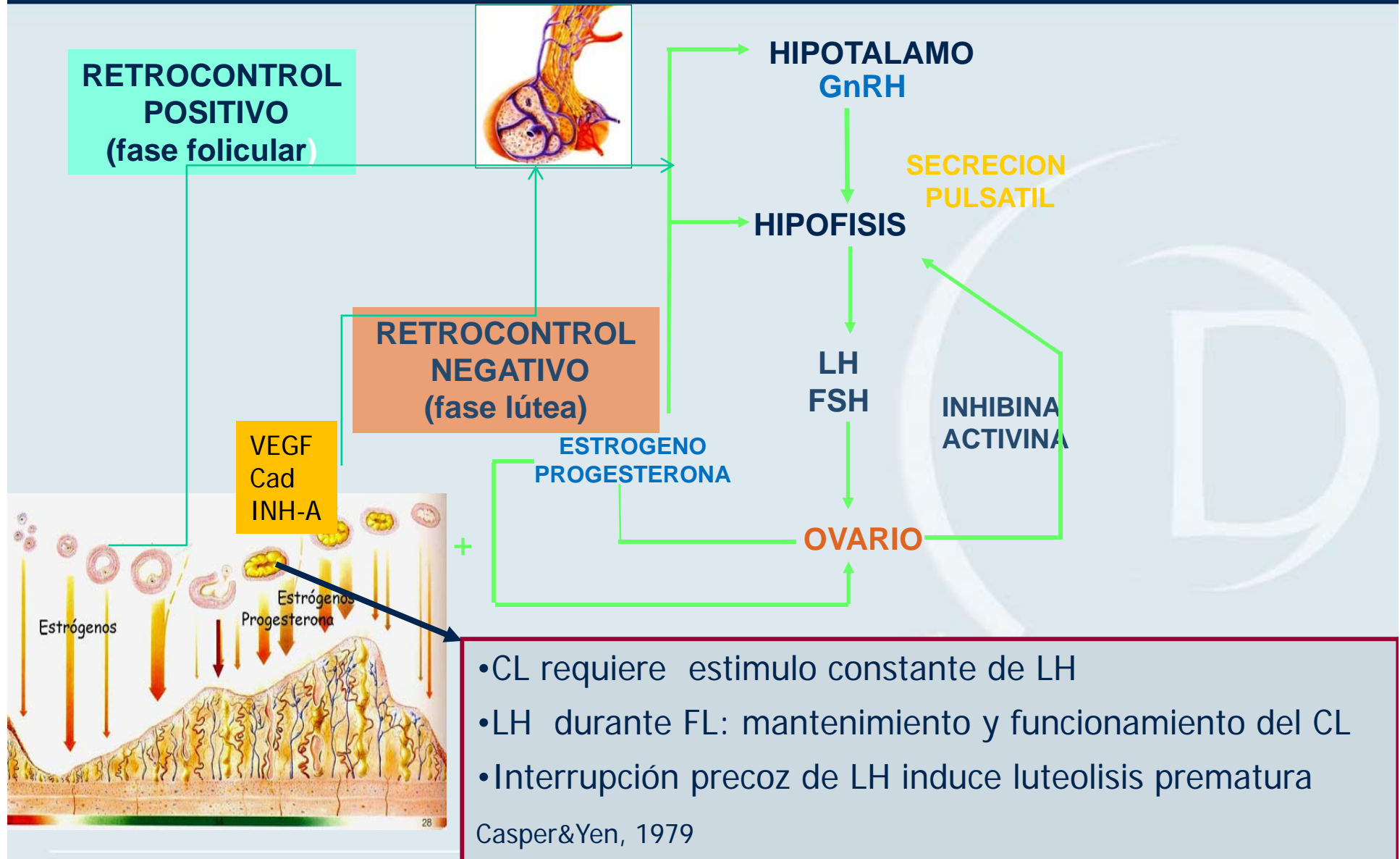


# Fase lútea en FIV tras bolo de GnRH

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**Servicio de Medicina de la Reproducción**

# Fase lútea en FIV



# Fase lútea en FIV

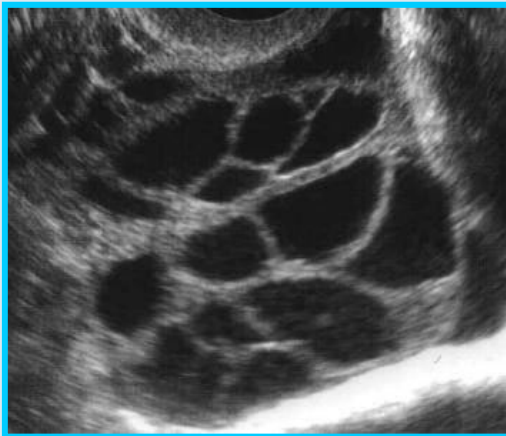
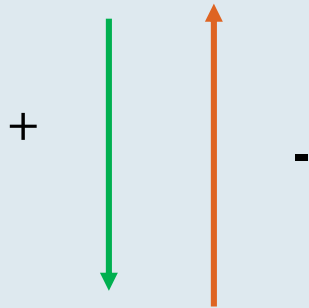
- La P producida por el CL es esencial para embarazo hasta 7s
- Lutectomía antes de 7 s aborto, evitable con P exógena
  - Csapo et al, 1972

## Fase Lútea Deficiente en los ciclos estimulados:

- No relación con el análogo
- En ciclos de IAC con gns con o sin antagonista, no efecto deletéreo del antag en los niveles de P ni en la duración de la FL
  - Ragni et al, 2001

# Fase lútea en FIV

## Fase Lútea Deficiente en los ciclos estimulados



- Desarrollo multifolicular y **niveles suprafisiológicos de esteroides** secretados por los múltiples CLs durante la fase lútea precoz que inhiben la liberación de LH vía **retroalimentación negativa** del eje Hipotálamo-hipofisario

- Fauser y Devroey, 2003
- Fatemi et al HRU, 2007

# Fase lútea en FIV

- En FIV y descarga con hCG está demostrado el beneficio de suplementar la FL en el período comprendido entre la desaparición de la hCG preovulatoria exógena y el aumento de la hCG del embrión implantado

Andersen et al, 2002

- HCG preovulatoria cubre hasta 7-8 días de FL, y después, la hCG del embrión implantado compensa la falta de LH endógena.

- La suplementación con P en FIV apoya el embarazo precoz hasta la 7<sup>a</sup>s, retrasando el aborto, pero no mejora las tasas de embarazo

Proctor et al, 2006; Kyrou et al, 2011

# Fase lútea en FIV

Apoyo de fase lútea entre ↓ hCG exógena y ↑ embrionaria

- hCG: riesgo de SHOS
- Progesterona:
  - Gel vaginal P micronizada 90 mg/d
  - Comprimidos vaginales P micronizada 400-600 mg/d
  - P i.m. 50 mg/d
- Dihidrogesterona
- Progesterona + hCG

# Fase lútea en FIV

**Table 2:** Comparison of the main differences of two meta-analysis using different LPS schemes

	HCG versus Progesterone		
	HCG versus vaginal progesterone (RR) Pritts and Atwood (2002)	HCG versus IM progesterone (RR) Pritts and Atwood (2002)	HCG versus Progesterone (vaginal and IM) (OR) Nosarka <i>et al.</i> (2005)
Number of patients	707	486	438
Clinical PR/ET	0.9 (95% CI 0.72–1.14)	0.98 (95% CI 0.68–1.42)	1.71 (95% CI 1.06–2.76)
Delivery rate	–	1.7 (95% CI 0.52–6.27)	–

No diferencias : hCG vs P vaginal  
hCG vs P i.m.

Mejor  
hCG vs P (v ó i.m)

Human Reproduction Update, Vol.13, No.6 pp. 581–590, 2007  
Advance Access publication July 11, 2007

doi:10.1093/humupd/

## An update of luteal phase support in stimulated IVF cycles

H.M. Fatemi<sup>1,3</sup>, B. Popovic-Todorovic<sup>1</sup>, E. Papanikolaou<sup>1</sup>, P. Donoso<sup>2</sup> and P. Devroey<sup>1</sup>

# Fase lútea en FIV

## Papel del Estradiol en la fase lútea

- El endometrio es sensible a las disminuciones de los niveles esteroideos y concentraciones de E subóptimas en la FL media.
- Efecto modulador de la concentración de RP en el endometrio secretor y puede servir para la reposición y mantenimiento del nivel de RP requerido para mediar y completar la respuesta a la P

Var et al, Fertil Steril 2011; 95:985

- E2 bajo en fase lútea media disminuye receptividad

Elgindy et al, Fertil Steril 2010; 93:2182-8



# Fase lútea en FIV

**Table 1:** Summary of studies evaluating the addition of E<sub>2</sub> to progesterone on LPS in different stimulation schemes

COH	Long GnRH agonist			GnRH antagonist	
	Smitz <i>et al.</i> (1993)	Fahri <i>et al.</i> (2000)	Lukaszuk <i>et al.</i> (2005)	Lewin <i>et al.</i> (1994)	Fatemi <i>et al.</i> (2006)
Number of patients	378	271	231	100	201
Dose of E <sub>2</sub> (mg)	6	2	6, 2 and 0	2	4
Implantation rate, % (Progesterone with E <sub>2</sub> versus progesterone)	32.8 versus 35.5	15.2* versus 10.2	29.9* versus 17.8 versus 9.8	–	42.4 versus 37.8
Clinical PR/ET, % (Progesterone with E <sub>2</sub> versus progesterone)	29.2 versus 29.5	39.5* versus 25.6	51.3* versus 32.8 versus 23.1	28 versus 26.5	32.6 versus 28.9

el uso rutinario de E además de P como apoyo de la FL no estaba justificado

Human Reproduction Update, Vol.13, No.6 pp. 581–590, 2007  
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Martínez, Endocrino, 2011

# Fase lútea en FIV

## A comparison of the effects of three different luteal phase support protocols on in vitro fertilization outcomes: a randomized clinical trial

Turgut Var, M.D., Esra Ayşın Tonguc, M.D., Melike Doğanay, M.D., Cavidan Gülerman, M.D., Tayfun Gungor, M.D., and Leyla Mollamahmutoglu, M.D.

**TABLE 2**

In vitro fertilization cycle characteristics of the three treatment groups.

Characteristic	Group 1 (E <sub>2</sub> + P), 4mg VE	Group 2 (hCG + P), 1500 IU	Group 3 (P only), 90mg P-Gel	P value
No. of oocytes retrieved	3.1 ± 0.3	3.0 ± 0.3	3.0 ± 0.3	.65
No. of embryos transferred	2.7 ± 1.0	2.6 ± 0.6	2.7 ± 0.4	.28
Implantation rate (%)	16.7 ± 22.7	20.0 ± 21.6	7.9 ± 15.4	.001 <sup>a</sup>
Clinical PR, % (no.)	40.6 (39/96)	38.9 (37/95)	21.6 (21/97)	.01 <sup>a</sup>
Miscarriage rate, % (no.)	12.8 (5/39)	13.5 (5/37)	38 (8/21)	.02 <sup>a</sup>
Multiple-pregnancy rate, % (no.)	2.3 (2/96)	14.7 (14/95)	0 (0/97)	.001 <sup>b</sup>

Note:  $P < .05$  was considered to be statistically significant. Data are expressed as mean ± SD or as percentage and number.

<sup>a</sup> Group 3 versus group 1 and group 2.

<sup>b</sup> Group 2 versus group 1 and group 3.

Var. Three different luteal phase supports. *Fertil Steril* 2011.

Mejor E + P y hCG + P que P sólo

Tras bolo GnRHa, E ↓ 50%  
Humaidan et al , 2005

# Fase lútea en FIV tras bolo GnRH

- EAC : bolo de agonista se asociaba a baja tasa de implantación , baja tasa de embarazo y alta tasa de abortos, atribuidos a la FLD, a pesar de apoyo estándar con P y VE
  - Humaidan et al, 2005; Kolibianakis et al, 2005
- Estrategias para apoyo de FL en el ciclo de FIV tras bolo de GnRha:
  1. dosis pequeñas de hCG periovulatoria + VE y P
  2. dosis bajas de hCG (1000, 500 ó 250 IU ) en días +1, +4 y +7
  3. LH recombinante
  4. dosis altas de E + P i.m.

# Fase lútea en FIV tras bolo GnRH

**Table I** Delivery rate in GnRH antagonist IVF cycles according to final oocyte maturation regimen (GnRHa versus HCG).

Studies	Study design	Patients type	Luteal support	Agonist used	AGONIST triggering arm	HCG triggering arm
Conventional luteal support						
Fauser <i>et al.</i> (2002)	RCT	Normovulatory	IM progesterone	Leuprorelin 0.5 Triptorelin 0.2	18.7% (06/32) <sup>a</sup>	13.3% (02/15) <sup>a</sup>
Humaidan <i>et al.</i> (2005)	RCT	Normovulatory	Vag progesterone Estrogen pos	Buserelin 0.5	3.9% (03/55)	36.0% (24/67)
Kolibianakis <i>et al.</i> (2005)	RCT	Normovulatory	Vag progesterone Estrogen pos	Triptorelin 0.2	3.9% (02/52) <sup>a</sup>	27.7% (15/54) <sup>a</sup>
			Rate difference: -0.18, 95% (CI: -0.36 to 0.01)		7.9% (11/139)	30.1% (41/136)
Modified luteal support						
Humaidan <i>et al.</i> (2006)	RCT	Normovulatory	Vag progesterone Estrogen pos 1500 bolus HCG	Buserelin 0.5	38.0% (05/13)	53.0% (08/15)
Babayof <i>et al.</i> (2006)	RCT	PCOS	IM progesterone Estrogen pos adjustable	Triptorelin 0.2	6.6% (01/15)	15.0% (02/13)
Pirard <i>et al.</i> (2006)	RCT	Normovulatory	Buserelin only Different doses	Buserelin 0.2	16.6% (02/12)	16.6% (01/06)
Engmann <i>et al.</i> (2008a,b)	RCT	PCOS	IM progesterone Estrogen patch + Estrogen pos	Leuprorelin 1.0	48.5% (16/33)	43.7% (14/32)
Humaidan <i>et al.</i> (2010)	RCT	Normovulatory	Vag progesterone Estrogen pos 1500 bolus HCG	Buserelin 0.5	23.7% (36/152)	31.3% (47/150)
Papanikolaou <i>et al.</i> (2011)	RCT	Normovulatory	Vag progesterone Rec-LH 6 doses	Triptorelin 0.2	22.2% (04/18)	23.5% (04/17)
			Rate difference: -0.06, 95% (CI: -0.14 to 0.02)		26.3% (64/243)	32.6% (76/233)

<sup>a</sup>Ongoing pregnancy rates (12–18 weeks) provided.

# Fase lútea en FIV tras bolo GnRH

hCG

RBM Online - Vol 13 No 2. 2006 173-178

Humaidan et al,

**Table 3.** Oocytes, embryos and clinical outcome in human chorionic gonadotrophin (HCG) group (1) versus gonadotrophin-releasing hormone agonist + HCG groups (2 and 3).

	HCG	GnRHa		P-value
	10.000 IU	1500 IU 12h	35h	
No. of patients	15	17	13	–
No. of oocytes (mean ± SD)*	105 (7.0 ± 3.5) <sup>a</sup>	184 (10.8 ± 7.7) <sup>b</sup>	163 (12.5 ± 4.0) <sup>b</sup>	<i>P</i> < 0.04
No. of embryos (% per oocyte)**	52 (50)	84 (46)	74 (45)	NS
Rate of transfer (%)	12/15 (80)	9/17 (53) <sup>a</sup>	12/13 (92) <sup>b</sup>	<i>P</i> < 0.05
No. of embryos transferred (mean ± SD)	1.9 ± 0.3	1.9 ± 0.3	1.8 ± 1.5	NS
Positive HCG per embryo transfer (%)	9/12 (75)	3/9 (33)	6/12 (50)	NS
Clinical pregnancy per embryo transfer (%)	8/12 (67)	2/9 (22)	6/12 (50)	NS
Clinical pregnancy per cycle (%)	8/15 (53) <sup>a</sup>	2/17 (12) <sup>b</sup>	6/13 (46) <sup>a</sup>	<i>P</i> < 0.02
Implantation rate, <i>n</i> (%)	12/23 (52)	3/17 (18)	9/21 (43)	NS
Early pregnancy loss (%)	1/9 (11)	1/3 (33)	0	NS

Crinone 90% + VE 4mg/d

# Fase lútea en FIV tras bolo GnRH

hCG

Crinone 90% + VE 4mg/d

**TABLE 3**

**Pregnancy outcome in GnRHa vs. hCG-group.**

Variable	GnRHa	hCG	OR (95% CI)	P Value
Patients, n	152	150		
Rate of transfer, n (%)	130/152 (86)	138/150 (92)	0.5 (0.4–0.7)	.054
Embryos transferred, median (range)	2 (1–2)	2 (1–2)		
Positive hCG per ET, n (%)	63/130 (48)	66/138 (48)	1.0 (0.9–1.2)	.36
Clinical pregnancy per patient, n (%)	50/152 (33)	55/150 (37)	0.8 (0.7–0.9)	.29
Ongoing pregnancy per patient, n (%)	40/152 (26)	49/150 (33)	0.7 (0.6–0.8)	.69
Delivery rate per patient, n (%)	36/152 (24)	47/150 (31)	0.7 (0.6–0.8)	.16
Early pregnancy loss, n (% of positive hCG)	13/63 (21)	11/66 (17)	1.3 (0.7–1.9)	.36

*Humaidan. GnRHa ovulation trigger and luteal rescue. Fertil Steril 2010.*

1500 IU hCG  
35 h post bolo

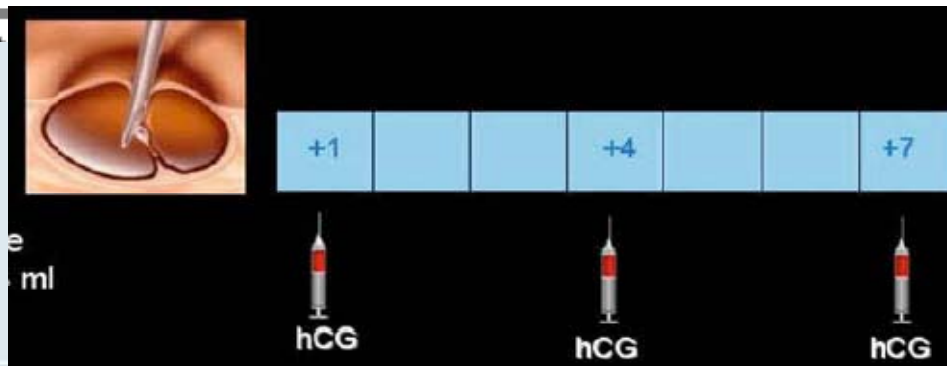
# Fase lútea en FIV tras bolo GnRH

hCG

Reproductive BioMedicine Online (2010) 20, 175–181

**Table 2** Treatment cycle outcomes.

	Group A (1000 IU HCG)	Group B (500 IU HCG)	Group C (250 IU HCG)	P-value <sup>a</sup>	Total
No. of patients	44	115	33	—	192
Oocytes recovered	15.9 ± 6.0 <sup>b</sup>	13.4 ± 7.1 <sup>c</sup>	17.8 ± 8.1 <sup>b</sup>	0.001	14.8 ± 7.2
Embryos per oocyte (%)	39 <sup>c</sup>	40 <sup>c</sup>	46 <sup>b</sup>	0.0001	41.6
Embryos transferred	2.6 ± 0.5 <sup>c</sup>	2.1 ± 0.4 <sup>b</sup>	1.9 ± 0.5 <sup>d</sup>	0.0001	2.1 ± 0.5
Pregnancy rate (%)	24/44 (54.5)	59/115 (51.3)	16/33 (48.5)	NS	99/192 (51.6)
Clinical pregnancy (%)	21/44 (47.7)	49/115 (42.6)	13/33 (39.4)	NS	83/192 (43.2)



# Fase lútea en FIV tras bolo GnRH

## LH recombinante

Pregnancy rates and stimulation/embryological data.		300IU /48d	
	Standard protocol recombinant hCG triggering (n = 17)	Luteal recombinant LH protocol agonist triggering (n = 18)	Statistics
Demographics and cycle parameters			
Age (y) <sup>a</sup>	30.6 ± 0.8	30.1 ± 0.7	.6
Days of stimulation <sup>a</sup>	9.6 ± 0.9	9.6 ± 1.0	.9
Total recombinant FSH dose (IU) <sup>a</sup>	1,767 ± 187	1,808 ± 209	.5
E <sub>2</sub> on OPU day (pg/mL)	1,179 ± 117	1,033 ± 91	.5
COC retrieved <sup>a</sup>	13.8 ± 1.8	11.7 ± 1.9	.4
2PN embryos <sup>a</sup>	8.3 ± 0.9	7.9 ± 1.0	.4
Blastocyst transferred	1 (15 patients underwent ET)	1 (16 patients underwent ET)	
Embryos cryopreserved <sup>a</sup>	1.2 ± 0.6	1.4 ± 0.8	.8
OHSS occurrence	0	0	n.a.
Pregnancy outcome			
Positive hCG test (per protocol analysis)	40.0% (6/15)	31.3% (5/16)	.7
Early pregnancy loss	33.3% (2/6)	20.0% (1/5)	n.a.
Clinical PR (per protocol analysis)	26.7% (4/15)	25.0% (4/16)	.9
Implantation rate (per protocol analysis)	26.7% (4/15)	31.2% (5/16) <sup>b</sup>	.9
Delivery rate (per intension to treat analysis)	23.5% (4/17)	22.2% (4/18) <sup>c</sup>	.9

Note: OPU = oocyte retrieval; COC = cumulus oocyte complex; 2PN = two pronuclear; OHSS = ovarian hyperstimulation syndrome; PR = pregnancy rate; n.a. = not available.

<sup>a</sup> Mean ± standard error of the mean.

<sup>b</sup> There was one monozygotic twin, therefore two heart beats.

<sup>c</sup> The patient with monozygotic twins underwent embryo reduction due to personal reasons.

Papanikolaou. *Correspondence. Fertil Steril* 2010.



# Fase lútea en FIV tras bolo GnRH

## Dosis altas de E+P

**TABLE 3**

**Outcome of cycle.**

	Study group	Control group	Odds ratio (95% CI)	P value
<b>Primary end points</b>				
<b>OHSS (intention to treat)</b>				
Total n, (%)	0/33 (0)	10/32 (31.3)	0 (0–0.26) <sup>a</sup>	<.01
Moderate/severe, n (%)	0/33 (0)	5/32 (15.6)	0 (0–0.74) <sup>a</sup>	.02
<b>OHSS (per protocol)</b>				
Total, n (%)	0/30 (0)	10/29 (34.5)	0 (0–0.26) <sup>a</sup>	<.01
Moderate/Severe, n (%)	0/30 (0)	5/29 (17.2)	0 (0–0.73) <sup>a</sup>	.02
<b>Secondary end point (per protocol)</b>				
Implantation rate, n (%)	22/61 (36)	20/64 (31)	1.18 (0.52–2.65)	.69
<b>Other end points (per protocol)</b>				
Positive pregnancy, n (%)	19/30 (63.3)	18/29 (62.1)	1.06 (0.37–3.0)	.92
Clinical pregnancy rate, n (%)	17/30 (56.7)	15/29 (51.7)	1.22 (0.4–3.4)	.45
Ongoing pregnancy rate, n (%)	16/30 (53.3)	14/29 (48.3)	1.22 (0.4–3.4)	.45

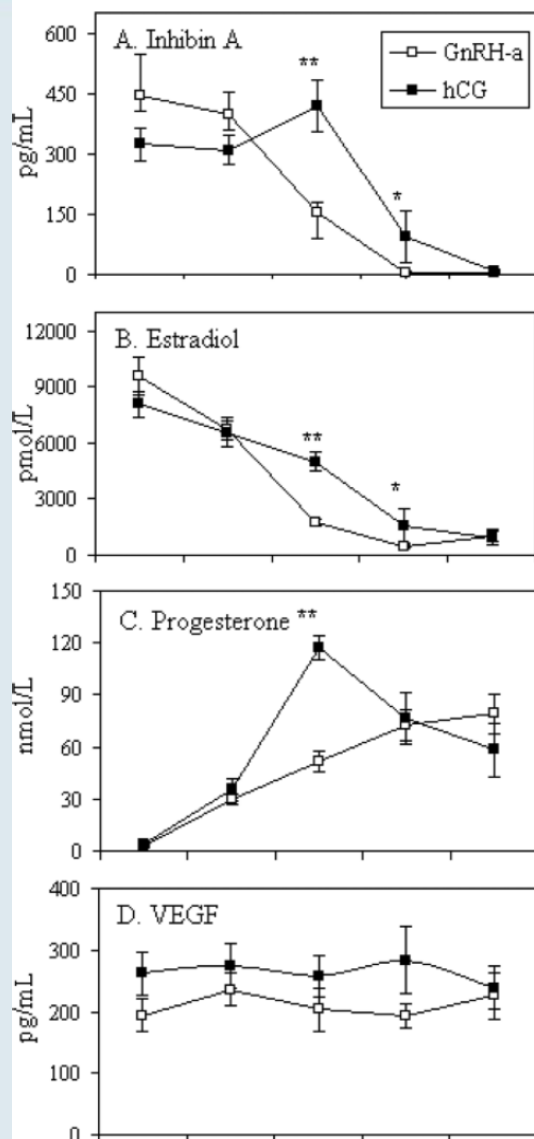
<sup>a</sup> The estimates of these odds ratios are zero, because no patient developed OHSS in the study group.

Engmann. GnRH agonist trigger and OHSS prevention. *Fertil Steril*

parche E 0.1 mg x 3/c2 d + P i.m. 50 mg/d  
 ± VE 2mg/12h, E2 > 200 pg/ml  
 Monitorizar E y P

Martínez, Endocrino, 2011

# Fase lútea en FIV tras bolo GnRH



Babayof et al, HR, 2006

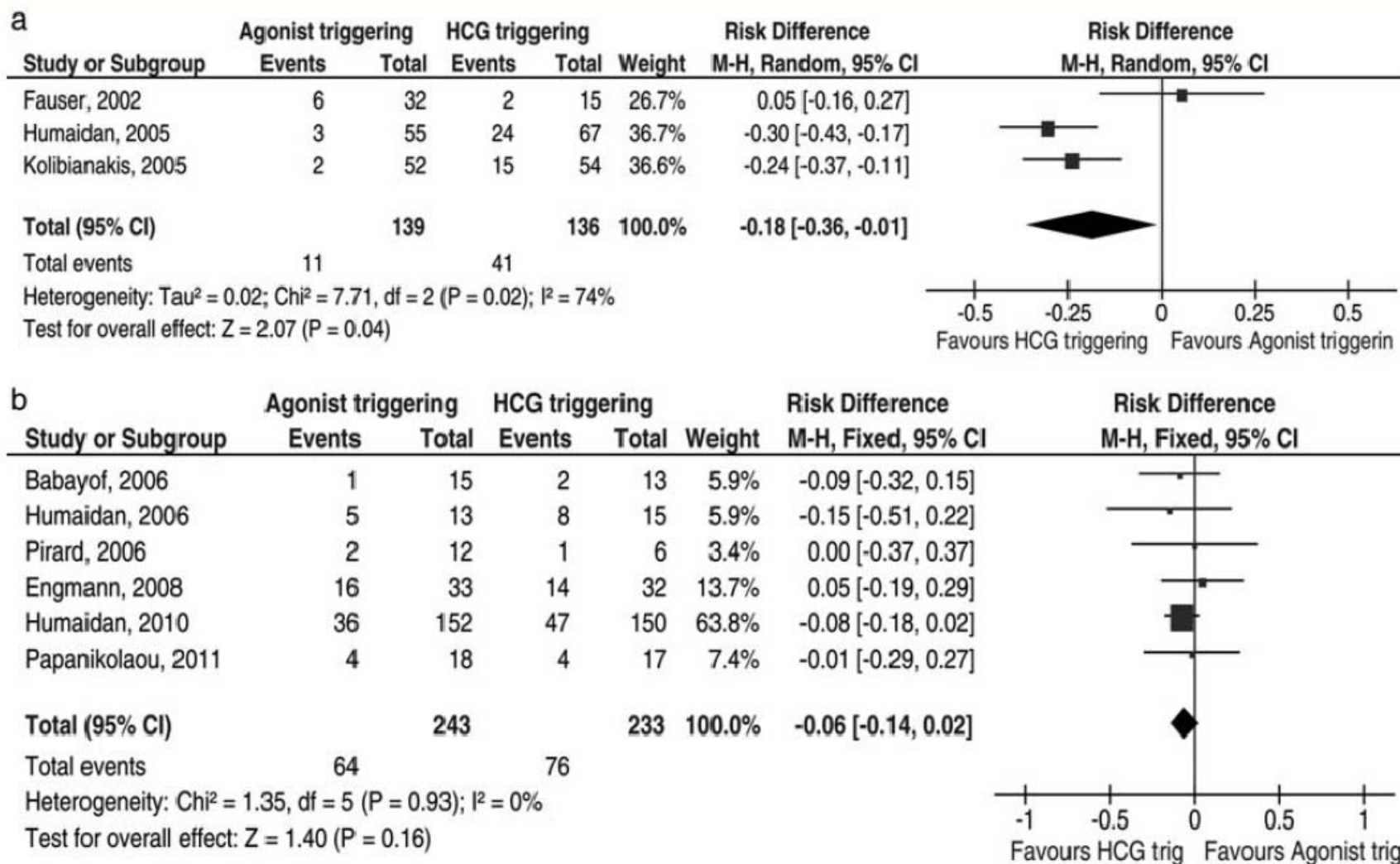
**TABLE 1**

Basal patient population, serum values of E<sub>2</sub>, P, LH, and vascular endothelial growth factor (VEGF), and ultrasonographic findings during the luteal phase (LP).

	hCG (n = 10)	E <sub>2</sub> + P (n = 10)	P value
Age (y)	28.2 ± 0.7	26.2 ± 0.5	.264
Body mass index (kg/m <sup>2</sup> )	22.1 ± 0.4	22.0 ± 0.4	.935
Total FSH (IU)	1980 ± 187	1965 ± 198	.912
No. of eggs retrieved	14.5 ± 1.1	15.9 ± 1.2	.734
LP duration (d)	15.0 ± 1.6	11 ± 1.1	.003
Serum E <sub>2</sub> (pg/mL)			
Day +4	761.7 ± 121	555.4 ± 129	.147
Day +7	1036.5 ± 195	357.6 ± 98	.001
Day +10	821.8 ± 103	190.3 ± 54	.002
Serum P <sub>4</sub> (ng/mL)			
Day +4	17.2 ± 4.1	19.0 ± 3.8	.732
Day +7	91.6 ± 15.2	12.0 ± 2.1	.003
Day +10	48.6 ± 8.7	10.6 ± 1.9	.001
Serum LH (IU/L)			
Day +4	0.03 ± 0.01	0.67 ± 0.11	.035
Day +7	0.06 ± 0.05	0.3 ± 0.14	.251
Day +10	0.4 ± 0.13	0.4 ± 0.09	1.0
Serum VEGF (pg/mL)			
Day +4	0.22 ± 0.1	0.26 ± 0.12	.489
Day +7	0.28 ± 0.11	0.26 ± 0.16	.758
Day +10	0.27 ± 0.09	0.25 ± 0.14	.694

Garcia-Velasco. Correspondence. Fertil Steril 2010.

# Fase lútea en FIV tras bolo GnRH



**Figure 2** (a) Ongoing pregnancy rate after conventional luteal support. (b) Delivery rate after modified luteal support.

# Fase lútea en FIV tras bolo GnRH

- Necesidad de apoyo más intenso de FL tras bolo de agonista
- hCG barata, eficaz, no comercializada
- LHr cara y no disponible
- Efectos secundarios de P i.m.
- Eficacia de P vaginal y disponibilidad
- Eficacia demostrada de E oral y parche
- Hasta cuando?
- Monitorizar niveles?
- Opción de congelar todos los embriones y CTS