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Comparison of GnRH Agonist, hCG, and Dual Trigger for Final Oocyte Maturation in IVF Cycle

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Abstract

Objectives: This study aims to analyze the effects of three types of triggers— human chorionic gonadotropin (hCG), GnRH-a, or a combination of them (dual)—on the quality of oocytes, embryos, and ovarian hyper-stimulation syndrome (OHSS) in the ICSI cycle.

Materials and Methods: A prospective case-control study was conducted on 320 women referred to Milad IVF Center, Mashhad, Iran, between May 2016 and June 2019. All the participants underwent an antagonist protocol and were classified according to the trigger type into three groups: 118 patients in the GnRH-a group, 49 in the hCG group, and 153 in a dual group. The outcome measures included the number of metaphase I and metaphase II oocytes, germinal vesicle (GV) oocytes, high-quality embryos, and the rate of OHSS.

Results: The three groups did not exhibit statistically significant differences concerning the quantities of retrieved oocytes: M II oocytes, M I oocytes, GV oocytes, and embryos. The dual trigger method resulted in significantly higher embryo quality ($P=0.017$). In comparison to dual and GnRH-a group triggers, it was observed that women administered with the hCG group trigger displayed an increased occurrence of OHSS, and the number of severe OHSS in the dual trigger was higher than in the GnRH-a and hCG groups.

Conclusions: The GnRH agonist alone and the dual trigger can be as effective as the hCG trigger. A GnRH agonist is preferable in high-risk patients. Therefore, it is imperative to administer the treatment based on the patient's status.

Keywords: In vitro fertilization, Human chorionic gonadotropin, Gonadotropin-releasing hormone agonist, Ovarian hyper-stimulation syndrome

Introduction

During in vitro fertilization (IVF), after ovarian stimulation and the development of follicles by gonadotropins, the final maturation of oocytes is achieved using an ovulation trigger (1). Over the past two decades, human chorionic gonadotropin (hCG) has been used as a conventional protocol for final follicular maturation due to its structural and biological similarities with endogenous luteinizing hormone (LH), which imitates the physiological LH surge for oocyte maturation (2,3).

However, the use of hCG is concomitant with an increase in the risk of ovarian hyperstimulation syndrome (OHSS) due to its long half-life in the luteal phase (4).Also, it is established that follicle-stimulating hormone (FSH) needs to improve the quality of oocytes, and hCG lacks FSH in the middle of the cycle (5,6). The presence of FSH in the oocyte maturation process has been demonstrated in a large number of studies; the GnRH agonist raises the proportion of mature oocytes (7,8). In contrast to hCG, the gonadotropin-releasing hormone agonists (GnRH-a) provide a more physiological trigger effect owing to a shorter half-life, resulting in a gonadotropin surge that lasts 34 hours, so there is often poor LH support for the corpora lutea after ovulation, so intensive luteal support is required to ensure implantation and ongoing pregnancy (9,10).This reduced duration of luteotropic activity greatly reduces the potential for OHSS (11).

Several researchers have reported that the rate of mature oocytes and the number of good-quality embryos were equivalent or greater when using the GnRH-a trigger than the hCG trigger (12).

Subsequent studies comparing clinical outcomes between GnRH-a and hCG triggers in oocyte donation cycles revealed comparable efficacy but with a significantly reduced rate of OHSS in GnRH-agonist-triggered cycles (13,14). Moreover, there is no significant difference between implantation, pregnancy, or miscarriage rates in GnRH agonist trigger and hCG trigger (14)

An alternative proposed trigger is a dual trigger, including a combination of GnRH-a and a low dose of hCG (1000–1500 units). One study has shown that the effect of a dual trigger in final oocyte maturation is similar to the GnRH agonist triggers in autologous cycles (15). A systematic review by Oliveira et al. showed that a dual

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Key Messages

- This study evaluated the effect of three triggers on the quality and quantity of oocytes and embryos in the ICSI cycle.
- It was found, the GnRH agonist alone and the dual trigger can be as effective as the hCG trigger.
- The viable embryos and quantity of grade 1 embryos were slightly higher in dual groups.
- This study suggests that it is more logical to use a GnRH agonist instead of HCG in high-risk patients.

trigger is an excellent alternative for final maturation in poor and normal respondents. Still, there is no indication of dual use among high respondents (16). Also, Ding et al and Chen et al performed two systematic reviews and meta-analyses, and both of them concluded that the quantity of oocyte M II and mature oocyte was identical in both dual trigger and hCG instances, and dual trigger has also improved clinical pregnancy rates considerably (17,18). However, Hu et al recently conducted a systematic review and meta-analysis of randomized trials. They found that dual trigger treatment improved the number of mature MII oocytes collected, the number of oocytes retrieved, viable embryos, and fertilized oocytes (19). These findings suggest that the GnRH-a component of trigger dual is beneficial in maturing oocytes, boosting pregnancy, and reducing OHSS syndrome.

Objectives

This study compares the number of retrieved oocytes, mature oocytes, top-quality embryos, and OHSS rate between three groups: GnRH-a, dual, and hCG triggers in antagonist IVF cycles.

Material and Methods

Study Design

A prospective case-control study enrolled individuals attending Mashhad University-affiliated Infertility and IVF Center (Milad), Mashhad, Iran, between May 2016 and June 2019 — 320 women who were referred for treatment of infertility enrolled in the study.

The sample size was calculated using G*Power software based on Haas et al study. Considering the number of eggs retrieved (11.1 versus 13.4), the total sample size in this study was calculated to be 213 people. Considering 20% of the confounding variables, 320 people were invited to the study and divided into three groups according to the conditions of drug consumption (20).

Study Participants

The inclusion criteria for participating in the study were women aged 18–40 years, body mass index (BMI, calculated as weight in kilograms divided by height in meters squared) <30, and high risk for OHSS (having more than 20 follicles > 12 mm on the day of trigger administration).

The exclusion criteria included having cardiovascular disease, liver disease, hyperprolactinemia, asthma, and hypertension, as well as age > 40 years old. Also, patient dissatisfaction with continued treatment was considered an exclusion criterion.

At the beginning of the study, women underwent complete evaluations such as clinical history, physical examination, laboratory test, transvaginal sonography, and profile hormone. If they met the inclusion criteria, they entered the study.

Ovarian Stimulation Protocols

The participants underwent GnRH antagonist protocol ovarian stimulation to prepare for IVF. On the second day of the menstrual cycle, all participants were investigated with transvaginal ultrasound at the onset of menses. If the endometrial thickness was less than 5 mm and the ovaries were quiet, ovarian stimulation would be started.

Stimulation protocol treatment was initiated on the third day of menses with the daily use of recombinant human FSH (Cinna Gen, Tehran, Iran) at 150-225 IU. The gonadotropin dose was individually adjusted according to prior cycles' ovarian reserve tests, BMI, age, and response.

Once the leading follicle reached a size of 12-13 mm, co-treatment with the GnRH antagonist 0.25 mg/d Cetrotide (Merck Serono, Mississauga, Canada) and highly purified human menopausal gonadotropin (Menotropin 75 IU, Darou Pakhsh Pharmaceutical Co., Tehran, Iran) was commenced. Follicle growth was continuously monitored using ultrasound, and the drug dose was adjusted based on ovarian response.

All ultrasound exams were performed by one researcher using a Phillips Affinity 70 device at the Milad infertility center.

When the dominant follicles reached an average diameter of 18–20 mm (the morning of the trigger day), the investigators recruited the patients for the study. After the participants provided written informed consent, based on the physician's preference (36.9%), 118 patients in the GnRH-a group (15.3%), 49 patients in the hCG group, and (47.8%), 153 patients in the dual group (GnRH-a and hCG) were assigned. In the hCG group, patients were triggered for final follicular maturation with hCG (Pregnil 5000 IU HCG; Pooyesh Darou, Tehran, Iran). When the serum estradiol level was lower than 4000 pg/mL in the dual trigger group, patients were triggered with a GnRH agonist (Decapeptyl 0.2 mg, Ferring, Germany) and a low-dose hCG of 1500 IU. In the GnRH agonist group, the GnRH agonist (Decapeptyl 0.2 mg) was used alone to trigger. Oocyte retrieval was performed via the transvaginal US-guided needle (K-OPSD-1730-A-L; Cook Australia Pty Ltd., Brisbane, Australia) puncture 36 hours after injection of the trigger.

Embryo quality was assessed on the third day of fertilization and evaluated according to Cummins et

al.'s standard as grade 1 (excellent embryos with eight blastomeres with cell regularity and size equality without necrosis and fragmentation), grade 2 (embryos 1–20% fragmentation), grade 3 (21–50% fragmentation), and grade 4 (fragmentation greater than 50%) (21).

Outcome Measures

The primary outcome measure was the number of oocytes derived in every group and the number of M II, M I, and germinal vesicle (GV) oocytes. The secondary outcome measures the rate of fertilization, the rate of embryos in grades 1 and 2, and the occurrence rate of OHSS. The fertilization rate was calculated as the ratio of the number of embryos fertilized over the number of oocytes inseminated.

The OHSS classification is based on the Humaidan et al. criteria (22). Mild OHSS was determined by the existence of pelvic discomfort, abdominal distension, and the presence of ascites in the Douglas pouch and enlarged ovaries in ultrasonography. Moderate OHSS was stated in the presence of pelvic discomfort, abdominal distension, ultrasonic evidence of fluid in Douglas's pouch and around the uterus (major pelvis), ovarian enlargement, and hemoconcentration (hematocrit > 45%).

Severe OHSS was defined in the presence of both objective criteria (fluid collection in the pelvic pouch and around intestinal loops, hematocrit >45%, white blood cells >15 000, urine outputs <600 mL per 24 hours) and subjective criteria (pelvic discomfort, abdominal distension, severe dyspnea, and enlarged ovaries).

Statistical Analysis

The mean and standard deviation (SD) were calculated for continuous variables. Continuous variables between groups were compared using one-way ANOVA, which depended on whether the data was normally distributed. For categorical variables, the chi-square test was used as the appropriate measure. An ANCOVA analysis was used to compare the three groups by adjusting for age and duration of infertility. Statistical analysis on all 320 patients was performed using the Statistical Package for Social Sciences (SPSS®) version 24. A P value of ≤0.05 was considered statistically significant for all statistical tests.

Results

Patients' Characteristics

A total of 320 patients underwent IVF/ICSI cycles and were referred to Milad Infertility Center.

The average age of participants receiving GnRH-a was 29.56 ± 4.91; in the hCG group, it was 31.18 ± 6.20, and the dual trigger was 30.40 ± 5.31. The mean age was not significantly different in the three groups (P = 0.178), but the average duration of infertility was significantly different in the three groups (P = 0.044). BMI was homogeneous in the three groups (P = 0.212). Additionally, there was no difference regarding serum FSH or LH between the three groups (Table 1).

The ovarian stimulation characteristics before oocyte retrieval were compared in three groups. There was no statistically significant difference in the total gonadotropin doses used in stimulation in the GnRH-a, hCG, and dual trigger groups (P = 0.098). Otherwise, no differences

Table 1. Demographic and Clinical Characteristics of the Study Participants in Three Groups

	GnRH-a (n=118)	hCG (n=49)	Dual trigger (n=153)	*P* Value[a]
Age in year	29.56±4.915	31.18±6.20	30.40±5.31	0.178
BMI (kg/m^2)	25.58±3.591	26.26±3.68	25.19±3.98	0.212
Duration of infertility (year)	6.96±4.40	8.48±4.67	6.74±3.99	0.044
Number of consumption drug	28.71±11.61	32.61±13.35	30.93±10.64	0.098
Total dose of gonadotrophins stimulation (IU/mL)	2153.84±870.85	2445.91±143.12	2320.27±798.92	0.098
Total days of gonadotrophins stimulation (days)	11.10±1.94	10.85±1.69	11.25±2.20	0.486
FSH (mIU/mL)	5.52±2.06	5.90±2.58	5.90±2.10	0.313
LH (mIU/mL)	8.10±5.07	6.69±4.60	6.93±4.76	0.095
Number of follicle	30.76±9.87	23.75±6.45	26.81±8.62	0.000
Pattern of the cycle — Irregular	71 (60.7)	32 (65.3)	90 (58.8)	0.721
Infertility—Primary	92 (78.6)	46 (93.9)	131(86.2)	0.035
Cause of infertility				
Female	58 (49.6)	14 (29.2)	65 (42.5)	0.019
Male	16 (13.7)	14 (29.2)	37 (24.2)	
Male and female	22 (18.8)	11 (22.9)	38 (24.8)	
Unexpected	21(17.9)	9 (18.8)	13 (8.5)	

hCG; human chorionic gonadotrophin, BMI; body mass index, FSH; follicle stimulating hormone, LH; luteinizing hormone.
Data are presented as mean ± SD, or n (%).
[a] ANOVA.

regarding the total days of gonadotrophin stimulation were found.

Finally, we compared the fertilization characteristics between the three groups. The majority of patients in the three groups had primary infertility, and there were significant differences between each group ($P=0.035$). Significant differences existed between the three groups in the cause of infertility ($P=0.019$). There was a statistically significant difference in the total number of follicles in the three groups: GnRH-a, hCG, and dual trigger groups (30.76 ± 9.87 vs. 23.75 ± 6.45, 26.81 ± 8.62, $P=0.000$).

Table 2 compares the number of follicles, retrieved oocytes, and mature and immature oocytes between the three groups. In the comparison of the three groups, women who received dual trigger and GnRH-a had a higher number of retrieved oocytes (17.86±7.49 and 17.37±6.70 vs. 15.43±6.21, $P=0.115$), but these differences were not significant. The number of embryos and values for metaphase II oocytes, metaphase I oocytes, and the number of GV oocytes were not significantly different between the three groups. Also, the total number of viable embryos was slightly higher in the dual trigger and GnRH-a groups than in the hCG group but was insignificant ($P=0.715$). The quantity of grade 1 embryos was found to be significantly higher in the dual trigger group, while the proportion of grade 2 embryos was observed to be higher in the GnRH trigger group.

Table 2 shows the difference between the three groups regarding the quality embryo percentile between the three groups ($P=0.017$).

Table 3 compares the OHSS between the three groups. There were no OHSS in the three groups. In comparison to dual trigger and GnRH-a, women who received the hCG group had a higher number of OHSS (15.2 % vs. 9.0%—7.1%, $P=0.506$). The number of severe OHSS in dual trigger was higher vs. GnRH-a alone and hCG groups alone (1.4% vs. 0%).

Discussion

This study identified no statistical difference in the number of retrieved and MII oocytes in three types of triggers in the GnRH antagonist protocol. Also, there was no difference in the number of high-quality embryos between groups, but the quality of embryos was higher in dual triggers.

The last two decades have seen a growing trend toward the use of GnRH agonist triggers to reduce the prevalence of OHSS (23,24). Also, the use of GnRH-a for triggering imitates the natural cycle by inducing a mid-cycle FSH surge and supposedly improves the quality of oocytes. FSH is a crucial element in stimulating the expression of LH receptors in oocyte granulosa cells, resumption of oocyte meiosis, and cumulus expansion (25,26). Consequently, increasing the proportion of metaphase II oocytes retrieved would be more advantageous than an hCG trigger.

Furthermore, Hassl et al conducted a study to assess the level of messenger RNA (mRNA) expression of reproduction-related genes in granulosa cells within the context of cycles triggered by hCG, or GnRH agonist, and hCG (double trigger). The researchers ultimately concluded that the quality of oocytes and embryos could

Table 2. Comparison of Embryological Data in Three Groups

	GnRH-a (n=118)	hCG (n=49)	Dual Trigger (n=153)	*P* Value
Number of oocytes	17.86±7.49	15.43±6.21	17.37±6.70	0.115[a]
Number embryo	10.66±6.55	9.86±5.63	10.55±5.43	0.715[a]
Number of MI oocytes	0.81±2.02	0.37±0.85	0.60±3.82	0.664[a]
Number of MII oocytes	14.74±7.49	13.76±5.68	15.02±6.58	0.505[a]
Gv oocyte	0.72 ± 1.57	0.51±1.37	0.65±1.38	0.696[a]
Fertilization rate	78.39%	72.42%	70.87%	0.483[a]
Quality embryo				
Grade 1	37 (33.0)	25 (52.1)	71 (47.7)	0.017[b]
Grade 2	74 (66.1)	22 (45.8)	74 (49.7)	

Data are presented as mean ± SD, or n (%).
[a] ANOVA; [b] Pearson chi-square.

Table 3. Comparison of OHSS in Three Groups

	GnRH-a (n=118)	hCG (n=49)	Dual Trigger (n=153)	*P* Value[a]
OHSS				
Mild	6 (5.3)	5 (10.9)	8 (5.5)	0.506
Moderate	2 (1.8)	2 (4.3)	3 (2.1)	
Severe	0 (0)	0 (0)	2 (1.4)	
Total	8 (7.1)	7 (15.2)	14 (9.0)_	

Data are presented as n (%).
[a] Pearson chi-square.

be enhanced in patients undergoing double triggers as a result of the reduced expression of conexin43 and increased expression of epiregulin (27).

Various studies have investigated the effectiveness of dual triggers on the number and quality of oocytes and embryos. These studies focus on high responders (15,28-30), poor responders (31), and normal responders (32-34). In some studies, the proportion of mature oocytes in the dual trigger was significantly higher than the hCG trigger (20,35). On the other hand, Zhou stated that an identical number of oocytes were collected in the two groups (32).

Our study shows an increasing number of mature oocytes in the dual trigger, but it was not significant. We compared three types of triggers; the difference between our findings and those of other studies may be due to the small sample size in each group. However, our results are consistent with Alleyassin et al and Decleer et al (33,35). In addition, our study demonstrated that high-quality embryos have a higher dual trigger than hCG or GnRH-a alone. However, there was no difference in the number of high-quality embryos between groups. Similar to our result, Ali and colleagues reported a considerable increase in grade I embryos in the dual trigger group without any difference in the number of embryos cryopreserved compared to the hCG group (34), but Hass et al and Zhou et al revealed dual triggers improve both the quality and proportion of top embryos (20-32).

Our study also showed that the risk of OHSS is highest with hCG triggers. OHSS is the most serious complication in the ART cycle, occurring in 1-5% of patients after gonadotropin stimulation (36). Two patients in the dual-trigger group developed severe OHSS. This is clinically important, but overall, there was no significant difference in the incidence of OHSS between the three groups.

Similar to our study, O'Neill et al found that dual triggers are associated with an increased number and maturity of oocytes collected compared to GnRH agonists alone. However, they concluded that dual triggers significantly increased the risk of early OHSS (8.6 vs. 0%) (37). Their result is almost consistent with our finding that the risk of OHSS in dual triggers is 9%.

Contrary to previous findings, Li and colleagues have demonstrated the efficacy of the dual trigger method in preventing severe OHSS in high-ovarian responders undergoing GnRH-antagonist protocols while also maintaining a high rate of high-quality embryos (29).

A recent study was conducted using three types of triggers: GnRH-a, dual trigger, and hCG in donor cycles. Ultimately, the number of mature oocytes in the GnRH-a and dual groups significantly increased compared to hCG. Additionally, the dual trigger method exhibited the highest likelihood of OHSS.

These conflicting consequences might be due to different methods, such as inconsistency in the research community and the type and dose of drugs. In addition, studies classified OHSS differently (22,38,39). As Hu et al mentioned, no agreement exists on the best dose of hCG and GnRH agonists in the dual trigger (19).

Strength and limitations of the study

A key strength of the present study was comparing three kinds of triggers together. However, several limitations of this study need to be acknowledged. First of all, our findings are limited by using a cross-sectional design. Therefore, the type of trigger was based on physician preference. Secondly, the study was conducted with limited sample sizes and performed in a single center in Iran, which may not be generalized for all patients. The relatively smaller size of the hCG patient group compared to the GnRH and dual groups undermines the robustness of the conclusions. Finally, the pregnancy outcomes were not evaluated due to the cryopreservation of all embryos. This limitation means that the study findings need to be interpreted cautiously.

Conclusions

The present study shows that three triggers yield similar effects on oocytes, albeit with a greater number of top-grade embryos observed in the dual trigger. GnRH-a alone may be a better trigger for reducing OHSS in high-risk patients.

Directions for Future Research

It is recommended that further research be undertaken in the following areas: As mentioned before, the study's main limitation is its design, which is better to perform as a clinical randomized trial focused on comparing the quality of oocytes and embryos between different triggers. Large randomized controlled trials could provide more definitive evidence. In addition, another question raised by this study is the effect of the type of trigger on the pregnancy outcome or complication of pregnancy that needs the follow-up of patients until the birth of a baby.

Authors' Contribution

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Conflict of Interests

Authors declare that they have no conflict of interests.

Ethical Issues
The study was approved by our institutional review board (IRB) in Mashhad, Iran, with the number approval code IR.MUMS.REC.1395.326. All participants provided written informed consent before entry.

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References

1. Smitz J, Platteau P. Influence of human chorionic gonadotrophin during ovarian stimulation: an overview. Reprod Biol Endocrinol. 2020;18(1):80. doi:10.1186/s12958-020-00639-3
2. Humaidan P, Kol S, Papanikolaou EG. GnRH agonist for triggering of final oocyte maturation: time for a change of practice? Hum Reprod Update. 2011;17(4):510-524. doi:10.1093/humupd/dmr008
3. Choi J, Smitz J. Luteinizing hormone and human chorionic gonadotropin: distinguishing unique physiologic roles. Gynecol Endocrinol. 2014;30(3):174-181. doi:10.3109/09513590.2013.859670
4. Yan MH, Cao JX, Hou JW, et al. GnRH agonist and hCG (dual trigger) versus hCG trigger for final oocyte maturation in expected normal responders with a high immature oocyte rate: study protocol for a randomized, superiority, parallel group, controlled trial. Front Endocrinol (Lausanne). 2022;13:831859. doi:10.3389/fendo.2022.831859
5. Zhou C, Yang X, Wang Y, et al. Ovulation triggering with hCG alone, GnRH agonist alone or in combination? A randomized controlled trial in advanced-age women undergoing IVF/ICSI cycles. Hum Reprod. 2022;37(8):1795-1805. doi:10.1093/humrep/deac114
6. Castillo JC, Haahr T, Martínez-Moya M, Humaidan P. Gonadotropin-releasing hormone agonist ovulation trigger-beyond OHSS prevention. Ups J Med Sci. 2020;125(2):138-143. doi:10.1080/03009734.2020.1737599
7. Abbara A, Clarke SA, Dhillo WS. Novel concepts for inducing final oocyte maturation in in vitro fertilization treatment. Endocr Rev. 2018;39(5):593-628. doi:10.1210/er.2017-00236
8. Qiu Q, Huang J, Li Y, et al. Does an FSH surge at the time of hCG trigger improve IVF/ICSI outcomes? A randomized, double-blinded, placebo-controlled study. Hum Reprod. 2020;35(6):1411-1420. doi:10.1093/humrep/deaa087
9. Gao F, Wang Y, Fu M, et al. Effect of a "dual trigger" using a GnRH agonist and hCG on the cumulative live-birth rate for normal responders in GnRH-antagonist cycles. Front Med (Lausanne). 2021;8:683210. doi:10.3389/fmed.2021.683210
10. Casper RF. Introduction: gonadotropin-releasing hormone agonist triggering of final follicular maturation for in vitro fertilization. Fertil Steril. 2015;103(4):865-866. doi:10.1016/j.fertnstert.2015.01.012
11. Youssef MA, Elashmawi H. GnRH antagonist for pituitary desensitization in IVF: is it a time for a change of practice? Middle East Fertil Soc J. 2011;16(4):254-256. doi:10.1016/j.mefs.2011.11.001
12. Orvieto R. Triggering final follicular maturation- hCG, GnRH-agonist or both, when and to whom? J Ovarian Res. 2015;8(1):60. doi:10.1186/s13048-015-0187-6
13. Dosouto C, Haahr T, Humaidan P. Gonadotropin-releasing hormone agonist (GnRHa) trigger - state of the art. Reprod Biol. 2017;17(1):1-8. doi:10.1016/j.repbio.2017.01.004
14. Humaidan P, Nelson SM, Devroey P, et al. Ovarian hyperstimulation syndrome: review and new classification criteria for reporting in clinical trials. Hum Reprod. 2016;31(9):1997-2004. doi:10.1093/humrep/dew149
15. Griffin D, Benadiva C, Kummer N, Budinetz T, Nulsen J, Engmann L. Dual trigger of oocyte maturation with gonadotropin-releasing hormone agonist and low-dose human chorionic gonadotropin to optimize live birth rates in high responders. Fertil Steril. 2012;97(6):1316-1320. doi:10.1016/j.fertnstert.2012.03.015
16. de Oliveira SA, Calsavara VF, Cortés GC. Final oocyte maturation in assisted reproduction with human chorionic gonadotropin and gonadotropin-releasing hormone agonist (dual trigger). JBRA Assist Reprod. 2016;20(4):246-250. doi:10.5935/1518-0557.20160047
17. Ding N, Liu X, Jian Q, Liang Z, Wang F. Dual trigger of final oocyte maturation with a combination of GnRH agonist and hCG versus a hCG alone trigger in GnRH antagonist cycle for in vitro fertilization: a systematic review and meta-analysis. Eur J Obstet Gynecol Reprod Biol. 2017;218:92-98. doi:10.1016/j.ejogrb.2017.09.004
18. Chen CH, Tzeng CR, Wang PH, et al. Dual triggering with GnRH agonist plus hCG versus triggering with hCG alone for IVF/ICSI outcome in GnRH antagonist cycles: a systematic review and meta-analysis. Arch Gynecol Obstet. 2018;298(1):17-26. doi:10.1007/s00404-018-4751-3
19. Hu KL, Wang S, Ye X, Zhang D, Hunt S. GnRH agonist and hCG (dual trigger) versus hCG trigger for follicular maturation: a systematic review and meta-analysis of randomized trials. Reprod Biol Endocrinol. 2021;19(1):78. doi:10.1186/s12958-021-00766-5
20. Haas J, Bassil R, Samara N, et al. GnRH agonist and hCG (dual trigger) versus hCG trigger for final follicular maturation: a double-blinded, randomized controlled study. Hum Reprod. 2020;35(7):1648-1654. doi:10.1093/humrep/deaa107
21. Cummins JM, Breen TM, Harrison KL, Shaw JM, Wilson LM, Hennessey JF. A formula for scoring human embryo growth rates in in vitro fertilization: its value in predicting pregnancy and in comparison with visual estimates of embryo quality. J In Vitro Fert Embryo Transf. 1986;3(5):284-295. doi:10.1007/bf01133388
22. Humaidan P, Quartarolo J, Papanikolaou EG. Preventing ovarian hyperstimulation syndrome: guidance for the clinician. Fertil Steril. 2010;94(2):389-400. doi:10.1016/j.fertnstert.2010.03.028
23. DiLuigi AJ, Engmann L, Schmidt DW, Maier DB, Nulsen JC, Benadiva CA. Gonadotropin-releasing hormone agonist to induce final oocyte maturation prevents the development of ovarian hyperstimulation syndrome in high-risk patients and leads to improved clinical outcomes compared with coasting. Fertil Steril. 2010;94(3):1111-1114. doi:10.1016/j.fertnstert.2009.10.034
24. Shen X, Yang Q, Li L, Lu W. Clinical pregnancy and incidence of ovarian hyperstimulation syndrome in high ovarian responders receiving different doses of hCG supplementation in a GnRH-agonist trigger protocol. Evid Based Complement Alternat Med. 2021;2021:2180933. doi:10.1155/2021/2180933
25. Richani D, Gilchrist RB. The epidermal growth factor network: role in oocyte growth, maturation and developmental competence. Hum Reprod Update. 2018;24(1):1-14. doi:10.1093/humupd/dmx029
26. Prochazka R, Blaha M, Nemcová L. Significance of epidermal growth factor receptor signaling for acquisition of meiotic and developmental competence in mammalian oocytes. Biol Reprod. 2017;97(4):537-549. doi:10.1093/biolre/iox112
27. Haas J, Ophir L, Barzilay E, et al. Standard human chorionic gonadotropin versus double trigger for final oocyte maturation results in different granulosa cells gene expressions: a pilot study. Fertil Steril. 2016;106(3):653-659.e1. doi:10.1016/j.fertnstert.2016.06.002
28. Shapiro BS, Daneshmand ST, Garner FC, Aguirre M, Hudson C. Comparison of "triggers" using leuprolide acetate alone or in combination with low-dose human chorionic gonadotropin. Fertil Steril. 2011;95(8):2715-2717. doi:10.1016/j.fertnstert.2011.03.109
29. Li S, Zhou D, Yin T, et al. Dual trigger of triptorelin and HCG optimizes clinical outcome for high ovarian responder in GnRH-antagonist protocols. Oncotarget. 2018;9(4):5337-5343. doi:10.18632/oncotarget.23916

30. Jones BP, Al-Chami A, Gonzalez X, et al. Is oocyte maturity influenced by ovulation trigger type in oocyte donation cycles? Hum Fertil (Camb). 2021;24(5):360-366. doi:10.1080/14647273.2019.1671614
31. Lin MH, Wu FS, Hwu YM, Lee RK, Li RS, Li SH. Dual trigger with gonadotropin releasing hormone agonist and human chorionic gonadotropin significantly improves live birth rate for women with diminished ovarian reserve. Reprod Biol Endocrinol. 2019;17(1):7. doi:10.1186/s12958-018-0451-x
32. Zhou X, Guo P, Chen X, Ye D, Liu Y, Chen S. Comparison of dual trigger with combination GnRH agonist and hCG versus hCG alone trigger of oocyte maturation for normal ovarian responders. Int J Gynaecol Obstet. 2018;141(3):327-331. doi:10.1002/ijgo.12457
33. Alleyassin A, Ghasemi M, Aghahosseini M, et al. Final oocyte maturation with a dual trigger compared to human chorionic gonadotropin trigger in antagonist co-treated cycles: a randomized clinical trial. Middle East Fertil Soc J. 2018;23(3):199-204. doi:10.1016/j.mefs.2018.01.001
34. Ali SS, Elsenosy E, Sayed GH, et al. Dual trigger using recombinant HCG and gonadotropin-releasing hormone agonist improve oocyte maturity and embryo grading for normal responders in GnRH antagonist cycles: randomized controlled trial. J Gynecol Obstet Hum Reprod. 2020;49(5):101728. doi:10.1016/j.jogoh.2020.101728
35. Decleer W, Osmanagaoglu K, Seynhave B, Kolibianakis S, Tarlatzis B, Devroey P. Comparison of hCG triggering versus hCG in combination with a GnRH agonist: a prospective randomized controlled trial. Facts Views Vis Obgyn. 2014;6(4):203-209.
36. Pfeifer S, Butts S, Dumesic D, Fossum G, Gracia C, La Barbera A, et al. Prevention and treatment of moderate and severe ovarian hyperstimulation syndrome: a guideline. Fertil Steril. 2016;106(7):1634-1647. doi:10.1016/j.fertnstert.2016.08.048
37. O'Neill KE, Senapati S, Maina I, Gracia C, Dokras A. GnRH agonist with low-dose hCG (dual trigger) is associated with higher risk of severe ovarian hyperstimulation syndrome compared to GnRH agonist alone. J Assist Reprod Genet. 2016;33(9):1175-1184. doi:10.1007/s10815-016-0755-8
38. Gaafar S, El-Gezary D, El Maghraby HA. Early onset of cabergoline therapy for prophylaxis from ovarian hyperstimulation syndrome (OHSS): a potentially safer and more effective protocol. Reprod Biol. 2019;19(2):145-148. doi:10.1016/j.repbio.2019.03.005
39. Du DF, Li MF, Li XL. Ovarian hyperstimulation syndrome: a clinical retrospective study on 565 inpatients. Gynecol Endocrinol. 2020;36(4):313-317. doi:10.1080/09513590.2019.1653275