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HCG mode of action versus GnRHa action for triggering of final oocyte maturation

Nick Macklon
Professor of Obstetrics and Gynaecology, University of Southampton

A hammer to crack a nut

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How hard does the hammer hit?

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1. LH and oocyte maturation
2. The real thing: Physiological LH midcycle dynamics
3. The imposters: Midcycle dynamics after GnRH or hCG?
4. Do different dynamics affect oocyte maturation?
5. The luteal phase after LH, GnRH and hCG

GMP/LH regulation of meiotic arrest and resumption

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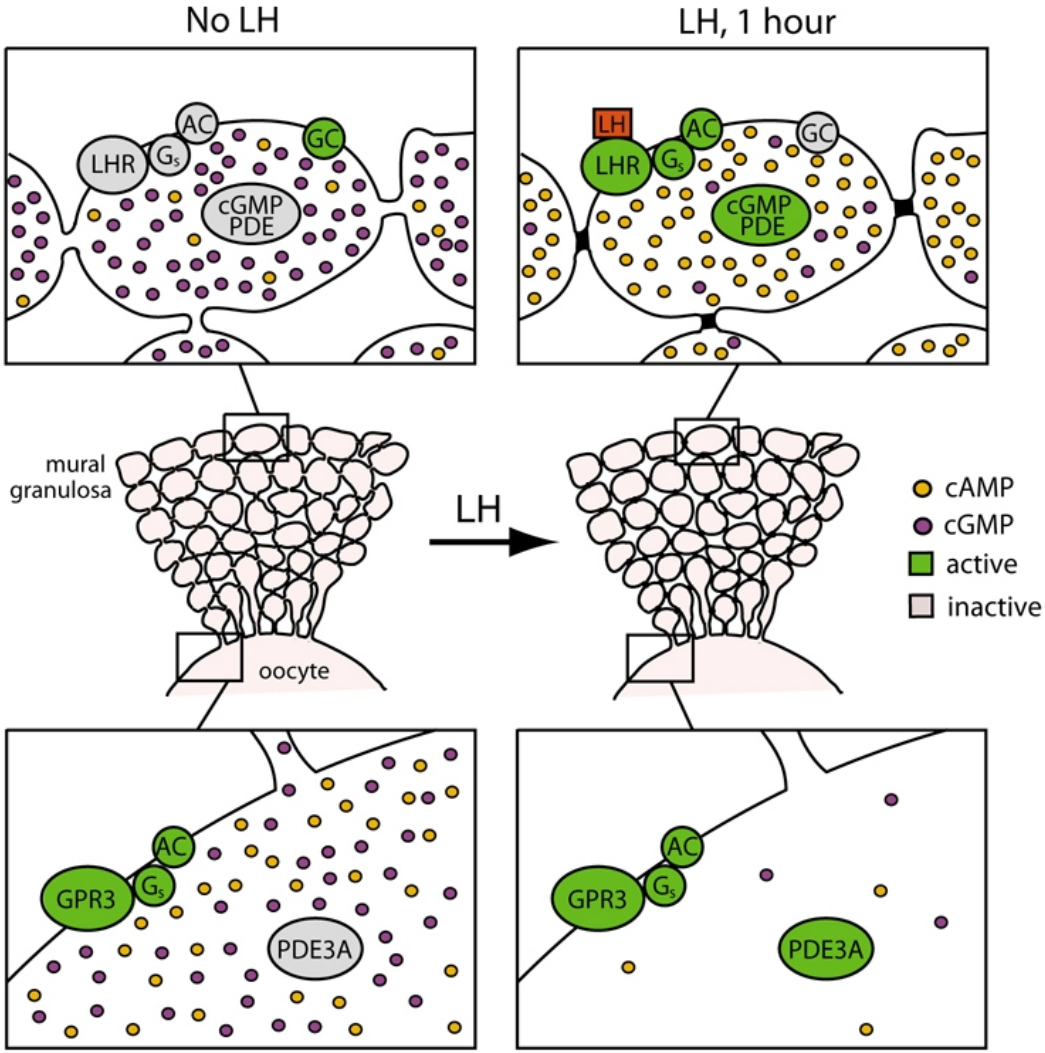

High cAMP in oocyte
Inhibits meiosis

No LH: high cGMP, diffuses into oocyte inhibits cAMP breakdown, and thus meiotic inhibition

LH: inhibits cGMP and raises cAMP
Gap junctions close
Low cGMP + Disinhib of PDE3A reduces cAMP

and Meiosis resumes.

Slide courtesy of Richard Anderson

Norris et al 2009 Development 136, 1869

HCG as a surrogate for LH

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.. it looks like LH

- Both glycoproteins
- Molecular weight approx 30kDa
- Identical α subunits
- High cysteine content

.. it acts like LH

- Granulosa cell luteinization
- Switch form E2 to P4 synthesis
- Resumption of meiosis and oocyte maturation
- Follicle rupture 36-40 hours later

.. but its not LH

- Sequence of β subunit
- Regulation of secretion
- Pharmacokinetics of clearance

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Pharmacokinetics of LH versus hCG

Test drug	rhLH	uhCG	rhCG
Subjects (n)	12	12	12
Route	i.v.	i.v.	i.v.
Dose (IU)	300	5000	5000
C_{max} (IU/l)	32	900	1400
Initial halflife(h)	0.8	5.5	4.7
Terminal halflife (h)	10.5	31	28

Le Cotonnec et al F&S 1998
Trinchard et al RBM Online 2002

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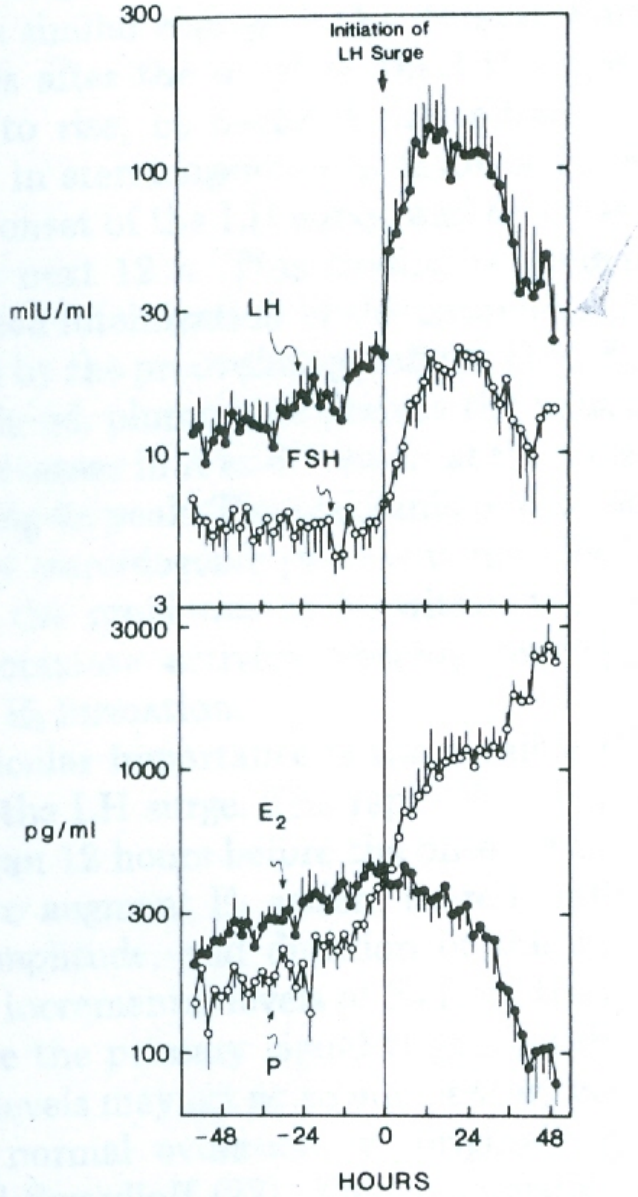
..and hCG does not inhibit the subsequent spontaneous LH surge

- Confirms that an ultrashort loop feedback of LH(by hCG) is not functional.
- hCG administration does not alter GnRH induced LH response
- Elevated P levels immediately after hCG injection induce LH surges in CC/hMG cycles

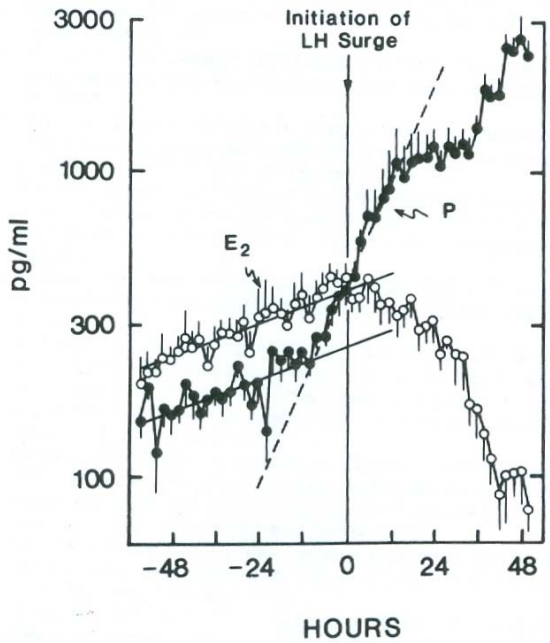
Kyle et al, JCEM 1989

Physiological midcycle hormone dynamics



LH:Short ascending phase (14 hrs)
:Peak plateau phase (14 hrs)
:Long descending phase (20 hrs)

FSH:Similar dynamics
:Slower rates of increase and decline



E2 :peak at onset LH surge
: rapid fall when LH falls

P4 :Multiphasic
:Phase 1 and 2 as LH
:Phase 3 plateau
: Phase 4 to luteal levels

Hoff et al JCEM 1983

Physiological versus GnRH induced LH rise

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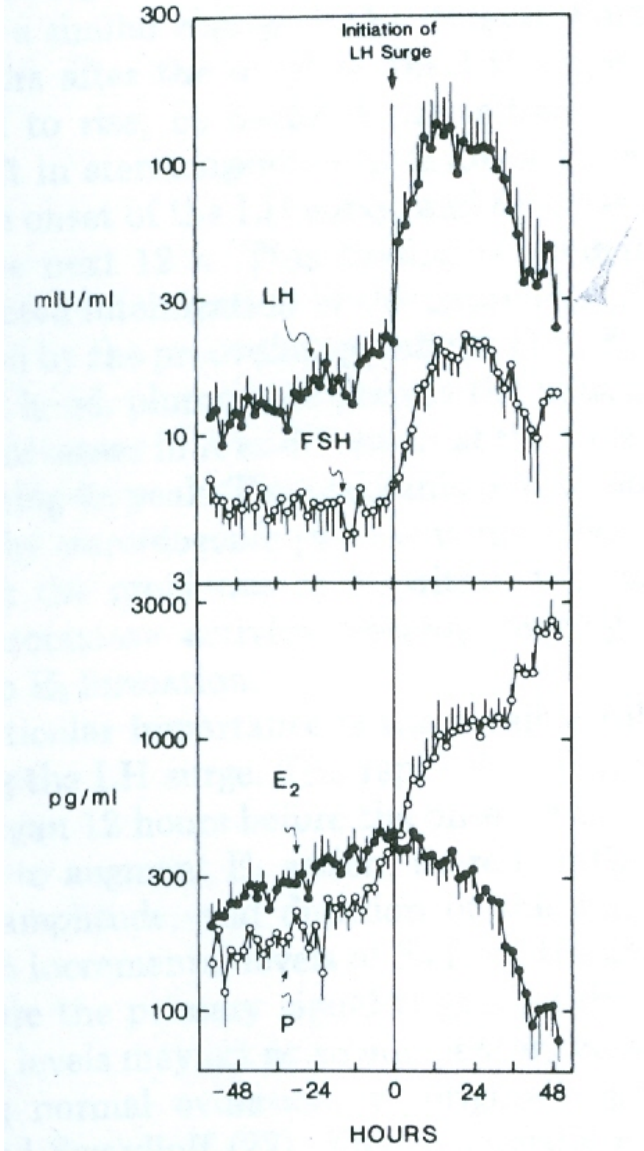
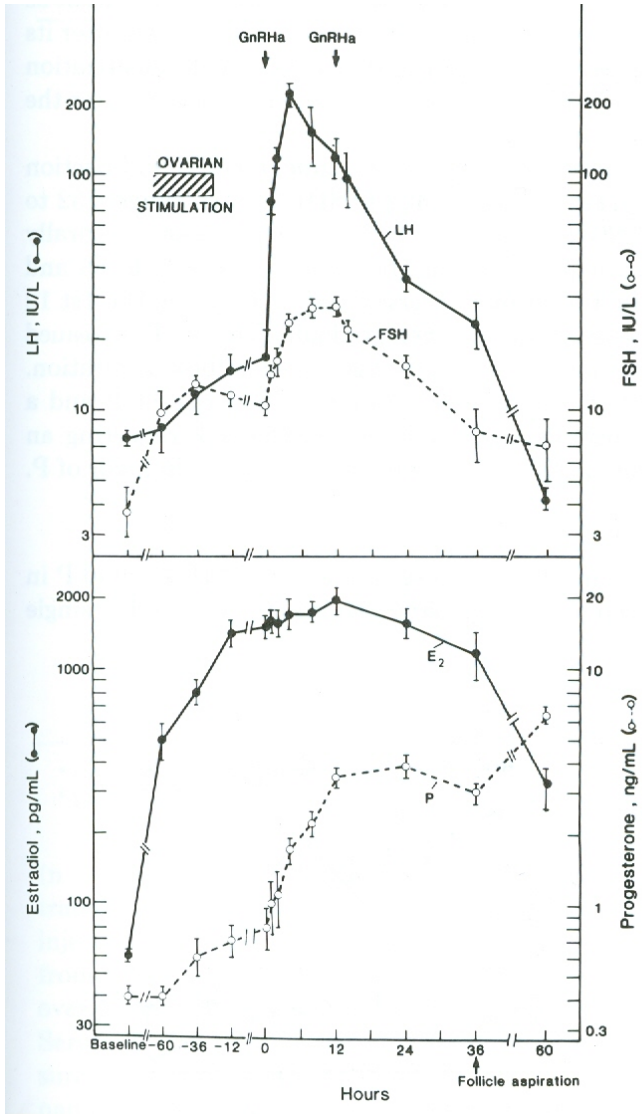
Hoff et a JCEM 1983



Itskowitz et al F&S 1991



Shorter ascending phase

Shorter plateau

Longer decending phase

..but similar P and E2 secretion patterns

Human Reproduction Vol.21, No.8 pp. 2126–2130, 2006 doi:10.1093/humrep/del119
Advance Access publication May 8, 2006.

Hormonal characteristics of follicular fluid from women receiving either GnRH agonist or hCG for ovulation induction

C.Yding Andersen[1,5], P.Humaid and L.G.Westergaard[4]

Table I. Hormonal concentrations in follicular fluid from women receiving either GnRH agonist or hCG for ovulation induction [mean ± SEM (range)]

	GnRH agonist group	hCG group
Number of follicular fluid samples	64	74
Number of women	32	37
FSH (IU/l)	6.3 ± 0.6* (0.4–5.7)	3.3 ± 0.2* (0.4–5.7)
LH (IU/l)	11.1 ± 0.6* (0.4–5.7)	3.6 ± 0.3* (0.4–5.7)
hCG (IU/l)	ND	139 ± 8
Estradiol (µmol/l)	1.9 ± 0.2 (0.4–5.7)	1.8 ± 0.2 (0.2–6.3)
Progesterone (µmol/l)	70 ± 4* (6.4–172)	94 ± 5* (16–289)
Inhibin-B (ng/ml)	35.6 ± 2.8 (5–120)	40.1 ± 3.1 (5–122)
Inhibin-A (ng/ml)	36.9 ± 3.1 (5–116)	37.1 ± 2.5 (12–114)

ND, not determined.
*$P < 0.001$.

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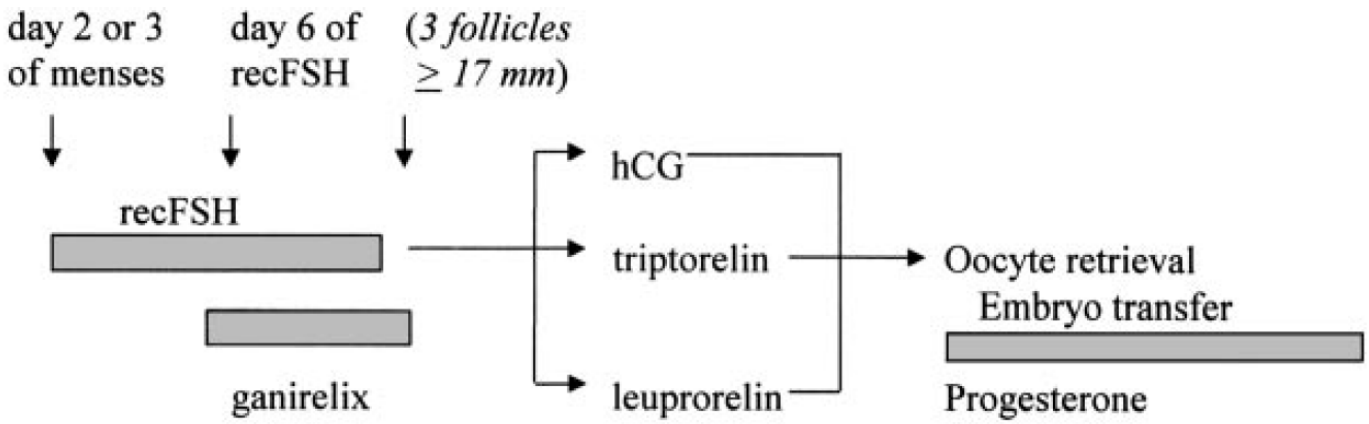
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 87(2):709–715

Endocrine Profiles after Triggering of Final Oocyte Maturation with GnRH Agonist after Cotreatment with the GnRH Antagonist Ganirelix during Ovarian Hyperstimulation for *in Vitro* Fertilization

B. C. FAUSER, D. DE JONG, F. OLIVENNES, H. WRAMSBY, C. TAY, J. ITSKOVITZ-ELDOR, H. G. VAN HOOREN

RCT, n=57



Number of follicles 11mm or larger

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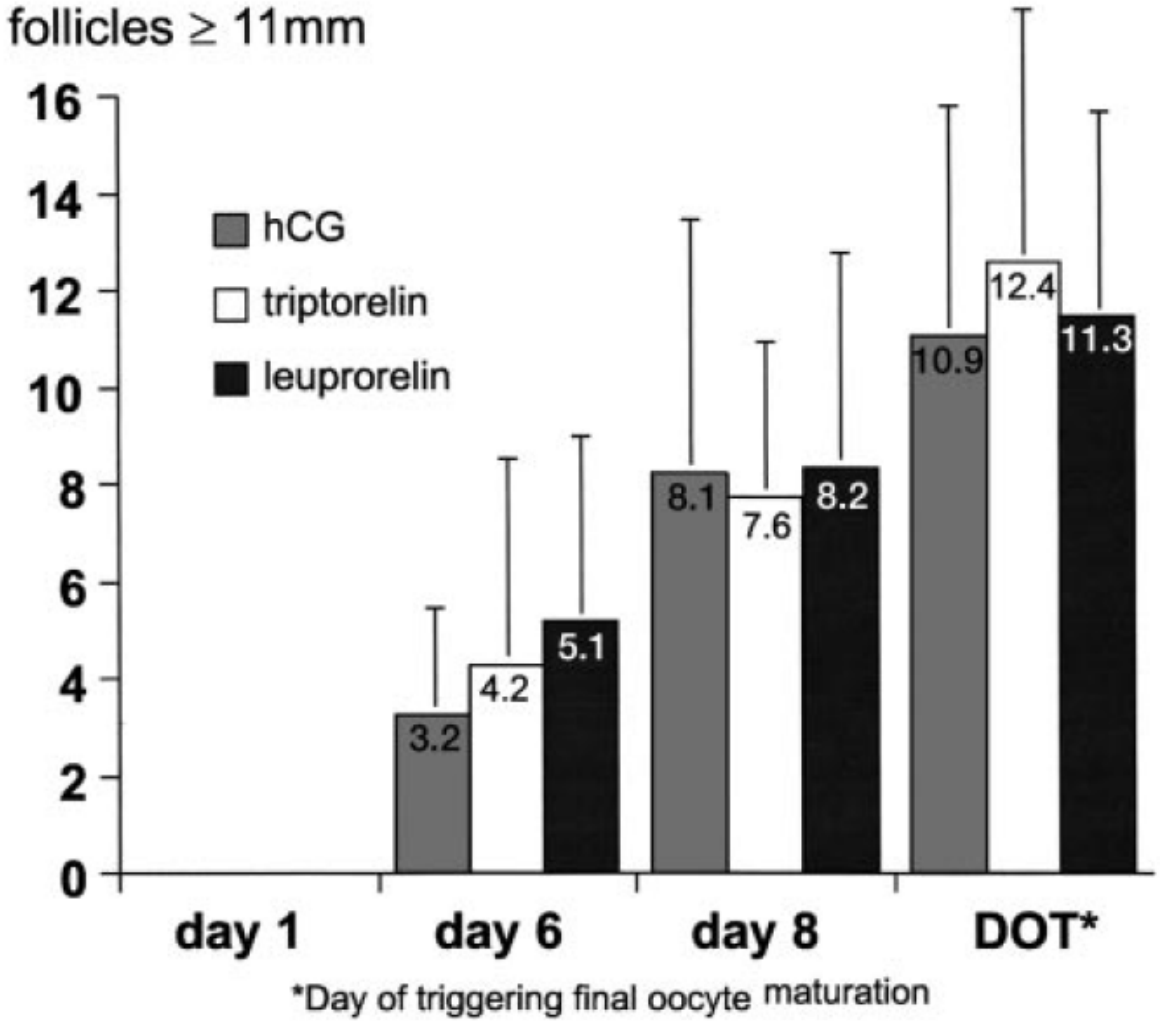
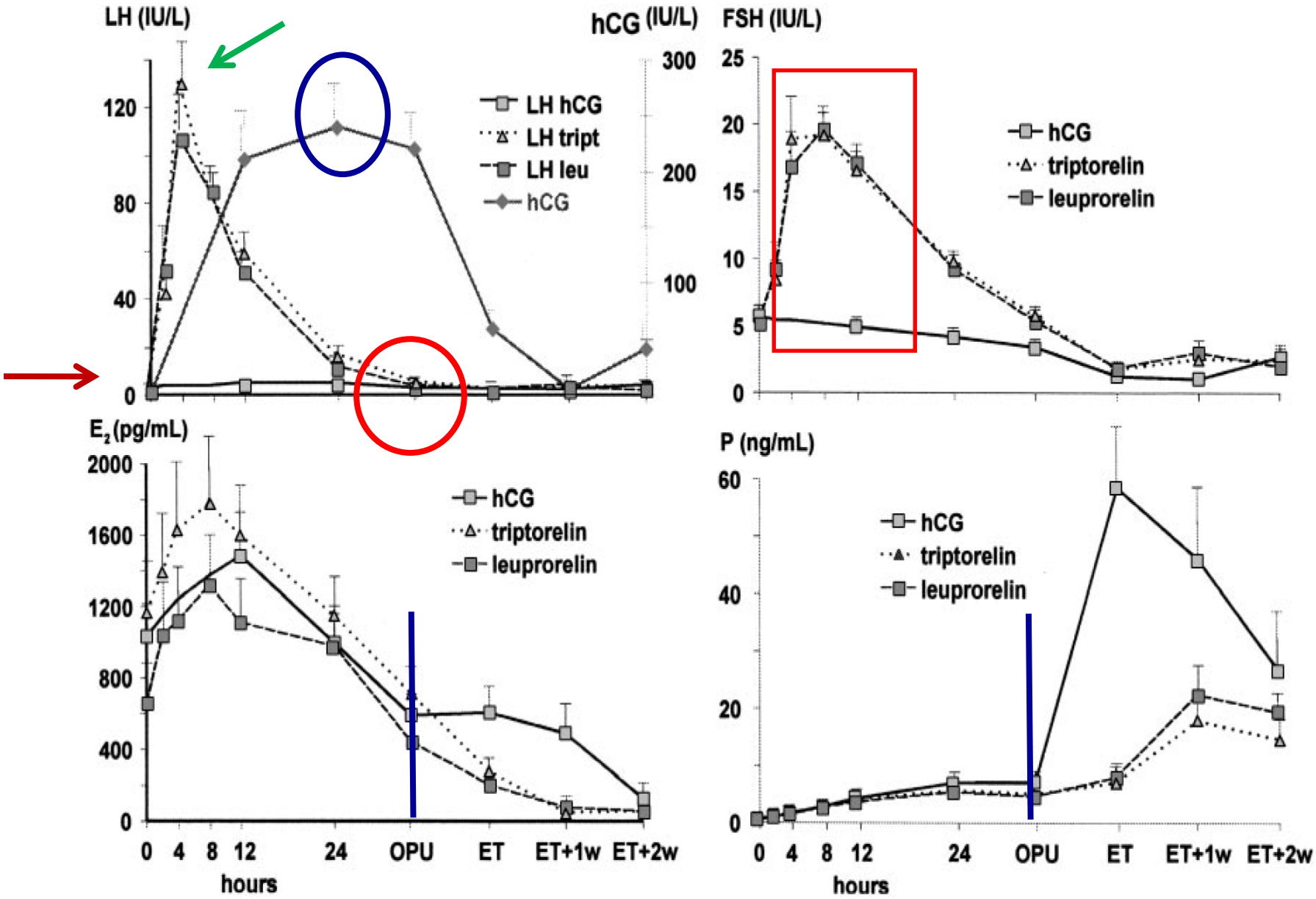


Endocrine measurements



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GnRH agonist LH surge vs natural

- Duration of LH surge shorter (24 vs 36 -40 hours)
- Due to immediate pituitary desensitization?
- No impact on oocyte maturation

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Clinical outcomes

	Triptorelin	Leuprorelin	hCG
No of oocytes	9.8±5.4	8.7±4.5	8.3±3.3
Proportion of MII oocytes	72±18%	85±17%	86±17%
Fertilization rate	61±30%	62±23% 56±18%	
Grade 1&2 embryos	2.7±1.9	3.2±2.6	3.3±2.0

Fauser et al JCEM 2002

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Role of midcycle FSH surge?

- Not obligatory
- Maturation of oocyte cumulus complex by suppression of intercellular coupling of cumulus cells
- Promotes secretion of glycosaminoglycans from granulosa cells

Moor et al J Embryol Exp Morph 1981
Yanagishita et al Endocrinology 1981

Clinical data

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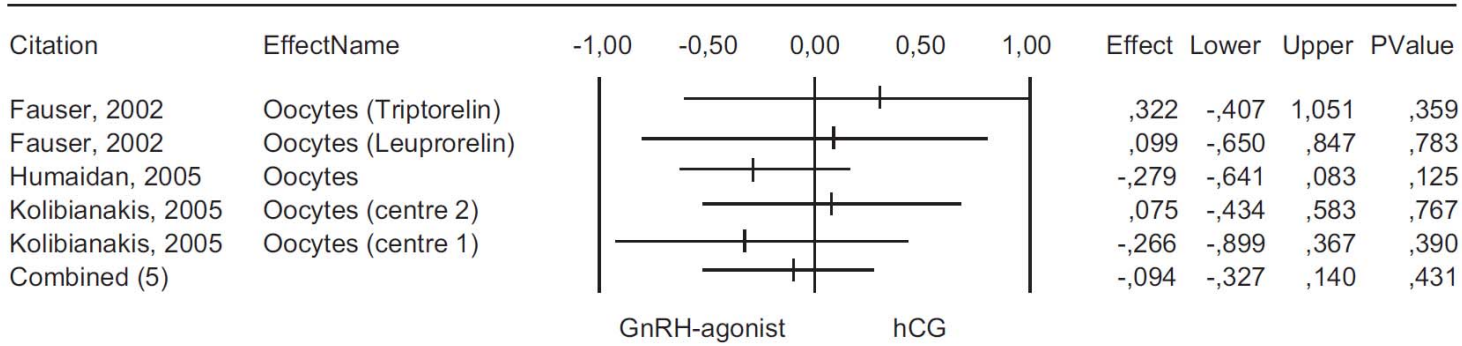
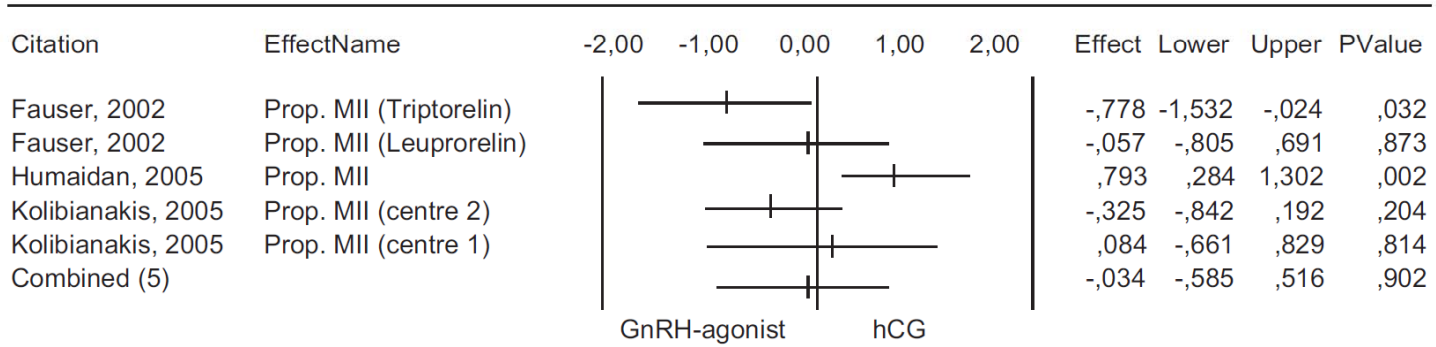
No. of oocytes retrieved



Proportion MII oocytes



Griesinger et al

Clinical data

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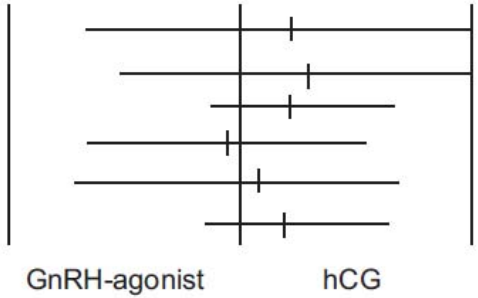
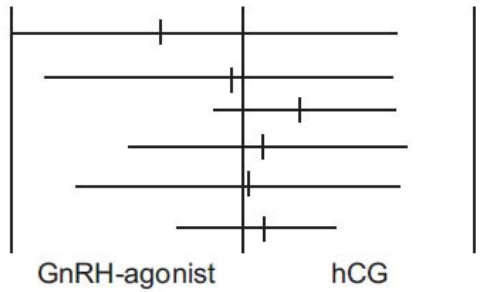
Fertilization rate

Citation	EffectName	Effect	Lower	Upper	PValue
Fauser, 2002	FR (Triptorelin)	,194	-,531	,919	,578
Fauser, 2002	FR (Leuprorelin)	,283	-,470	1,035	,433
Humaidan, 2005	FR	,218	-,143	,579	,231
Kolibianakis, 2005	FR (centre 2)	-,033	-,550	,484	,899
Kolibianakis, 2005	FR (centre 1)	,081	-,573	,736	,799
Combined (5)		,150	-,086	,385	,212



Embryo score

Citation	EffectName	Effect	Lower	Upper	PValue
Fauser, 2002	E-score (Triptorelin)	-,300	-1,028	,428	,391
Fauser, 2002	E-score (Leuprorelin)	-,042	-,790	,706	,907
Humaidan, 2005	E-score	,172	-,189	,533	,344
Kolibianakis, 2005	E-score (centre 2)	,070	-,461	,601	,789
Kolibianakis, 2005	E-score (centre 1)	,013	-,682	,708	,969
Combined (5)		,053	-,185	,291	,663



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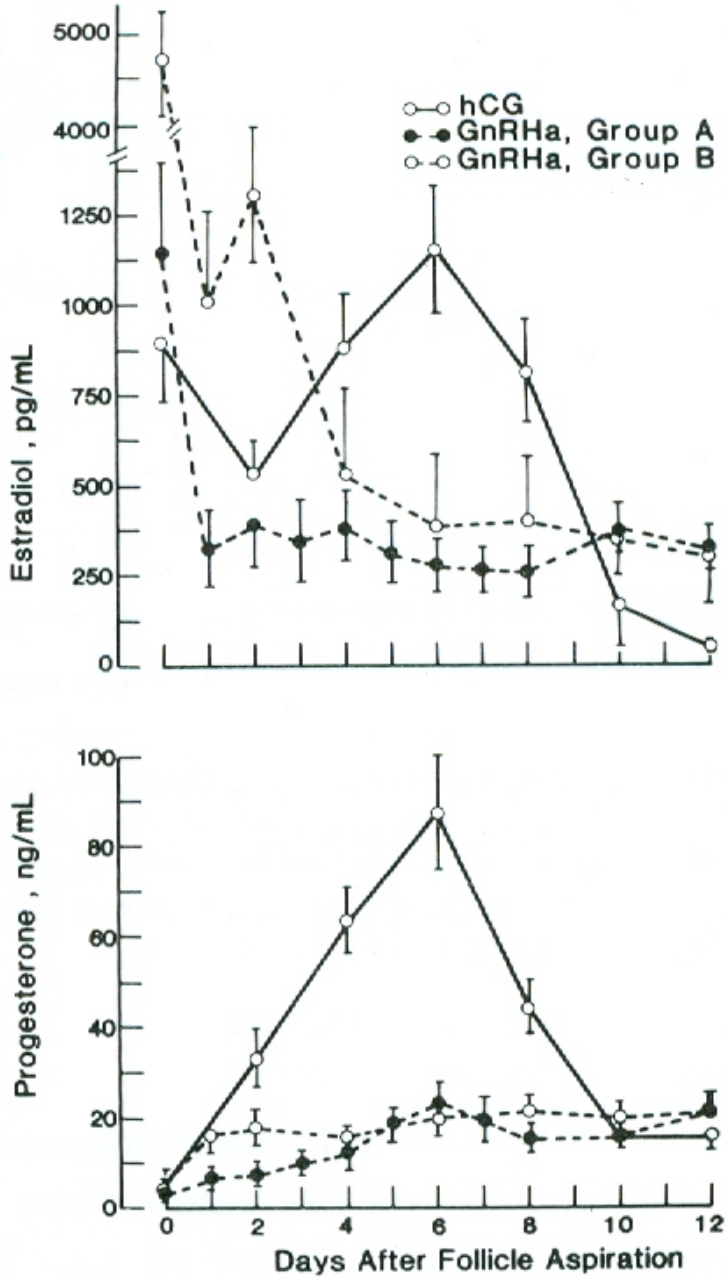
What about the luteal phase?

The luteal phase after hCG and after GnRH

Despite multiple preovulatory follicles, luteal phase E2 ans P levels close to Physiological after GnRH



Itskowitz et al F&S 1991

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Good news?

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No.

0021-972X/03/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 88(9):4186–4192

doi: 10.1210/jc.2002-021953

Nonsupplemented Luteal Phase Characteristics after the Administration of Recombinant Human Chorionic Gonadotropin, Recombinant Luteinizing Hormone, or Gonadotropin-Releasing Hormone (GnRH) Agonist to Induce Final Oocyte Maturation in *in Vitro* Fertilization Patients after Ovarian Stimulation with Recombinant Follicle-Stimulating Hormone and GnRH Antagonist Cotreatment

NICOLE G. M. BECKERS, NICHOLAS S. MACKLON, MARINUS J. EIJKEMANS, MICHAEL LUDWIG, RICARDO E. FELBERBAUM, KLAUS DIEDRICH, SHELLY BUSTION, ERNEST LOUMAYE, AND BART C. J. M. FAUSER

The luteal phase after hCG,LH & GnRH-a

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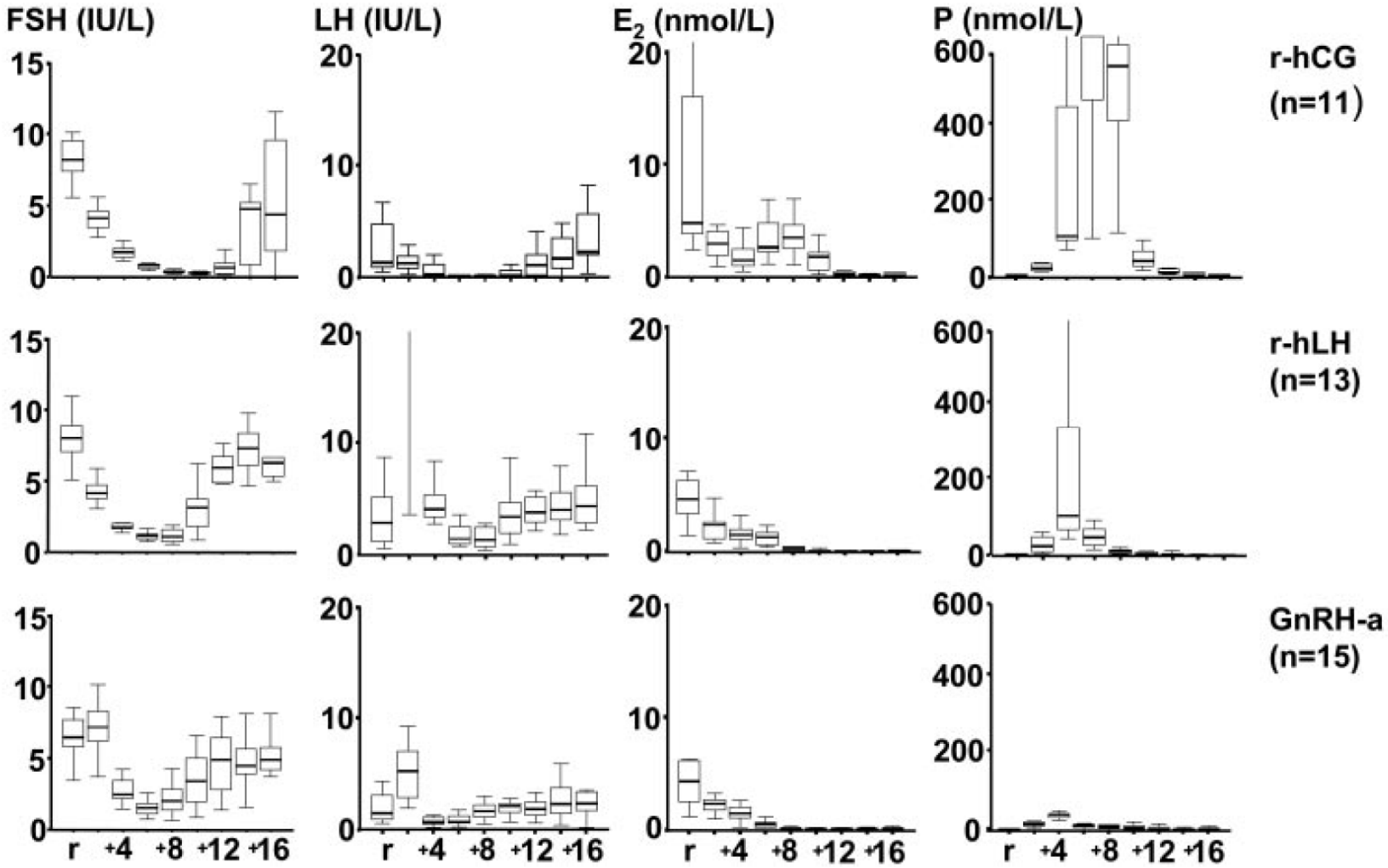

Beckers et al JCEM 2002

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The bad news..

TABLE 1. Follicular and luteal phase characteristics (median and ranges) of 39 subjects undergoing ovarian stimulation for IVF using r-hFSH/GnRH antagonist, randomized for three different strategies for the induction of final oocyte maturation

	r-hCG (n = 11)	r-LH (n = 13)	GnRH agonist (n = 15)	*P* value[a]
Duration follicular phase (d)	11 (9–14)	12 (10–14)	12 (9–16)	0.9
No. days GnRH antagonist	4 (3–8)	4 (3–6)	4 (2–7)	1.0
No. follicles ≥ 11 mm	7 (5–16)	8 (2–18)	9 (3–13)	0.8
No. oocytes retrieved	7 (3–23)	7 (1–26)	10 (1–17)	0.9
No. patients achieving embryo transfer[b]	9	11	14	0.4
Pregnancy[b]	2 (18%)	1 (8%)	2 (13%)	0.8
Ongoing pregnancy[b]	2 (18%)	0 (0%)	1 (7%)	0.3
$LH_{(\text{day of oocyte retrieval})}$ (IU/liter)	1.3 (0.3–2.9)	50.6 (3.7–54.1)	5.5 (2.0–9.6)	<0.001
Day of P_{maximum}	6 (6–8)	4 (4–6)	4 (4–6)	<0.001
Day of decrease of P	8 (6–8)	4 (4–8)	4 (4–8)	<0.001

[a] Parameters were tested for significance using Kruskal Wallis test.
[b] Calculated per randomized group and tested for significance using a two-tailed Fisher's exact test.

The impact of GnRH agonist versus hCG on the SUPPLEMENTED luteal phase in PCOS

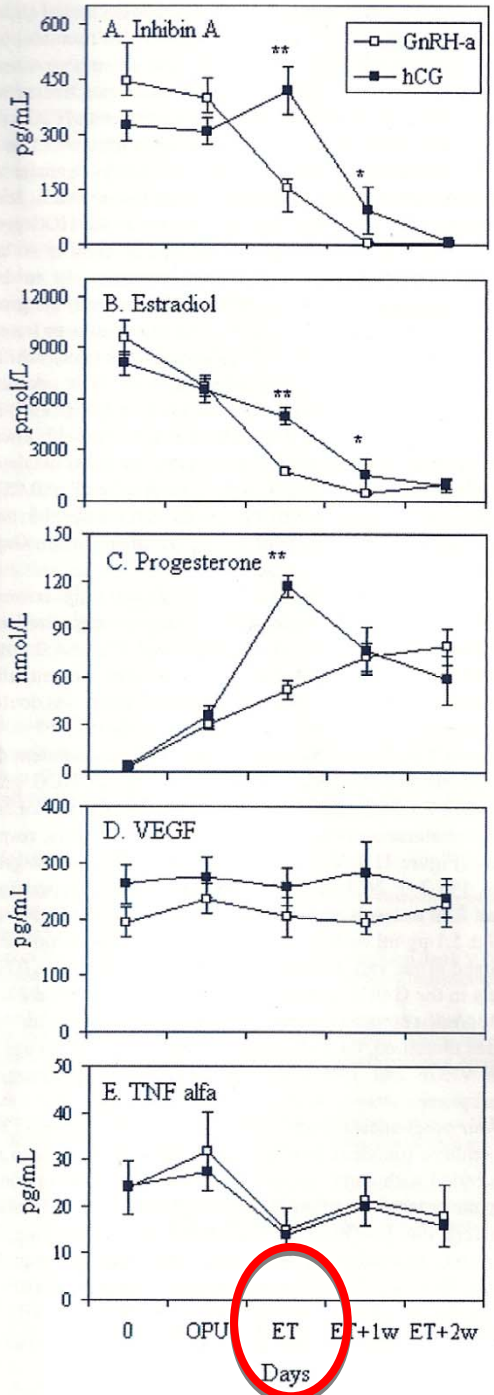
Inhibin A ↓

Estradiol ↓

Progesterone ↓

VEGF≈

TNF alpha≈



Babayof et al, Hum Rep 2006

Hcg versus GnRH agonist

- Causes rise in intrafollicular P4 *(Yding Andersen et al 1993)*
- Development of multiple corpora lutea
- Supraphysiological estradiol and progesterone synthesis
- hCG increase LH activity but does not reconstitute the midcycle physiologic FSH surge.
- Higher luteal phase levels of E2 and P induced by supraphysiological hCG concentrations

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GnRH agonist versus hCG

- More physiological mid-cycle dynamics, but still different from rec LH.
- Similar oocyte and embryo quality
- A more physiological luteal phase, but impacted more severely by ovarian stimulation
- So remove ovarian stimulation and then…..?

Cryopreserved-thawed human embryo transfer: spontaneous natural cycle is superior to human chorionic gonadotropin–induced natural cycle

Human Mousavi Fatemi, M.D., Ph.D.,[a] *Dimitra Kyrou, M.D.,*[a] *Claire Bourgain, M.D., Ph.D.,*[b] *Etienne Van den Abbeel, Ph.D.,*[c] *Georg Griesinger, M.D., Ph.D.,*[d] *and Paul Devroey, M.D., Ph.D.*[a]

	Spontaneous LH (n = 61)	hCG group (n = 63)	*P* value
Day 3			
FSH (IU/L)	7.3 ± 1.7	7.4 ± 4.9	NS
LH (IU/L)	5.1 ± 1.9	4.7 ± 1.3	NS
E_2 (pg/mL)	41.7 ± 18.6	39 ± 14.4	NS
P (ng/mL)	0.6 ± 0.3	0.7 ± 0.4	NS
Day of hCG administration/LH rise			
FSH (IU/L)	9.9 ± 5	7 ± 4.1	NS
LH (IU/L)	34.6 ± 18.3	17.5 ± 16.7	.001
E_2 (pg/mL)	275.4 ± 121.3	252.7 ± 91.3	NS
P (ng/mL)	0.93 ± 0.45	0.91 ± 1.6	NS

Note: Data are given as mean ± SD. NS = not significant.

Treatment outcomes in spontaneous LH and hCG group.

	Spontaneous LH (n = 61)	hCG group (n = 63)	Difference, % (95% CI)	*P* value
Ongoing pregnancy rate–ET (%)	31.1 (19)	14.3 (9)	16.9 (2.1–30.9)	.025
Miscarriage rate–ET (%)	0 (0)	3.2 (2)	−3.2 (−10.9 to 3.2)	NS
Biochemical rate–ET (%)	3.3 (2)	3.2 (2)	0.1 (−7.9 to 8.3)	NS
Positive hCG–ET(%)	34.4 (21)	20.6 (13)	13.8 (−1.9 to 28.7)	NS

Note: CI = confidence interval; NS = not significant.

Fatemi. Natural cycle vs. hCG induced for frozen ET. Fertil Steril 2010.

SEPTEMBER 2007

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