THE NEBULA OF IMPAIRED OOCYTE MATURATION: IS THE DUAL TRIGGERING AN OPTION?

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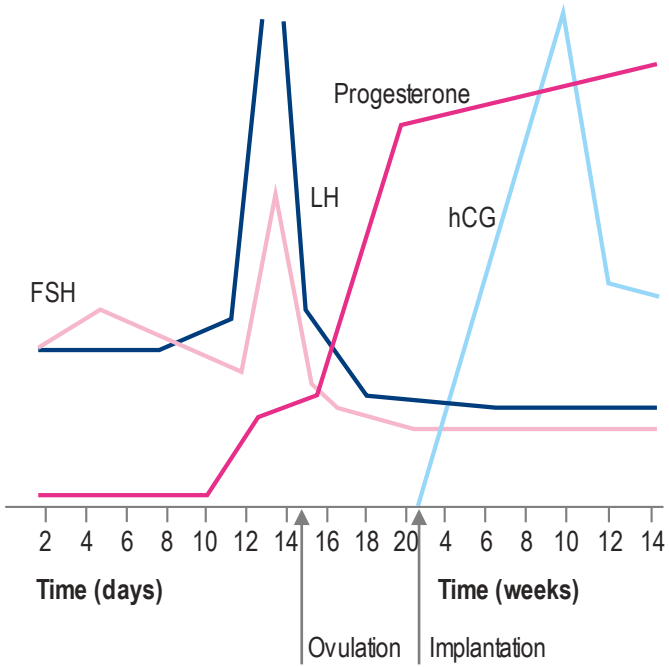
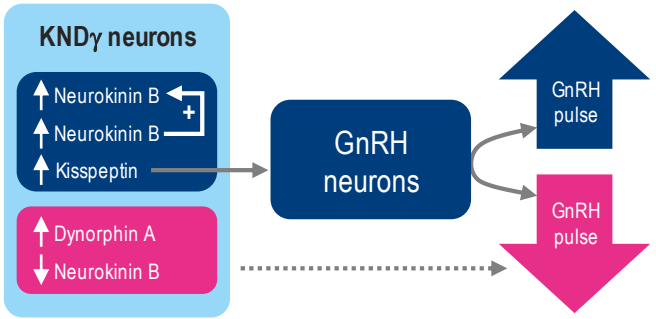
Educational objectives

- Identify the prevalence of impaired oocyte maturation among women undergoing ART
- Summarize the pathophysiology for oocyte maturation failure
- Discuss available therapeutic interventions including the rationale for dual triggering and evidence from clinical data/case reports

Serum hormone levels from a natural cycle





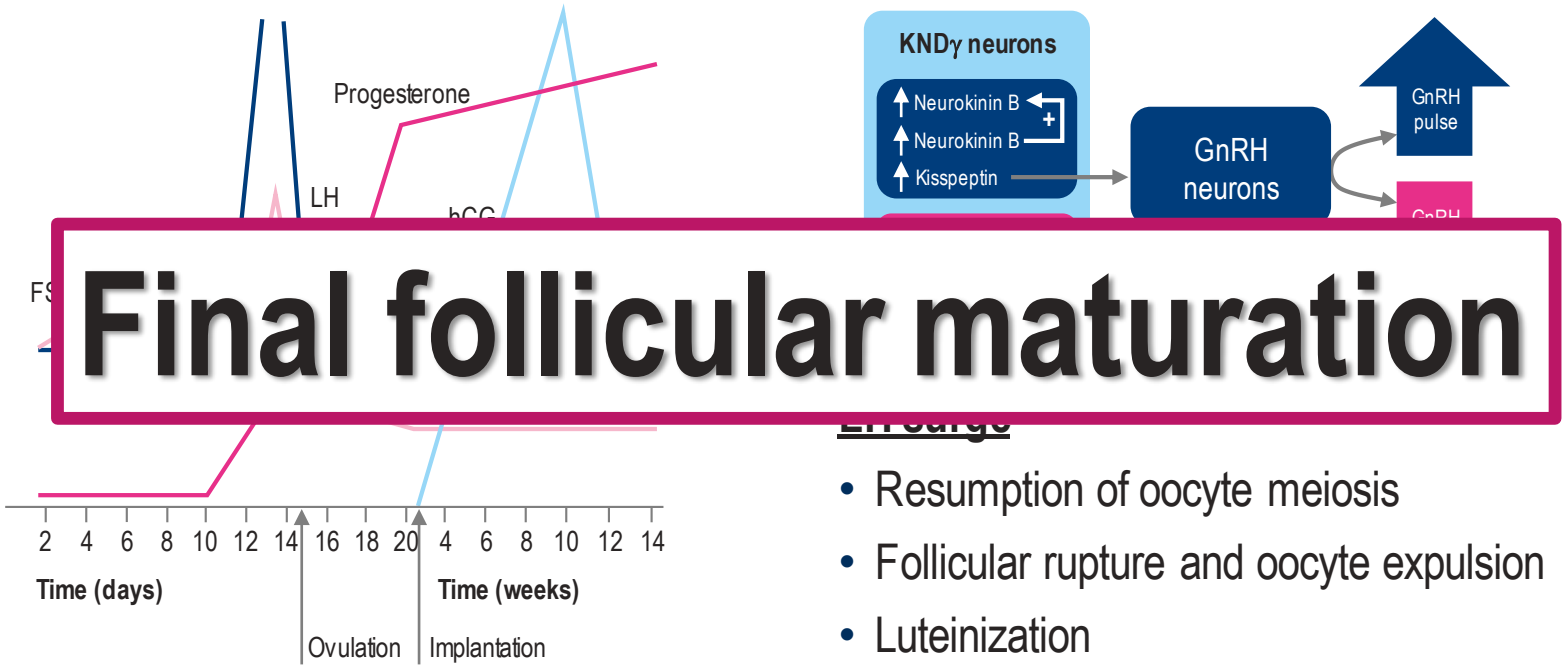
LH surge

- Resumption of oocyte meiosis
- Follicular rupture and oocyte expulsion
- Luteinization

FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; hCG, human chorionic gonadotropin; IVF, in vitro fertilization; KND, kisspeptin/neurokinin B/dynorphin; LH, luteinizing hormone.

Fritz MA, Speroff, L. Clinical gynecologic endocrinology and infertility. 8th ed. Philadelphia: Lipincott Williams & Wilkins; 2011.
Kasum M, et al. Gynecol Endocrinol. 2017;33:583-7.

Serum hormone levels from a natural cycle



Final follicular maturation

LH surge

- Resumption of oocyte meiosis
- Follicular rupture and oocyte expulsion
- Luteinization

FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; hCG, human chorionic gonadotropin; IVF, in vitro fertilization; KND, kisspeptin/neurokinin B/dynorphin; LH, luteinizing hormone.

Fritz MA, Speroff, L. Clinical gynecologic endocrinology and infertility. 8th ed. Philadelphia: Lipincott Williams & Wilkins; 2011.
Kasum M, et al. Gynecol Endocrinol. 2017;33:583-7.

Empty follicle syndrome

EFS is a phenomenon in which no oocytes are retrieved after ovarian stimulation, despite apparently normal follicular development and E2 levels

- Genuine – in the presence of optimal hCG levels on the day of oocyte retrieval
- False – when hCG levels are low
- Borderline form – in cases in which very few mature or immature oocytes are recovered from several mature follicles

Stevenson TL, Lashen H. Fertil Steril. 2008;90:691-8.
Işik AZ, Vicdan K. Eur J Obstet Gynecol Reprod Biol. 2000;88:213-5.
Nikolettos N, et al. Clin Exp Obstet Gynecol. 2004;31:79-80.
Duru NK, et al. J Reprod Med. 2007;52:858-63.
Desai N, et al. Hum Reprod. 2009;24:1171-5.
Vutyavanich T, et al. Case Rep Med. 2010;2010:367505.

E2, estradiol; EFS, empty follicle syndrome.

Incidence of EFS

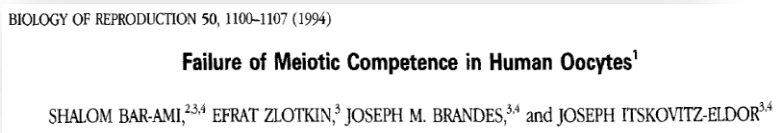
The incidence of EFS is 0.045–3.4%; genuine EFS prevalence is 0–1.1%

Author (year)	No. of OPU cycles	No. of EFS cycles (genuine)	EFS prevalence (%) (genuine%)	No. of patients with EFS	Recurrent EFS
Ben-Shlomo et al. (1991)	1,321	26 (NM)	2 (NM)	26	1/21
Harrison, Fawzy (1996)	1,418	1 (NM)	0.07 (NM)	1	
Ndukwe et al. (1996)	716	6 (0)	0.8 (0)	6	
Fiszbain et al. (1997)	376	9 (0)	2.4 (0)	9	
Awonuga et al. (1998)	2,059	11 (3)	0.92 (0.58)	11	0/5
Driscoll et al. (1998)	4,236	43 (NM)	1.01 (NM)	42	
Quintans et al. (1998)	1,118	5 (0)	0.44	5	
Zreik et al. (2000)	3,004	57 (NM)	1.89	37	55/200
Aktas et al. (2005)	3,060	25 (14)	0.81 (0.45)	25	0/12
Coskun et al. (2010)	5,238	NM (58)	NM (1.1)	26	4/13
Reichman et al. (2010)	15,729	7 (0)	0.045 (0)	7	
Griesinger et al. (2006)	51	1 (NM)	2 (NM)	1	
Mesen et al. (2011)	12,359	11 (2)	0.089 (0.016)	11	
Baum et al. (2011)	8,292	163 (NM)	2 (NM)	136	16/101
Castillo et al. (2012)	3,467	118	3.4	118	

NM, not measured; OPU, ovum pickup.

Beck-Fruchter R, et al. Hum Reprod. 2012;27:1357-67.

Incidence of patients with high proportion of immature oocytes is unknown

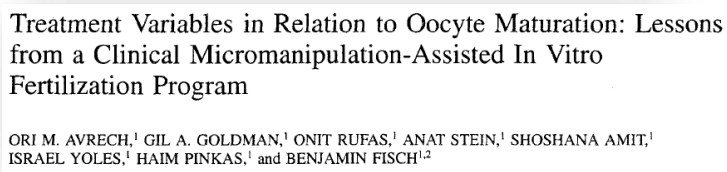


BIOLOGY OF REPRODUCTION 50, 1100–1107 (1994)

Failure of Meiotic Competence in Human Oocytes[1]

SHALOM BAR-AMI,[2,3,4] EFRAT ZLOTKIN,[3] JOSEPH M. BRANDES,[3,4] and JOSEPH ITSKOVITZ-ELDOR[3,4]

- Of the 703 scored menstrual cycles of 487 women, only 58 menstrual cycles of 42 women (8.6%) were found to yield ≥ 1 immature oocyte[1]



Treatment Variables in Relation to Oocyte Maturation: Lessons from a Clinical Micromanipulation-Assisted In Vitro Fertilization Program

ORI M. AVRECH,[1] GIL A. GOLDMAN,[1] ONIT RUFAS,[1] ANAT STEIN,[1] SHOSHANA AMIT,[1] ISRAEL YOLES,[1] HAIM PINKAS,[1] and BENJAMIN FISCH[1,2]

- 154 of the 3,520 oocytes studied (4.4%) were in the GVII stage[2]
  - These oocytes were found in 66 of the treatment cycles (15.2%) and in 54 of the 221 patients (24.4%)

During IVF cycles, patients who have > 25% of immature oocytes retrieved have a reduced pregnancy rate

GV, germinal vesicle.

1. Bar-Ami S, et al. Biol Reprod. 1994;50:1100-7.
2. Avrech OM, et al. J Assist Reprod Genet. 1997;14:337-42.

Causes of failure to retrieve oocytes

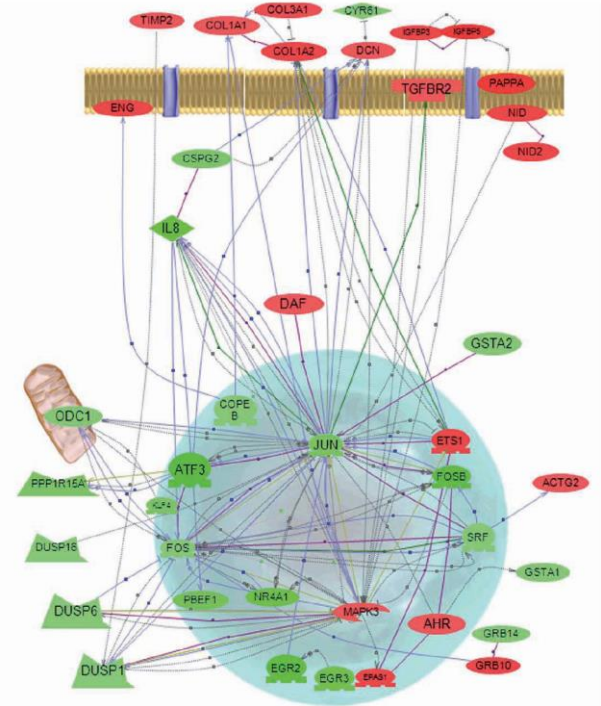
- Low hCG bioavailability resulting from variation in the absorption or clearance of hCG
- Variation in the threshold for follicular response to hCG
- Variation in the time needed from hCG exposure to maturation of oocyte–cumulus complexes
- Intrinsic defects in the biological activity of hCG preparation

Other suggested aetiologies

- Ovarian aging
- Dysfunctional folliculogenesis due to increased apoptosis
- Defective granulosa cell function
- Faulty oocyte development and maturation
- Strong attachment of cumulus cell complexes to the follicular wall
- Dysfunctional ovulation induction

Beck-Fruchter R, et al. Hum Reprod. 2012;27:1357-67.

A genetic cause?

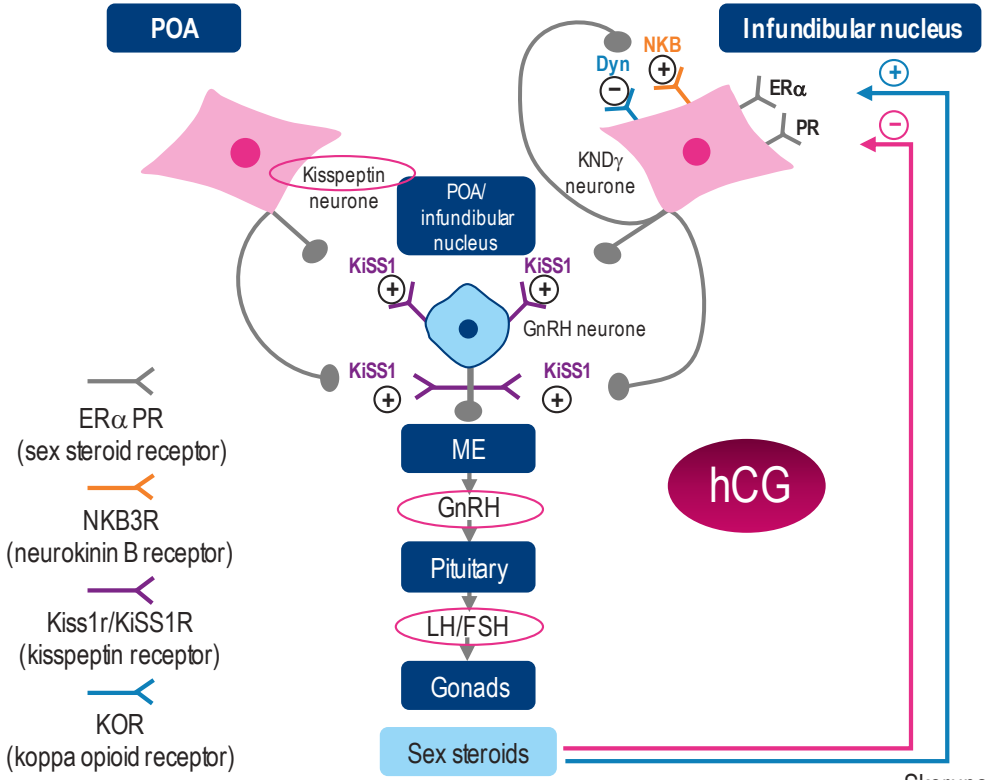


Inherited mutation of the luteinizing hormone/ choriogonadotropin receptor (*LHCGR*) in empty follicle syndrome

Kemal O. Yariz, Ph.D.[a], **Tom Walsh, Ph.D.**[b], **Asli Uzak, M.D.**[c], **Michail Spiliopoulos, M.D.**[a], **Duygu Duman, Ph.D.**[d], **Gogsen Onalan, M.D.**[e], **Mary-Claire King, Ph.D.**[b], and **Mustafa Tekin, M.D.**[a]

Inan MS, et al. Reprod Biomed Online. 2006;13:481-91.
Yariz KO, et al. Fertil Steril. 2011;96:e125-30.

Neuroendocrine control of final follicular maturation



Dyn, dynorphin;
ER, estrogen receptor;
ME, median eminence;
POA, preoptic area;
PR, progesterone receptor.

Skorupskaite K, at al. Hum Reprod Update. 2014;20:485-500.

hCG is a surrogate of the naturally occurring LH surge

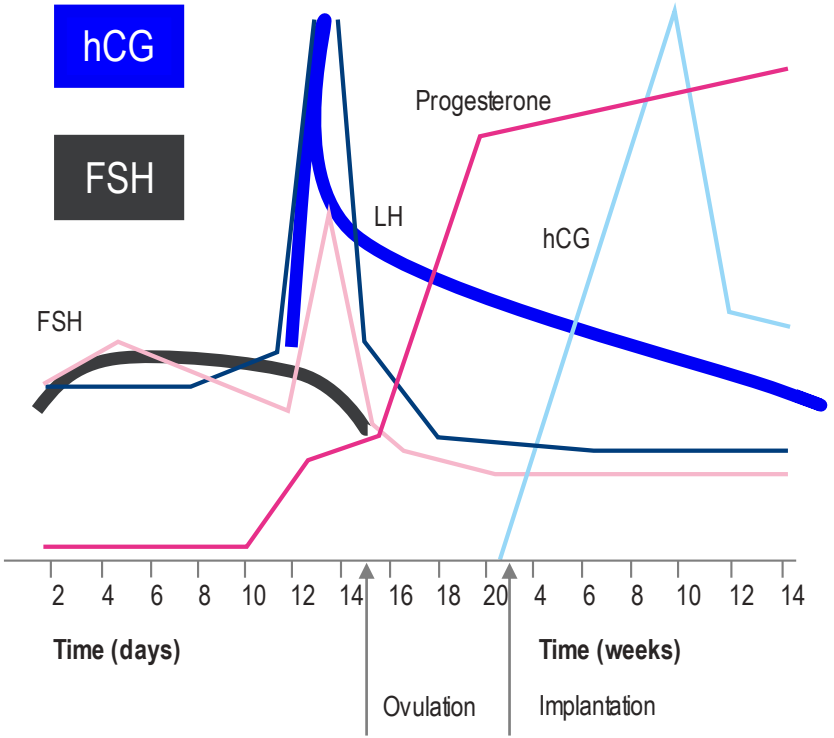
- hCG induces luteinization of the granulosa cells, final oocyte maturation, and resumption of meiosis
- Final follicular maturation is usually triggered by one bolus of hCG (5,000–10,000 units)
  - This is administered as close as possible to the time of ovulation (i.e. 36 hours before oocyte recovery)

Orvieto R. J Ovarian Res. 2015;8:60.

Serum hormone levels from a natural cycle superimposed on a typical stimulation cycle

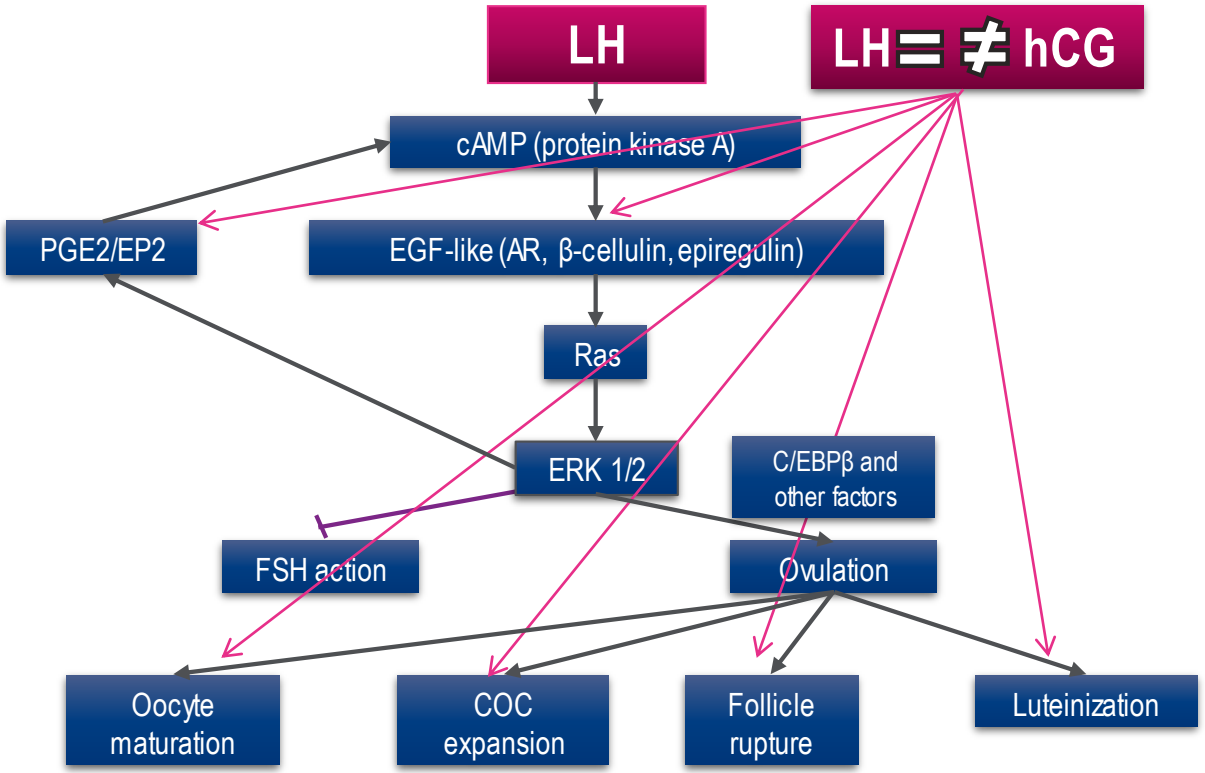
LH
hCG
FSH

?



Lamb JD, et al. Fertil Steril. 2011;95:1655-60.
Fritz MA, Speroff, L. Clinical gynecologic endocrinology and infertility. 8th ed. Philadelphia: Lipincott Williams & Wilkins; 2011.

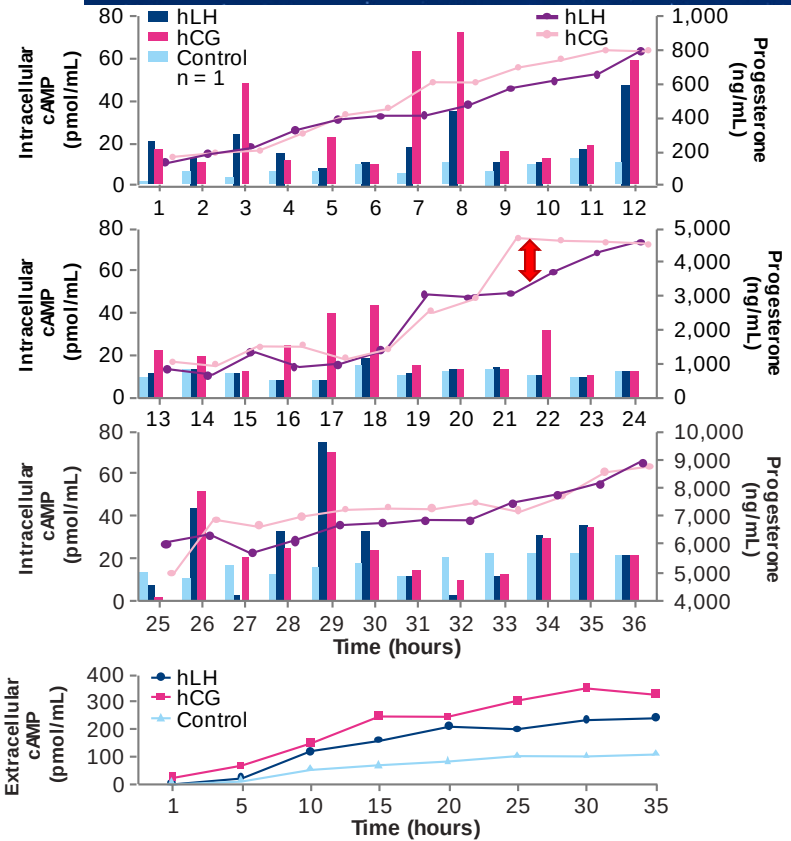
LH versus hCG signalling

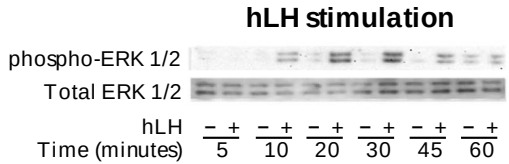


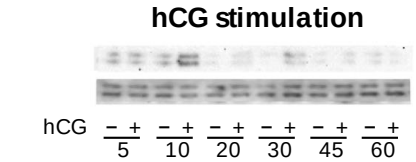
AR, amphiregulin;
cAMP, cyclic AMP;
COC, cumulus cell-oocyte complex;
EBP, enhancer binding protein;
EGF, epidermal growth factor;
EP, epiregulin;
PgE2, prostaglandin E2.

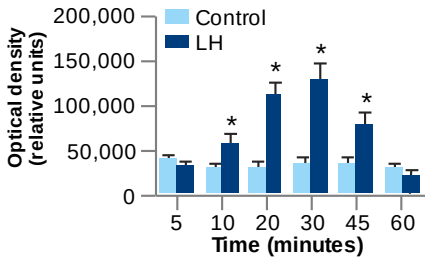
Fan HY, et al. Science. 2009;324:938-41.

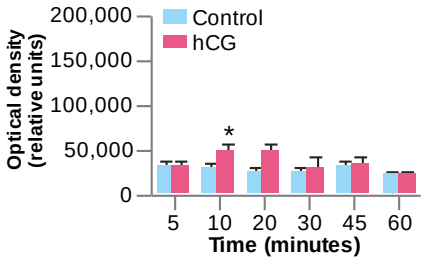
LH and hCG action on the same receptor: differences in intracellular signaling

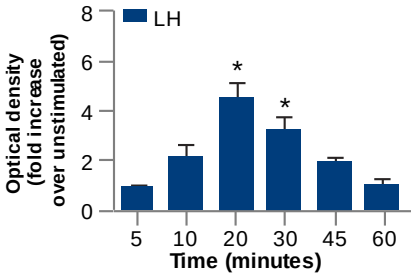


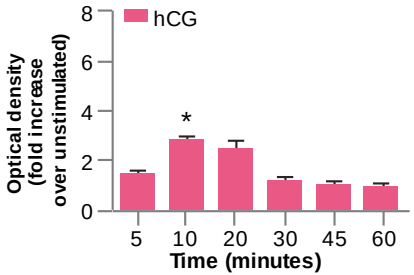






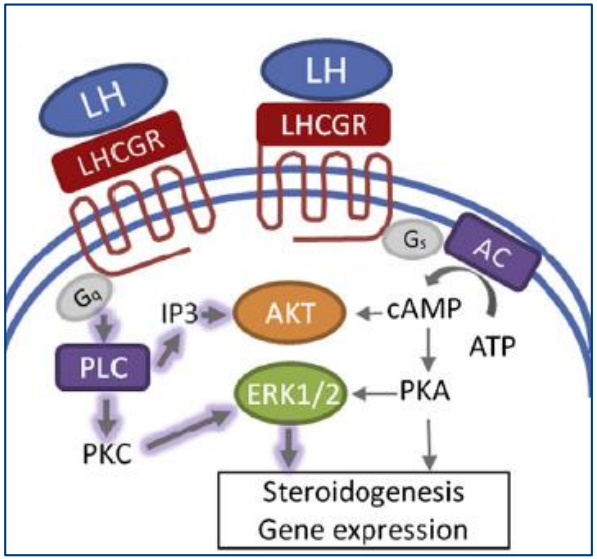


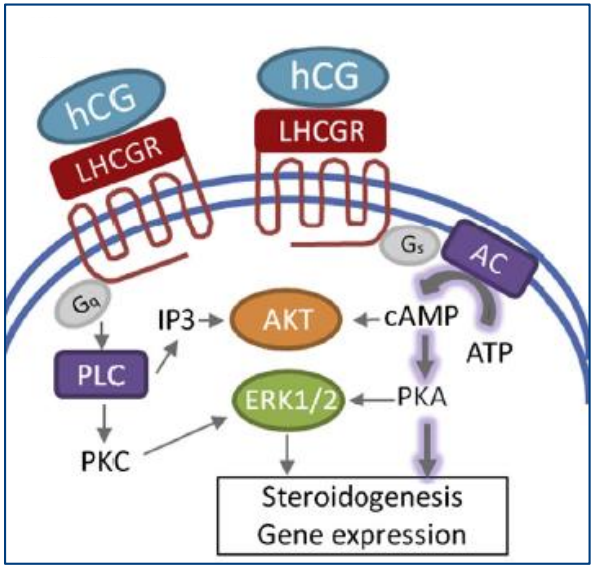




Casarini L et al. LoS ONE 7(10): e46682.
Choi J and Smitz J. Mol Cell Endocrinol. 2014;383:203-13.

LH and hCG action on the same receptor: differences in intracellular signaling



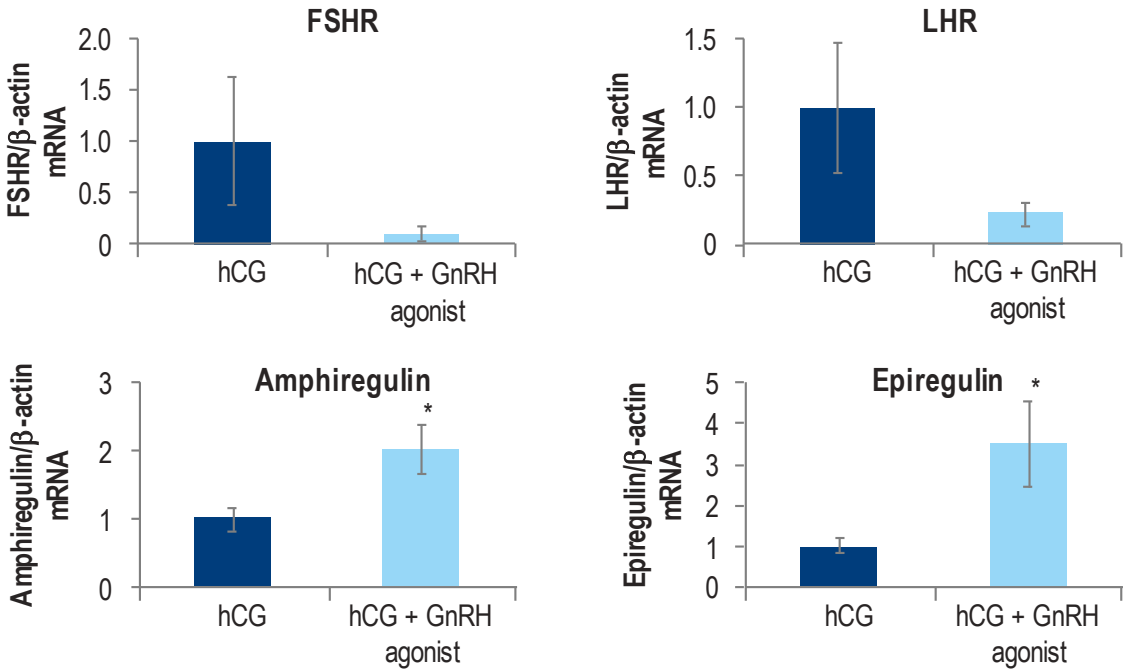


Choi J and Smitz J. Mol Cell Endocrinol. 2014;383:203-13.

hCG versus double trigger for final oocyte maturation in granulosa cells

Standard human chorionic gonadotropin versus double trigger for final oocyte maturation results in different granulosa cells gene expressions: a pilot study

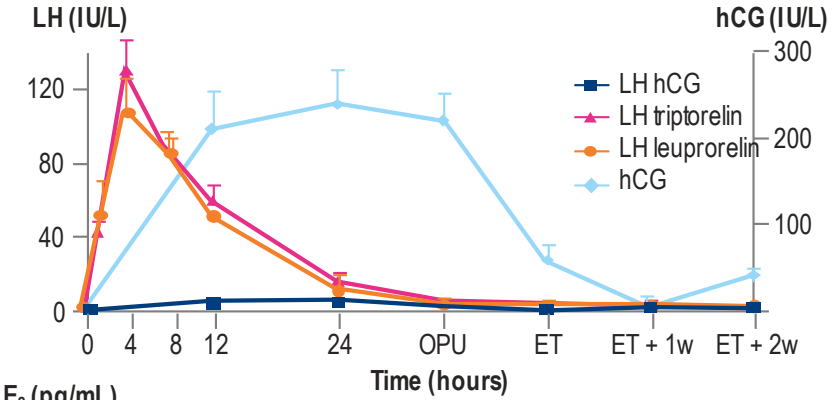
Jigal Haas, M.D., Libby Ophir, B.Sc., Eran Barzilay, M.D., Ph.D., Ronit Machtinger, M.D., Ph.D., Yuval Yung, Ph.D., Raoul Orvieto, M.D., and Ariel Hourvitz, M.D.

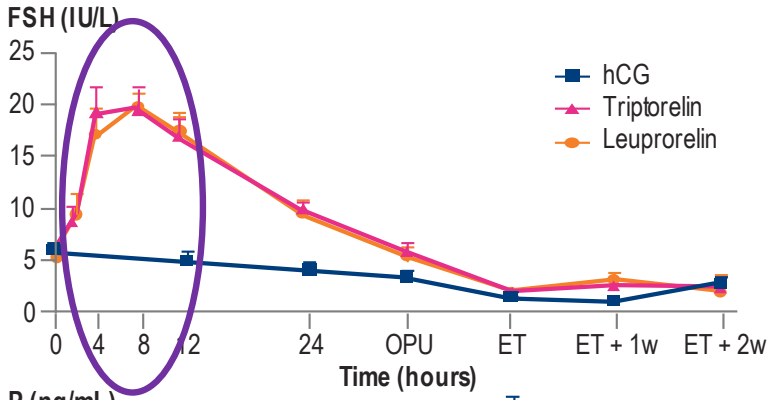


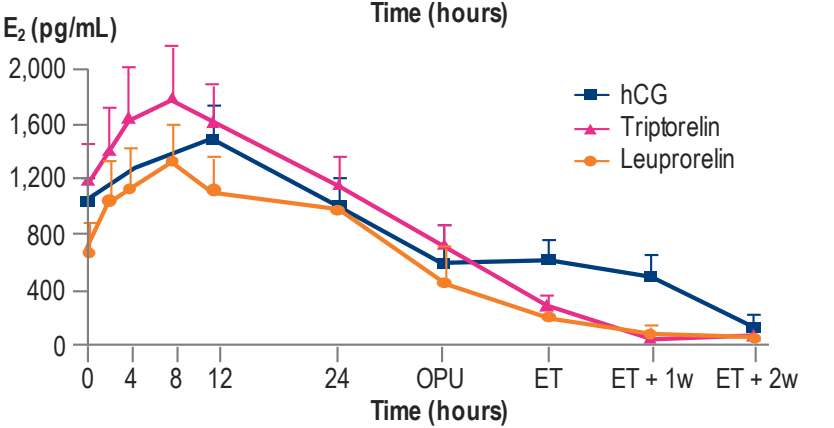
*$p < 0.05$.
FSHR, FSH receptor.

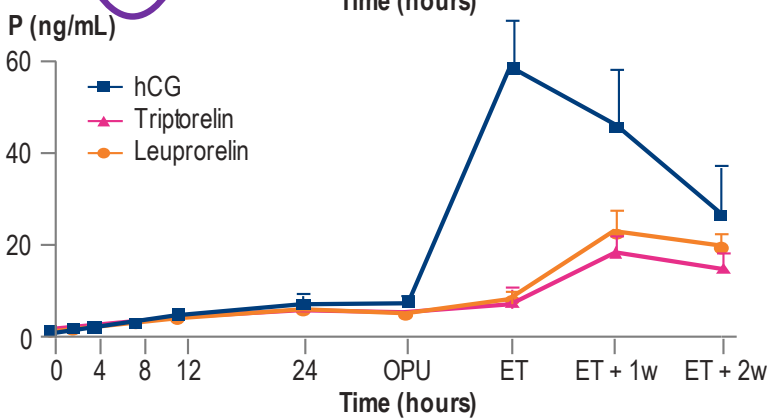
Haas J, et al. Fertil Steril. 2016;106:653-59.

LH, FSH, estradiol, and progesterone levels following triggering of final oocyte maturation





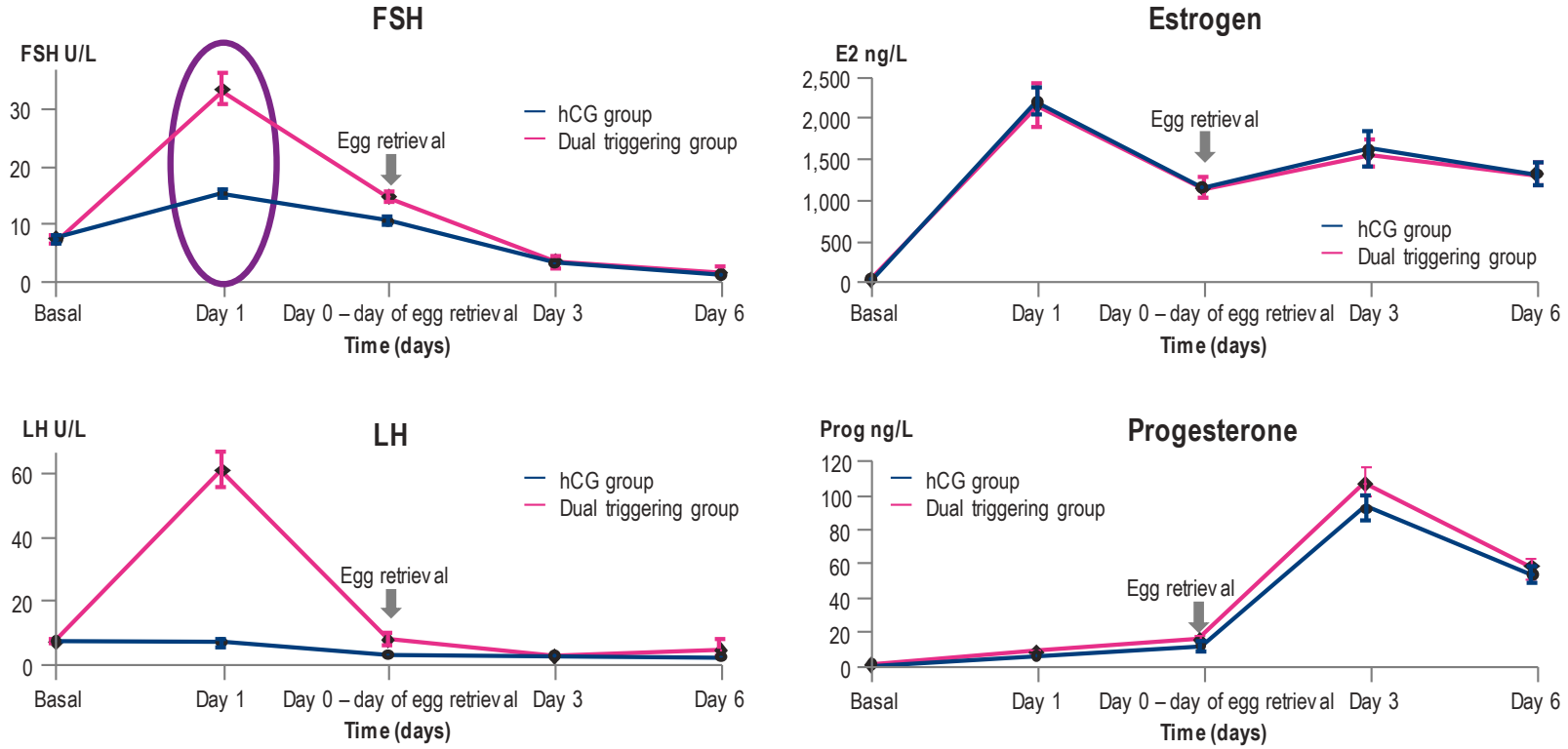




ET, embryo transfer; w, week(s).

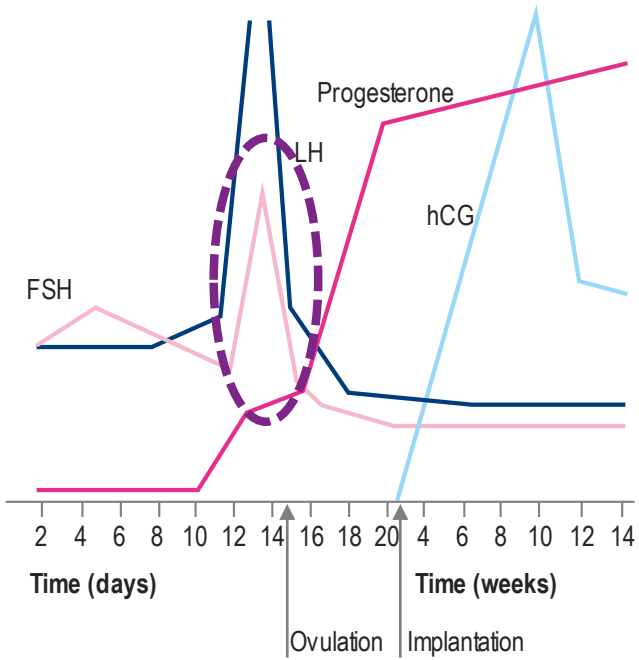
Fauser BC, et al. J Clin Endocrinol Metab. 2002;87:709-15.

Evolution of FSH, LH, estradiol, and progesterone levels following triggering of final oocyte maturation



Decleer W, et al. Facts Views Vis Obgyn. 2014;6:203-9.

FSH administered at the time of hCG trigger improves oocyte developmental competence in in vitro IVF



Comparison of outcomes of FSH bolus group vs placebo

Outcome (450 IU)	FSH (n = 95)	Placebo (n = 93)	p value
Oocyte recovery rate	69.9%	57.1%	0.04
Mean fertilization proportion (2PN/oocytes collected)	0.63	0.55	0.01
ICSI fertilization rate (2PN/MII)	0.79	0.73	0.086
IVF fertilization rate (2PN/oocytes collected)	0.62	0.48	0.04
Mean implantation rate	0.40	0.35	0.35
Clinical pregnancy rate	56.8%	46.2%	0.15
Live birth or ongoing pregnancy rate	51.6%	44.1%	0.30

ICSI, intracytoplasmic sperm injection; MII, metaphase II stage; PN, pronuclei.

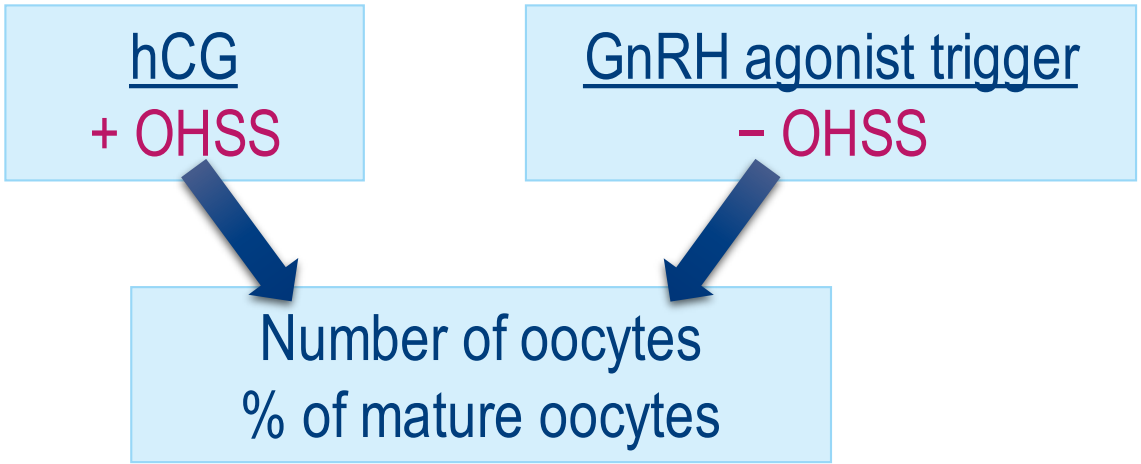
Lamb JD, et al. Fertil Steril. 2011;95:1655-60.

Role of FSH surge

- Promotes formation of LH receptors
- Nuclear maturation
- Cumulus expansion
- Stimulates plasminogen activator leading to dissociation of the oocyte from the follicular wall
- Keeps the gap junctions open between the oocyte and cumulus cells

Role of LH surge

- Resumption of oocyte meiosis
- Follicular rupture and oocyte expulsion
- Luteinization



OHSS, ovarian hyperstimulation syndrome.

GnRH agonist vs hCG

Studies	Oocytes, n	MII, n	MII/ oocytes, n	Top quality embryo, n
Fauser et al, 2002[1]	=		=	=
Kolibianakis et al, 2005[2]	=	=	=	
Humaidan et al, 2005[3]	=		>	
Acevedo et al, 2006[4]	=	=	=	=
Erb et al, 2010[5]	>	>		>

When effects are observed across studies, they are always in the same direction – **consistently improved**

1. Fauser BC, et al. J Clin Endocrinol Metab. 2002;87:709-15.
2. Kolibianakis EM, et al. Hum Reprod. 2005;20:2887-92. 3. Humaidan P, et al. Hum Reprod. 2005;20:1213-20.
4. Acevedo B, et al. Fertil Steril. 2006;86:1682-7. 5. Erb TM, et al. Fertil Steril. 2010;93:374-8.

Dual trigger with GnRH agonist and hCG improves LBR for normal responders

Normal responders

- hCG trigger standard dosage: 6,500 IU rhCG
- Dual trigger: 0.2 mg triptorelin and 6,500 IU rhCG

Outcomes of IVF/ICSI cycles

Variable	Control (hCG)	hCG + triptorelin	p value
Implantation rate, %	18.43	29.68	< 0.001
Clinical pregnancy rate per ET, %	40.11	50.79	0.047
Abortion rate, %	18.67	16.49	NS
LBR per ET, %	30.49	41.36	0.042
Blastocyst progression rate, %	55.6	52.9	NS
OHSS rate, %	0.005	0	NS

Characteristics of ovarian stimulation

Variable	Control (hCG)	hCG + triptorelin	p value
Total dose of gonadotropins, IU	4,062	3,851	NS
Duration of stimulation, days	10.3	9.6	NS
E2 on trigger day, pg/mL	2,139	2,083	NS
Progesterone on trigger day, ng/mL	1.84	2.09	NS
Duration of GnRH-antagonist treatment, d	3.5	3.4	NS
Endometrial thickness on trigger day, mm	9.8	10.1	NS
Oocytes retrieved, n	10.10	12.36	< 0.01
MII oocytes retrieved, n	8.03	10.53	< 0.01
Embryos obtained, n	5.3	5.8	NS
Top quality embryos obtained, n	2.9	2.9	NS
Embryos transferred, n	2.84	2.79	NS
Embryos cryopreserved, n	1.60	1.97	< 0.01

LBR, live birth rate; NS, not significant; rhCG, recombinant hCG.

Lin MH, et al. Fertil Steril. 2013;100:1296-302.

Comparison of hCG vs hCG and GnRH agonist

Embryological parameters between patients triggered with hCG vs GnRH agonist + hCG

	hCG triggering	Dual triggering	p value
MII oocytes, n	9.2	10.3	NS
Cumulus oocyte complexes, n	12.0	13.9	NS
2PN oocytes, n	6.0	7.4	NS
Cryopreserved embryos, n	1.5	2.2	NS
Patients with ≥ 1 top quality embryo, n/N (%)	28/59 (47.5)	45/61 (73.8)	0.001
Patients with embryos for cryopreservation, n/N (%)	21/59 (35.6)	33/61 (54.1)	0.04

In this prospective randomized controlled trial, there were no significant differences in the number of COCs or pregnancy rates

Decleer W, et al. Facts Views Vis Obgyn. 2014;6:203-9.

Dual trigger in patients with mild male factor infertility, unexplained infertility, or tubal factor infertility: retrospective, case-control cohort study

Ovarian stimulation and cycle characteristics[a]

	Standard group (n = 72)	Dual trigger group (n = 84)	p value
Total dose of gonadotropins, IU	2,009	2,021	0.86
Duration of stimulation, days	10.3	10.4	0.63
Total dose of antagonist, IU	417	423	0.70
Duration of GnRH antagonist, days	5.5	5.6	0.71
E2 on trigger day, pg/mL	2,059	2,143	0.77
P on trigger day, ng/mL	0.98	1.02	0.72
Endometrial thickness on trigger day, mm	8.8	8.9	0.75
Oocytes retrieved, n	9.2	10.8	0.07
MII oocytes retrieved, n	6.3	7.9	0.02
Embryos obtained, n	4.6	5.0	0.24
Grade A embryos obtained, n	1.1	1.6	0.01
Embryos transferred, n	1.5	1.5	0.45
Blastocyst transfer, n (%)	10 (13.8)	14 (16.6)	0.63
Mild OHSS, n (%)	2 (2.7)	2 (2.3)	0.87
Cycle cancellation, n (%)	6 (8.3)	5 (5.9)	0.56
Clinical pregnancy rate, n (%)	27 (37.5)	46 (54.8)	0.006
Implantation rate, %	27.4	41.0	0.01

[a] Retrospective, case-control cohort study.

Seval MM, et al. Obstet Gynaecol Res. 2016;42:1146-51.

Effect of dual trigger vs hCG alone on clinical outcomes: retrospective cohort study

Outcome	hCG group (n = 101)	Dual trigger group (n = 224)	Odds ratio (95% CI)	p value
Embryos transferred, n	2.07	1.9		0.082
Live deliveries, n/N (%)	31/76 (40.8)	95/175 (54.3)	1.64 (0.94–2.85)	0.083
Clinical pregnancy, n/N (%)	40/76 (52.6)	109/175 (62.3)	0.71 (0.41–1.24)	0.225
Early spontaneous abortion, n/N (%)	4/40 (10.0)	5/109 (4.6)	2.20 (0.55–8.77)	0.264
Implantation, n/N (%)	57/157 (36.3)	154/364 (42.3)		0.200
OHSS, n/N (%)	1/101 (1.0)	0/224 (0)		0.311
Mature oocyte rate, n/N (%)	286/387 (73.9)	247/326 (75.8)		0.568
Embryos, n				
2PN	5.0	5.9		0.004
Available	3.4	4.2		0.001
High quality	2.3	2.8		0.011
Normal fertilization rate				
IVF, n/N (%)	313/535 (58.5)	1111/1785 (62.2)		0.119
ICSI, n/N (%)	182/286 (63.6)	171/247 (69.2)		0.173

CI, confidence interval.

Zhou X, et al. Int J Gynaecol Obstet. 2018;141:327-31.

Dual trigger with GnRH agonist and hCG improves oocyte maturity rates

Patients with a history of > 25% immature oocytes retrieved. GnRHa and hCG 5,000/10,000 IU

Variable	Prior cycle (n = 27)	Dual trigger (n = 27)	p value
Outcome of ovarian stimulation			
Total days of stimulation	10	10	NS
Total dose of gonadotropins, IU	4,200	5,400	0.02
Oocytes retrieved, n	9	11	0.02
Mature oocytes, n	3	7	< 0.01
Mature oocytes,%	38.5	75.0	< 0.01
Fertilization rate, %	66.7	83.3	NS
Embryos transferred, n	1	2	NS

Dual trigger in patients with low oocyte maturation improves the rate of oocyte maturation; however, implantation and pregnancy rates remained low, suggesting underlying oocyte dysfunction

[a] Patients with a history of > 25% immature oocytes retrieved; GnRHa and hCG 5,000/10,000 IU.
GnRHa, GnRH agonist.

Griffin D, et al. Fertil Steril. 2014;102:405-9.

Dual trigger in patients with high immature oocyte rates

Non-interventional retrospective study, final oocyte maturation was triggered with hCG in patients with > 50% immature oocytes

	hCG trigger (n = 81)	Dual trigger (n = 81)	p value
Total oocytes,n	5.5	7	0.02
MII, n	2.4	5.3	< 0.001
MII rate, %	43.6	72.9	< 0.001
Fertilized eggs, n	2.9	4.8	< 0.001
Fertilization rate, %	79.6	82.5	0.7
Transferred embryos, n	1.2	1.3	0.5
Frozen embryos, n	0.8	1.3	0.2
Implantation rate, %	17.3	30.8	0.1
Clinical pregnancy rate, %	26.9	43.6	0.2
Ongoing pregnancy rate, %	15.3	31.6	0.1

Fabris AM, et al. Reprod Sci. 2017;24:1221-5.

Dual trigger vs hCG alone: a meta-analysis

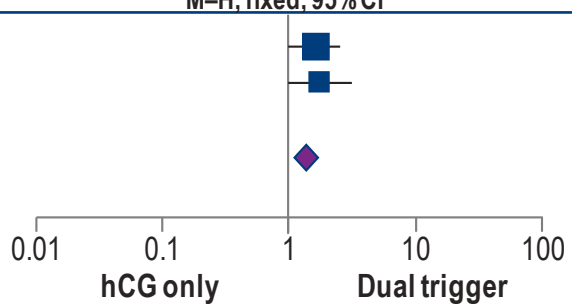
Study (year)	Study design	Country	Patients, n	Cycles, n
Schachter 2008	RCT	Israel	105	97
			106	103
Decleer 2014	RCT	Belgium	61	61
			59	59
Kim 2014	RCT	Korea	60	60
			60	60
Mahajan 2016	RCT	India	38	38
			38	38

No significant differences for:

- Number of oocytes retrieved
- Number of mature oocytes retrieved
- Number of fertilized oocytes
- Number of good quality embryos
- Implantation rate

Forest plot of pregnancy rate associated with comparing dual trigger with hCG alone for IVF

	Experimental		Control			Risk ratio	
Study or subgroup	Events	Total	Events	Total	Weight	M–H, fixed, 95% CI	Year
Schachter 2008	43	97	30	103	59.3%	1.52 (1.05–2.21)	2008
Kim 2014	32	60	20	60	40.7%	1.60 (1.04–2.46)	2014
Total (95% CI)		**157**		**163**	**100.0%**	**1.55 (1.17–2.06)**	
Total events	75		50				



M–H, Mantel–Haenszel; RCT, randomized controlled trial.

Ding N, et al. Eur J Obstet Gynecol Reprod Biol. 2017;218:92-8.

human reproduction

CASE REPORT *Infertility*

Empty follicle syndrome: successful treatment in a recurrent case and review of the literature

R. Beck-Fruchter[1,*], A. Weiss[1], M. Lavee[1,2], Y. Geslevich[1], and E. Shalev[1,2]

Double trigger

- GnRH agonist: 40 hours prior to OPU
- hCG: 34 hours prior to OPU

This trigger combines the advantages of both

- Prolongation of the time between ovulation triggering and OPU
- GnRH agonist trigger with the consequent simultaneous induction of an FSH surge

Beck-Fruchter R, et al. Hum Reprod. 2012;27:1357-67.

Comparison between IVF cycles with double trigger vs hCG: a preliminary report

Low (< 50%) number of oocytes retrieved per number of preovulatory follicles, despite normal response to COH

	hCG	Double trigger	p value
Gonadotropin ampoules used, n	38.5	49.8	NS
Length of stimulation, days	10.7	10.7	NS
Total gonadotropin used, n	39	49	NS
Peak E2 levels on day of hCG administration, pmol/L	5402	4642	NS
Progesterone levels on day of hCG administration, nmol/L	1.7	1,5	NS
Follicles of > 14 mm on day of hCG administration, n	8.0	6.4	NS
Follicles of > 10 mm on day of hCG administration, n	10.6	8.2	NS
Oocytes retrieved, n	2.3	7.0	< 0.02
2PN embryos, n	1.7	6.0	< 0.002
Top quality embryos, n	0.4	3.7	0.06
Embryos transferred, n	0.85	2.2	< 0.002
Oocytes retrieved per number follicles of > 14 mm on day of hCG administration, %	23.7	118.0	< 0.01
Oocytes retrieved per number follicles of > 10 mm on day of hCG administration, %	18.5	80.3	< <0.001
Positive hCG, % (n/N)	0 (0/8)	62.5 (5/8)	< 0.001
Clinical ongoing pregnancy, % (n/N)	0 (0/8)	37.5 (3/8)	< 0.03

COH, controlled ovarian hyperstimulation.

Haas J, et al. J Ovarian Res. 2014;7:77.

Double trigger in patients with low proportion of mature oocytes

Low proportion of mature MII oocytes (< 66%) per number oocytes retrieved despite normal response to COH

	hCG (n = 12)	Double trigger (n = 12)	p value
Length of stimulation, days	10.0	10.2	NS
Peak E2 levels on day of hCG administration, pmol/L	5737	6389	NS
Progesterone levels on day of hCG administration, nmol/L	2.1	2.2	NS
Follicles of > 14mm on day of hCG administration, n	6.6	8.6	NS
Follicles of > 10mm on day of hCG administration, n	9.7	10.9	NS
Oocytes retrieved, n	8.0	10.4	< 0.03
MII oocytes, n	3.67	6.5	< 0.008
MI oocytes, n	1.8	0.16	< 0.003
2PN embryos, n	2.8	6.6	< 0.001
Number of MII per number of oocytes retrieved, %	47.1	69.7	< 0.03
Top quality embryos, n	1	3.16	< 0.02
Embryos transferred, n	1.16	2.41	< 0.03
Ongoing clinical pregnancy rate, n/N (%)	0/12 (0)	6/12 (50)	< 0.001

MI, metaphase I.

Zilberberg E, et al. Gynecol Endocrinol. 2015;31:145-7.

Poor ovarian response: Bologna criteria

POR involves the presence of at least 2 of 3 of the following features:

1) Advanced maternal age (≥ 40 years) or any other risk factor for POR
2) A previous POR (≤ 3 oocytes with a conventional stimulation protocol)
3) An abnormal ovarian reserve test

High prevalence of premature luteinization/ovulation

POR, poor ovarian response.

Ferraretti AP, et al. Hum Reprod. 2011;26:1616-24.

High prevalence of premature luteinization/ovulation

May be overcome by:

1) Early triggering of final follicular maturation while approaching a follicular size of 15–16 mm
2) Shortening the duration between the trigger and OPU

May decrease the percentage of mature oocytes

Dual/double trigger

Dual trigger of final oocyte maturation in poor ovarian responders undergoing IVF/ICSI cycles

Retrospective cohort study: progesterone-primed ovarian stimulation in combination with a freeze-all policy

	Group A: 5,000 IU hCG (n = 328)	Group B: 0.1 mg GnRHa + 5,000 IU hCG (n = 386)	Group C: 10,000 IU hCG (n = 363)	Group D: 0.1 mg GnRHa + 10,000 IU hCG (n = 312)	p value[a]	p value[b]
Duration of HMG treatment, days	8.55	8.5	8.6	8.6	NS	NS
Total dose of gonadotrophins, IU	1,562.4	1,559.7	1,547.3	1,601.4	NS	NS
Estradiol on trigger day, pg/mL	1,066.3	1,094.5	1,070.5	1,140.0	NS	NS
Progesterone on trigger day, ng/mL	0.4	0.4	0.4	0.4	NS	NS
Estradiol on day after trigger, pg/mL	1,178.7	1,265.5	1,191.9	1,285.7	NS	NS
Progesterone on day after trigger, ng/mL	14	1.8	1.4	1.9	< 0.001	< 0.001
Oocytes retrieved, n	2	3	2	3	< 0.001	< 0.001
Mature oocytes, n	2	3	2	3	< 0.001	<0.001
Top quality embryos, n	1	1	1	1	NS	NS
Viable embryos, n	1	1	1	1	NS	NS
ICSI rate, n (%)	106	116	118	97	NS	NS
Oocyte retrieval rate, n/N(%)	784/1373 (57.1)	1119/1623 (68.9)	886/1532 (57.8)	936/1372 (68.2)	< 0.001	< 0.001
Mature oocyte rate, n/N (%)	638/784 (81.4)	990/1119 (88.5)	717/886 (80.9)	820/936 (87.6)	< 0.001	< 0.001

[a] Group A vs Group B. [b] Group C vs Group D.
HMG, human menopausal gonadotropin.

Zhang J, et al. Reprod Biomed Online. 2017;35:701-7.

Diminished ovarian reserve: effect of dual triggering on pregnancy outcomes

- Retrospective cohort study, diminished ovarian reserve was defined as the presence of both serum AMH ≤ 1.1 ng/mL and low AFC ≤ 5 at the time of initiation of ovarian stimulation

Comparison between hCG and dual trigger protocols: outcomes of IVF–ICSI cycles

	Control group (hCG)	Study group (hCG + triptorelin)	p value
Cancellation of embryo transfer, %	15.4	6.1	0.003
Implantation rate, %	10.58	15.02	NS
Biochemical pregnancy rate per cycle, %	4.6	2.0	NS
Clinical pregnancy rate per cycle, %	20.7	33.0	0.035
Live birth rate per cycle, %	13.1	27.2	0.014
Abortion rate, %	37.0	17.4	0.037
Twin pregnancy rate, %	1.5	4.4	NS

AFC, antral follicle count; AMH, anti-Müllerian hormone.

Lin MH, et al. Reprod Biol Endocrinol. 2019;17:7.

Does double trigger improve outcomes in poor responders? A pilot study

Patients demographics and IVF-cycle-related variables in the different study groups

Study group	hCG trigger	GnRHa trigger	Double trigger	p value
Patients, n	11	10	12	-
Age, years	39.4	42.2	40.3	NS
BMI, kg/m^2	26.0	25.9	24.6	NS
Days of stimulation, n	10.1	11.2	9.3	NS
E2 levels on the trigger day, (pmol/L)	2,707	3,243	2,236	NS
Follicles between 10 mm and 14 mm, n	2.1	1.5	1.7	NS
Number of follicles ≥ 15 mm	2.5	2.9	2.5	NS
Cases without any oocytes retrieved, n	3	1	1	NS
Oocytes retrieved, n	2	3	2.8	NS
2PN, n	1.4	2.1	1.8	NS
Top quality embryo (Day 3), n	0.3	0.5	1.1	0.02[a]
Ongoing pregnancy, n/N (%)	1/11 (9.1)	0/10	2/11 (18.2)	NS

[a] hCG vs double trigger.

Haas J, et al. Gynecol Endocrinol. 2019 Feb 27:1-3 [Epub ahead of print].

Conclusion for current clinical practice

Normal responders

- Standard hCG dose alone, or concomitant with GnRH agonist (**dual trigger**) 35–37 hours before oocyte retrieval
- Aim is to improve oocyte yield, number of matured oocytes, and top quality and cryopreserved embryos

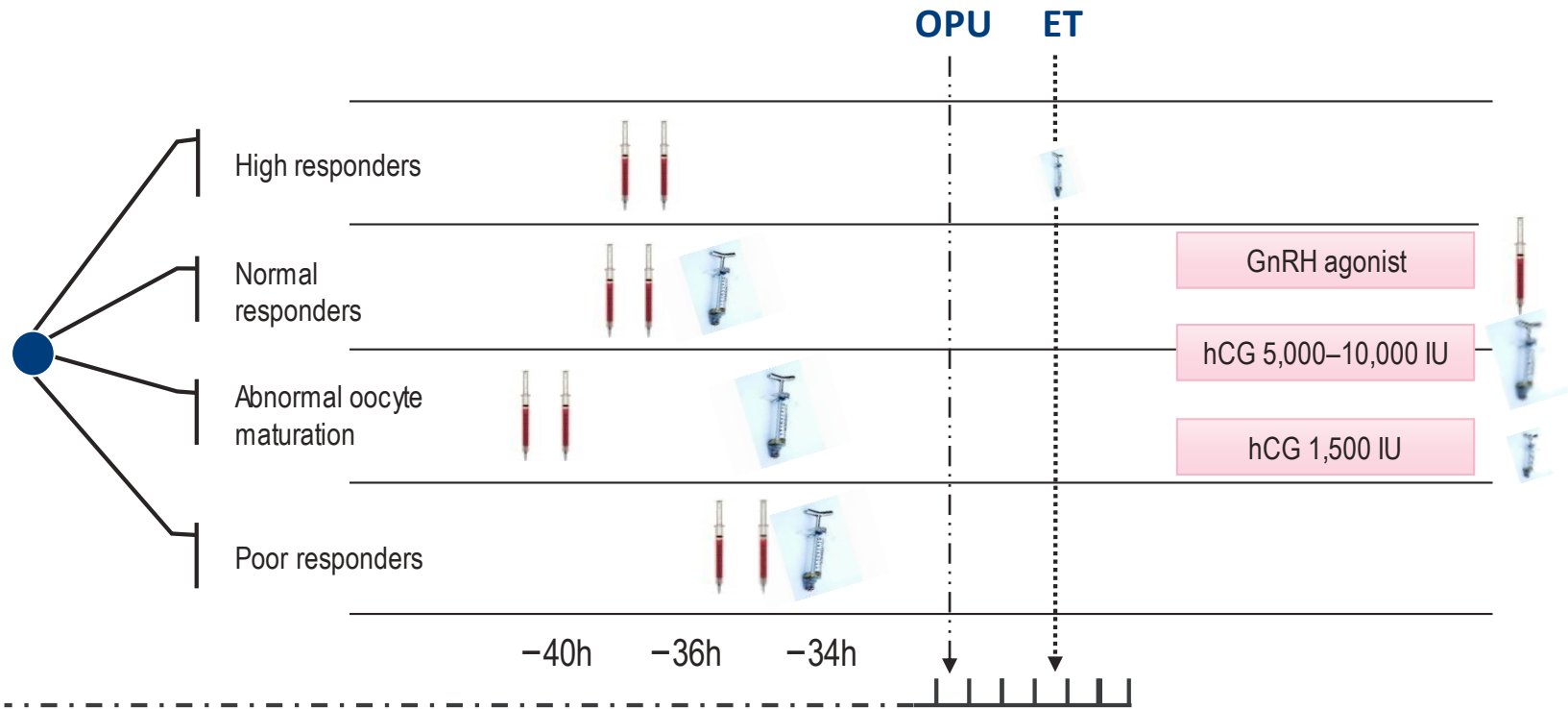
Patients demonstrating abnormal final follicular maturation despite normal response to COH

- Those with low (< 50%) number of oocytes retrieved per number of dominant follicles > 14 mm on day of hCG administration and those with low proportion of MII oocytes (< 66%) per number of oocytes retrieved
- GnRH agonist 40 hours and standard hCG added 34 hours prior to OPU (**double trigger**)

Poor responders

- Standard hCG dose concomitant with GnRH agonist (**dual or double trigger**)
- Aim is to improve oocyte yield and maturation, and prevent premature luteinization

Triggering final follicular maturation



h, hours.