GnRH Agonist Ovulation Trigger in Patients Undergoing Controlled Ovarian Hyperstimulation for IVF with Stop GnRH-agonist Combined With Multidose GnRH-antagonist Protocol.

Raoul Orvieto (✉ raoul.orvieto@sheba.health.gov.il)

Sheba Medical Center at Tel Hashomer

Ravit Nahum

Sheba Medical Center at Tel Hashomer

Judith Frei

Sheba Medical Center at Tel Hashomer

Orit Zandman

Sheba Medical Center at Tel Hashomer

Yulia Frenkel

Sheba Medical Center at Tel Hashomer

Jigal Haas

TRIO fertility partners <https://orcid.org/0000-0001-5274-7358>

Research

Keywords: Stop GnRH-agonist, Multidose GnRH-antagonist, COH, GnRH-agonist, Ovulation trigger, Suboptimal response, LH

Posted Date: January 22nd, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-151943/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Version of Record: A version of this preprint was published at Gynecologic and Obstetric Investigation on September 17th, 2021. See the published version at <https://doi.org/10.1159/000517177>.

Abstract

Background: Recently, the Stop GnRH agonist protocol has been used successfully in poor responder patients, those with poor embryos quality and those with elevated peak serum progesterone levels. The aim of the present study was to evaluate, whether GnRH-agonist trigger in patients undergoing the Stop protocol combined, will result in an optimal response/trigger, as reflected by post trigger LH >15 mIU/mL

Methods: A retrospective cohort study. All consecutive women admitted to our IVF unit from February 2020 through November 2020 who reached the ovum pick-up stage. Patients triggered with GnRH-ag alone, or combined with hCG for final oocyte maturation were included in the study. LH levels were measured 12 hours post trigger.

Results: Five out of the 32 patients (15.6%) demonstrated suboptimal response as reflected by LH levels <15 IU/L 12 hrs post GnRH-agonist trigger. Moreover, while no differences were observed in oocytes recovery rate, maturity or embryos quality between the different study groups, those achieving a suboptimal response to the GnRH-agonist trigger (post trigger LH <15 mIU/mL) demonstrated significantly higher number of follicles and peak estradiol levels at the day of trigger.

Conclusions: The Stop GnRH-agonist combined with GnRH-antagonist protocol, enables the substitution of HCG with GnRH-ag for final oocyte maturation. However, caution should be taken in high responders, where the dual trigger with small doses of hCG (1000-1500IU) should be considered, aiming to avoid suboptimal response (post trigger LH levels <15IU/L).

Background

Controlled ovarian hyperstimulation (COH) enables the recruitment of multiple healthy fertilizable oocytes in patients undergoing in vitro fertilization-embryo transfer (IVF-ET) (1). However, despite the great improvements in ovarian stimulation protocols and fertilization procedures, live birth rates per embryo transferred remain at approximately 15–50% and severe ovarian hyperstimulation syndrome (OHSS) remains one of their major threats (2–3).

Moreover, while there are no precise methods to completely prevent severe OHSS, except by withholding human chorionic gonadotropin (hCG), during the last decade, observations have suggested that gonadotropin-releasing hormone agonist (GnRH-ag) by its consequent LH surge, may effectively trigger oocyte maturation and ovulation, with the consequent elimination of severe OHSS (4–5). It is noteworthy, that previous studies have shown that patients receiving a GnRH-agonist trigger alone, who have a post trigger LH < 15 mIU/mL, were more likely to have suboptimal response or a cancelled retrieval (6–9).

Recently, we introduced the Stop GnRH-Agonist combined with multiple-dose GnRH-antagonist protocol to our COH armamentarium. The rationale behind the sequential treatment stems from the advantages of its components. The mid-luteal GnRH-ag pre-treatment causes down regulation of the GnRH receptors with the consequent suppression of pituitary LH secretion for as long as 10 days after the last dose of the

agonist. This effect, together with the immediate LH suppression provided by the GnRH-ant, will eliminate premature LH surge and might improve the quality of the embryos generated (10).

This protocol was successfully used in poor responder patients (10), those with poor embryos quality (11) and those with elevated peak serum progesterone levels (12). Moreover, following the observations of comparable or improved oocyte/embryos quality following GnRH-a trigger as compared to hCG, and the different effects of LH and hCG on the downstream signaling of the LH receptor, GnRH-a is now offered concomitantly with the standard hCG trigger dose (dual trigger), to improve oocyte/embryo yield and quality (13), or solely, instead of HCG, aiming to eliminate the risk to develop severe OHSS (3).

The aim of the present study was to evaluate, whether GnRH-agonist trigger in patients undergoing the Stop GnRH-Agonist combined with multiple-dose GnRH-antagonist protocol, will result in an optimal response/trigger, as reflected by post trigger LH < 15 mIU/mL (6–9).

Patients And Methods

We reviewed the computerized files of all consecutive women admitted to our IVF unit from February 2020 through November 2020 who reached the ovum pick-up stage. Exclusion criteria were use of donor oocytes or transfer of frozen-thawed embryos, and use of other than the Stop GnRH-Agonist combined with multiple-dose GnRH-antagonist protocol [as previously described (10)]. Of whom, only those patients who underwent triggering of final follicular maturation with GnRH-agonist trigger, either solely or combined with hCG (dual trigger), were included. LH levels were measured 12 hours post GnRH-agonist trigger injection. Those with post trigger LH < 15 mIU/mL were considered as achieving a suboptimal response. The study was approved by the institutional research ethics board of Sheba Medical Center.

Data on patient age and infertility-treatment-related variables were collected from the files. The decision regarding final follicular maturation triggering was based on physician judgement. Generally, patients exhibiting Estradiol level > 10,000 pmol/L were prescribed the GnRH-agonist only trigger, as were patients developing > 15 follicles of > 10 mm diameter. LH level 12 hours post trigger, embryological parameters and number of oocyte retrieved and oocyte recovery rate (defined as the number of oocyte retrieved per number of follicles > 10 mm in diameter at the day of trigger) were also retrieved and analyzed. Classification of embryo quality was based on previously published scoring parameters (14); a top-quality embryo was defined as four to five blastomeres on day 2, seven or more blastomeres on day 3, equally-sized blastomeres and $\leq 10\%$ fragmentation on day 3 and no multinucleation.

Statistical analysis was performed with Student's t-test and Chi square, as appropriate. Results are presented as means $\pm$ standard deviations; p value < 0.05 was considered significant.

Results

Of the 1070 cycles performed in our IVF unit from February 2020 through November 2020, 32 IVF cycles were eligible for analysis. Patients' age, BMI and basal Day-3 FSH levels were 39.3 ± 3.9 yrs, 22.7 ± 4.2

kg/M², and 11.0 ± 4.7 IU/L, respectively. Five patients underwent the GnRH-agonist trigger solely, and 27 the dual trigger, of whom 1 and 4 presented a suboptimal LH rise following the GnRH-agonist trigger, respectively. The clinical characteristics of the IVF cycles of these two groups are shown in Table 1. As expected, those undergoing the GnRH-agonist solely trigger demonstrated significantly higher peak Estradiol level (10303 ± 9354 vs 4507 ± 3924 , respectively. $P < 0.02$) and more follicles < 14 mm in diameter at the trigger day (8.4 ± 6.4 vs 4.6 ± 3.3 , respectively. $P < 0.03$). These differences are biased owing to the fact that we offered the GnRH-agonist solely trigger approach mainly to patients at risk to develop OHSS or those destined to freeze-all (such as those undergoing preimplantation genetic testing). No in-between groups difference were observed in the number of oocytes retrieved, oocytes recovery rates or the percentage of MII oocytes per oocytes retrieved, nor the percentages of 2PN per MII oocytes or TQE per 2PN.

Table 1

	GnRH-agonist trigger (n = 5)	Dual trigger (n = 27)	P value
Age	38.6 ± 3.2	39.5 ± 4.1	0.32
Day-3 FSH (IU/L)	8.9 ± 2.1	11.5 ± 5.2	0.21
BMI (kg/m ²)	20.5 ± 3.3	23.1 ± 4.3	0.13
Duration of stimulation (days)	11.2 ± 1.9	11.2 ± 2.3	0.49
Total dose of FSH used (IU)	4310 ± 2309	5068 ± 1312	0.15
Peak E2 levels (pmol/L)	10303 ± 9354	4507 ± 3924	0.02
Peak Progesterone level (nmol/L)	2.5 ± 1.2	1.75 ± 0.66	0.08
# follicles > 14 mm in diameter at day of trigger	8.4 ± 6.4	4.6 ± 3.35	0.03
# follicles > 10 mm in diameter at day of trigger	10.2 ± 8.4	7.3 ± 5.2	0.12
Post trigger LH levels (IU/L)	48 ± 29	38 ± 20	0.18
Interval between last GnRH-agonist and trigger day (days)	15.4 ± 1.3	13.9 ± 2.6	0.12
# of oocytes retrieved	7 ± 5.6	7.5 ± 6.5	0.4
Oocyte recovery rate	0.66 ± 0.28	0.99 ± 0.49	0.14
% of MII oocytes per oocytes retrieved	0.8 ± 0.18	0.8 ± 0.2	0.48
% of 2PN per MII oocytes retrieved	0.52 ± 0.27	0.62 ± 0.29	0.29
% of TQE per 2PN	0.62 ± 0.2	0.56 ± 0.54	0.43

While comparing those with post trigger LH < 15 mIU/mL, who were considered as achieving a suboptimal response to those with optimal response (LH > 15 IU/L), no in-between groups differences were observed in the number of oocytes retrieved, oocytes recovery rates or the percentage of MII oocytes per oocytes retrieved, nor the percentages of 2PN per MII oocytes or TQE per 2PN (Table 2). While considering ovarian-stimulation characteristics, those achieving a suboptimal response to the GnRH-agonist trigger demonstrated significantly higher number of follicles and peak estradiol levels (11413 ± 8106 vs 4301 ± 3601 pmol/L, respectively. $p < 0.003$) at the day of trigger (Table 2).

Table 2

	Suboptimal response (n = 5)	Optimal response (n = 27)	P value
Age	39.2 ± 5.2	39.3 ± 3.5	0.46
Day-3 FSH (IU/L)	7.8 ± 0.8	11.5 ± 4.8	0.16
BMI (kg/m ²)	24.2 ± 4.1	22.5 ± 4.2	0.23
Duration of stimulation (days)	11.6 ± 1.0	11.1 ± 2.3	0.32
Total dose of FSH used (IU)	5000 ± 1558	4940 ± 1445	0.46
Peak E2 levels (pmol/L)	11413 ± 8106	4301 ± 3601	< 0.003
Peak Progesterone level (nmol/L)	1.8 ± 0.9	1.8 ± 0.66	0.47
# follicles > 14 mm in diameter at day of trigger	9.2 ± 6.1	4.5 ± 2.9	< 0.008
# follicles > 10 mm in diameter at day of trigger	13 ± 7.1	6.7 ± 4.7	< 0.02
Post trigger LH levels (IU/L)	10.4 ± 2.1	44.9 ± 19.1	< 0.001
Interval between last GnRH-agonist and trigger day (days)	13.4 ± 1.7	14.3 ± 2.5	0.22
# of oocytes retrieved	11 ± 7.2	6.7 ± 5.7	0.08
Oocyte recovery rate	0.85 ± 0.44	0.97 ± 0.48	0.29
% of MII oocytes per oocytes retrieved	0.92 ± 0.07	0.78 ± 0.21	0.09
% of 2PN per MII oocytes retrieved	0.63 ± 0.2	0.605 ± 0.29	0.43
% of TQE per 2PN retrieved	0.6 ± 0.37	0.59 ± 0.52	0.48

Discussion

In the present study of patients undergoing the Stop GnRH-Agonist combined with multiple-dose GnRH-antagonist protocol, who underwent triggering of final follicular maturation with GnRH-agonist trigger, either solely or combined with hCG (dual trigger), 5 out of the 32 patients (15.6%) demonstrated suboptimal response as reflected by LH levels < 15 IU/L 12 hrs post GnRH-agonist trigger. This figure is higher than the reported 5.2% in patients undergoing the multiple-dose GnRH-antagonist protocol (9). GnRH-agonist causes suppression of pituitary LH secretion for as long as 10 days after the last dose of

the agonist (15). It might be therefore assumed that a residual prolonged pituitary suppression following the Stop GnRH-agonist protocol might be the culprit of the observed higher suboptimal response.

We could not observe any differences in oocytes recovery rate, maturity or embryos quality between the different study groups. The reason is that the aforementioned variables are affected by the trigger mode, and most of our patients were triggered with both GnRH-agonist and hCG (dual trigger). On the other hand, we could indeed demonstrate significantly higher number of follicles and peak estradiol levels at the day of trigger in those achieving a suboptimal response to the GnRH-agonist trigger (post trigger LH < 15 mIU/mL).

Therefore, it might be suggested that high responders undergoing the Stop GnRH-agonist combined with GnRH-antagonist are at risk to a suboptimal response to GnRH-agonist solely trigger. To avoid this suboptimal response, we recommend considering the dual trigger with low-dose hCG (1000-1500IU), in this subgroup of patients, aiming to prevent the suboptimal response.

The Stop GnRH-agonist combined with GnRH-antagonist was successfully used several groups of patients (10–12). The rationale behind the sequential treatment stems from the advantages of its components: (a) The long GnRH-ag protocol pretreatment results in better synchronized response and a scheduled cycle (16–17); (b) Since continuing the GnRH-ag during COH is often associated with a significant increase in the number of gonadotropin ampoules required for achieving adequate follicular development, its cessation might improve ovarian response and avoids the need of increasing gonadotropin daily dose. GnRH-ag causes suppression of pituitary LH secretion for as long as 10 days after the last dose of the agonist (15); and (c) The Stop GnRH-ag together with the multiple-dose GnRH-ant provide immediate LH suppression, eliminating premature LH surge and might improve the quality of the embryos generated. In the present study we could demonstrate another advantage, by the feasibility of triggering final oocyte maturation by GnRH agonist together with hCG (Dual trigger), with improved IVF outcome (13).

In conclusion, the Stop GnRH-agonist combined with GnRH-antagonist protocol, has been successfully used in poor responder patients (10), those with poor embryos quality (11) and those with elevated peak serum progesterone levels (12). In the present study we could demonstrate that it also enables the substitution of HCG with GnRH-ag for final oocyte maturation. However, caution should be taken in high responders, where the addition of small doses of hCG (1000-1500IU) should be considered (dual trigger), aiming to avoid suboptimal response (post trigger LH levels < 15IU/L). Further studies are required to identify other risk factors for suboptimal response to GnRH-agonist trigger.

Declarations

Ethics approval and consent to participate:

The study protocol was approved by the "Sheba Medical Center" Institutional Review Board.

Availability of data and materials:

Data will be made available from the corresponding author on request.

Competing interests:

The authors have nothing to declare.

Funding:

This manuscript was not supported by specific funding.

Consent for publication:

Not applicable (cohort historical)

Authors' contributions:

RO- wrote the paper and edited it in all its revisions., performed the statistical evaluations took part in discussions regarding the results.

RN- Participated in designing the study, retrieved the data proof read the paper and took part in discussions regarding the results.

JF- Retrieved the data, proof read the paper and took part in discussions regarding the results.

YF- Retrieved the data, proof read the paper and took part in discussions regarding the results.

OZ- Retrieved the data, performed laboratory work, proof read the paper and took part in discussions regarding the results.

JH- Participated in designing the study, assisted in writing the paper and edited it, proof read the paper and took part in discussions regarding the results.

Acknowledgment:

NA

References

1. [Penzias AS](#). Improving results with assisted reproductive technologies: individualized patient-tailored strategies for ovulation induction. *Reprod Biomed Online* 2004;9:43-6.
2. Mersereau J, Stanhiser J, Coddington C, Jones T, Luke B, Brown MB. Patient and cycle characteristics predicting high pregnancy rates with single-embryo transfer: an analysis of the Society for Assisted Reproductive Technology outcomes between 2004 and 2013. *Fertil Steril* 2017;108(5):750-756.

3. The Practice Committee of the American Society for Reproductive Medicine (ASRM). Prevention and treatment of moderate and severe ovarian hyperstimulation syndrome: a guideline. *Fertil Steril* 2016;106(7):1634-1647
4. Kol S. Luteolysis induced by a gonadotropin-releasing hormone agonist is the key to prevention of ovarian hyperstimulation syndrome. *Fertil Steril* 2004;81:1-5
5. Orvieto R. Ovarian hyperstimulation syndrome- an optimal solution for an unresolved enigma. *J Ovarian Res* 2013;6(1):77.
6. Kummer NE, Feinn RS, Griffin DW, Nulsen JC, Benadiva CA, Engmann LL. Predicting successful induction of oocyte maturation after gonadotropin-releasing hormone agonist (GnRHa) trigger. *Hum Reprod* 2013;28:152–9.
7. Chen SL, Ye DS, Chen X, Yang XH, Zheng HY, Tang Y, et al. Circulating luteinizing hormone level after triggering oocyte maturation with GnRH agonist may predict oocyte yield in flexible GnRH antagonist protocol. *Hum Reprod* 2012;27:1351–6.
8. Shapiro BS, Daneshmand ST, Restrepo H, Garner FC, Aguirre M, Hudson C. Efficacy of induced luteinizing hormone surge after “trigger” with gonadotropin-releasing hormone agonist. *Fertil Steril* 2011;95:826–8.
9. Meyer L, Murphy LA, Gumer A, Reichman DE, Rosenwaks Z, Cholest Risk factors for a suboptimal response to gonadotropin-releasing hormone agonist trigger during in vitro fertilization cycles. *Fertil Steril* 2015;104:637–642.
10. Orvieto R, Kirshenbaum M, Galiano V, Elkan-Miller T, Zilberberg E, Haas J, Nahum R. Stop GnRH-Agonist Combined With Multiple-Dose GnRH-Antagonist Protocol for Patients With "Genuine" Poor Response Undergoing Controlled Ovarian Hyperstimulation for IVF. *Front Endocrinol (Lausanne)*. 2020;11:182.
11. Orvieto R, Kirshenbaum M, Galiano V, Zilberberg E, Haas J, Nahum R. Stop GnRH-agonist combined with multiple-dose GnRH-antagonist for patients with elevated peak serum progesterone levels undergoing ovarian stimulation for IVF: A proof of concept. *Gynecol Obstet Invest* 85: 357-361.
12. Orvieto R, Kirshenbaum M, Galiano V, Zilberberg E, Haas J, Nahum R. Stop GnRH-Agonist Combined with Multiple-Dose GnRH-Antagonist for Patients with Elevated Peak Serum Progesterone Levels Undergoing Ovarian Stimulation for IVF: A Proof of Concept. *Gynecol Obstet Invest* 2020;85(4):357-361.
13. Orvieto R. Triggering final follicular maturation–hCG, GnRH-agonist or both, when and to whom? *J Ovarian Res*. 2015;8:60.
14. Ziebe S, Lundin K, Janssens R, Helmgaard L, Arce JC, Group M. Influence of ovarian stimulation with HP-hMG or recombinant FSH on embryo quality parameters in patients undergoing IVF. *Hum Reprod* 2007;22:2404-13.
15. Pritts EA, Atwood AK. Luteal phase support in infertility treatment: a meta-analysis of the randomized trials. *Hum Reprod* 2002;17:2287-99.

16. Huirne JA, Homburg R, Lambalk CB. Are GnRH antagonists comparable to agonists for use in IVF? *Hum Reprod.* 2007;22(11):2805-13.
17. Orvieto R, Patrizio P. GnRH agonist versus GnRH antagonist in ovarian stimulation: an ongoing debate. *Reprod Biomed Online.* 2013;26(1):4-8.