TYPES OF OVULATION TRIGGER IN IVF

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Triggering final follicular maturation–hCG, GnRH-agonist or both, when and to whom?

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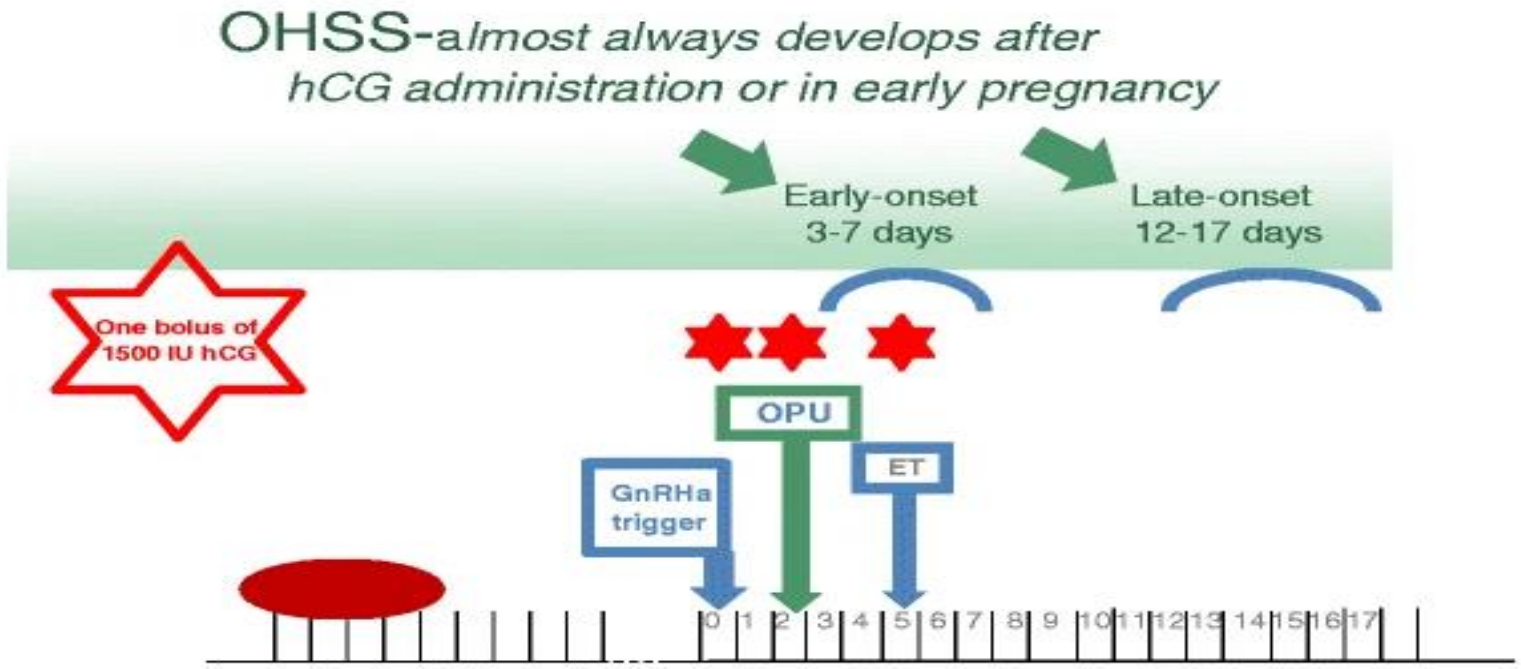
Raoul Orvieto

GnRHa and hCG in patients at risk to develop severe OHSS (Fig. 1)

Fig. 1



GnRHa and hCG trigger in patients at risk to develop severe OHSS

GnRHa versus hCG trigger- the physiological perspectives

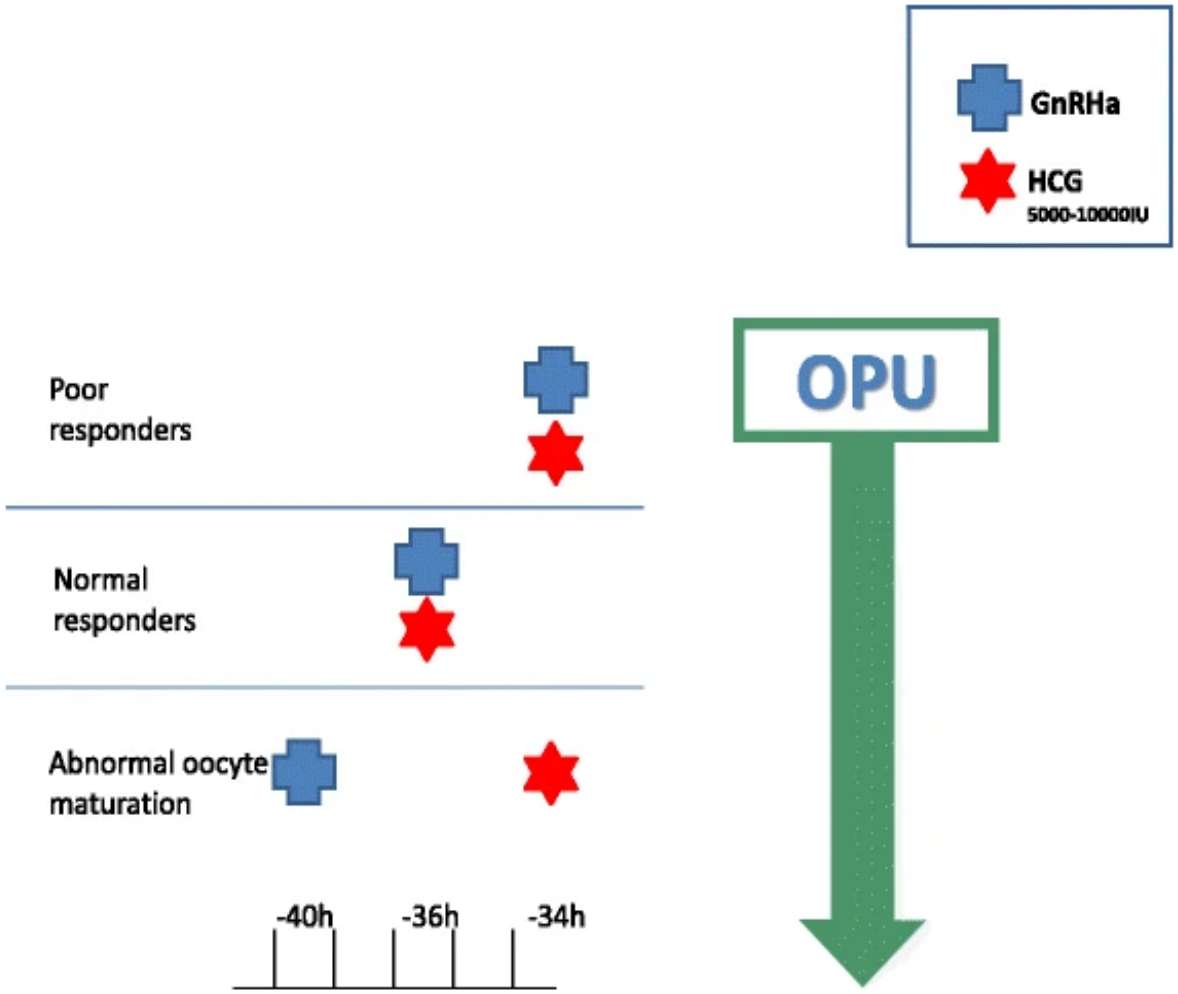
The number of oocytes retrieved, percentage of mature oocytes and number of top-quality embryos were either comparable or in favor of the GnRHa trigger (Table 1) and might be explained by the following observations:

1.Unlike the GnRHa-induced mid-cycle surge of LH and FSH, terminating 24 h after its onset, the HCG-mediated LH activity, with no FSH rise, and spans several days into the luteal phase

2.While both LH and hCG act on the same LH receptor, accumulating evidence suggests that LH has a greater impact on AKT and extracellular signal regulated protein kinase (ERK1/2) phosphorylation, responsible for granulosa cells proliferation, differentiation and survival, while hCG generates higher intracellular cAMP accumulation, which stimulates steroidogenesis (progesterone production)

Fig. 2

From: Triggering final follicular maturation- hCG, GnRH-agonist or both, when and to whom?



GnRHa and hCG trigger in patients not at risk to develop severe OHSS

Decleer et al. [25] compared IVF outcome following either, 5000 IU of hCG trigger or a combination of GnRHa plus 5000 IU of hCG concomitantly, 36 h prior to oocyte retrieval. While no in between groups differences were observed in the mean number of oocytes retrieved, mature oocytes or pregnancy rates, the number of patients who received at least one embryo of excellent quality and the number of cryopreserved embryos were significantly higher following the dual trigger.

Griffin et al. [26] evaluated the effect of the dual trigger (GnRHa and hCG 5,000 IU or 10,000 IU, 35–37 h) prior to oocyte retrieval in patients with a previous history of >25 % immature oocytes retrieved. Despite a significantly higher proportion of mature oocytes retrieved with the dual trigger, the observed IVF outcome remained poor, probably due to patients' underlying oocyte dysfunction.

In the group of patients with low (<50 %) number of oocytes retrieved per number of dominant follicles, following the double trigger (GnRHa 40 h and standard hCG added 34 h prior to OPU (double trigger), respectively) patients had significantly higher number of oocytes retrieved, number of 2PN, number of embryos transferred and significantly higher proportions of the number of oocytes retrieved to the number of follicles >10 mm and >14 mm in diameter on day of hCG administration

Moreover, in those with low proportion of MII oocytes (<66 %) per number oocytes retrieved, following the double trigger, patients yielded significantly higher number of MII oocytes and proportion of MII oocytes per number of oocytes retrieved, with the consequent significantly increased number of top-quality embryos, as compared to the hCG-only trigger cycles

To conclude, when the effects of the dual and double triggers are observed across the aforementioned studies (Table 2), they are always in the same direction- consistently improved

Table 2 The effect of Standard hCG dose concomitant with GnRHa (dual-double trigger) versus hCG alone on the different follicular maturation variables following an IVF treatment cycle

From: Triggering final follicular maturation- hCG, GnRH-agonist or both, when and to whom?

Authors	#oocytes	#MII oocytes	# embryos cryopreserved	#top quality embryos	Pregnancy rate
Lin et al. [24]	>	>	>	=	>
Decleer et al. [25]	=	=	=	=	=
			>patients with embryos	>patients with at least	
			Cryopreserved	one top quality embryo	
Griffin et al. [26]	>	>			=
Haas et al. [29]	>	>		>	>
Zilberberg et al. [30]	>	>		>	>

>In favor of the dual/double trigger

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JOURNAL ARTICLE

Ovulation triggering with hCG alone, GnRH agonist alone or in combination? A randomized controlled trial in advanced-age women undergoing IVF/ICSI cycles

FREE

Chengliang Zhou, Xinyue Yang, Yong Wang, Ji Xi, Hong Pan, Min Wang, Yuzhong Zhou, Yu Xiao ✉ Author Notes

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Article Contents

Comparison of embryo outcomes between the trigger groups.

	hCG	GnRH agonist	Dual trigger	*P*-value		
				hCG vs GnRH agonist	hCG vs Dual trigger	GnRH agonist vs Dual trigger
Number of mature oocytes[a]	2.78±2.10	3.15±2.95	3.54±2.51	0.376	0.061	0.353
Mature oocyte rate[a]	85.4	81.1	87.3	0.181	0.501	0.041
Number of 2PN embryos	2.77±2.30	2.79±2.53	3.04±2.24	0.944	0.302	0.337
Fertilization method				0.121	0.277	0.634
IVF	82 (50.0)	96 (58.5)	94 (56.0)			
ICSI	82 (50.0)	68 (41.5)	74 (44.0)			
Fertilization rate						
IVF	81.8	78.9	76.7	0.350	0.096	0.457
ICSI	83.3	80.8	82.1	0.494	0.711	0.733
Number of cleaved embryos	2.70±2.27	2.71±2.49	2.93±2.23	0.943	0.350	0.388
Cleavage rate	97.1	97.2	96.5	0.986	0.558	0.546
Number of good-quality embryos	1.19±1.45	1.20±1.67	1.74±1.90	0.362	0.016	0.003
Good-quality embryo rate	44.1	44.3	59.2	0.964	<0.001	<0.001
Number of viable embryos	1.56±1.66	1.45±1.75	2.19±2.11	0.277	0.008	0.001
Viable embryo rate	57.9	53.5	74.6	0.184	<0.001	<0.001

We conducted this study for the first time to simultaneously compare the hCG trigger, GnRHa trigger and dual trigger in women older than 35 years, in order to investigate whether dual trigger can be generally applicable to this population.

Our study showed no significant differences in the number of retrieved oocytes or mature oocytes in favor of any of the three trigger methods. However, we found that dual trigger was associated with more good-quality embryos and more viable embryos.

In all three groups in our study, there were patients in whom no oocytes were retrieved, and the proportions were not significantly different between the groups, although the number in the GnRHa trigger group was higher.

the two cases with more than three follicles and no oocyte retrieved were in the GnRHa trigger group. This suggests that the risk of no response or suboptimal response to GnRHa should not be ignored.

. In the present study, we found that the dual trigger group did not allow more oocytes to be retrieved but produced more good-quality embryos than the two single trigger groups,

suggesting that it was the combined effect of the two components that improved oocyte maturation and embryo development when compared with single hCG trigger. However, this finding could be only limited to some specific group of patients, such as older women, but not younger women or normal responders

ACADEMIC

human reproduction

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Article Contents

JOURNAL ARTICLE

Does an FSH surge at the time of hCG trigger improve IVF/ICSI outcomes? A randomized, double-blinded, placebo-controlled study FREE

Qi Qiu, Jia Huang, Yu Li, Xiaoli Chen, Haiyan Lin, Lin Li, Dongzi Yang, Wenjun Wang, Qingxue Zhang ✉ Author Notes

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Patients aged ≤42 years who were treated with IVF/ICSI owing to tubal factor, male factor, unexplained, endometriosis and multiple factors were enrolled in this trial.

Subjects all received a standard **long GnRHa protocol** for IVF/ICSI and hCG 6000–10 000 IU to trigger oocyte maturation. A total of 364 and 368 patients were randomized to receive a urinary FSH (uFSH) bolus (6 ampules, 450 IU) and placebo, respectively, at the time of the hCG trigger.

The primary outcome measure was clinical pregnancy rate. The secondary outcome measures were FSH level on the day of oocyte retrieval, number of oocytes retrieved, good-quality embryo rate, live birth rate and rate of OHSS

Table V Sensitivity analysis for pregnancy outcomes of the participants (ITT).

Open in new tab

IVF outcome	FSH co-trigger	Placebo	Absolute rate difference, % (95% CI)	Risk ratio (95% CI)	*P*-value
Under the worst outcome hypothesis					
Clinical pregnancy rate	52.7% (192/364)	55.4% (204/368)	−2.7 (−9.9 to 4.5)	0.95 (0.83 to 1.09)	0.47
Live birth rate	44.5% (162/364)	47.6% (175/368)	−3.1 (−10.2 to 4.2)	0.94 (0.80 to 1.10)	0.41
Under the best outcome hypothesis					
Clinical pregnancy rate	56.3% (205/364)	51.6% (190/368)	4.7 (−2.5 to 11.8)	1.09 (0.95 to 1.25)	0.20
Live birth rate	48.1% (175/364)	43.8% (161/368)	4.3 (−2.9 to 11.5)	1.10 (0.94 to 1.29)	0.24

The worst outcome hypothesis: the missing values in the FSH co-trigger group were imputed as

In this randomized, placebo-controlled, double-blinded study, we compared final oocyte maturation with hCG alone or with FSH co-trigger (uFSH + hCG) in women undergoing a GnRHa protocol for the treatment of infertility

. Our study showed no clinically relevant or statistically significant differences in clinical pregnancy rates in favor of treatment with additional FSH for oocyte triggering.
The serum FSH on the day of OR was significantly higher in the FSH co-trigger group, reflecting the effect of the study medication, but there was no clear clinical relevanc

CLINICAL ENDOCRINOLOGY

ORIGINAL ARTICLE | Open Access

Clinical parameters of ovarian hyperstimulation syndrome following different hormonal triggers of oocyte maturation in IVF treatment

A. Abbara, R. Islam, S.A. Clarke, L. Jeffers, G. Christopoulos, A.N. Comninos, R. Salim, S.A. Lavery, T.N.L. Vuong, P. Humaidan, T.W. Kelsey, G.H. Trew, W.S. Dhillo

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Funding information

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Clinical Trials Registration Number: NCT01667406.

A. Abbara and R. Islam are joint first authors.

- We conducted a retrospective single-centre cohort study investigating symptoms and clinical parameters of early OHSS in women at high risk of OHSS (antral follicle count or total number of follicles on day of trigger ≥23)

  triggered with human chorionic gonadotrophin (hCG) (n = 40), GnRH agonist (GnRHa; n = 99) or kisspeptin (n = 122) at Hammersmith Hospital IVF unit, London, UK

kisspeptin has been evaluated as a novel trigger of oocyte maturation.
Kisspeptin acts to stimulate the release of endogenous GnRH from the hypothalamus. The peak serum LH level following kisspeptin occurs at a similar interval to GnRHa (~4 hours following administration), but to a lower amplitude,
as kisspeptin only stimulates the release of an endogenous pool of GnRH. To date, there has been no direct comparison of markers of early OHSS following these triggers of oocyte maturation.

Mild OHSS occurred in 45% of patients following hCG, 30% following GnRHa and 12% following kisspeptin (Table 2). Moderate to severe OHSS occurred in 37.5% of patients following hCG, 3% following GnRHa and no patient following kisspeptin (Table 2). The likelihood of OHSS was increased at least ~33-fold following hCG ($P < .0001$) and ~3-fold following GnRHa ($P < .0001$) when compared to kisspeptin

N	Normal	Mild OHSS	Moderate OHSS	Severe OHSS	Odds ratio of mild-severe OHSS (95% CI)	Odds ratio of moderate-severe OHSS (95% CI)
hCG (n = 40)	7 (18%)	18 (45%)	9 (23%)	6 (15.0%)	33.6 (12.6-89.5) $P < .0001$	80.7 [a] (10.2-637.5) $P < .0001$
GnRHa (n = 99)	66 (67%)	30 (30%)	3 (3%)	0 (0%)	3.6 (1.8-7.1) $P < .0001$	5.1 [a] (0.6-46.3) $P = .15$
Kisspeptin (n = 122)	107 (88%)	15 (12%)	0 (0%)	0 (0%)	-	-

Journal of
Human Reproductive Sciences

ORIGINAL ARTICLE

Repeat Dose of Gonadotropin-releasing Hormone Agonist Trigger in Polycystic Ovarian Syndrome Undergoing *In Vitro* Fertilization Cycles Provides a Better Cycle Outcome - A proof-of-concept Study

Deepika, Krishna; Baiju, Pookilath; Gautham, Praneesh; Suvarna, Rathore; Arveen, Vohra; Kamini, Rao

Author Information

Journal of Human Reproductive Sciences 10(4):p 271-280, Oct–Dec 2017. | ***DOI:*** 10.4103/jhrs.JHRS_102_17

This prospective randomized study was conducted in a university-affiliated tertiary care center. A total of 227 patients diagnosed with PCOS, undergoing IVF in an antagonist protocol

COH was started from 112.5 to 175 IU daily for 4 days

GnRH antagonist, Ganirelix (Orgalutran, Organon) 0.25 mg/day subcutaneous (s.c) was started when the leading follicle was >14 mm and/or serum E2 concentration was >300 pg/mL.

When three lead follicles achieved 17-mm diameter, the final oocyte maturation was triggered with a single dose of 0.2 mg s.c triptorelin (decapeptyl, Ferring) 35 h prior to oocyte retrieval in both the groups and in Group B, a repeat dose of 0.1 mg 12 h following the first dose. We preferred using triptorelin as GnRHa trigger,

a significantly higher proportion of the number of oocytes' retrieved to the number of preovulatory follicles was seen in Group A, yet a significantly higher yield of MII oocytes was obtained in Group B with an odds of 0.47 ($P < 0.001$)
This was associated with a statistically significant lesser number of MIs and GV oocytes in Group B, suggestive of a better maturity with a repeat dose of GnRHa 12 h following the first dose

Our study demonstrates a trend toward better fertilization, higher number of G1 embryos available on day 3 and better blastocyst conversion, yielding a greater number of blastocysts in Group B.

Following transfer of frozen embryos in the subsequent HT cycle, a trend toward **a higher clinical pregnancy rate** was observed in Group B (58% vs. 44%) who received a repeat dose of GnRHa 12 h later, though not statistically significant.

ELSEVIER

Reproductive BioMedicine Online

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Article

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

Jie Zhang [1], Yun Wang [1], Xiaoyan Mao [1], Qiuju Chen, Qingqing Hong, Renfei Cai, Shaozhen Zhang, Yanping Kuang

https://doi.org/10.1016/j.rbmo.2017.09.002

. Our data showed that dual trigger with GnRHa and standard dosage of HCG significantly increased the **number of oocytes retrieved** and the **egg maturity** versus conventional HCG trigger alone

The results indicated that the gene expression of **epiregulin (Ereg)** and **amphiregulin (Areg)**) in the GC from patients receiving the double trigger were significantly higher than that from the patients triggered by HCG alone (Haas et al., 2016).

More specifically, Ereg and Areg have been shown to mediate the LH signal and partially take part in the process of cumulus expansion and oocyte maturation

JBRA Assisted Reproduction

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Dual trigger *vs.* Conventional trigger outcomes in *In Vitro* Fertilization. Systematic review and meta-analysis

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Abstract

Go to: ▸

Objective

The aim of this study is to analyze the efficacy of the dual trigger (human chorionic gonadotropin (hCG) + GnRH agonists) compared to the conventional trigger (hCG) in terms of oocyte retrieval (number and oocyte maturity), fertilization rate or number of embryos with two pronuclei, number of high-quality embryos, number of transferred embryos, number of cryopreserved embryos, implantation rate, positive β-hCG rate, ongoing pregnancy rate, abortion rate, and live birth rate.

Table 3

Controlled ovarian hyperstimulation regimens.

Study	Type of protocol	Dual trigger group	hCG group
Schachter *et al.*, 2008	Antagonist	hMG + Cetrorelix	HMG + Cetrorelix
Kim *et al.*, 2014	Antagonist	150-225 UI rFSH + Cetrorelix	150-225 UI rFSH + Cetrorelix
Decleer *et al.*, 2014	Antagonist	200 UI rFSH + Ganirelix	200 UI rFSH + Ganirelix
Mahajan *et al.*, 2016	Antagonist	FSH + hMH-HP + Cetrorelix	FSH + hMH-HP + Cetrorelix
Maged *et al.*, 2021	Antagonist	300 UI r-FSH + 150 UI LH+FSH + Cetrorelix	300 UI r-FSH + 150 UI LH+FSH + Cetrorelix
Haas *et al.*, 2020	Antagonist	150-225 UI r-FSH + Ganirelix	150-225 UI r-FSH + Ganirelix

Table 4

Interventions and dosage in COH and triggering.

Study	Dual group		hCG group	
	Total FSH dose	Triggering	Total FSH dose	Triggering
Schachter et al., 2008	N/A	0.2 mg triptorelin + 5000 UI hCG	N/A	5000 UI hCG
Kim et al., 2014	1879.4±457.2	0.1 mg triptorelin + 250 μg hCG	1859.6±462.8	250 μg hCG + placebo
Decleer et al., 2014	2083±590	0.2 mg triptorelin + 5000 IU hCG	2006±457	5000 UI hCG
Mahajan et al., 2016	2851.6±573	0.2 mg triptorelin + 250 μg hCG	2879.6±809.9	250 μg hCG
Maged et al., 2021	N/A	0.2 mg triptorelin + 10000 UI hCG	N/A	10000 UI hCG
Haas et al., 2020	N/A	1 mg leuprolide acetate + 1000UI hCG	N/A	1000UI hCG

in favor of the dual trigger protocol when compared to hCG activation in terms of number of oocytes retrieved and live birth rate. No statistically significant differences were found for the other analyzed variables, although a trend favoring the dual trigger was identified in every parameter considered.

All studies reported an increase in the number of total oocytes retrieved and in the number of mature oocytes favoring the dual trigger. They also reported a higher number of high-quality embryos with the dual trigger protocol compared with the conventional trigger. Nevertheless, statistically significant differences were observed only in the total number of oocytes. Despite the increased number of mature oocytes and high quality embryos associated with the dual trigger, no statistically differences were observed in the analysis, with an MSD of 0.23 (IC: 0.06 - 0.53) in the study of mature oocytes

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JOURNAL ARTICLE

GnRH agonist and hCG (dual trigger) versus hCG trigger for final follicular maturation: a double-blinded, randomized controlled study FREE

J Haas ✉, R Bassil, N Samara, E Zilberberg, C Mehta, R Orvieto, R F Casper

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Article Contents

A prospective, randomized, double-blinded clinical trial enrolled patients between May 2016 and June 2018.

The inclusion criteria for participating in the study were: women age 18–41 years, with BMI (body mass index) of 18–35 kg/m2, AMH (anti-Müllerian hormone) >1 ng/ml, AFC (antral follicular count) 6–20 and FSH <20 IU/l undergoing one of their first three IVF cycle attempts.

We excluded patients with poor ovarian reserve (AMH <1 ng/ml), patients at high risk of developing ovarian hyperstimulation syndrome (OHSS; E2 levels >15 000 pmol/l or AFC >20), patients with BMI >35 and patients with moderate–severe endometriosis.

In our present RCT, we found a higher number of oocytes, mature oocytes, blastocysts, top-quality blastocysts, implantation rate, ongoing pregnancy rate and higher live birth rate in the dual trigger group