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REVIEW

GnRH agonist for triggering final oocyte maturation in patients at risk of ovarian hyperstimulation syndrome: still a controversy?

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Abstract

Purpose An update on the subject of ovarian hyperstimulation syndrome (OHSS) prevention with GnRH agonist ovulation trigger.

Methods Review of pertinent English language studies published during the past 4 years.

Results Randomized prospective studies support the notion that agonist trigger completely eliminates OHSS. Conflicting results regarding on going pregnancy rate probably reflect different approaches to luteal phase support. Embryos obtained and frozen after agonist trigger yield good clinical outcome in subsequent thaw cycles.

Conclusions The notion that agonist trigger can eliminate OHSS is strongly supported by randomized controlled trials. Further research is needed to assess optimal luteal support post agonist trigger.

Keywords GnRH agonist · Luteal support · OHSS · Ovulation · Prevention

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Introduction

Ovarian hyperstimulation syndrome (OHSS) is a pure iatrogenic complication of ART, affecting young healthy women seeking fertility. According to a WHO report this syndrome is responsible to 1 death for every 50,000 treatment cycles, while the incidence of severe OHSS is 1%. [1]. Despite all efforts to lower OHSS occurrence, it remains a relentless companion of IVF. Even GnRH antagonist-based mild stimulation still resulted in >2% incidence of OHSS [2]. Numerous strategies have been suggested in the context of OHSS prevention, with only limited success.

Previously [3], the mechanism of OHSS prevention by GnRH agonist trigger instead of hCG was emphasized, i.e. complete luteolysis. However, clinical data supporting the notion that agonist trigger eliminates OHSS were based on case-series studies only. Unfortunately, in the era of "evidence-based medicine" the fantastic power of agonist trigger to prevent OHSS is also its weakness. Can we randomize patients with extreme ovarian response to the hCG arm???

Two groups gathered the courage and performed randomized controlled studies with patients at high risk of OHSS [4, 5]. These groups, with their respective Review Boards can be praised for the courage, or condemned for putting patients at excessive risk, depending on your individual point of view. However, their work is of paramount importance in our efforts to eliminate OHSS. Moreover, Review Boards will probably be reluctant to approve similar studies in the future; hence we will be left with only these two studies to draw conclusions from. The third group [6] used the donor–recipient model to elucidate the role of agonist trigger in terms of OHSS incidence and pregnancy rate, while neutralizing the

"endometrial factor". The main conclusion, as we will see, is crystal clear: agonist trigger prevents OHSS. No further research seems necessary. Good clinical outcome (pregnancy rate) probably depends on aggressive luteal support; further research is needed in that direction.

Randomized controlled studies comparing agonist and hCG trigger in OHSS-high risk patients

The 3 relevant publications are summarized in Table 1.

OHSS incidence The first two studies [4, 5] included patients at high risk for OHSS, the third [6] included donors. None of the 78 patients in the agonist groups developed OHSS. Of the 75 patients triggered with hCG, 19 (25%) developed OHSS (Table 2).

Clinical pregnancy rate No statistically significant difference in clinical pregnancy rate between hCG and agonist trigger was observed in any of the individual studies. Furthermore, no differences were found with other cycle variables: number of oocytes retrieved, proportion of metaphase II oocytes, or fertilization rate.

Table 1 Characteristics of the randomized controlled trials

Study	Methods	Participants	Intervention	Outcomes
Engmann et al. [5]	RCT; single center; two armed; 1:1 randomization ratio; randomization by computer-generated random numbers; randomization at recruitment; number of patients at intention-to-treat, 60; number of patients at randomization, 66 (34 agonist, 32 hCg); number of subjects at oocyte retrieval and ET, 59 (30 agonist, 29 hCG). Sample size analysis—yes. Main outcome measures: OHSS incidence and implantation rate	Inclusion criteria: age 20–39, normal early follicular phase FSH, first IVF with PCOS or PCOM, or a history of high response in a previous IVF cycle. Exclusion: hypogonadotropic hypogonadism	Study group: OCP for 21 days, ovarian stimulation with rec-FSH (112–225 IU), Ganirelix when leading follicle >14 mm. Trigger: leuprolide 1 mg. Luteal phase: 50 mg P in oil 0.1 mg transdermal E2 patch every other day Control group: Dual pituitary suppression: OCP and 1 mg leuprolide acetate. ovarian stimulation with rec-FSH (112–225 IU), Trigger: hCG (3,300 – 10,000 IU)Luteal phase: 50 mg P in oil	Incidence of OHSS; implantation rate; number of oocyte retrieved; proportion of mature oocyte retrieved; fertilization rate; mid luteal mean ovarian volume; clinical and ongoing pregnancy rates; luteal phase E2 and P
Babayof et al. [4]	RCT; single center; two armed; 1:1 randomization ratio; randomization by a randomization list; randomization on last stimulation day; sample size analysis — yes; main outcome measures: hormonal markers of OHSS. Number of patients at randomization: 28 (15 agonist, 13 hCG); number of subjects at oocyte retrieval and ET: 28	Inclusion criteria: women with PCO undergoing IVF treatment	Both groups: recFSH 225 IU from cycle day 2 or 3. Cetyrorelix 0.25 mg daily when leading follicle=14 mm Study group: Decapeptyl 0.2 mg. Control group: Ovitrelle 250 μg. Luteal support (both groups): 50 mg P in oil. If E2<200 pmol/l, Estrofem 4 mg/day. If serum *P*<40 nmol/l—100 mg P in oil	Incidence of OHSS; number of oocyte retrieved; proportion of mature oocyte retrieved; fertilization rate; day of ET ovarian volume; luteal phase inhibin A, E2, P, VEGF, TNFα
Acevedo et al. [6]	RCT; single center; two armed; 1:1 randomization ratio; randomization by a computer-generated list; randomization before ovarian stimulation; main outcome measures: pregnancy and implantation rate, OHSS in an IVF-donor program. Number of patients at randomization: 60; number of subjects at oocyte retrieval and ET: 60	Inclusion criteria: Female donors following guidelines of Spanish Committee of ART	Both groups: recFSH 150 IUI from cycle day 3–4, Ganirelix 0.25 mg/d from stimulation day 6, with Menopur 75 IU instead of 75 IU recFSH. Study group: Decapeptyl 0.2 mg. Control group: Ovitrelle 250 μg Recipients: endometrial preparation with E2 (Progynova) and natural P (600 mg/d).	Incidence of OHSS; number of oocyte retrieved; proportion of mature oocyte retrieved; fertilization rate; embryo quality, luteal phase duration, clinical pregnancy rate, implantation rate

Table 2 Incidence of ovarian hyperstimulation syndrome

Reference	No patients with agonist trigger	No of patients with hCG trigger	Patients with OHSS post agonist	Patients with OHH post hCG (%)	*P* value
Babayof et al. [4]	15	13	0/15	4/13 (31%)	<0.05
Engmann et al. [5]	33	32	0/33	10/32 (31%)	<0.001
Acevedo et al. [6]	30	30	0/30	5/30 (17%)	<0.05
TOTAL	78	75	0/78	19/75 (25%)	<0.001

Statistical analysis was performed using Chi-square test.

Randomized controlled studies comparing agonist and hCG trigger in OHSS-low risk patients

Following suggestions to replace hCG with agonist trigger in the general IVF population, two groups [7, 8] published the results of randomized controlled studies in OHSS-low risk patients. These studies are comparable in design to previous publication by Fauser et al. [9]. A meta-analysis of these studies [10] clearly demonstrated low pregnancy rate with agonist trigger. Poor clinical outcome probably has to do with deficient luteal support, as will be discussed herein.

Low pregnancy rate in high-responders

The question of pregnancy rate in high responders was previously addressed in cycles during which hCG was used as trigger. Pellicer et al. [11] found that implantation rate was significantly higher in normal (18.5%) as compared with high (0%) responders. These researchers concluded that a different endocrine milieu between normal and high responders is detected by daily steroid measurements up to the preimplantation period, suggesting that this difference could be responsible for an impaired implantation in high responder patients undergoing IVF. An increase in serum E_2 levels seems to be the cause of this difference. Simon et al. [12] reached similar conclusions, stating that their clinical results demonstrate that high serum estradiol concentration on the day of hCG injection in high and normal responder patients, regardless of the number of oocytes retrieved and the serum progesterone concentration, is detrimental to uterine receptivity without affecting embryo quality.

The question of luteal support

As for agonist trigger, if estradiol levels are not extremely high, pregnancy rate becomes a matter of adequate luteal support, as can be seen in Table 3. Indeed, while the question of OHSS prevention is solved, further research is needed to elucidate the best approach to luteal support following agonist trigger, in order to maximize pregnancy rate. According to Acevedo et al. [6], agonist trigger has no

Table 3 Pregnancy rate and luteal support

reference	*N*	E2 Trigger day (nmol/l)	No of oocytes retrieved (Mean±SEM)	Clinical pregnancy (%)	Ongoing pregnancy (%)	Luteal support
Humaidan et al. [8]	55	7,100	8.4	6	*	Vag gel P 8%, p.o. estradiol 4 mg for 12 days
Kolibianakis et al. [7]	50	7,067	10.2±7.0	*	5.6 (Brussels) 2.9 (Lubeck)	Vag tab P 600 mg, p.o. estradiol 4 mg until 7 w
Fauser et al. [9]	15 15	4,070 (trip) 2,590 (leu)	9.8±5.4 8.7±4.5	*	18 (trip) 20 (leu)	IM P 50 mg for 2 weeks
Babayof et al. [4]	15	9,595	19.8±2.5	20	*	IM P 50 mg, p.o. estradiol 4 mg
Engmann et al. [5]	30	8,410	20.2±9.9	60	56	IM P 50 mg 0.1 mg E2 patches until 7 w
Acevedo et al. [6]	30	8,501	9.1±4.01	46	*	Embryo recipients: E2, 600 mg natural P

*Not avaliable

adverse effect at the level of embryo quality and implantation potential. Hence, low pregnancy rates reported after agonist trigger have to do with the type of luteal support given and its duration. Aggressive luteal support which uses IM progesterone overcomes the agonist-induced luteolytic effect, resulting in good clinical outcome [5]. Vaginal P may be adequate in a donor-recipient setup [6], but results in poor outcome in the normal IVF setup [7, 8].

Agonist trigger and its effect on subsequent thaw cycles

Since agonist trigger should be used in OHSS-high risk situation, a large number of oocytes is expected, leading to a large number of embryos to be cryopreserved. The outcome of subsequent thaw cycles is important in terms of patient counseling regarding per-retrieval success rate (combining "fresh" and "thaw" cycles originating from single oocyte retrieval). Agonist trigger in normal responders yielded good clinical outcome in subsequent thaw cycle, with live birth rate of 18.5% per ET [13]. The question remains whether similar results can be obtained with embryos frozen after agonist trigger in high responders.

A recent "proof of concept" study by Griesinger et al. [14] produced very promising results. Twenty OHSS-high risk patients (≥20 follicles or estradiol ≥4000 pg/ml on trigger day) were triggered with agonist, all 2 pronucleate (2PN) oocyte were cryopreserved. None of the patients developed OHSS. Subsequent thaw cycles (mean of 2.3 embryos transferred) resulted in 29.2% ongoing pregnancy rate. Each patient had an average of 7.4 2 PN cryopreserved, allowing for an average 3 subsequent thaw cycle. With a 29.2% ongoing pregnancy rate per thaw cycle each patient has an excellent chance of achieving ongoing pregnancy from single oocyte retrieval, with complete safety as far as OHSS is concerned. Indeed, this is great news to our high responder patients.

Conclusion

GnRH agonist trigger totally prevents OHSS. This conclusion is based now on randomized prospective studies. Given the clear cut conclusion that emerges from the 3 studies described regarding OHSS prevention, Review Boards will probably not approve similar studies in the future. Further studies must concentrate on luteal phase support following agonist trigger, and on per retrieval pregnancy rate, taking into account subsequent thaw cycles.

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References

1. Hugues J. Ovarian stimulation for assisted reproductive technologies, In: Current practices and controversies in assisted reproduction. Geneva, Switzerland: WHO; 2001, p. 102–126.
2. Papanikolaou EG, Pozzobon C, Kolibianakis EM, Camus M, Tournaye H, Fatemi HM, et al. Incidence and prediction of ovarian hyperstimulation syndrome in women undergoing gonadotropin-releasing hormone antagonist in vitro fertilization cycles. Fertil Steril. 2006;85:112–20.
3. 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.
4. Babayof R, Margalioth EJ, Huleihel M, Amash A, Zylber-Haran E, Gal M, et al. Serum inhibin A, VEGF and TNFalpha levels after triggering oocyte maturation with GnRH agonist compared with HCG in women with polycystic ovaries undergoing IVF treatment: a prospective randomized trial. Hum Reprod. 2006;21:1260–5.
5. Engmann L, DiLuigi A, Schmidt D, Nulsen J, Maier D, Benadiva C. The use of gonadotropin-releasing hormone 9GnRH) agonist to induce oocyte maturation after cotreatment with GnRH antagonist in high-risk patients undergoing in vitro fertilization syndrome: a prospective randomized controlled study. Fertil Steril. 2008;89:84–91.
6. Acevedo B, Gomez-Palomares JL, Ricciarelli E, Hernandez ER. Triggering ovulation with gonadotropin-releasing hormone agonists does not compromise embryo implantation rates. Fertil Steril. 2006;86:1682–7.
7. Kolibianakis EM, Schultze-Mosgau A, Schroer A, van Steirteghem A, Devroey P, Diedrich K, et al. A lower ongoing pregnancy rate can be expected when GnRH agonist is used for triggering final oocyte maturation instead of HCG in patients undergoing IVF with GnRH antagonists. Hum Reprod. 2005;20:2887–92.
8. Humaidan P, Bredkjaer HE, Bungum L, Bungum M, Grøndahl ML, Westergaard L, et al. GnRH agonist (buserelin) or hCG for ovulation induction in GnRH antagonist IVF/ICSI cycles: a prospective randomized study. Hum Reprod. 2005;20:1213–20.
9. Fauser BC, de Jong D, Olivennes F, Wramsby H, Tay C, Itskovitz-Eldor J, et al. Endocrine profiles after triggering of final oocyte maturation with GnRH agonist after cotreatment with the GnRH antagonist ganirelix during ovarian hyperstimulation for in vitro fertilization. J Clin Endocrinol Metab. 2002;87:709–15.
10. Griesinger G, Diedrich K, Devroey P, Kolibianakis EM. GnRH agonist for triggering final oocyte maturation in the GnRH antagonist ovarian hyperstimulation protocol: a systematic review and meta-analysis. Hum Reprod Updat. 2006;12:159–68.
11. Pellicer A, Valbuena D, Cano F, Remohi J, Simon C. Lower implantation rates in high responders: evidence for an altered endocrine milieu during the preimplantation period. Fertil Steril. 1996;65:1190–5.
12. Simon C, Cano F, Valbuena D, Remohi J, Pellicer A. Clinical evidence for a detrimental effect on uterine receptivity of high serum oestradiol concentrations in high and normal responder patients. Hum Reprod. 1995;10:2432–7.
13. Griesinger G, Kolibianakis EM, Papanikolaou EG, Diedrich K, Van Steirteghem A, Devroey P, et al. Triggering of final oocyte maturation with gonadotropin-releasing hormone agonist or human chorionic gonadotropin. Live birth after frozen–thawed embryo replacement cycles. Fertil Steril. 2007;88:616–21.
14. Griesinger G, von Otte S, Schroer A, Ludwig AK, Diedrich K, Al-Hasani S, et al. Elective crypreservation of all pronuclear oocytes after GnRH agonist triggering of final oocyte maturation in patients at risk of developing OHSS: a prospective, observational proof-of-concept study. Hum Reprod. 2007;22:1348–52.