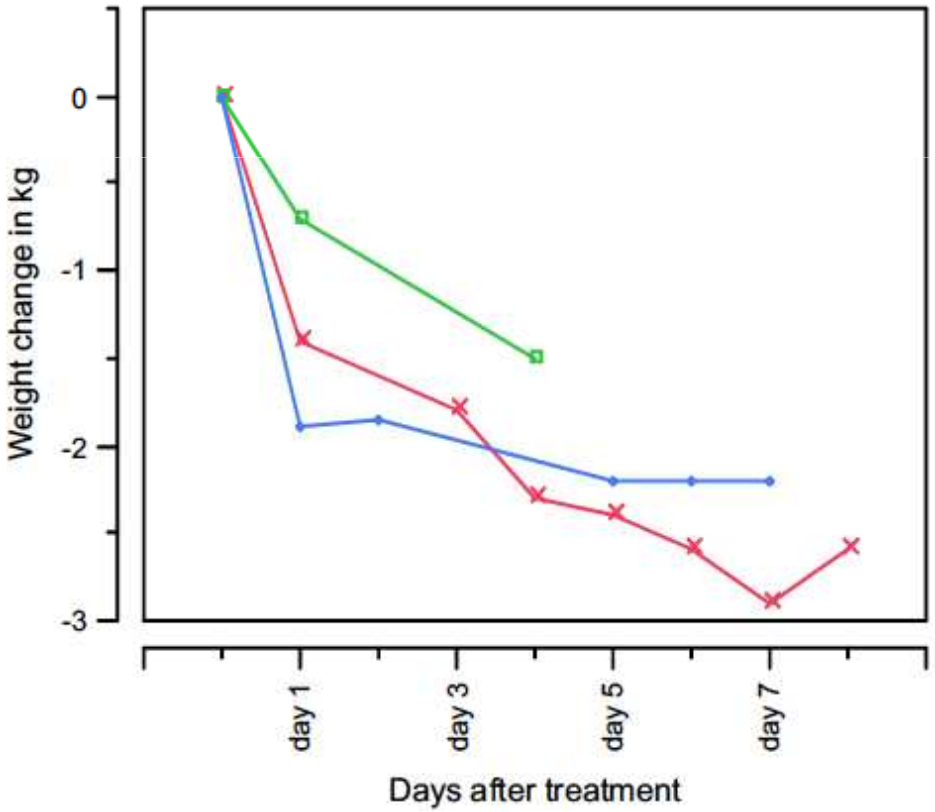
Antagonistes GnRH:

- Estratègia per evitar la cancelació de la transferència embrionària en la majoria de pacients d'alt risc (88.7%)
- Regresió ràpida de SHO severa a moderada
- Ús en pacients d'alt risc per prevenir SHO?? Ús en cicles amb TE fresc??

Combinació d'estratègies preventives

4 pacients amb diagnòstic de SHO previ a transferència embrionària

CP embrionària + cabergolina 0.5 mg/dia (7d) + ganirelix 250mcg sc/dia



Rollene et al. Fertil Steril, 2009

TABLE 3

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

Note: RCT = randomized controlled trial. Hierarchy of evidence: 1a = systematic review and meta-analysis of RCTs; 1b = at least one RCT; 2a = at least one well-designed controlled study without randomization; 2b = at least one other type of well-designed quasi-experimental study; 3 = well-designed nonexperimental descriptive studies, e.g., comparative studies, correlation studies, case studies; 4 = expert commentary reports or opinions and/or clinical experience of respected authorities.

Humaidan. Prevention strategies for OHSS. Fertil Steril 2010.