Benefits of GnRH agonist triggering in oocyte donation cycles

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Conflict of interest: none

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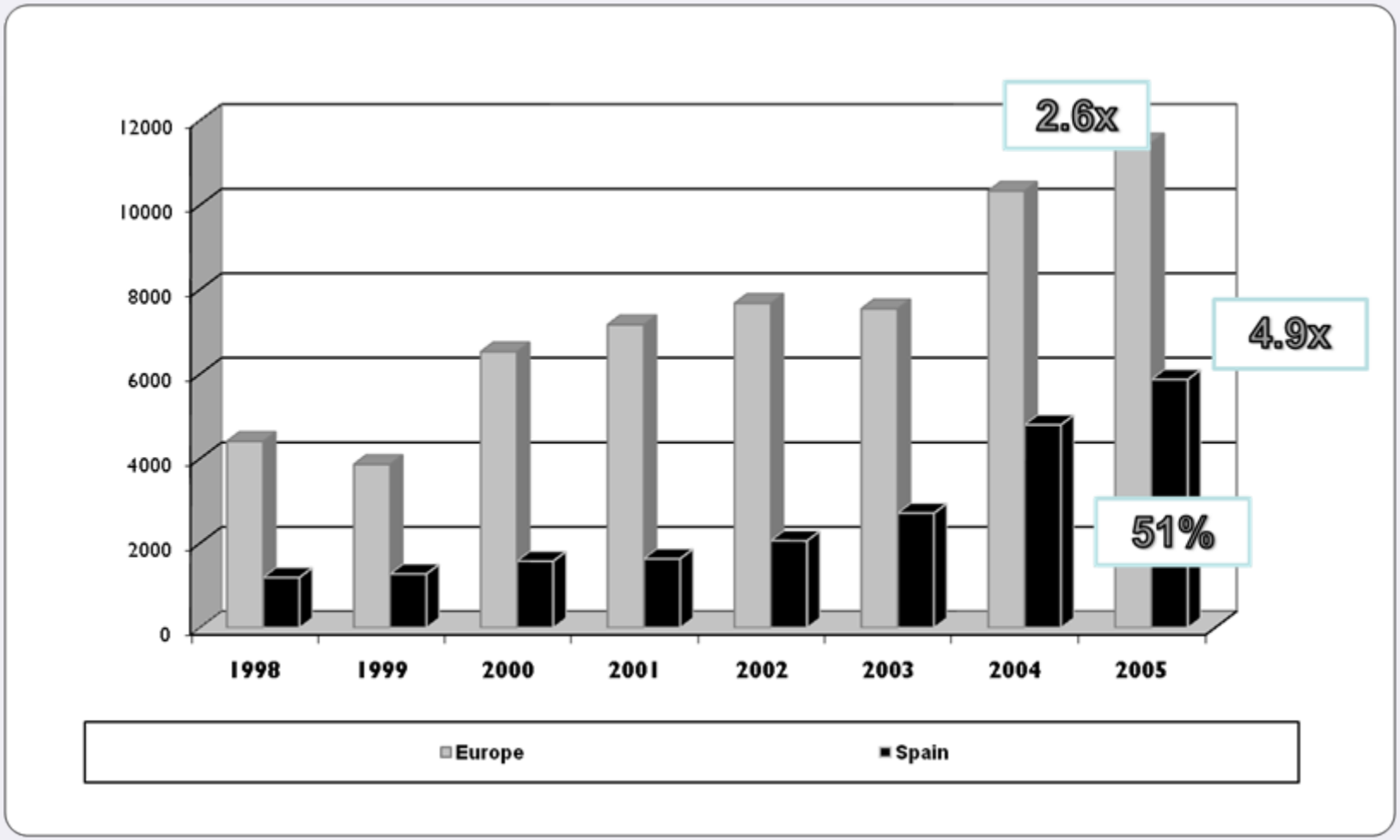
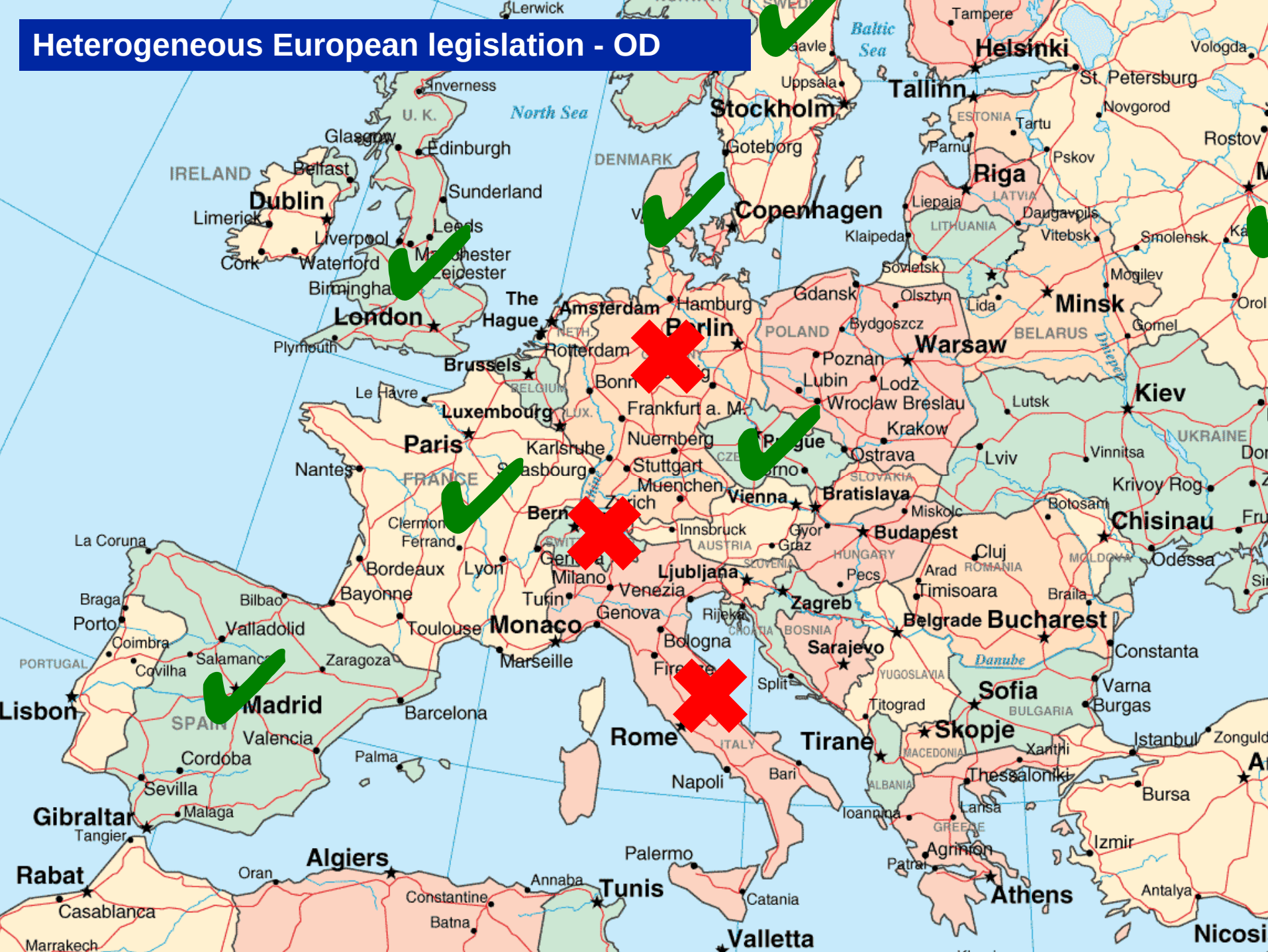
Outline

- Oocyte donation's worldwide evolution
- Donor complications
- Which is the ideal stimulation protocol for oocyte donors?
- GnRH antagonist protocol
- GnRH agonist triggering
- Practical consequences
- Oocyte donation guidelines
- Future directions
- Conclusion

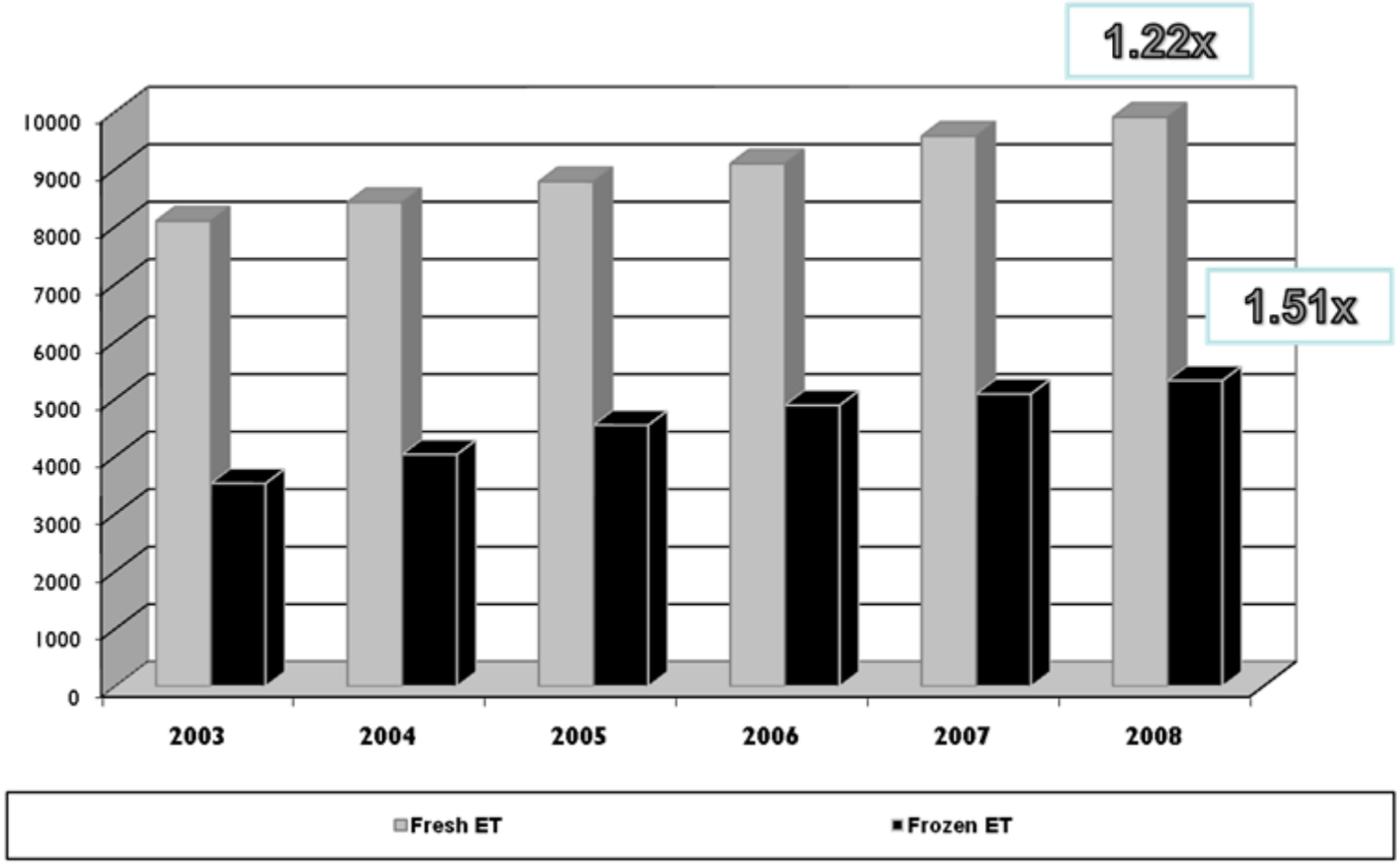
- Oocyte donation is on the rise in Europe *(ESHRE register)*



Heterogeneous European legislation - OD



- Oocyte donation is also on the rise in the US *(SART register)*



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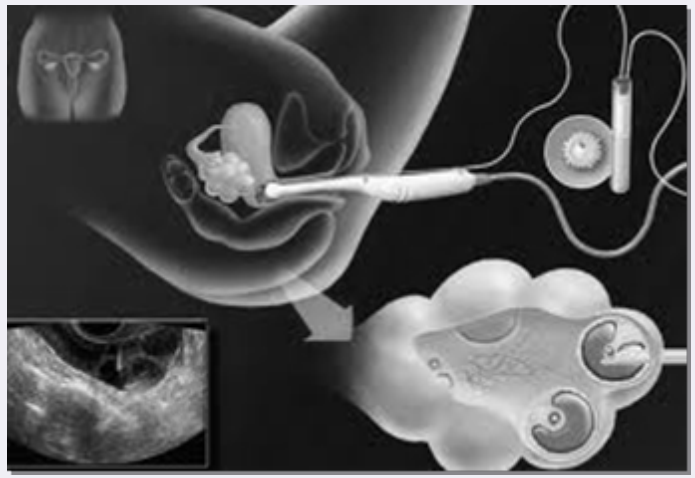
Donor complications – Oocyte retrieval

- Serious and minor complications in oocyte donors *(Maxwell 2007)*
  0.7% (6/886) serious complications
  (moderate OHSS, ovarian torsion, cyst rupture)
  8.5% (75/886) minor complications
  (mild-moderate OHSS, self-limiting intraabdominal bleeding, other)

- Complications related to **oocyte retrieval** *(Bodri 2008)*
  0.42% (17/4052)

Intra-abdominal bleeding:	14 (6 op.)
Severe pain:	2
Ovarian torsion:	1 (op.)



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Donor complications - OHSS

- Lower OHSS risk (only **early-onset**) no pregnancy *(Sauer 1996, 2001)*
- Young women who are screened to have a **high ovarian reserve** *(Melo 2008)*
- Oocyte donation programme based on **long GnRH agonist** protocol *(Melo 2009)*

TABLE 1

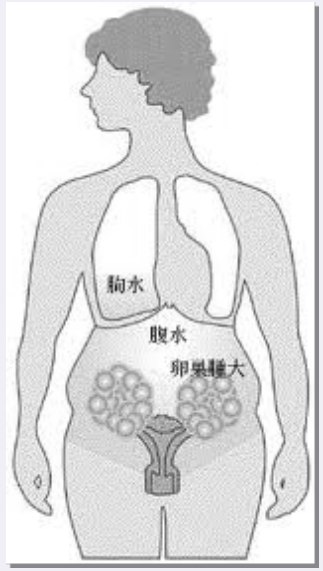
Oocyte donor characteristics and controlled ovarian stimulation parameters.

	Group 1, rFSH	Group 2, HP-hMG	Group 3, rFSH + HP-hMG	*P* value
No.	346	333	349	
Age (y)	24.9 ± 2.8	23.9 ± 3.7	23.2 ± 3.4	NS
BMI (kg/m^2)	22.5 ± 2.9	23.9 ± 3.1	23.7 ± 2.5	NS
Antral follicle count (mean ± SD)	16.3 ± 5.2	17.1 ± 3.9	17.5 ± 3.5	NS
Days of stimulation (mean ± SD)	10.4 ± 0.8	10.6 ± 0.7	10.5 ± 1.0	NS
Gonadotropin dose (IU) (mean ± SD)	2,500 ± 240	2,450 ± 310	2,350 ± 210	NS
E_2 level—hCG day (pg/mL) (mean ± SD)	2,850 ± 740	2,710 ± 690	2,740 ± 810	NS
P level—hCG day (ng/mL) (mean ± SD)	1.01 ± 0.4	0.9 ± 0.3	0.9 ± 0.3	NS
Oocytes retrieved (mean ± SD)	19.3 ± 7.2	18.7 ± 6.4	19.5 ± 7.0	NS
Cancellation rate (%)	62/346 (18)	53/333 (16)	59/349 (17)	NS
Oocyte pickup (%)	284/346 (82)	280/333 (84)	290/349 (83)	NS
Mild and moderate OHSS rate (%)	20/284 (7.04)	19/280 (6.78)	16/290 (5.52)	NS
Severe OHSS rate (%)	—	—	—	

Melo. Gonadotropin regimens and IVF outcome. Fertil Steril 2009.

Donor complications - OHSS

- Lower OHSS risk (OR: 0.46-0.60) with **GnRH antagonists** in IVF patients *(Kolibianakis 2006, Al-Inany 2007)*
- OHSS risk in GnRH antagonist-treated IVF patients *(Papanikolaou 2006)*
  2.524 cycles in 1801 patients
  early-onset OHSS in 31 patients (**1.2%**)
  late-onset OHSS in 22 patients (0.9%)
- OHSS risk in GnRH antagonist-treated donors *(Bodri 2008)*
  1.031 cycles triggered with hCG
  early-onset OHSS in 13 patients (**1.26%**)



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Which is the ideal stimulation protocol for donors?

Protocol type / trigger type	Advantages	Drawbacks
Long GnRH agonist / **hCG**	Depot agonist	**OHSS risk** Longer duration Side effects
Short GnRH agonist / **hCG**	Less gonadotropin requirement (flare-up)	**OHSS risk**
GnRH antagonist / **GnRHa**	**No OHSS** Shorter duration Depot antagonist	Higher cost
No GnRH analogue or extended CC / **GnRHa**	**No OHSS** Shorter duration less expensive	LH surge? Oocyte quality?

GnRH agonists (short flare-up)

- RCT: 118 egg donors *(Bodri 2006)*

Table I. Description of donors and donor cycle outcomes

	GnRH antagonist	GnRH agonist	*P*
Number	58	55	–
Age (years)	25.9 ± 3.3	24.7 ± 3.4	0.065[a]
BMI	22.6 ± 2.8	22.6 ± 3.0	0.92[a]
Basal FSH (IU/ml)	6.8 ± 1.5	7.3 ± 1.5	0.062[a]
Days of stimulation[b]	9.9 ± 1.6	10.2 ± 2.1	0.32[a]
Total rFSH (IU) used[b]	2179 ± 367	1828 ± 459	<0.0001[a]
Days of antagonist/agonist administration	5.6 ± 1.7	13.3 ± 2.1	–
Estradiol on the day of HCG (pg/ml)	2428 ± 1318	4634 ± 1903	<0.0001[a]
COC retrieved[c]	11.6 ± 6.8	12.1 ± 6.7	0.69[a]
Mature oocytes retrieved[c]	8.4 ± 4.4	8.9 ± 5.3	0.52[a]
Proportion of mature oocytes[b] (%)	70.8 ± 23.8	75.7 ± 14	0.20[a]

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GnRH agonists (short flare-up)

Table III. Recipient outcome

	GnRH antagonist	GnRH agonist	*P*
Embryo replacements (*n*)	86	76	–
Transferred embryos per recipient mean ± SD	1.92 ± 0.38	1.92 ± 0.39	0.97[a]
Quality of transferred embryos			
Grade 1 [*n* (%)]	54/165 (32.7)	49/146 (33.6)	0.252[b]
Grade 2 [*n* (%)]	37/165 (22.4)	39/146 (26.7)	
Grade 3 [*n* (%)]	18/165 (10.9)	22/146 (15.1)	
Grade 4 [*n* (%)]	50/165 (30.3)	31/146 (21.2)	
Clinical pregnancy rate[c,d] [*n* (%)]	35/87 (40.2) (30.5–50.7)	36/79 (45.6) (35.0–56.5)	0.66[b]
Clinical pregnancy rate[e,d] [*n* (%)]	35/58 (60.3) (47.4–71.9)	36/55 (65.4) (52.2–76.6)	0.78[b]
Implantation rate[d] [*n* (%)]	43/165 (26.1) (19.9–33.2)	44/146 (30.1) (23.2–38.0)	0.54[b]
Miscarriage rate[d] [*n* (%)]	7/35 (20) (10.0–35.9)	6/36 (16.7) (7.9–31.9)	0.76[b]
Ongoing pregnancy rate[c,d] [*n* (%)]	28/87 (32.2) (23.3–42.6)	30/79 (37.9) (28.1–49.0)	0.58[b]
Ongoing pregnancy rate[e,d] [*n* (%)]	28/58 (48.3) (35.9–60.8)	30/55 (54.5) (41.5–66.9)	0.70[b]
Twins[d] [*n* (%)]	8/35 (22.9) (12.1–39.0)	8/36 (22.2) (11.7–38.1)	0.95[b]
Triplets	0	0	–

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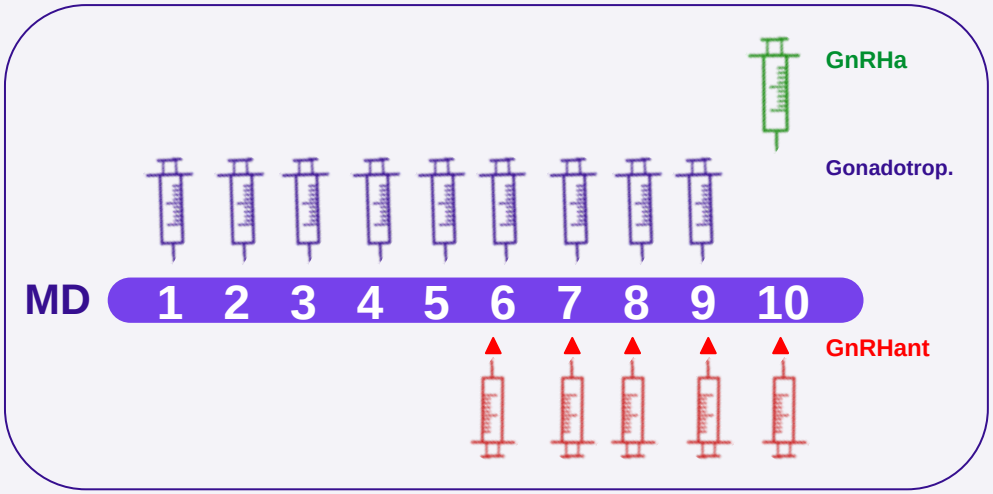
GnRH antagonists - publications

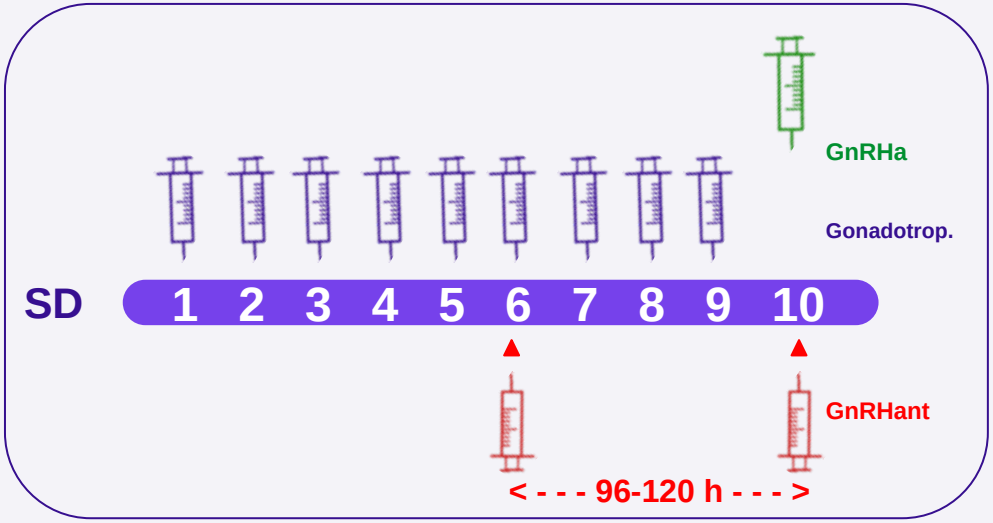
- First descriptions *(Meldrum 1994, Sauer 1997)*
- Small retrospective series *(Thong 2003, Lindheim 2003, Vlahos 2005)*
- LH supplementation *(Acevedo 2004)*

- GnRH short agonist versus antagonist *(Bodri 2006, Wei 2010)*
- GnRH long agonist versus antagonist *(Prapas 2005, Martínez 2008, 2010)*
- Depot GnRH antagonist - 3 mg *(Erb 2008, Martínez 2010)*

- Meta-analysis *(Bodri 2010)*

Single-dose GnRH antagonist protocol





Achieving a single antagonist injection in 61-90% of cycles

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Single-dose GnRH antagonist protocol

TABLE 1

Characteristics of egg donors and response to stimulation treatment and corresponding recipients and outcomes.

Egg donor	Group DI (n = 44)	Group DII (n = 40)
Age	28.4 ± 4.2	27.9 ± 3.8
BMI	21.3 ± 2.7	22.9 ± 2.6
Baseline FSH	6.2 ± 1.9	5.1 ± 1.1
Antral follicle count	13.8 ± 4.5	14.4 ± 4.3
Dose of hpHMG, IU	2,021 ± 671	2,172 ± 568
Dose of rFSH, IU	1,726 ± 430	1720 ± 501
Days of stimulation	10.7 ± 1.7	11.2 ± 1.2
E_2 level on day of hCG, pg/mL	1,986 ± 1,051	2,449 ± 1,091
No. of oocytes retrieved	14.0 ± 5.7	16.3 ± 6.8
Cancellation rate, %	29.5 (13/44)	20.0 (8/40)
Recipient	**Group RI (n = 31)**	**Group RII (n = 30)**
Age	40.95 ± 5.29	40.83 ± 4.96
BMI	21.64 ± 2.3	22.02 ± 2.13
E_2, pg/mlL	171.8 ± 6.52	224.0 ± 166
P, ng/mL	15.43 ± 6.52	15.25 ± 10.52
Endometrial thickness, mm	10.97 ± 2.64	11.55 ± 4.04
No. of oocytes inseminated	9.74 ± 3.24	10.70 ± 4.96
Fertilization rate, %	76.4	74.9
No. of embryos transferred	1.97 ± 0.30	1.97 ± 0.32
Score for embryo quality	7.32 ± 1.23	7.04 ± 1.34
Pregnancy rate per transfer, %	71.0 (22/31)	46.7 (14/30)
Implantation rate, %	42.3 (25/59)	30.5 (18/59)

Pilot RCT: 84 donors
(Martínez 2010)

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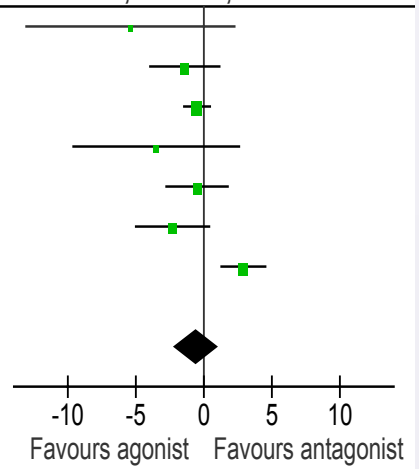
OD meta-analysis *(Bodri 2010)*

Study or Subgroup	GnRH antagonist Mean	SD	Total	GnRH agonist Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Shamma 2003	20.5	9.8	12	25.9	11.1	17	4.0%	-5.40 [-13.05, 2.25]	2003
Lan 2004	14.9	8.3	98	16.3	11.1	124	15.6%	-1.40 [-3.95, 1.15]	2004
Prapas 2005	13.8	3.2	73	14.3	2.7	75	22.8%	-0.50 [-1.46, 0.46]	2005
Shamma 2006	25.4	9.2	31	28.9	13.7	27	5.7%	-3.50 [-9.60, 2.60]	2006
Bodri 2006	11.6	5.8	60	12.1	6.7	58	16.9%	-0.50 [-2.76, 1.76]	2006
Martínez 2008b	14	5.7	44	16.3	6.8	40	15.0%	-2.30 [-5.00, 0.40]	2008
Martínez 2008a	17.9	8.6	163	15	6.1	160	20.0%	2.90 [1.28, 4.52]	2008
Total (95% CI)			**481**			**501**	**100.0%**	**-0.60 [-2.26, 1.07]**	

Heterogeneity: Tau² = 2.91; Chi² = 20.49, df = 6 (P = 0.002); I² = 71%

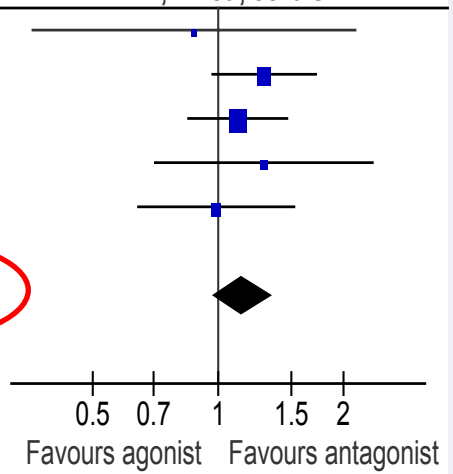
Test for overall effect: Z = 0.70 (P = 0.48)



Study or Subgroup	GnRH antagonist Events	Total	GnRH agonist Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bodri 2006	7	33	8	33	5.3%	0.88 [0.36, 2.14]
Lan 2004	51	98	50	124	29.3%	1.29 [0.97, 1.72]
Martínez 2008a	67	163	59	160	39.5%	1.11 [0.85, 1.47]
Martínez 2008b	17	44	12	40	8.3%	1.29 [0.71, 2.35]
Prapas 2005	26	73	27	75	17.7%	0.99 [0.64, 1.52]
Total (95% CI)		**411**		**432**	**100.0%**	**1.15 [0.97, 1.36]**
Total events	168		156			

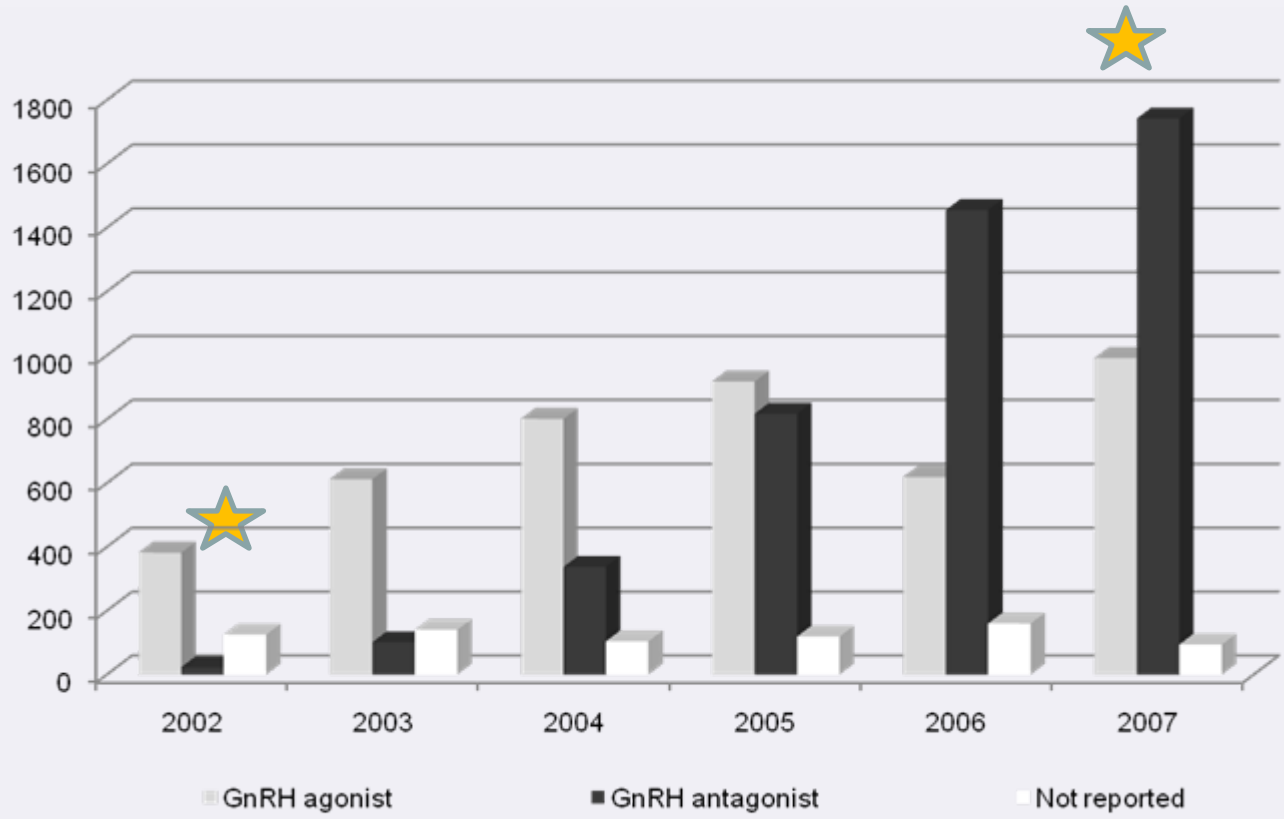
Heterogeneity: Chi² = 1.64, df = 4 (P = 0.80); I² = 0%

Test for overall effect: Z = 1.57 (P = 0.12)



IVF registry data from Catalonia, Spain (2002-2007)

- Increase of GnRH antagonist-treated donor cycles (4.3 to 65,1%)



GnRH agonist triggering

- Comparable proportion of mature oocytes and fertilization rates *(Bodri 2008)*

TABLE 1

Description of donor cycles according to the triggering agent.

Triggering agent	rhCG	GnRH agonist	*P*
No. of cycles	624	547	—
Mean donor age	26.5 ± 4.1	25.5 ± 4.1	<.0001[a]
Days of stimulation	10 ± 1.68	9.9 ± 1.5	.61[a]
Total FSH used, IU	2256 ± 536	2175 ± 529	.1[a]
Final E_2 level, pg/mL	2241 ± 1099	3128 ± 1520	<.0001[a]
No. of follicles ≥18 mm	3.1 ± 1.8	4.1 ± 2.6	<.0001[a]
No. of follicles ≥16 mm	6.0 ± 2.5	8.5 ± 3.6	<.0001[a]
No. of follicles ≥14 mm	9.2 ± 3.8	13.5 ± 4.9	<.0001[a]
No. of follicles ≥10 mm	14.5 ± 6.1	21.5 ± 7.4	<.0001[a]
No oocytes retrieved, n (%)	3 (0.48%)	6 (1.09%)	.23[b]
No attributed recipient (≤2 MII oocytes) n, (%)	86 (13.7%)	36 (6.5%)	.0002[b]
Retrieved oocytes (COC)	9.8 ± 5.8	13.6 ± 7.3	<.0001[a]
Mature (MII) oocytes	6.9 ± 4.3	9.2 ± 4.8	<.0001[a]
Proportion of MII oocytes (%)	69.6 ± 24.1	68.9 ± 18	.56[a]
Fertilized (2PN) oocytes	5.1 ± 3.2	6.8 ± 3.8	<.0001[a]
Fertilization rate (%)	65 ± 24	69 ± 20.1	.003[a]
Fertilization failure, n (%)	9 (1.67%)	5 (0.97%)	.33[b]

Note: Values are mean ± SD.
[a] Independent *t*-test.
[b] χ^2-square test.

Bodri. GnRHa versus hCG trigger in donor cycles. Fertil Steril 2008.

GnRH agonist triggering

- Comparable recipient pregnancy rates *(Bodri 2008)*

TABLE 2

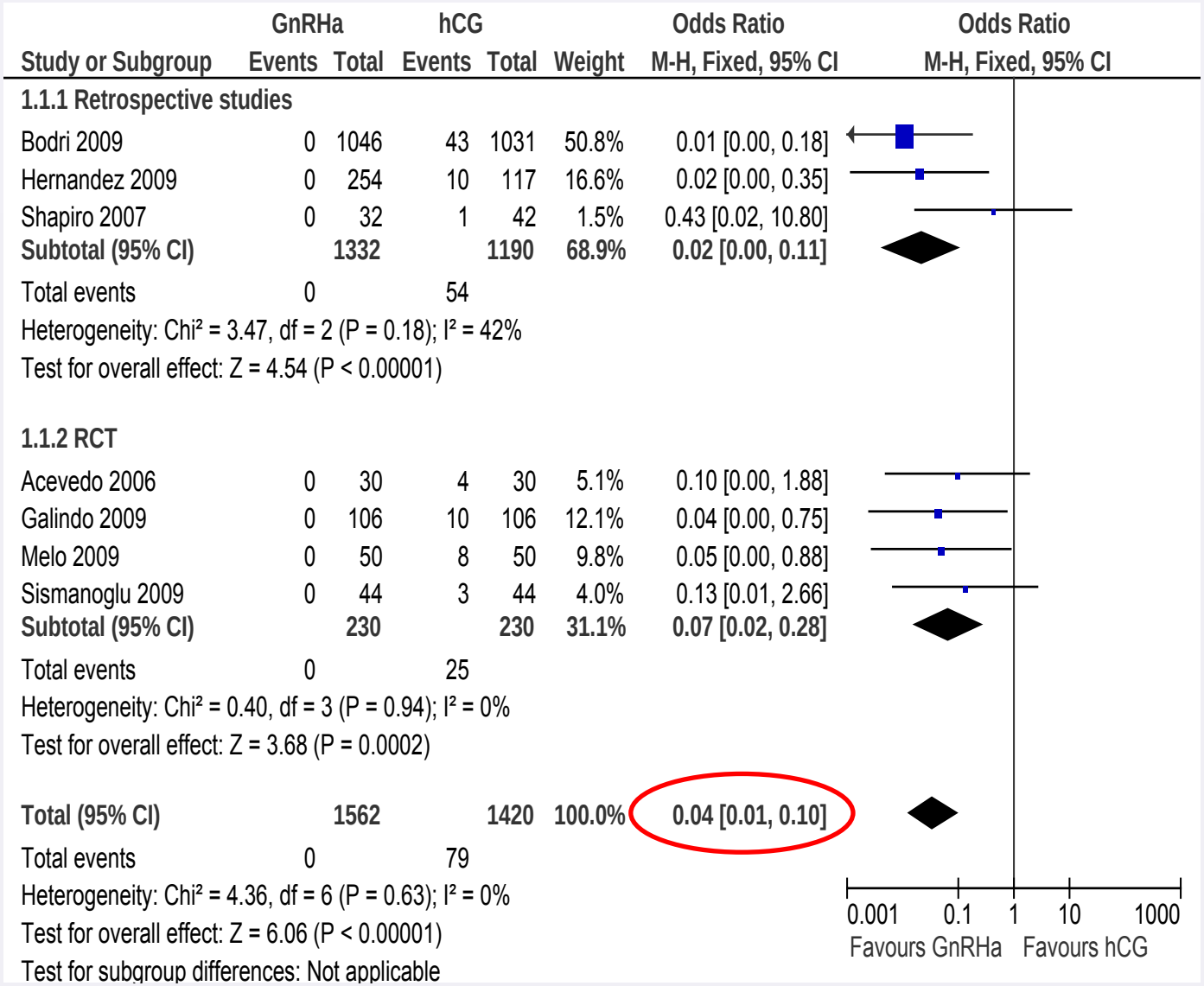
Recipient outcome.

	rhCG	GnRH agonist	*P*
Number of allocated recipients, n	763	878	—
Cancelled cycles, n	45	38	.16[a]
Embryo replacements, n	718	840	—
Transferred embryos per recipient, mean ± SD	1.93 ± 0.4	1.93 ± 0.32	.87[b]
Mean embryo score, mean ± SD[c]	8.5 ± 1.2	8.6 ± 1.1	.3[b]
Clinical pregnancy rate,[d] n (%) (95% CI)	305/718 (42.4) (38.9–46.1)	326/840 (38.8) (35.5–42.1)	.33[a]
Implantation rate,[e] n (%) (95% CI)	404/1386 (29.1) (26.8–31.6)	421/1624 (25.9) (23.8–28.1)	0.13[a]
Miscarriage rate n (%) (95% CI)	55/305 (18) (14.1–22.7)	56/326 (17.1) (13.4–21.6)	.81[a]
Ongoing pregnancy rate,[d] n (%) (95% CI)	250/718 (34.8) (31.4–38.3)	270/840 (32.1) (29–35.3)	.43[a]
Twins,[e] n (%) (95% CI)	93/305 (30.4) (25.5–35.8)	93/326 (28.5) (23.9–33.6)	.69[a]
Triplets,[e] n (%) (95% CI)	3/305 (0.98) (0.34–2.85)	1/326 (0.31) (0.05–1.72)	.28[a]

[a] χ^2-square test.
[b] Independent *t*-test.
[c] To calculate the mean embryo score, only cleavage-stage embryos (day 2–3) were taken into account (out of 3010 embryos, 43 compacted embryos and four blastocysts could not be scored with the combined embryo score).
[d] Per ET.
[e] According to gestational sacs observed at the sixth – seventh gestational week's ultrasound scan.

Bodri. GnRHa versus hCG trigger in donor cycles. Fertil Steril 2008.

- "Reduced" OHSS incidence after GnRHa triggering



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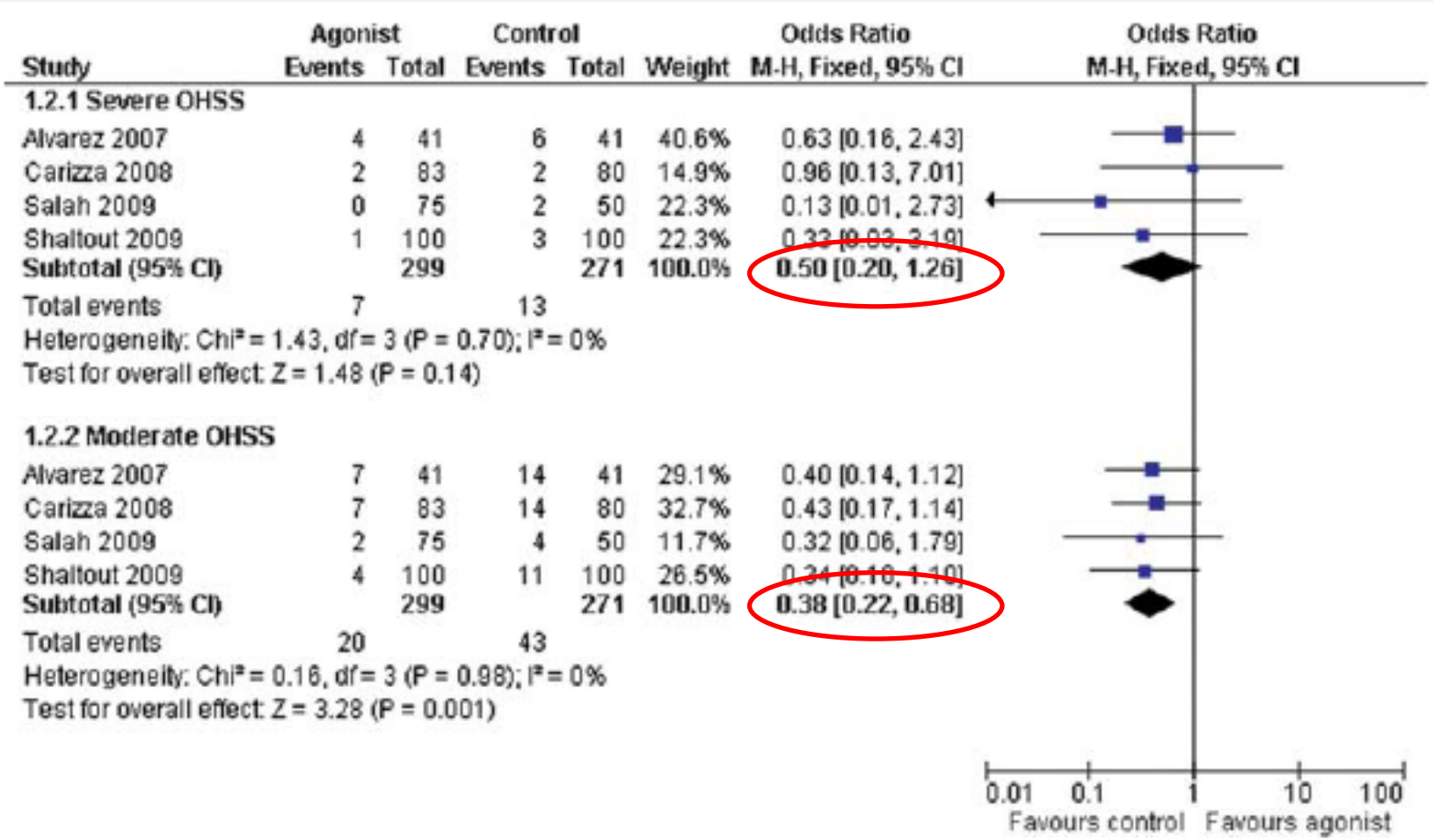
Dopamine agonists meta-analysis *(Youssef 2010)*



Study	Agonist Events	Agonist Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.2.1 Severe OHSS						
Alvarez 2007	4	41	6	41	40.6%	0.63 [0.16, 2.43]
Carizza 2008	2	83	2	80	14.9%	0.96 [0.13, 7.01]
Salah 2009	0	75	2	50	22.3%	0.13 [0.01, 2.73]
Shaltout 2009	1	100	3	100	22.3%	0.33 [0.03, 3.19]
Subtotal (95% CI)		**299**		**271**	**100.0%**	**0.50 [0.20, 1.26]**
Total events	7		13			
Heterogeneity: Chi² = 1.43, df = 3 (P = 0.70); I² = 0%						
Test for overall effect: Z = 1.48 (P = 0.14)						
1.2.2 Moderate OHSS						
Alvarez 2007	7	41	14	41	29.1%	0.40 [0.14, 1.12]
Carizza 2008	7	83	14	80	32.7%	0.43 [0.17, 1.14]
Salah 2009	2	75	4	50	11.7%	0.32 [0.06, 1.79]
Shaltout 2009	4	100	11	100	26.5%	0.34 [0.10, 1.10]
Subtotal (95% CI)		**299**		**271**	**100.0%**	**0.38 [0.22, 0.68]**
Total events	20		43			
Heterogeneity: Chi² = 0.16, df = 3 (P = 0.98); I² = 0%						
Test for overall effect: Z = 3.28 (P = 0.001)						

Early ovarian hyperstimulation syndrome is completely prevented by gonadotropin releasing-hormone agonist triggering in high-risk oocyte donor cycles: a prospective, luteal-phase follow-up study

- Prospective, observational study
- 102 egg donors at high OHSS risk
- Study period: April -September 2008
- Institutional Review Board approval

High OHSS risk

≥ 20 follicles ≥10 and/or E2 ≥4000 pg/ml and/or ≥20 retrieved COC

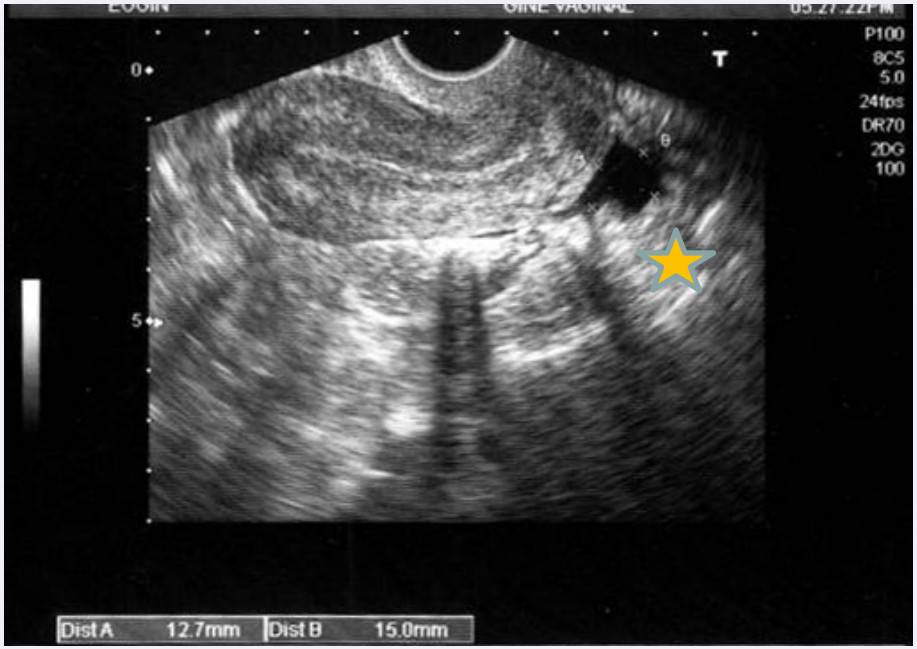
No preventive measures (coasting, iv. albumin administration)

GnRH agonist triggering

- **NO** moderate/severe OHSS cases

- Seven patients (6.8%) – transient pain and moderate abdominal distension *(without any concomitant biochemical or ultrasound sign of OHSS)*

- No ascitis - Douglas fluid pocket 3.1±3.8 cm^2
- Ovarian diameter 49.7±10.7 mm (right) mm 46.9±9 mm (left)



GnRH agonist triggering

TABLE 1

Donor cycles and luteal phase follow-up evaluation.

	Mean ± standard deviation	Range
Mean donor age (years)	25.9 ± 4.4	18–35
Starting FSH dose (IU)	203.0 ± 35.0	112.5–300
Days of stimulation	10.1 ± 1.3	7–15
Total FSH (IU) used	1983.0 ± 476.0	1012.5–3375
Final estradiol level (pg/mL)	3337.0 ± 1825.0	143–8474
Number of follicles ≥10 mm	25.1 ± 6.2	13–42
Retrieved oocytes (COC)	19.8 ± 7.2	5–40
Basal hematocrit	39.7 ± 2.5[a]	34.1–45.7
Luteal phase hematocrit	37.7 ± 2.8[a]	26.5–46.4
Luteal leukocytes	7880.0 ± 1980.0	4240–13580
Serum ALAT (IU/mL)	20.0 ± 7.0	7–104
Serum ASAT (IU/mL)	16.0 ± 8.0	9–60
Serum creatinine	0.8 ± 0.1	0.6–1.1
Diameter, right ovary (mm)	49.7 ± 10.9	29.5–79
Diameter, left ovary (mm)	48.9 ± 9.0	28–71
Douglas pouch fluid pocket (cm^2)	3.1 ± 3.8	0–19.6

[a] Independent *t*-test ($P=.0001$).

Bodri. Correspondence. Fertil Steril 2009.

GnRH agonist triggering

Massive and irreversible luteolysis after GnRHa triggering *(Kol 2004)*

Completely prevents early-onset OHSS

(absence of hemoconcentration and pelvic fluid accumulation)

However in a few patients - some milder symptoms

(related to the oocyte retrieval and/or a high ovarian response)

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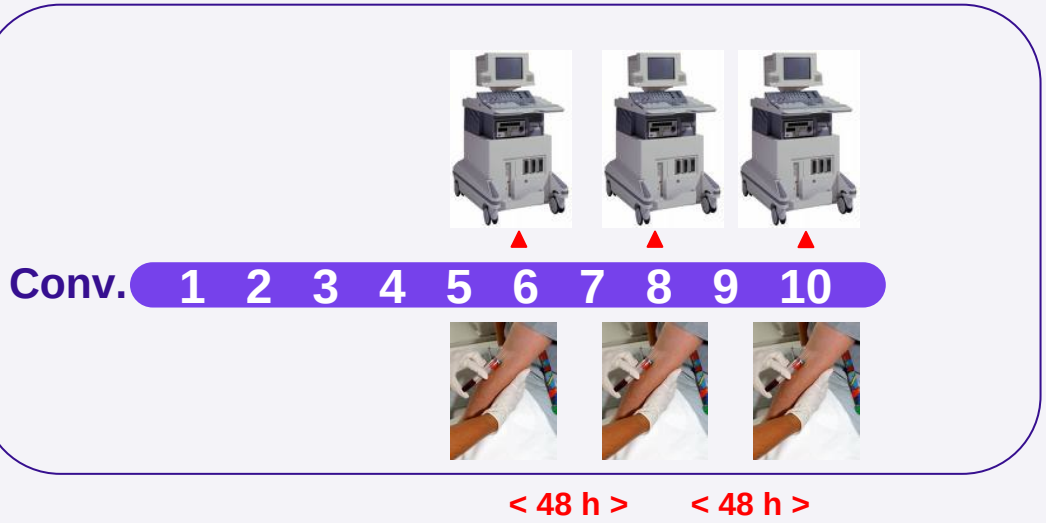
Practical consequences

- No coasting or cycle cancellation *(Hernández 2009)*
- Simpler cycle monitoring
- Reduced workload, improved cost-effectiveness
- Better safety record
- OHSS-free OD programme *(Bodri 2008)*
- Improved donor commodity, shortened luteal phase *(Cerillo 2008)*

Practical consequences



Simplification of monitoring:

Less or no E2 assays
Longer control intervals
More flexible OPU scheduling (+ 1 day)

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Complications related to ovarian stimulation and oocyte retrieval in 4052 oocyte donor cycles

Table 2. The incidence of moderate/severe ovarian hyperstimulation syndrome (OHSS) according to the stimulation protocol and triggering agent used in donor oocyte cycles.

Stimulation protocol/triggering agent	*No. of cycles*	*Moderate/ severe OHSS (n)*	*Incidence % (95% CI)*
GnRH agonist/HCG	1238	8	0.65[a] (0.33–1.27)
GnRH antagonist/HCG	1295	14	1.08[a] (0.64–1.80)
GnRH antagonist/GnRH agonist	1519	0	0 (0–0.25)

[a]Chi-squared test (not statistically significant).
CI = confidence interval; GnRH = gonadotrophin-releasing hormone; HCG = human chorionic gonadotrophin.

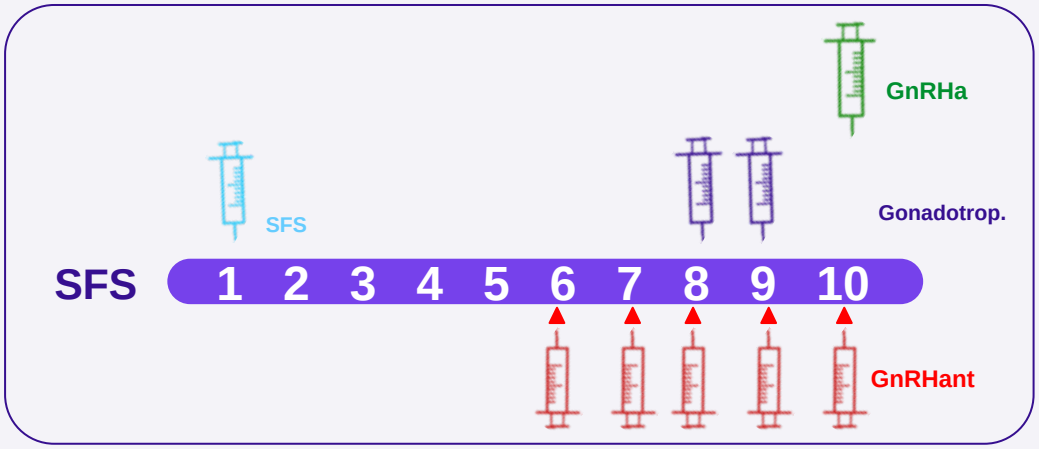
Guidelines

- **ESHRE 2002**: recruitment, screening, payment, informed consent
- **HFEA 8th Code of practice (UK)**: donor recruitment, assessment, screening, 10 family limit
- **ASRM 2008:** donor screening and testing, payment, repetitive OD, informed consent

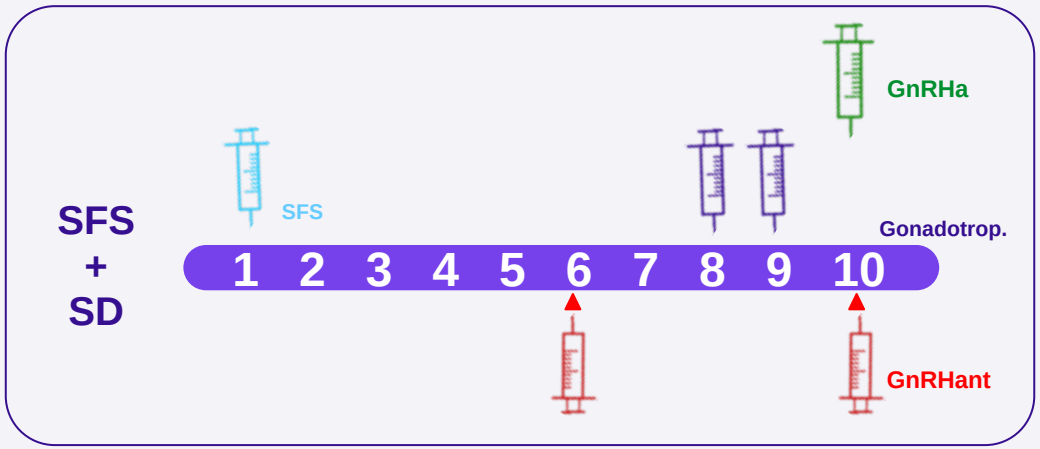
  "involves significant inconvenience, discomfort and risks for the oocyte donor"

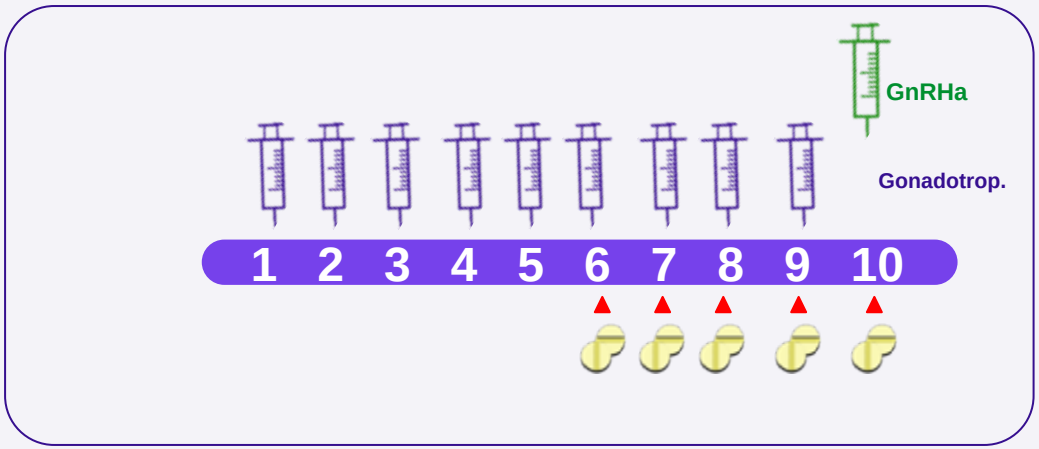
No specific recommendation to donor management or stimulation protocols

Future directions



Long acting drugs (SFS, depot antagonist)





Oral compounds (oral LMW FSH/LH agonists, CC)

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GnRH antagonist protocol coupled with GnRHa triggering

- **Efficient**
- **Safe**
- **Simple**

1st choice treatment for oocyte donors

Thank you for your attention

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