XXXVII SABATO DELL'ANDROLOGIA

Colloqui in PMA tra ginecologi e andrologi

L'uso di triptorelina, il doppio trigger e l'avvento della kisspeptina

Katarzyna Litwicka

European Hospital

17 Febbraio 2018, Paderno Dugnano

GnRHa and hCG trigger- physiological basis

The hCG-mediated LH activity, with no FSH rise, spans several days into the luteal phase. The hCG endocrine effect on the corpus luteum is well known but the sustained luteotrophic effect of HCG is associated with increased chances for OHSS . GnRHa and hCG act on the same LH receptor but HCG generates higher intracellular cAMP accumulation which stimulates steroidogenesis production (Barski, 2006).

GnRH agonist induces endogenous LH and FSH surges which rise after 4 and 12 h, respectively, and are elevated for 24–36 h. The endogenous surge of FSH after GnRH agonists' trigger has been reported to have important role in ovulation and oocyte maturation (Downs, 2005; Prochazka, 2012).

GnRHa has a greater impact on AKT and extracellular signal regulated protein kinase (ERK1/2) phosphorylation, responsible for granulosa cells proliferation, differentiation and survival. Although previous studies have observed higher mature oocytes yield using GnRH agonist for ovulation triggering (Humaidan, 2005), lower pregnancy rates were also reported (Kolibianakis, 2005; Griesinger, 2006) probably due to the luteal phase insufficiency caused by luteolysis and the consequent lower luteal P levels.

The endogenous LH surge caused by GnRH agonist induces milder secretion of VEGF having a fundamental role in the pathophysiology of OHSS (Pellicer, 1999).

Gonadotropin-releasing hormone agonist versus HCG for oocyte triggering in antagonist-assisted reproductive technology

Youssef MAFM, Van der Veen F, Al-Inany HG, Mochtar MH, Griesinger G, Nagi Mohesen M, Aboulfoutouh I, van Wely M

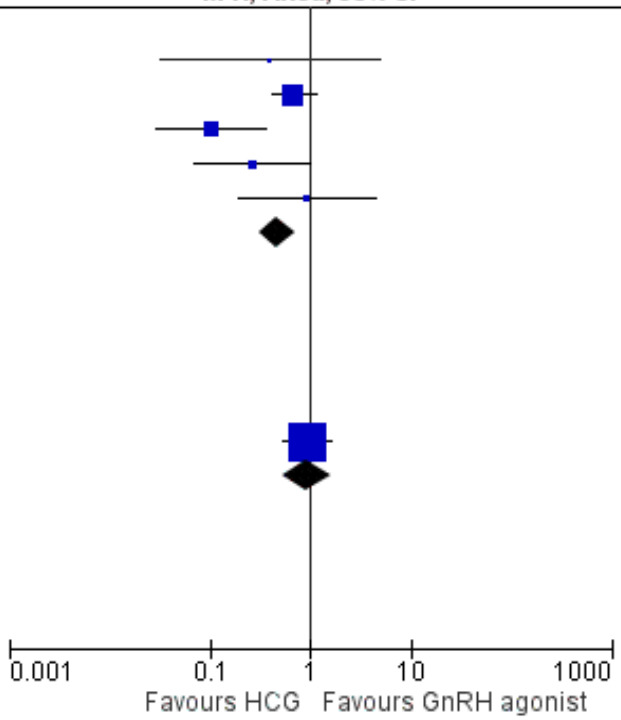
Seventeen RCTs, 13 in fresh autologous cycles and four in donor-recipient cycles, including 1847 randomly assigned women, met the inclusion criteria and were fully reviewed.

Analysed studies included 791 women in the intervention groups and 779 in the control groups. All were women with subfertility from 18 to 40 years of age. All participants were undergoing IVF treatment cycles followed by fresh ET in autologous or donor cycles.

Cochrane database Syst Rev, 2014

GnRH agonist vs HCG for oocyte maturation triggering: Live birth rate

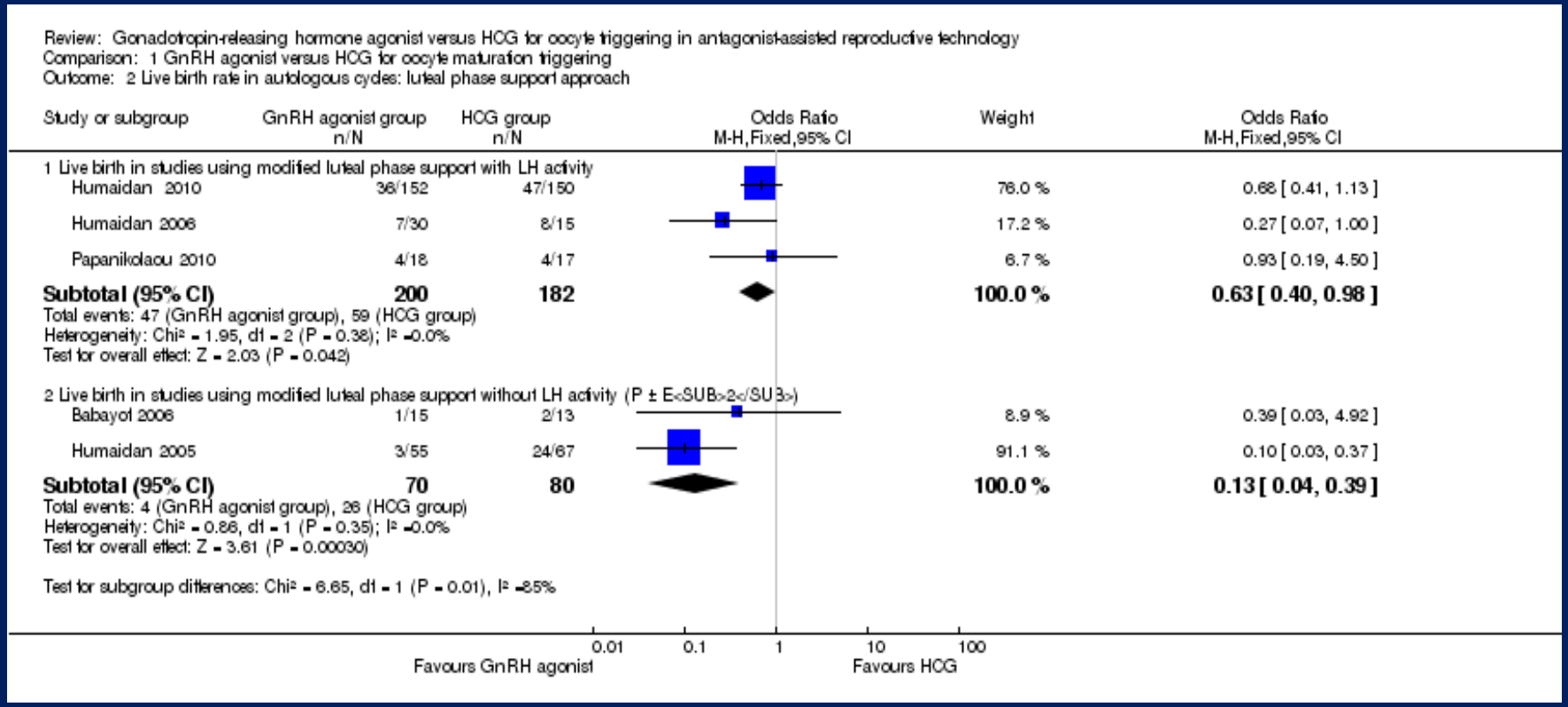
Study or Subgroup	GnRH agonist group Events	Total	HCG group Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.1.1 Fresh autologous cycles						
Babayof 2006	1	15	2	13	2.9%	0.39 [0.03, 4.92]
Humaidan 2010	36	152	47	150	51.6%	0.68 [0.41, 1.13]
Humaidan 2005	3	55	24	67	29.3%	0.10 [0.03, 0.37]
Humaidan 2006	7	30	8	15	11.7%	0.27 [0.07, 1.00]
Papanikolaou 2010	4	18	4	17	4.6%	0.93 [0.19, 4.50]
Subtotal (95% CI)		**270**		**262**	**100.0%**	**0.47 [0.31, 0.70]**
Total events	51		85			
Heterogeneity: Chi² = 8.99, df = 4 (P = 0.06); I² = 56%						
Test for overall effect: Z = 3.69 (P = 0.0002)						
1.1.2 Donor cycles						
Galindo 2009	40	106	42	106	100.0%	0.92 [0.53, 1.61]
Subtotal (95% CI)		**106**		**106**	**100.0%**	**0.92 [0.53, 1.61]**
Total events	40		42			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.28 (P = 0.78)						
Test for subgroup differences: Chi² = 3.82, df = 1 (P = 0.05), I² = 73.8%						



In fresh autologous cycles GnRH agonist trigger was associated with a lower LBR than was seen with HCG (OR 0.47, 95% CI 0.31 to 0.70; five RCTs, 532 women, I^2 = 56%). %. The live birth rate varied from 15% to 53% in the HCG group and from 5% to 24% in the agonist group. This means that for a woman with a 31% chance of achieving live birth with the use of HCG, the chance of a live birth with the use of a GnRh agonist will be between 12% and 24%.

Cochrane database Syst Rev, 2014

GnRH agonist vs HCG for oocyte maturation triggering: Live birth rate and luteal phase support

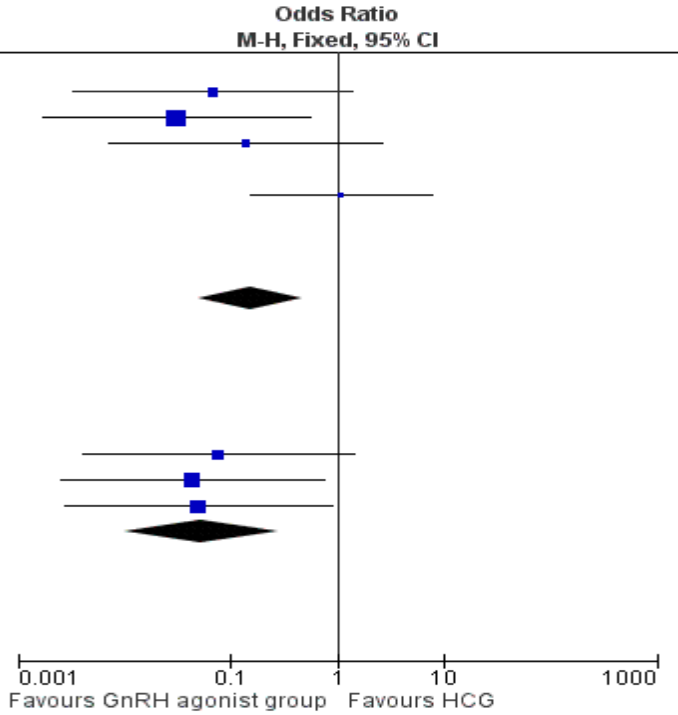


The subgroup analysis based on luteal phase support used revealed differences in LBR between trials that used luteal phase support with LH activity and trials that used luteal phase support without LH activity. Both groups showed evidence of differences in LBR in favour of HCG, but this difference was significantly greater in studies that used luteal support without LH.

Cochrane database Syst Rev, 2014

GnRH agonist vs HCG for oocyte maturation triggering: OHSS incidence

Study or Subgroup	GnRH agonist group Events	Total	HCG group Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.3.1 Fresh autologous cycles						
Babayof 2006	0	15	4	13	22.4%	0.07 [0.00, 1.41]
Engmann 2008 (1)	0	34	10	32	51.4%	0.03 [0.00, 0.56]
Humaidan 2010	0	152	3	150	16.9%	0.14 [0.01, 2.70]
Humaidan 2006	0	30	0	15		Not estimable
Humaidan 2013	2	185	2	199	9.2%	1.08 [0.15, 7.72]
Kolibianakis 2005	0	52	0	54		Not estimable
Papanikolaou 2010	0	18	0	17		Not estimable
Pirard 2006	0	17	0	6		Not estimable
Subtotal (95% CI)		**503**		**486**	**100.0%**	**0.15 [0.05, 0.47]**
Total events	2		19			
Heterogeneity: Chi² = 5.21, df = 3 (P = 0.16); I² = 42%						
Test for overall effect: Z = 3.29 (P = 0.0010)						
1.3.2 Donor cycles: mild, moderate or severe OHSS						
Acevedo 2006	0	30	5	30	22.3%	0.08 [0.00, 1.44]
Galindo 2009	0	106	10	106	43.0%	0.04 [0.00, 0.75]
Melo 2009	0	50	8	50	34.7%	0.05 [0.00, 0.88]
Subtotal (95% CI)		**186**		**186**	**100.0%**	**0.05 [0.01, 0.28]**
Total events	0		23			
Heterogeneity: Chi² = 0.08, df = 2 (P = 0.96); I² = 0%						
Test for overall effect: Z = 3.46 (P = 0.0005)						



Test for subgroup differences: Chi² = 1.09, df = 1 (P = 0.30), I² = 8.6%

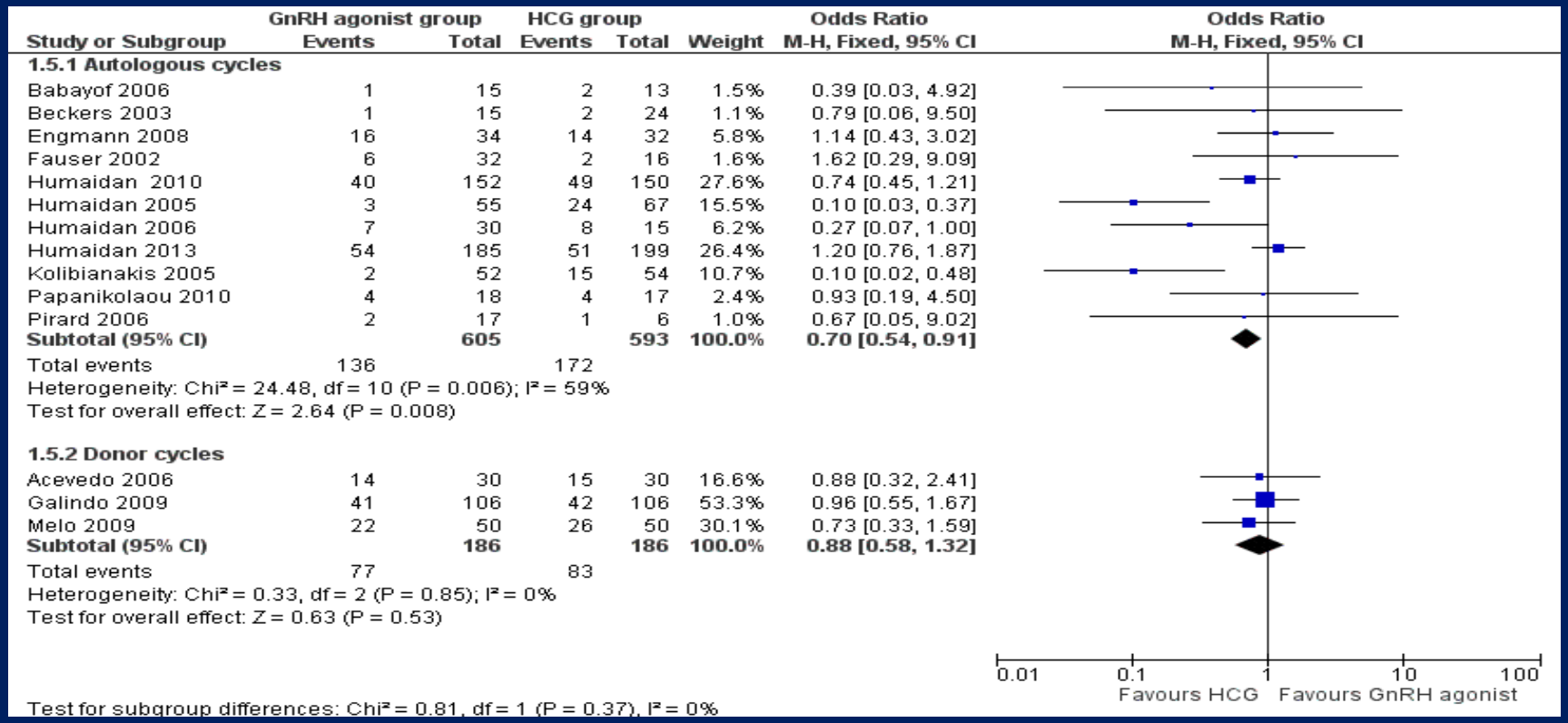
Footnotes

(1) A sensitivity analysis without Engman 2008 (as has high number of events) results in pooled OR (95% CI) 0.28 [0.08, 1.02]

In women undergoing fresh autologous cycles GnRH agonist was associated with lower risk of OHSS than was seen with HCG (OR 0.15, 95% CI 0.05 to 0.47; eight RCTs, 989 women, I^2 = 42%). This suggests that for a woman with a 5% risk of OHSS using HCG, the rate would be between nil and 2% with use of a GnRH agonist.

Cochrane database Syst Rev, 2014

GnRH agonist vs HCG for oocyte maturation triggering: ongoing pregnancy rate



Study or Subgroup	GnRH agonist group Events	Total	HCG group Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.5.1 Autologous cycles						
Babayof 2006	1	15	2	13	1.5%	0.39 [0.03, 4.92]
Beckers 2003	1	15	2	24	1.1%	0.79 [0.06, 9.50]
Engmann 2008	16	34	14	32	5.8%	1.14 [0.43, 3.02]
Fauser 2002	6	32	2	16	1.6%	1.62 [0.29, 9.09]
Humaidan 2010	40	152	49	150	27.6%	0.74 [0.45, 1.21]
Humaidan 2005	3	55	24	67	15.5%	0.10 [0.03, 0.37]
Humaidan 2006	7	30	8	15	6.2%	0.27 [0.07, 1.00]
Humaidan 2013	54	185	51	199	26.4%	1.20 [0.76, 1.87]
Kolibianakis 2005	2	52	15	54	10.7%	0.10 [0.02, 0.48]
Papanikolaou 2010	4	18	4	17	2.4%	0.93 [0.19, 4.50]
Pirard 2006	2	17	1	6	1.0%	0.67 [0.05, 9.02]
Subtotal (95% CI)		**605**		**593**	**100.0%**	**0.70 [0.54, 0.91]**
Total events	136		172			
Heterogeneity: Chi² = 24.48, df = 10 (P = 0.006); I² = 59%						
Test for overall effect: Z = 2.64 (P = 0.008)						
1.5.2 Donor cycles						
Acevedo 2006	14	30	15	30	16.6%	0.88 [0.32, 2.41]
Galindo 2009	41	106	42	106	53.3%	0.96 [0.55, 1.67]
Melo 2009	22	50	26	50	30.1%	0.73 [0.33, 1.59]
Subtotal (95% CI)		**186**		**186**	**100.0%**	**0.88 [0.58, 1.32]**
Total events	77		83			
Heterogeneity: Chi² = 0.33, df = 2 (P = 0.85); I² = 0%						
Test for overall effect: Z = 0.63 (P = 0.53)						
Test for subgroup differences: Chi² = 0.81, df = 1 (P = 0.37), I² = 0%						

In women undergoing fresh autologous cycles, GnRH agonists were associated with a lower ongoing pregnancy rate than was seen with HCG (OR 0.70, 95% CI 0.54 to 0.91; 11 studies, 1198 women, I^2 = 59%, low-quality evidence) and a higher early miscarriage rate. However, the effect was dependent on the type of luteal phase support provided (with or without luteinising hormone activity.

Cochrane database Syst Rev, 2014

GnRH agonist vs HCG for oocyte maturation triggering: results from donor cycles

Donor-recipient cycles:

- No difference between groups in live birth rate (OR 0.92, 95% CI 0.53 to 1.61; one RCT, 212 women) and ongoing pregnancy rate (OR 0.88, 95% CI 0.58 to 1.32; three RCTs, 372 women, $I^2 = 0\%$)
- Lower incidence of OHSS was found in the GnRH agonist group than in the HCG group (OR 0.05, 95% CI 0.01 to 0.28; three RCTs, 374 women, $I^2 = 0\%$*).*

Cochrane database Syst Rev, 2014

GnRH agonist vs HCG for oocyte maturation triggering: taken together…..

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk HCG for oocyte maturation triggering	Corresponding risk GnRH agonist	Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)
Live birth	313 per 1000	176 per 1000 (124 to 242)	OR 0.47 (0.31 to 0.70)	532 (5 studies)	⊕⊕⊕⊖ Moderate
OHSS: overall risk	5 per 1000	1 per 1000 (0 to 2)	OR 0.15 (0.05 to 0.47)	989 (8 studies)	⊕⊕⊕⊖ Moderate
OHSS: in women at high risk of OHSS	308 per 1000	26 per 1000 (4 to 131)	OR 0.06 (0.01 to 0.34)	212 women (3 studies)	⊕⊕⊕⊖ Moderate
Ongoing pregnancy	256 per 1000	194 per 1000 (157 to 238)	OR 0.7 (0.54 to 0.91)	1198 (11 studies)	⊕⊕⊖⊖ Low
Miscarriage	67 per 1000	111 per 1000 (73 to 165)	OR 1.74 (1.10 to 2.75)	1198 (11 studies)	⊕⊕⊕⊖ Moderate

*The basis for the **assumed risk** is the median control group risk across studies. The **corresponding risk** is based on the assumed risk in the comparison group and the **relative effect** of the intervention

Gonadotropin-releasing hormone agonist versus HCG for oocyte triggering in antagonist-assisted reproductive technology

Youssef MAFM, Van der Veen F, Al-Inany HG, Mochtar MH, Griesinger G, Nagi Mohesen M, Aboulfoutouh I, van Wely M

Authors' conclusions:

Final oocyte maturation triggering with GnRH agonist instead of HCG in fresh autologous GnRH antagonist cycles prevents OHSS but is associated with a lower live birth rate, a lower ongoing pregnancy rate and a higher rate of early miscarriage. GnRH agonist as an oocyte maturation trigger could be useful for women who choose to avoid fresh transfers, women who donate oocytes to recipients or women who wish to freeze their eggs for later use in the context of fertility preservation.

Cochrane database Syst Rev, 2014

GnRH Agonist Trigger and LH Activity Luteal Phase Support versus hCG Trigger and Conventional Luteal Phase Support in Fresh Embryo Transfer IVF/ICSI Cycles—A Systematic PRISMA Review and Meta-analysis

Haahr T, Roque M, Esteves CS, Humaidan P

In this review, The Authors aimed to evaluate once again the role of GnRHa triggering in view of new evidence that has emerged after the publication of Cochrane review.

A meaningful comparison between GnRH agonist and HCG trigger must naturally be confined to outcome measure that are not affected by the luteal support used. Thus the variables to compare or meta-analyse should also be the number of oocytes obtained, percentage of mature oocytes, the fertilization rate and the embryo quality.

Front Endocrinol, 2017

frontiers in Endocrinology

Study results

- LBR rate in the GnRHa and hCG groups were 26.1 and 28.8%, respectively. The corresponding OR for LBR was 0.84 (95% CI 0.62, 1.14, I^2 = 22%)

- The OHSS rates in the GnRHa and hCG groups were 0.9 and 1.7%, respectively. The corresponding OR was 0.48 (95% CI 0.15, 1.60, I^2 = 0%)

- The ongoing pregnancy rate in the GnRHa and hCG groups were 27.9 and 28.7%, respectively (OR 0.95, 95% CI 0.59, 1.53; I^2 = 50%)

- The clinical pregnancy rate in the GnRHa and hCG groups were 33 and 34%. Overall, pooled results indicated that the clinical pregnancy rate was similar comparing GnRHa + LPS and hCG trigger

- The miscarriage rate was 20.0% in GnRHa group and 12.5% in hCG group, respectively (p = 0.06)

Front Endocrinol, 2017

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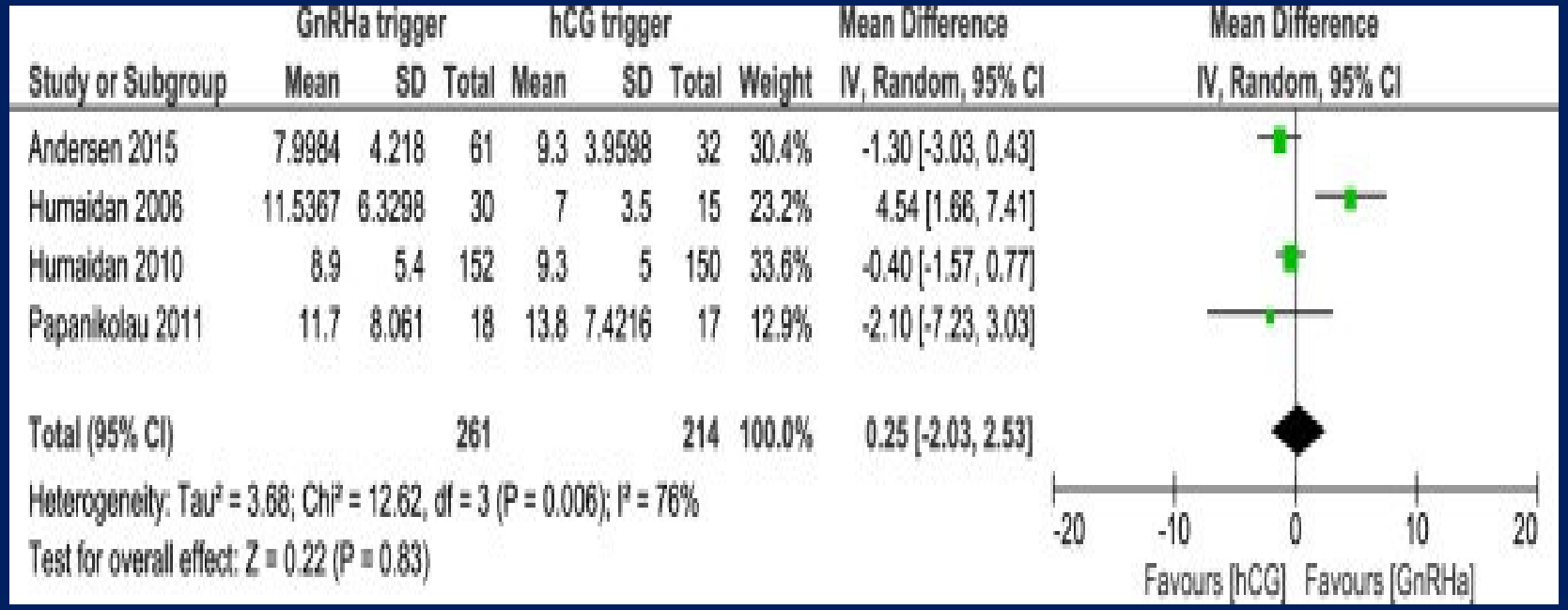
GnRHa trigger vs hCG trigger: oocytes retrieved



The mean number of oocytes retrieved was 8.0 and 9.3 in the GnRHa and hCG groups, respectively. Overall, the results indicated that the number of oocytes retrieved was not different between groups (OR 0.98, 95% CI 0.73, 1.30; I^2 = 76%)

Front Endocrinol, 2017

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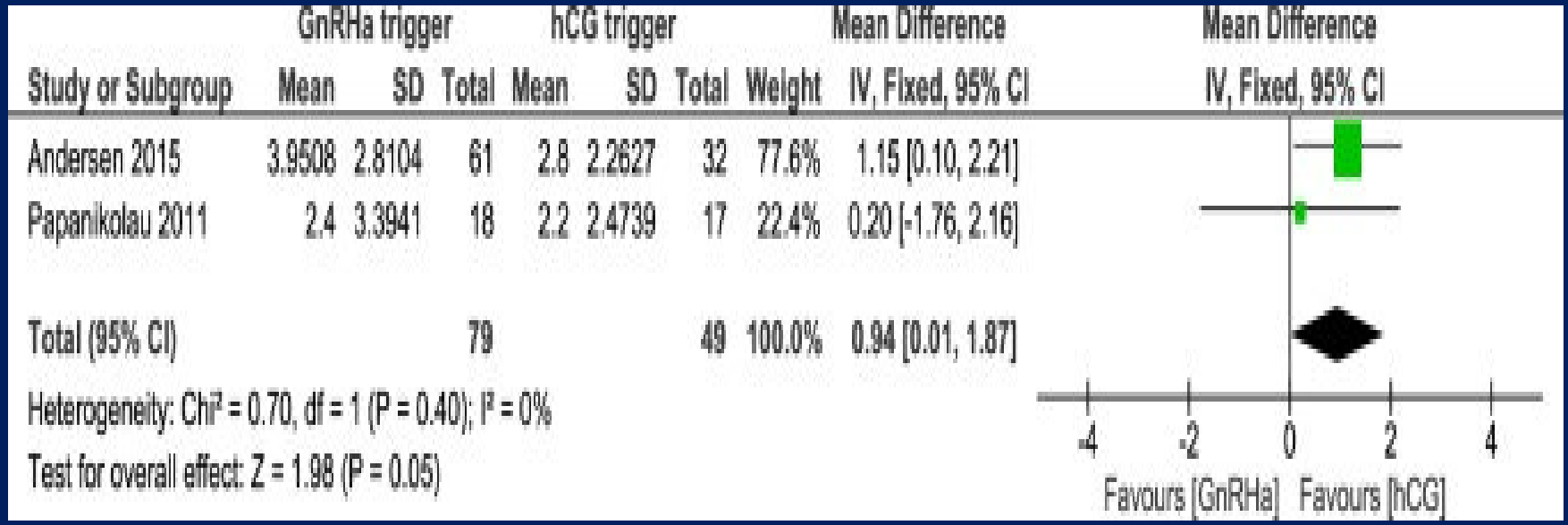
GnRHa trigger vs hCG trigger: good quality embryos



A significant difference was observed in favor of GnRHa trigger regarding the number of good quality embryos (MD 0.94, 95% CI 0.01, 1.87)

Front Endocrinol, 2017

Final oocyte maturation with two different GnRH agonists in antagonist co-treated cycles at risk of ovarian hyperstimulation syndrome

Sukur YE, Ozmen B, Ozdemir ED, Seval MM, Kalafat E, Sonmezer M et al.

Groups A (n = 63): 0.2 mg triptorelin, E2 level >3000 pg/ml
Group B (n=74): 1 mg leuprolide , E2 level >3000 pg/ml
Group C (n=131): 10.000 IU HCG, E2 level <3000 pg/ml

Demographic parameters were comparable between the groups.
No cases of severe or moderate OHSS occurred in any group.
The clinical pregnancy rates were 31.7%, 37.8% and 32.8% in groups A, B and C, respectively.
Both injections had comparable efficacy in clinical outcome and OHSS risk.

Regardless of preferred drug, GnRH agonist trigger for final oocyte maturation seems to be safe for patients with high OHSS risk, and can be safely used in fresh embryo transfer cycles

Reprod Biomed Online, 2017

Gonadotropin-releasing hormone agonist trigger in oocyte donors co-treated with a gonadotropin-releasing hormone antagonist: a dose-finding study.

Voung TN, Ho MT, Ha TD, Phung HT, Huynh GB, Humaidan P

Which dose….0.2, 0.3, or 0.4 mg triptorelin ?

There were no significant differences in 66 oocyte donors between the triptorelin 0.2, 0.3, and 0.4 mg trigger groups with respect to:

- number of metaphase II oocytes (16.0 ± 8.5, 15.9 ± 7.8, and 14.7 ± 8.4, respectively),
- number of embryos (13.2 ± 7.8, 11.7 ± 6.9, 11.8 ± 7.0),
- number of top-quality embryos (3.8 ± 2.9, 3.6 ± 3.0, 4.1 ± 3.0).

Luteinizing hormone levels at 24 hours and 36 hours after trigger was significantly higher with triptorelin 0.4 mg

Progesterone level at oocyte pick-up +6 days was significantly higher in the 0.4-mg group

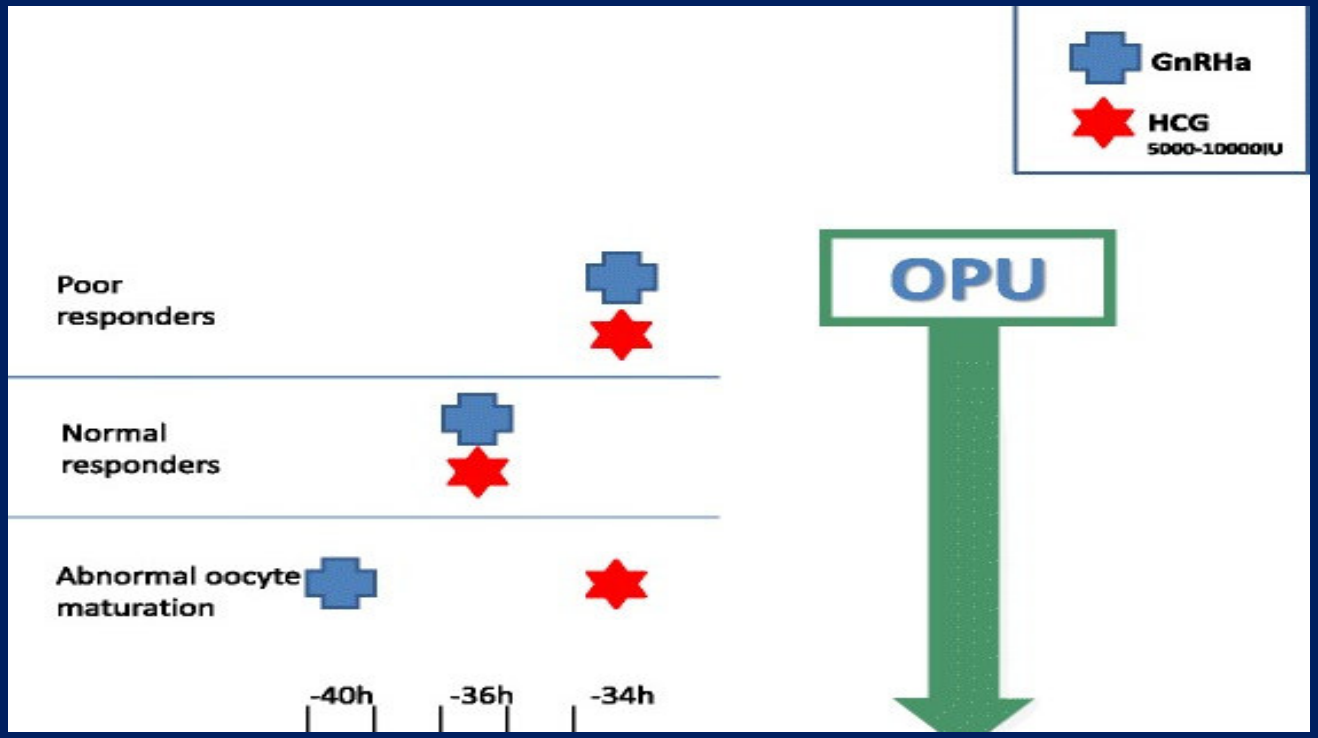
One patient developed early-onset severe OHSS.

CONCLUSION

No significant differences between triptorelin doses of 0.2, 0.3, and 0.4 mg used for ovulation trigger in oocyte donors were seen with regard to the number of mature oocytes and top-quality embryo

Fertil Steril, 2016

Dual-double trigger: a novel strategy



It was assumed that ovulation induction by GnRHa administered together with hCG could overcome any existing impairments in granulosa cell function, oocyte meiotic maturation, cumulus expansion and luteal phase resulting in successful aspiration of mature oocytes, pregnancy and delivery.

GnRHa and hCG may be administered concomitantly, 34–37 h prior to oocyte retrieval (dual trigger) or 40 h and 34 h prior to oocyte retrieval, respectively (double trigger).

Orvieto R, J Ovarian Res, 2015

Dual trigger for normal responders

Dual trigger with combination of gonadotropin-releasing hormone agonist and human chorionic gonadotropin significantly improves the live-birth rate for normal responders in GnRH-antagonist cycles

Study objective:

To evaluate if dual triggering improve the live-birth rate in IVF cycles

Study participants:

Inclusion criteria: normal responders undergoing IVF with a GnRH antagonist protocol
Exclusion criteria: age ≥40 years, abnormal BMI, FSH concentration of ≥10 IU/L, AMH ≤1.0 ng/mL, endocrine disorders or uterine abnormalities

378 women were eligibile. In 187 the finnal oocyte maturation was triggered by either 250 µg of recombinant hCG which was considered as equivalent to approximately 6,500 IU hCG according to the manufacturer's data. Remaing 191 patients **received 250µg of recombinant hCG plus 0.2 mg of triptorelin**

Study outcomes:

Primary outcome: live-birth, clinical pregnancy, and implantation rates per cycle.
Secondary outcomes: oocyte maturation, fertilization rate, embryo transfer rate, clinical PR

Lin et al., Fertil Steril, 2013

Dual trigger for normal responders

Study results

Variable	HCG group	Dual trigger	*P* value
No. of oocytes retrieved	10.10 ± 4.58	12.36 ± 6.64	.01
No. of MII oocytes retrieved	8.03 ± 4.51	10.53 ± 6.47	.01
No. of top quality embryos	2.9 ± 2.3	2.9 ± 3.1	NS
Implantation rate (%)	18.43 (106/575)	29.68 (160/539)	.001
Clinical pregnancy rate (%)	40.11 (75/187)	50.79 (97/191)	.047
Abortion rate (%)	18.67 (14/75)	16.49 (16/97)	NS
Live-birth rate (%)	30.49 (57/187)	41.36 (79/191)	.042
Blastocyst rate (%)	55.6 (299/538)	52.9 (379/720)	NS
OHSS rate (%)	0.005 (1/187)	0 (0/191)	NS

The mean number of all and mature oocytes were significantly greater in the dual-trigger group. The mean number of top quality embryos obtained as well as the rate of blastocyst progression were similar between the groups. The dual-trigger group demonstrated significantly higher implantation and clinical pregnancy rate. The abortion rate was similar in both groups. No OHSS occurred in the study group.

Lin et al., Fertil Steril, 2013

Oocyte retrieval

The genuine empty follicle syndrome (Stevenson, 2008) is defined as no oocyte recovery during ovum pick-up following COH with an apparently normal follicular development, E2 levels and optimal hCG levels on the day of OPU. It's a rare entity with an estimated prevalence of 0–1.1% (Mese, 2011; Beck, 2012)

More frequently encountered situation in the normally responding patients is a low oocytes yield defined as a low ratio (<50%) between the number of oocytes retrieved to the number of follicles >14 mm in diameter on the day of hCG administration

It was also obsereved that patients with ≥25% of immature oocytes retrieved have a reduced pregnancy rate (Avrech, 1997, Bar-Ami, 1994)

It can be assumed that in these circumstances the "double trigger" could overcome eventual impairments in granulosa cell function, oocyte meiotic maturation or cumulus expansion, resulting in successful aspiration of mature oocytes, pregnancy and delivery (Fruchter, 2012).

Double trigger and “empty follicles”

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

A patient with primary infertility who underwent seven assisted reproductive technique cycles is described. In spite of a satisfactory ovarian response, aspiration yielded no oocytes in four cycles and 1–4 low quality oocytes in three cycles.

In the index treatment cycle, ovulation was triggered using **GnRH agonist (Triptorelin acetate, decapeptyl 0.1 mg) 40h prior to ovum pickup and hCG (Choriogonadotropin alfa, ovitrelle 250 µg)** was added 6h after.

Eighteen oocytes were recovered, of which 16 were mature and were inseminated by ICSI. Two embryos were transferred 48h after aspiration and nine embryos were cryopreserved. The patient conceived and delivered a healthy boy at 38 weeks of gestation.

Beck-Further, et al., Hum Reprod, 2012

Double trigger and low oocyte yield

Co-administration of GnRH-agonist and hCG for final oocyte maturation (double trigger) in patients with low number of oocytes retrieved per number of preovulatory follicles-a preliminary report

Study participants:

All consecutive patients with poor oocytes yield (<50%) number of oocytes retrieved per number of follicles > 14 mm in diameter on day of hCG administration) despite normal response to COH and E2 level who received in the subsequent IVF cycle a double trigger (GnRH-agonist and hCG) for final follicular maturation

Previous cycles: recombinant hCG (Choriogonadotropin alfa, ovitrelle 250 mcg), 36 hours prior to OPU

Present cycle: the co-administration of **GnRH-agonist (Triptorelin acetate, decapeptyl 0.2 mg) and recombinant hCG (250 mcg), 40 and 34** hours prior to oocyte retrieval, respectively

Study outcomes:

Primary outcome: oocyte yield evaluation

Haas, et al., J Ovarian Res, 2014

Double trigger and low oocyte yield

Study results

	HCG	Double trigger	P values
Oocytes retrieved	2.3 ± 2.5	7.0 ± 4.6	p < 0.02
2PN embryos	1.7 ± 1.2	6.0 ± 4.6	p < 0.002
top quality embryos	0.4 ± 0.5	3.7 ± 0.8	p = 0.06
embryos transferred	0.85 ± 0.9	2.2 ± 0.7	p < 0.002
Oocytes yield (%)	23.7 ± 21.5	118.0 ± 71.2	p < 0.01
Positive hCG (%)	0 (0/8)	62.5% (5/8)	p < 0.001
Clinical PR(%)	0 (0/8)	37.5% (3/8)	p < 0.0

Patients who received the double trigger had a significantly higher number of oocytes retrieved, number of 2PN, number of embryos transferred and significantly higher oocyte yield with a tendency toward a higher number of top quality embryo respectively, as compared to the hCG-only trigger cycles. Five pregnancies were recorded in the study group and none in the hCG-only trigger group.

Haas, et al., J Ovarian Res, 2014

Dual trigger low oocyte yield

Dual trigger with gonadotropin-releasing hormone agonist and standard dose human chorionic gonadotropin to improve oocyte maturity rates

Study participants:

Patients eligible for the study had a prior IVF cycle with >25% immature oocytes retrieved and a subsequent IVF cycle using a dual trigger to induce oocyte maturation.

Exclusion criteria included patients who used a standard IVF insemination technique for oocyte fertilization.

Previous IVF cycles: HCG only

Present IVF cycle: Patients were triggered when at least 3 follicles reached ≥17 mm in diameter, with a combination of **1 mg SC leuprolide acetate plus 5,000–10,000 IU SC hCG**

Study outcomes:

Primary outcome: number and percentage of mature oocytes

Secondary outcome fertilization rate, implantation rate, clinical and ongoing PR, live birth rate

Griffin et al., Fertil Steril, 2014

View Table in HTML

Dual trigger and low oocyte yield

Study results

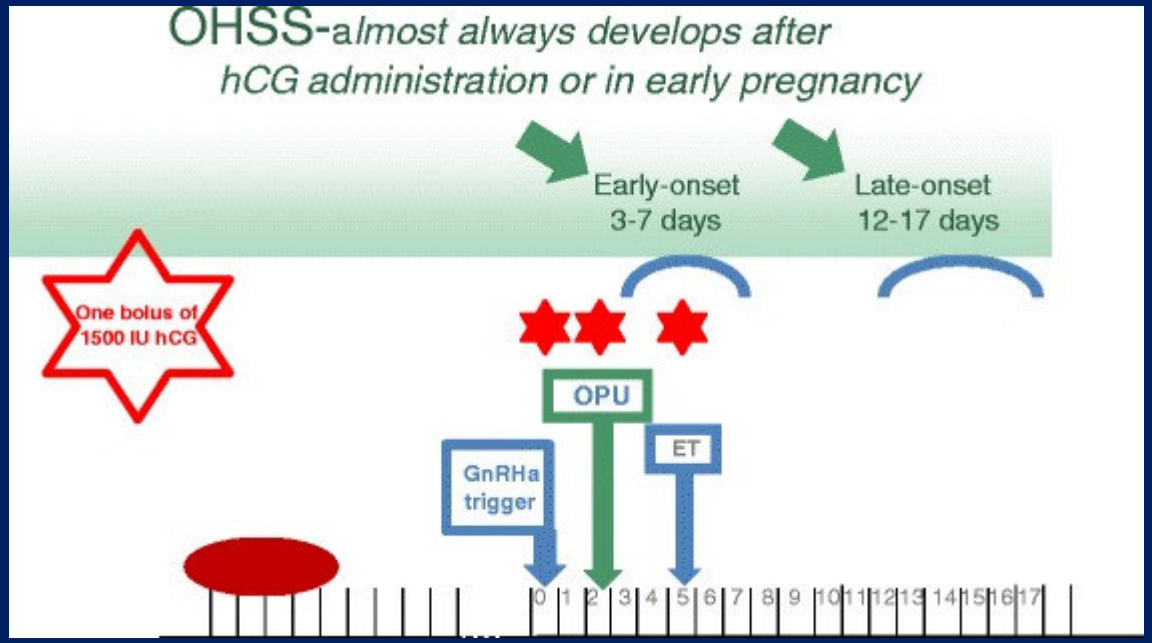
Variable	Prior cycle (n = 27)	Dual trigger (n = 27)	*P* value
Oocytes retrieved (n)	9 (4–14)	11 (5–16)	.02
Mature oocytes (n)	3 (1–5)	7 (4–9)	.01
Mature oocytes (&)	38.5 (16.7–55.6)	75.0 (55.6–80.0)	.01
Fertilization rate (%)	66.7 (40.0–100.0)	83.3 (72.4–93.8)	NS
Embryos transferred (n)	1 (0–2)	2 (2–3)	NS

The logistic regression determined that the odds of having a mature oocyte using a dual trigger was 2.51 times higher. The implantation, clinical, and live birth rates per ET for the dual trigger were 11.8% (7 of 59); 26.1% (6 of 23); and 17.4% (4 of 23), respectively.

A dual trigger in patients with a history of low oocyte maturation is a viable treatment to improve the rate of oocyte maturation. However, despite the improvement in mature oocytes retrieved, the clinical results remain low probably due to the underlying oocyte dysfunction.

Griffin et al., Fertil Steril, 2014

Dual trigger and OHSS



One bolus of 1500 IU hCG concomitant with GnRHa (dual trigger), 34–36 h before oocyte retrieval was suggested as a method which improves oocyte maturation, while providing more sustained support for the corpus luteum than could be realized by the GnRHa-induced LH surge alone. However, while acceptable rates of fertilization, implantation, clinical and ongoing pregnancy rates were achieved in high responders after dual trigger, the incidence of clinically significant OHSS was not eliminated, but rather reduced to 0.5 % (Shapiro, 2011).

Orvieto R, J Ovarian Res, 2015

Dual trigger and OHSS

GnRH agonist with low-dose hCG (dual trigger) is associated with higher risk of severe ovarian hyperstimulation syndrome compared to GnRH agonist alone.

Purpose

The purpose of this study was to compare rates of OHSS after GnRHa alone and GnRHa in combination with low-dose hCG (dual trigger) for final oocyte maturation in women undergoing IVF

Methods

108 women who received GnRHa trigger and 66 women who received dual trigger (GnRHa + low-dose [1000 IU] hCG trigger). The main outcome measure was OHSS. Secondary outcomes included total oocyte yield and oocyte maturity.

Results

The incidence of early OHSS was significantly higher after dual trigger than GnRHa trigger (8.6 vs 0 %). Moreover, four of the six patients that developed OHSS developed severe OHSS. Adjusted analyses revealed that dual trigger was associated with a higher number of total oocytes (adjusted OR 1.27; 95 % confidence interval, 1.18, 1.38) and percentage of mature oocytes (AOR 1.10; 95 % confidence interval, 1.03, 1.17) obtained compared to GnRHa trigger alone.

Conclusions

Dual trigger for final oocyte maturation using GnRHa and low-dose hCG is associated with a significantly increased risk of severe OHSS compared to GnRH alone. However, dual trigger may be associated with a modest increase in oocyte yield, both in terms of number and maturity.

O' Neil et al., J Assist Reprod Genet, 2016

Dual trigger and OHSS

Study results

	GnRHa trigger (*n* = 108)	Dual trigger (*n* = 66)
Maximum E2 (pg/mL)	4360 (3517–5704)	3541 (2943–5014)
Follicles >15 mm	13 (10–16)	14 (12–16)
Total follicles	31 (25–35)	28 (22–34)
E2 levels on day of trigger (pg/mL)	3604 (2843–4536)	2993 (2597–4280)
Oocytes retrieved	16.5 (11–21.5)	17.5 (12–24)
Oocyte maturity (%)	70 (56–85)	82 (74–91)
OHSS (%)	0	6 (9)
Severe OHSS (%)	0	4 (6

Patients who developed OHSS were less than 35 years of age and had a BMI ≤23 kg/m^2 . 4 of them had E2 levels on the day of trigger > 4000 pg/mL and 2 had E2 levels <3500 pg/mL. Only two individuals had a baseline AFC >20.

The percentage of patients having blastocyst transfer was significantly higher in the dual trigger (88%) compared to the GnRHa trigger (45%). No significant differences in clinical pregnancy (44 vs 63 %, $p = 0.12$) or miscarriage rates (7 vs 6 %, $p = 0.90$) were observed in the GnRHa and dual trigger group.

O' Neil et al., J Assist Reprod Genet, 2016

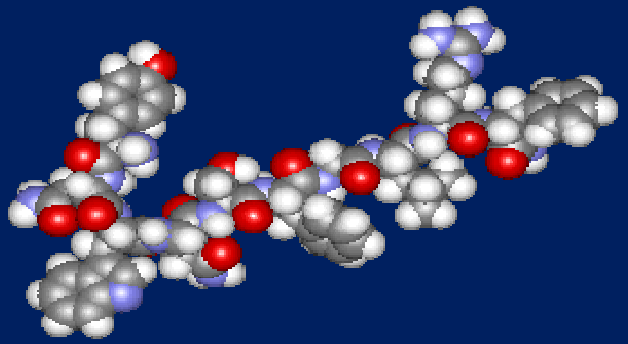
Dual-Double trigger

Conclusions:

Dual trigger may be a useful tool to increase oocyte yield after COH and may be particularly valuable in patients who have a higher proportion of immature oocytes retrieved in previous cycles.

Importantly, the improvement observed in the number and percentage of mature oocytes retrieved in this cohort came at the cost of increased rates of moderate and severe OHSS.

Therefore clinicians must carefully weigh these factors when selecting the most appropriate agent(s) used to trigger oocyte maturation.

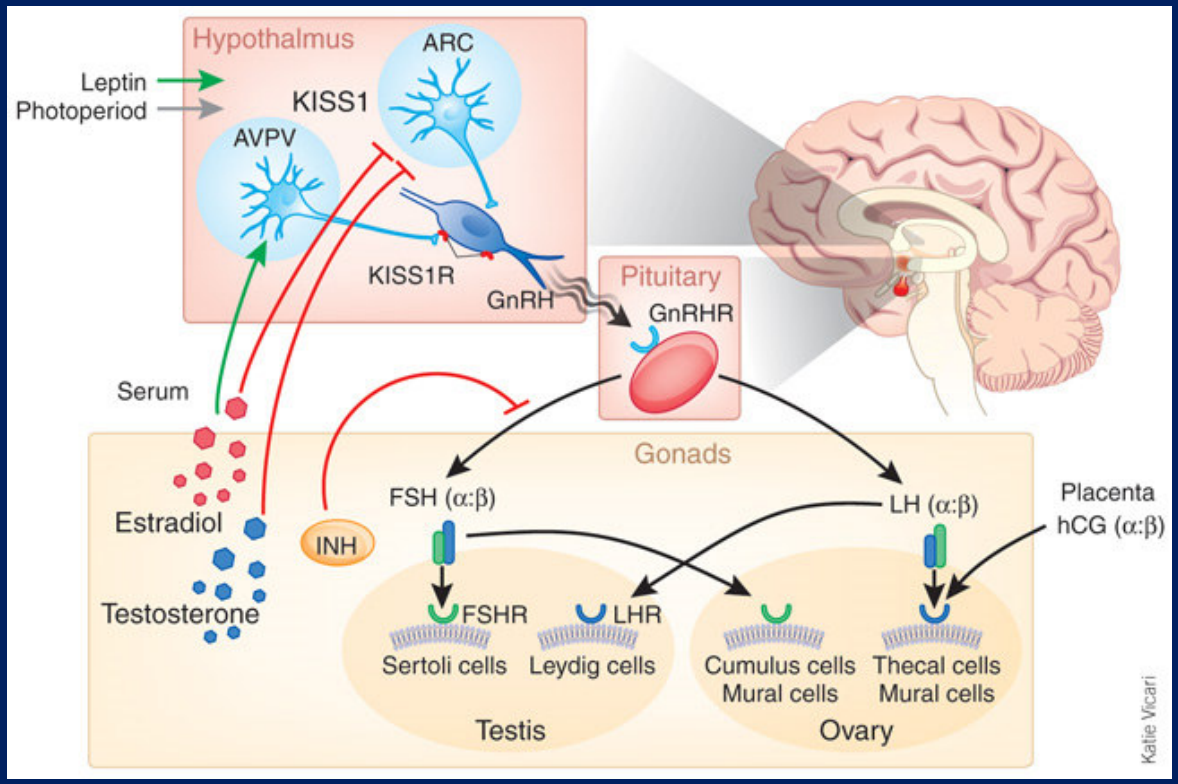


Kisspeptin

- Human *KISS1* gene maps to chromosome 1q32 and consists of 4 exons, of which only parts of the third and fourth exons are translated to a 145-amino acid precursor peptide subsequently cleaved to 54 amino acids in length (West, 1998)

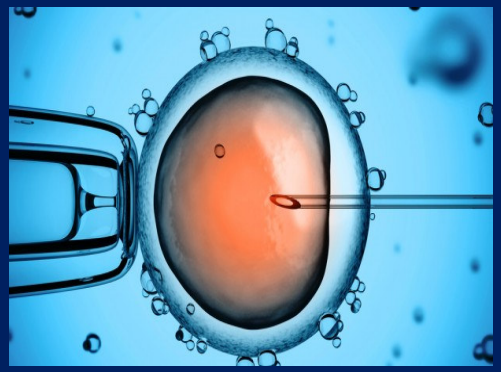
- Like most genes, *KISS1* may be subjected to mutations and polymorphisms. Patients with genetic inactivation of the kisspeptin signaling pathway fail to undergo puberty and are infertile (Topaloglu, 2012).

Kisspeptin and female reproduction



Kisspeptin released by neurons in the AVPV (anteroventral periventral nucleus) and Arc (arcuate nucleu) stimulates GnRH release, which induces the release of LH and FSH. The gonads respond secreting sex steroids, which then feed back to inhibiting Kiss1 expression in the Arc and inducing its expression in the AVPV. This inductive effect may contribute to the preovulatory LH surge in females (Kauffman, 2007).

Kissspeptin has been implicated in puberty onset, ovarian function, delivery, and lactation. Important increase in Kisspeptin concentration was also seen in human plasma during pregnancy, which was mainly produced in the placenta suggesting its possible role in the regulation of trophoblast invasion.



Kisspeptin in IVF treatment

A number of clinical studies have demonstrated that kisspeptin can be safely administered to human subjects without any observed adverse effects (Dhillo, 2007 ; Jajasena, 2009 and 2013)

Using kisspeptin as a trigger for egg maturation exposes the patient to only a very short duration of kisspeptin, since the half-life of exogenously administered kisspeptin is 28 minutes (Dhillo, 2007)

Kisspeptin-54 triggers egg maturation in women undergoing in vitro fertilization

Study objective:
To evaluate if kisspeptin-54 could be used to trigger egg maturation in IVF therapy

Study participants:
Inclusion criteria: age, 18–34 years; FSH ≤ 12 mIU/ml; AMH, 10–40 pmol/l (1.4–5.6 ng/ml); both ovaries intact, regular menstrual cycles of 24 to 35 days duration; BMI 18–29 kg/m^2

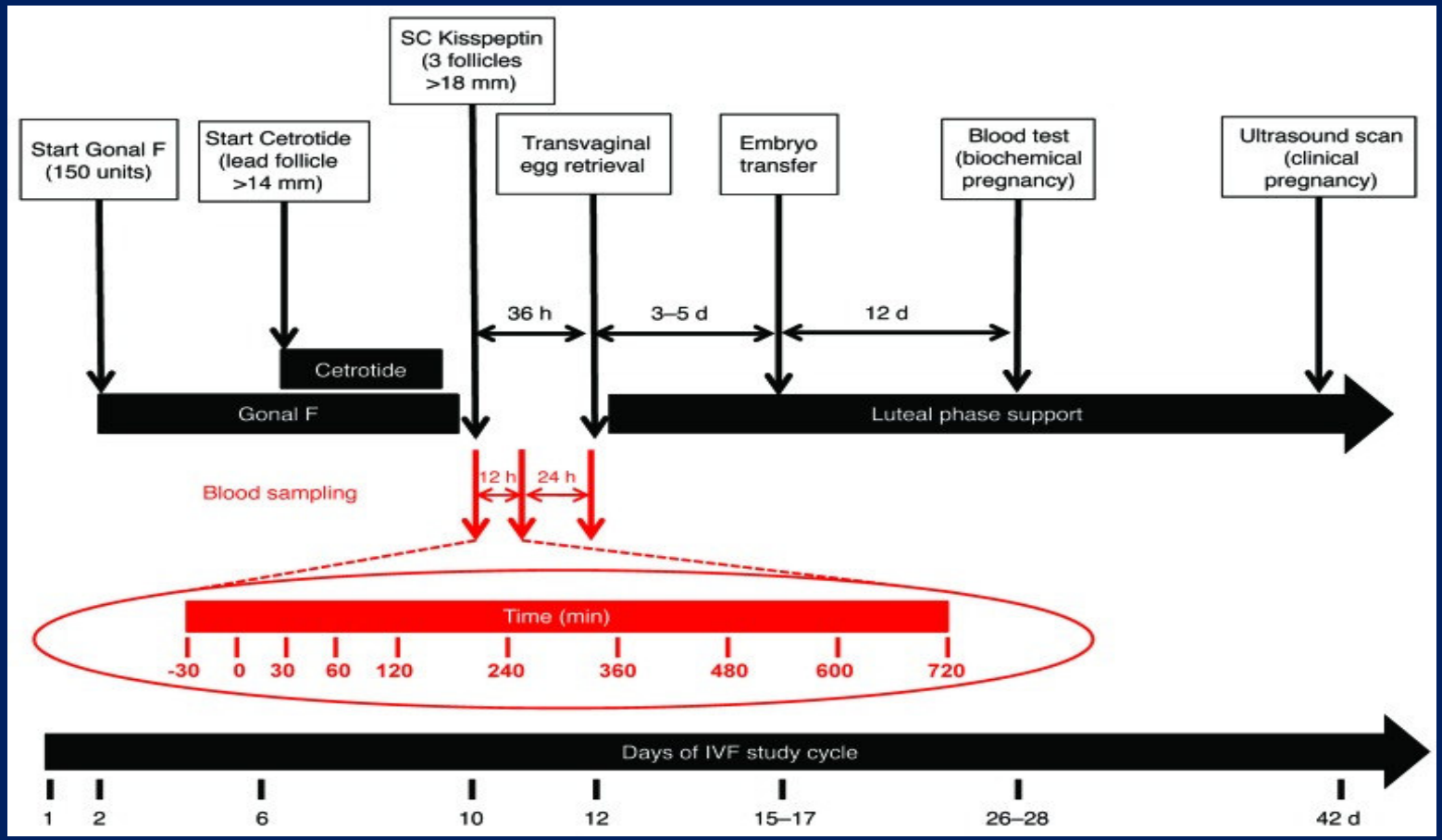
Exclusion criteria: moderate/severe endometriosis; poor response in previous IVF cycle; clinical or biochemical hyperandrogenemia; polycystic ovarian syndrome.

53 eligibile women received a single subcutaneous injection of kisspeptin-54 (1.6 nmol/kg, *n* = 2; 3.2 nmol/kg, *n* = 3; 6.4 nmol/kg, *n* = 24; 12.8 nmol/kg, *n* = 24) to induce a luteinizing hormone surge and egg maturation

Study outcomes:
Primary outcome: number and percentage of mature oocytes
Secondary outcomes: reproductive hormones levels, fertilization rate, embryo transfer rate, embryo quality, biochemical and clinical PR

Javasena et al.,J Clin Invest, 2014

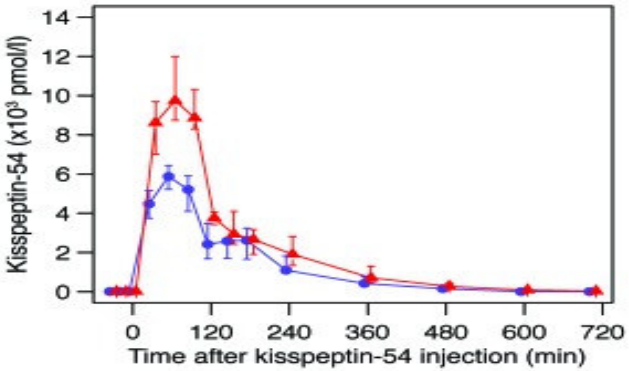
Study protocol

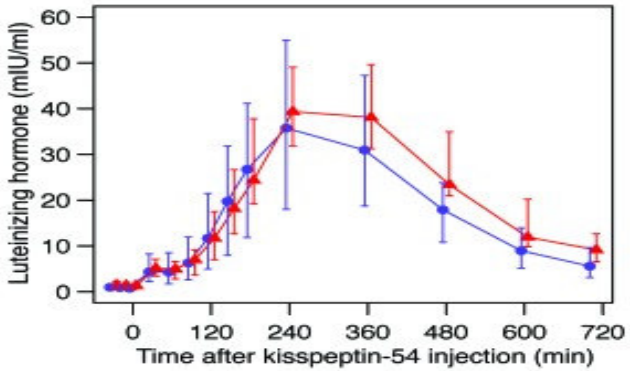


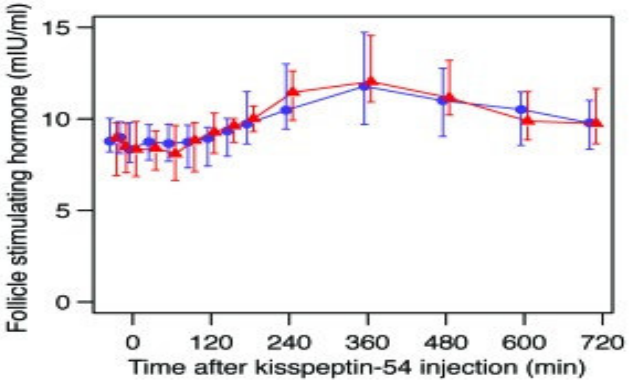
A subcutaneous bolus injection dose of kisspeptin-54 (1.6, 3.2, 6.4, or 12.8 nmol/kg) was administered to trigger egg maturation. A subgroup of women receiving the two highest doses of kisspeptin-54 (6.4 or 12.8 nmol/kg, *n* = 10/dose) underwent overnight measurements of serum LH, FSH, estradiol and progesterone, and plasma kisspeptin just prior to and during the 12 hours following kisspeptin-54 injection

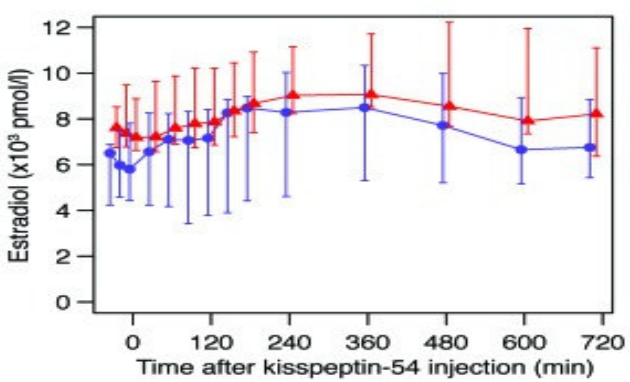
Javasena et al.,J Clin Invest, 2014

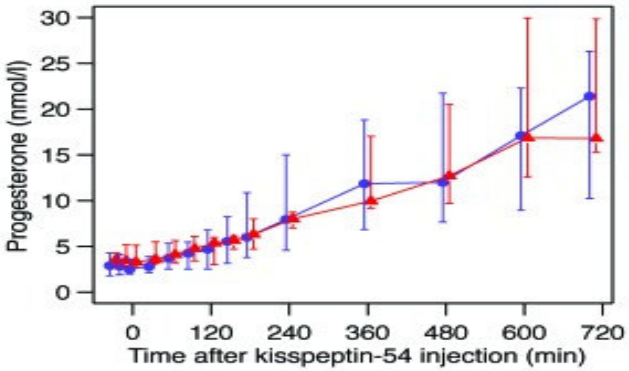
Study results











Peak levels of plasma kisspeptin were observed one hour after injection and then fell to preinjection levels by 12 hours. Serum LH levels peaked 4 to 6 hours following kisspeptin-54 injection and decreased thereafter. Similar but less prominent elevation pattern were observed in FSH and estradiol secretion. In contrast, progesterone levels rose continually during the 12 hours following kisspeptin-54 injection

Javasena et al.,J Clin Invest, 2014

Study results

Table 3. Summary of egg maturation following administration of kisspeptin-54

	Kisspeptin-54 dose (nmol/kg): mean (SD)							
	1.6 (n = 2)		3.2 (n = 3)		6.4 (n = 23/24[A])		12.8 (n = 24)	
M2[B]	4.5	(3.5)	4.3	(1.5)	7.5	(3.8)	8.8	(4.0)
%M2[C]	75	(35)	79	(36)	79	(22)	85	(16)
Oocyte yield[D]	49	(29)	36	(18)	76	(49)	103	(53)

[A]n = 24 for M2, n = 23 for %M2, and n = 24 for oocyte yield. [B]Absolute number of mature eggs per patient. [C]Percentage of collected eggs that were mature. [D]Percentage of M2 oocytes collected from the number of follicles greater than 14 mm in diameter on final ultrasound prior to kisspeptin trigger injection. Oocyte yield of more than 100% can occur where eggs are additionally retrieved from follicles just under 14 mm.

Similar rates of egg maturation, between 75% and 85%, were observed following all doses of kisspeptin-54. However, the number of mature eggs and mature oocyte yield appeared to increase with increasing dose of kisspeptin

Javasena et al.,J Clin Invest, 2014

Study results

Table 6. Egg maturation in patients following administration of kisspeptin-54

	Kisspeptin-54 dose (nmol/kg)			
	1.6 (*n* = 2)[A]	3.2 (*n* = 3)[A]	6.4 (*n* = 24)[B]	12.8 (*n* = 24)[B]
2PN fertilized oocytes	2, 0	5, 1, 2	5.1 (2.9)	6.8 (3.8)
Cleaved embryos at day 3	2, 0	5, 1, 2	5.0 (2.9)	6.3 (3.4)
Embryos at day 3 graded as 633 or above	0, 0	5, 1, 1	3.8 (2.7)	4.5 (2.7)
Patients with day 5 transfer (*n*)	0	1	18	17
Embryos at day 5[C]		4	5.2 (2.0)	6.9 (2.3)
High-quality embryos at day 5[C]		3	1.9 (1.4)	2.4 (1.7)
High-quality embryos (> 3A/B) transferred at day 5[C]		1	1.3 (0.8)	1.5 (0.7)

[A]List of raw values for individual subjects, unless otherwise stated. [B]Mean (SD), unless otherwise stated. [C]Calculated using only patients with day 5 transfer.

The fertilization rate defined as at least one fertilized egg and subsequent embryo transfer occurred in 92% of women. 58% of patients had a high-quality embryo transfer and 49% had blastocyst formation. The biochemical pregnancy rate was 40%, and the clinical pregnancy rate was 23%. In this study 12 healthy babies have been born without any abnormalities.

Javasena et al., J Clin Invest, 2014

The role of kisspeptin in OHSS prevention

Kisspeptin-54 has some characteristics suggesting it may reduce the incidence of OHSS due to:

- shorter duration of action compared to hCG (Abbara *et al.*, 2015; Thomsen and Humaidan, 2015)
- induces an LH surge that is dependent upon the patient's individual endogenous GnRH/gonadotropin reserves (Dhillo *et al.*, 2005; Jayasena *et al.*, 2015, Abbara *et al.*, 2015)
- kisspeptin-54 directly inhibits the production from the ovaries of VEGF (Cho *et al.*, 2009)

Efficacy of Kisspeptin-54 to Trigger Oocyte Maturation in Women at High Risk of Ovarian Hyperstimulation Syndrome (OHSS) During In Vitro Fertilization (IVF) Therapy

Study objective:

To evaluate if kisspeptin-54 could be used to trigger egg maturation women undergoing in IVF at high risk of developing OHSS.

Study participants:

Inclusion criteria: age, 18–34 years; FSH ≤ 12 mIU/ml; AMH of at least 40 pmol/l; AFC greater than 23; both ovaries intact, regular menstrual cycles of 24 to 35 days duration; BMI 18–29 kg/m^2

Exclusion criteria: moderate/severe endometriosis; poor response in previous IVF cycle; clinical or biochemical hyperandrogenemia; polycystic ovarian syndrome.

60 elligible patients underwent the adaptive design for kisspeptin-54 dose allocation to induce a luteinizing hormone surge and egg maturation (n = 5, 3.2 nmol/kg; n = 20, 6.4 nmol/kg; n = 15, 9.6 nmol/kg; n = 20, 12.8 nmol/kg)

Study outcomes:

Primary outcome: oocyte yield

Secondary outcomes: OHSS occurence, fertilization rate, embryo transfer rate, embryo quality, biochemical and clinical PR

Abbara et al., J Clin Endocrinol Metab, 2015

Study results

Outcome Measures	Kisspeptin-54 Dose (nmol/kg)				
	3.2	**6.4**	**9.6**	**12.8**	**All Doses**
n	**5**	**20**	**15**	**20**	**60**
All oocytes	8.8	14.6	11.9	17.5	14.4
M2 oocytes	6.8	11.6	8.3	14.1	11.2
Maturation rate, %	62	79	66	78	74
Oocyte yield, %	53	86	86	121	95
Fertilization rate, %	68	76	74	73	74
Biochemical PR , %	50.0	64.7	**84.6**	47.1	62.7
Clinical PR , %	25.0	58.8	**76.9**	35.3	52.9
Implantation rate, %	25.0	47.1	**57.7**	29.4	42.2
Live birth rate , %	25.0	52.9	**61.5**	29.4	45.1

Oocyte maturation (≥ 1 mature oocyte) occurred in 95% patients. The highest oocyte yield (121%) was observed after 12.8 nmol/kg kisspeptin-54. Oocyte maturation did not occur in 3 women, 3 women had fertilization failure and 3 women didn't have embryo transfer because of OHSS.

J Clin Endocrinol Metab, 2015

Study results

Rates of OHSS

- In the study, only three (5%) were diagnosed with mild early OHSS and one with mild late OHSS (2%),
- No woman had moderate, severe and no woman required medical intervention for OHSS.
- None of the three women who had segmentation because of a very high risk of OHSS prior to kisspeptin-54 administration had any features of early OHSS on screening

J Clin Endocrinol Metab, 2015

A second dose of kisspeptin-54 improves oocyte maturation in women at high risk of ovarian hyperstimulation syndrome: a Phase 2 randomized controlled trial

Study objective

To evaluate if a second dose of kisspeptin-54 10 h after the first could further increase oocyte maturation and the proportion of women achieving an oocyte yield of at least 60%

Study participants

Inclusion criteria: age, 18–34 years; FSH ≤ 12 mIU/ml; AMH of at least 40 pmol/l (≥5.6 ng/mL) ; AFC greater than 23; both ovaries intact, regular menstrual cycles of 24 to 35 days duration; BMI 18–29 kg/m^2

Exclusion criteria: moderate/severe endometriosis; poor response in previous IVF cycle

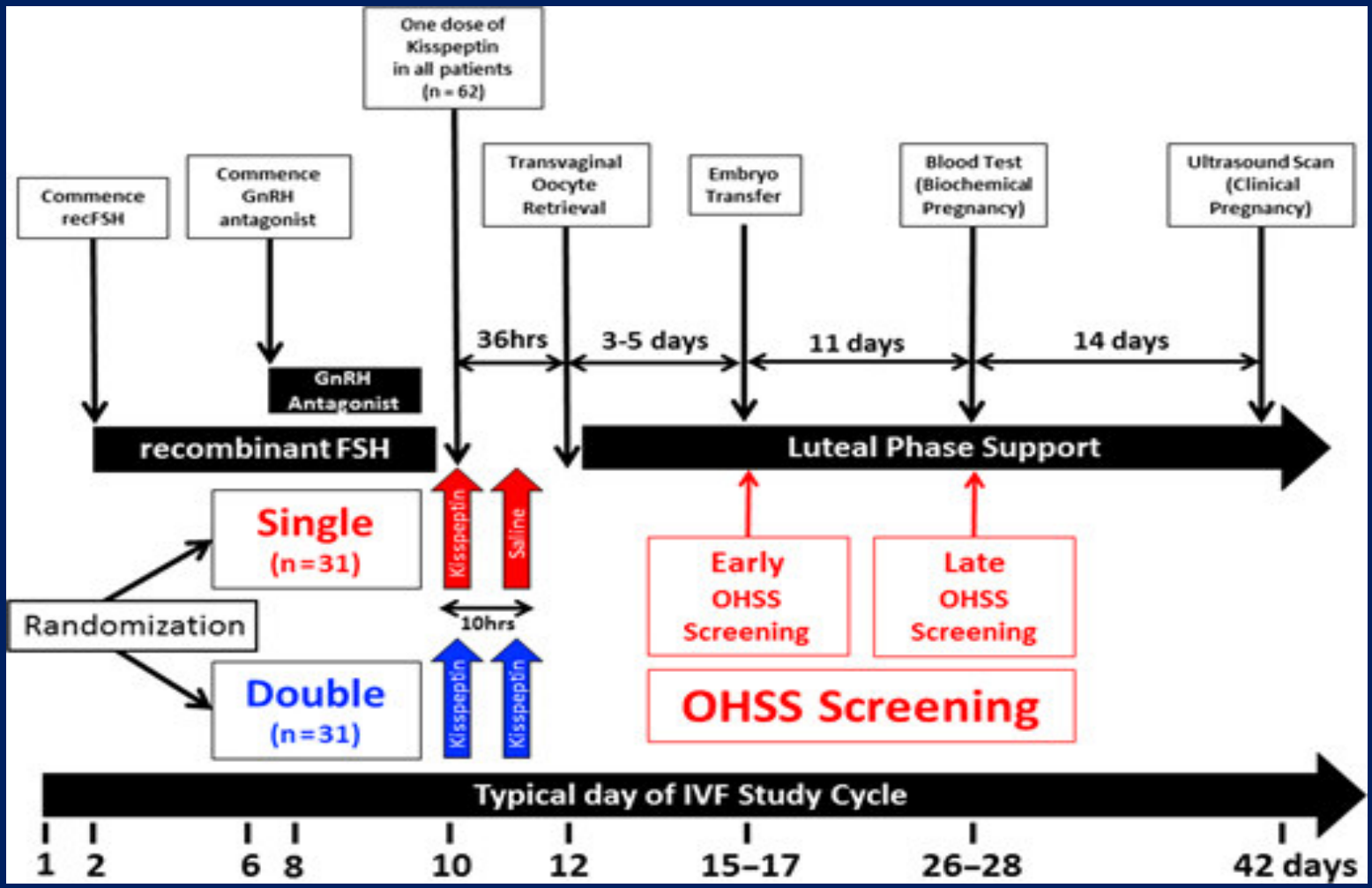
Sixty-two eligible patients underwent a single IVF treatment cycle and were randomized to receive either one (single; *n*= 31) or two doses (double; *n* = 31) of kisspeptin-54 to trigger oocyte maturation

Study outcomes

Primary outcome: the proportion of patients achieving an oocyte yield of at least 60%.
Secondary outcomes: reproductive hormone levels, IR and occurrence of OHSS

Abbara et al., Human Reproduction , 2017

Study protocol



62 patients received a subcutaneous injection of kisspeptin-54 (9.6 nmol/kg) 36 h prior to oocyte retrieval. All patients were randomized 1:1 to receive either a second dose of kisspeptin-54 10 h after the first injection.

Human Reproduction , 2017

Study results

	Single (*n*= 31)	Double (*n*= 31)	Both (*n* = 62)
Patients achieving ≥60% oocyte yield (%)	45.2%	71.0%*	58.1%
Number of oocytes	12	13	12
MII oocytes	10	10	10
Oocyte maturation rate (%)	83.0%	80.0%	82.0%
Oocyte yield as percentage	52.9%	63.6%	58.1%
Clinical PR (%)	23.0%	39.0%	30.6%
Implantation rate %	23.3%	37.1%	30.3%
Live birth rate (%)	19.4%	39%	29 %

The proportion of patients achieving an oocyte yield ≥60% was improved from 45% in the single kisspeptin-54 group to 71% in the double kisspeptin-54 group (*P* = 0.042). The implantation and live birth were increased in the double group. All patients who achieved an oocyte yield ≥60% had an embryo available for transfer and 25/36 (69%) had a high quality blastocyst available for transfer. By contrast, 1 of 26 (3.8%) patients with an oocyte yield ≤60% did not have an embryo available for transfer and 10 of 26 (38%) patients had a high quality embryo available for transfer

Human Reproduction , 2017

Study results

Rates of OHSS

- Despite 48% of patients in our trial having more than 25 follicles ≥11 mm on the day of trigger, almost all patients (61/62; 98.4%) were still able to safely receive fresh embryo transfer following kisspeptin-54 triggering

- There was one moderate early OHSS in single group (1.6%), and one mild late OHSS (1.6%) in the double group

Human Reproduction , 2017

Clinical parameters of ovarian hyperstimulation syndrome (OHSS) following different hormonal triggers of oocyte maturation in IVF treatment.

DESIGN:

We conducted a retrospective single-centre cohort study investigating symptoms and clinical parameters of early OHSS in women at high risk of OHSS triggered with hCG (n=40), GnRH agonist (GnRHa; n=99), or kisspeptin (n=122).

RESULTS:

Clinical Parameters of OHSS: Median ovarian volume was larger following hCG (138mls) than GnRHa (73mls; P<0.0001), and in turn kisspeptin (44mls; P<0.0001). Median ovarian volume remained enlarged 20-fold following hCG, 8-fold following GnRHa and 5-fold following kisspeptin compared to pre-stimulation ovarian volumes. Mean (±SD) ascitic volumes were lesser following GnRHa (9±44mls) and kisspeptin (5±8mls) than hCG (62±84mls; p<0.0001). Symptoms of OHSS were most frequent following hCG and least frequent following kisspeptin. Diagnosis of OHSS: The odds ratio for OHSS diagnosis was 33·6 (CI 12·6-89·5) following hCG and 3·6 (CI 1·8-7·1) following GnRHa, when compared to kisspeptin.

CONCLUSION:

Triggering oocyte maturation by inducing endogenous gonadotropin release is preferable to the use of exogenous hCG in women at high risk of OHSS.

Conclusioni

- GnRHa trigger and subsequent individualized luteal phase support with LH activity drugs may improve the clinical results. Therefore, GnRHa trigger can be used to assure both a high live birth rate and a low OHSS rate.

- Dual-double trigger con be useful for ovulation induction in normal and poor responders women with oocyte abnormalities. However, its application in woman at high risk of OHSS must be further evaluated.

- The data regarding the use of kisspeptin for oocyte maturation induction are still very limited and further large prospective studies are needed.

Centro di Medicina della Riproduzione
European Hospital – Roma

Direttore: Ermanno Greco

Ginecologia:

Maria Teresa Varricchio
Cristiana Arrivi
Katarzyna Litwicka
Alina Caragia
Maria Laura Tartaglia

Endocrinologia:

Cecilia Mencacci

Andrologia:

Ermanno Greco
Maria Chiara Greco

Psicologia:

Alessia Greco

Laboratorio:

Maria Giulia Minasi
Valentina Casciani
Alessandro Colasante
Elisabetta Cursio
Erika Iovine
Alessandra Ruberti
Filomena Scarselli
Vincenzo Zazzaro
Simona Gatti
Melania Riccio
Andrea Pristerà
Saverio Muzzi
Romualdo Polese