# Coasting Versus GnRH Antagonist administration in Patients at High Risk of Ovarian Hyper stimulation Syndrome and its impact on the ICSI Outcome

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## Abstract

**Objectives:** study the value of GnRH antagonist administration as an alternative protocol to coasting in preventing severe OHSS in cases of long agonist ovarian stimulation protocol and its impact on embryos quality &positive pregnancy in women undergoing ICSI.

**Study design:** A prospective randomized control trial is done at the assisted Reproduction unit, Al-Azhar university, Egypt to compare Coasting group (n = 150) and GnRH antagonist group (n = 150) in patients detected to be at risk of OHSS during the process OHSS in cases of long agonist ovarian stimulation protocol before ICSI. The primary outcome was high quality embryos, the secondary outcome was days of intervention, number of oocytes, pregnancy outcome, number of cryopreserved embryos and incidence of severe OHSS.

**Results:** There were statistical significant deference between quality embryos (2.3±1.2 versus 1.6±0.7; P value = 0.001) and more oocytes number (8.2±3.1) versus (6.7±3.2; P value = 0.01) in Antagonist group as compared with coasting group. There were more number of coasting days than with antagonist administration days (2.9±1.4 versus 2.2±1.1; P value = 0.001).

**Conclusion:** GnRH antagonist was superior to coasting in producing higher numbers of mature oocytes, high quality embryos and reducing the number of days till the HCG injection. There was no statistical significant difference in chemical pregnancy rate between two groups. No early or late OHSS developed in either group.

## Introduction

Infertility affects 10%–15% of couples worldwide and has become a public health problem in recent decades(1). In vitro fertilization (IVF) and Intracytoplasmic sperm injection (ICSI) are commonly used in the management of infertility attributable to tubal factor, endometriosis, male factor and unexplained infertility (2).Recruitment and development of multiple follicles in response to go-

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nadotrophin stimulation are necessary for successful assisted reproductive treatment. The response of ovulating women to gonadotrophin therapy is quite variable and difficult to predict. Patient characteristics, rather than the stimulation protocol, seem to determine the individual response; although the dose and duration of gonadotropin treatment required to induce successful ovulation vary among women, even among cycles within a woman. In young ovulating women undergoing IVF treatment, the standard stimulation protocol can result in either poor response or in ovarian hyper-stimulation syndrome (OHSS) (3).

OHSS is considered a menacing prospective to the patients' health elaborated by iatrogenic influence of controlled ovarian hyper stimulation (COH) thus, it is a particularly alarming complication of IVF-related ovarian stimulation, that has a well-being threatening compass that ranges between admitting the patient to a hospital and in ultimate adverse impact may lead to lethal complication. (4) IVF cycles correspondence to OHSS intensity is outlined with the majority of cases exhibiting mild symptoms (around 33%) (1) The approximate value of moderate OHSS varies between 3%-6%, and the severe forms take place in about 0.1%-3% of all IVF cycles (5). Patients observed (based on undesirable regulatory factors) with elevated chances of OHSS are evaluated up to 20% (6).

OHSS foundation is directly proportional to the enhancement of multiple follicles, a critical phase for evolving a severe OHSS is supplied either by an exogenous human chorionic gonadotrophin (HCG) administration for final occasion of oocytes maturity peak or by endogenous production of HCG as a result of embryo-maternal signaling (pregnancy) (4)Exhibition of severe OHSS is displayed through extensive ovarian enlargement, peritoneal effusion, pleural effusion, hypo uresis, hemoconcentration, and thromboembolism (7).Coasting implies a refraining exogenous gonadotrophin therapy that maintains a realizing hormone agonist/antagonist administration to the point where serum E2 levels set down to a safe level. GnRH antagonists could disaffect the phenomenon of OHSS in by assigning a fast E2 levels suppression. (8) Aboulghar et al studied the anticipation of women with high risk of OHSS throughout the consequences of utilizing coasting and GnRH antagonist administration during randomized controlled cycles of ovarian stimulation for IVF, accompanied by a GnRH agonist long protocol, with a scouting prospect of preventing a downside outcome of prolonged coasting (9).

## Aim of the Work

The aim of this study is to evaluate the GnRH antagonist subcutaneous administration as an alternative protocol to coasting in prevention of OHSS and its impact on embryos number, quality and ICSI outcome.

## Patients and Methods

A prospective randomized control study was done after approval by the internal ethical committee. All women gave an informed written consent at the beginning of the research. The study population consists of 300 infertile women at high risk of developing OH, during COH using long GnRH agonist protocol for ICSI-ET. They were recruited from the International Islamic Centre for population studies and researches, assisted reproduction unit, Al- Azhar University during the period from January 2013 to June 2014.

***Inclusion criteria:***

During the ovarian stimulation process using long GnRH agonist protocol, women were considered at high risk of developing OHSS if they have a large number of follicles (>20) on both ovaries, with 90% of the follicles being small (<14 mm in mean diameter), and E2 concentration $\geq$ 3500 pg/ml. These women were included in the study. All women were subjected to: Full history taking general examination specially body mass index; Pelvic examination and full Investigations: FSH, LH, E2,prolactin,TSHusing ELFA technique

(Enzyme linked Fluorescent Assay) (Vidas-Biomerieux). Routine preoperative investigations (HB%, fasting blood sugar, 2 hours postprandial blood sugar, liver function ,kidney function tests, HBS Ag and HCV Ab). TVS for determination of AFC, folliculometry and detection of normally stimulated and hyper stimulated ovaries.E2 levels monitoring to ensure pituitary down regulation and for follow up during folliculometry) using ELFA technique (Enzyme linked Fluorescent Assay) (VidasBiomerieux).

**Female patients in the study were divided randomly into 2 groups:**

## Coasting group

Involves 150 patients who experienced gonadotropin administration for no less than 24 hours prior to ovulation triggering, aided with HCG injection GnRH agonist in a quotidian manner. E2test is performed uniformly up to a descending desired concentration of ≤ 3000 pg/ml, 5000 IU of HCG was then supplied.

## Antagonist group

Involved 150 patients that sustained a daily intake of GnRH antagonist (subcutaneous injection Cetrorelix acetate 0.25 mg (Cetrotide, Serono, UK)) up to the point in time for HCG administration. A daily E2 level assessment was carried out until the required concentration was achieved: ≤ 3000 pg/ml and vouched with TVS that visualized the follicles diameter of ≥ 18 mm, subsequently 5000 IU of HCG was given.

## Oocyte Retrieval

TVS directed oocyte recovery was performed UGA, 34-36 hours after HCG administration, under full aseptic technique. The oocytes then were assessed for maturity (quality) according to **Hill et al. (10)** grading system.

## Semen assessment

All semen parameters were recorded and evaluated in accordance to the WHO standards 2010 of semen evaluation.

## ICSI

The ICSI procedure involved the injection of a single motile sperm into the cytoplasm of mature oocyte. The assessment of fertilization and cleavage was evaluated depends on the numbers, sizes of blastomeres and presence of a cytoplasmic fragments. The cleavage embryos are scored according to equality of size of the blastomeres and proportion of a nucleate fragments(10).

## Embryo Transfer

On day 3, the embryos that would be transferred were loaded into the ETcatheter. The catheter used is Labotect catheter that is a 150 mm long atraumatic catheter having a precurved guiding cannula with spherical finish). (Labotect GmbH, Labor -Technik - Gottingen - Germany).

**Luteal phase support (LPS)**was given to all females, Prontogest (Shire Pharmaceuticals Ltd., Andover, UK) 100 mg intramuscular injection once daily for 2 weeks was give till the day of pregnancy test after two weeks. If the pregnancy test came positive; Prontogest 400 vaginal or rectal suppository was given instead of the injections until 8 weeks gestation. Clinical pregnancy was confirmed at 5-6 weeks gestation by visualization of a viable fetus by U/S examination.

***Main outcome measure***

Good quality embryos

***Secondary outcome measures***

number of intervention days, number of mature oocytes, pregnancy rate (PR), number of cryopreserved embryos and the incidence of severe OHSS.

***Statistical analyses***

- **Descriptive analysis** of the results in the form of percentage distribution for qualitative data.
- **Student t- test: Fisher's exact test and the Chi-square test.**
- **P:** The probability/significance value
- Statistical analysis: Statistical package was used for social science (SPSS) software version 17

## Results

**Table 1:** Biodemographic 'characteristics for female patients at risk of OHSS in Coasting versus GnRH antagonist groups:

| | Coasting | Antagonist | P value |
|---|---|---|---|
| Females age (years) | 28.2±4.6 | 28.3±5.3 | 0.889 |
| Duration of Infertility (years) | 6.9±4.9 | 6.5±4.1 | 0.444 |
| Primary infertility (%) | 116(77.3%) | 120(80%) | 0.573 |
| Secondary infertility (%) | 34(22.7%) | 30(20%) | 0.573 |
| PCO cases(%) | 44(29.3%) | 40(26.7%) | 0.607 |
| BMI | 33.1±35.0 | 28.9±5.2 | 0.144 |
| Basal FSH (mIU/ml) | 6.1±2.0 | 7.6±9.7 | 0.070 |
| Basal LH (mIU/ml) | 4.8±3.5 | 4.5±2.5 | 0.409 |
| Basal PRL (ng/mL) | 17.6±7.3 | 18.7±9.5 | 0.277 |
| Basal E2 (pg/ml) | 46.4±18.6 | 46.0±16.7 | 0.845 |
| Basal TSH (mIU/L) | 2.0±1.0 | 1.8±1.0 | 0.212 |

**Table 2:** The distribution of the underlying aetiology of infertility

| (%) | Coasting | Antagonist | P value |
|---|---|---|---|
| Male factor | 92(61.3%) | 84(56%) | 0.348 |
| Azoospermia | 18(12%) | 22(14.7%) | 0.497 |
| Ovarian factor | 4(2.7%) | 6(4%) | 0.520 |
| Tubal factor | 16(10.7%) | 22(14.7%) | 0.298 |
| Endometriosis | 2(1.3%) | 2(1.3%) | 1 |
| Asherman syndrome | 2(1.3%) | 0(0%) | 0.156 |
| Adhesions | 4(2.7%) | 6(4%) | 0.520 |
| Unexplained infertility | 30(20%) | 34(22.7%) | 0.573 |

**Table 3:** Comparison between Coasting and Antagonist groups regarding the stimulation characteristics of the cycle.

| | Coasting | Antagonist | P value |
|---|---|---|---|
| No. of HMG injections | 26.7±8.3 | 28.8±10.4 | 0.133 |
| Days of stimulation | 10.8±1.8 | 11.4±2.7 | 0.124 |
| Peak E2 (pg/ml) | 4759.5±1160.8 | 4953.9±1301.2 | 0.322 |
| E2 on day of hCG (pg/ml) | 2257.8±715.3 | 2120.0±715.0 | 0.342 |
| Days of intervention | 2.9±1.4 | 2.2±1.1 | 0.001** |

The table represents a significantly prolonged coasting period in variance to antagonist pattern. The GnRH antagonist injections delivered a median value of 2.2±1.1. The average E2 concentration within the antagonist criteria manifested a decline continuously after 24 hours till the day of hCG administration. Inceptive observation acknowledges the ascending concentration of E2 within the first 24 hours of coasting, followed by a falling pursuit of E2 concentration until the day of hCG administration.

**Table 4:** %Coasting and Antagonist groups in relation to the number of days of intervention.

| No. Days of intervention | Coasting No. (%) | Antagonist No. (%) |
|---|---|---|
| 1 | 16(10.7) | 44(29.3) |
| 2 | 48(32) | 62(41.3) |
| 3 | 50(33.3) | 18(12) |
| 4 | 16(10.7) | 22(14.7) |
| 5 | 16(10.7) | 4(2.7) |
| 7 | 2(1.3) | 0(0) |
| 8 | 2(1.3) | 0(0) |

In Antagonist group, 44 women (29.3%) required only one injection of GnRH antagonist, 62 women (41.3%) required two injections of GnRH antagonist and 44 women (29.4%) required more than two injections before hCG administration. In coasting group, only 16 women (10.7%) underwent coasting for 1 day, 48 women (32%) were coasted for 2 days, and 86 women (57.3%) were coasted for 3 days or more.

**Table 5:** Comparison between Coasting and Antagonist groups regarding the embryology lab characteristics:

| % | Coasting | Antagonist | P value |
|---|---|---|---|
| Sperm collection by ejaculate | 130(86.7%) | 130(86.7%) | 1 |
| Sperm collection by PESA | 4(2.7%) | 2(1.3%) | 0.409 |
| Sperm collection by TESE | 16(10.7%) | 18(12%) | 0.716 |
| No. of oocytes | 6.7±3.2 | 8.2±3.1 | 0.001** |
| No. of MII oocytes | 3.7±2.0 | 4.7±2.3 | 0.001** |
| No. of MI oocytes | 1.8±1.0 | 1.9±1.3 | 0.487 |
| No. of GV oocytes | 2.4±1.9 | 1.9±0.8 | 0.059 |
| No. of atretic oocytes | 2.4±1.4 | 2.3±1.6 | 0.583 |
| No. of fertilized oocytes | 2.9±1.8 | 3.8±2.4 | 0.001** |
| No. of grade 1embryos | 1.6±0.7 | 2.3±1.2 | 0.001** |
| No. of embryos grade 2 | 1.5±0.7 | 1.7±0.8 | 0.179 |
| No. of embryos grade 3 | 2.0±1.3 | 1.7±1.3 | 0.415 |
| No. of embryos transferred | 1.9±0.8 | 2.1±0.8 | 0.042* |
| No. of cryopreserved embryos | 0.0±0.0 | 0.1±0.6 | 0.157 |

The table displays a notable difference of average oocytes number picked up from the antagonist group that was higher by almost 18% compared to the coasting group. An elevated value of the number of metaphase II oocytes obtained from the antagonist group is distinguished in contrast to the coasting group. The antagonist group regarding fertilization rate of oocytes is distinctly advanced in figures compared to the coasting group. Amount of the developed high-quality embryos in the antagonist group exceeds that of the coasting group by around one-third the number of embryos (grade1). The mean

number of embryos transferred was significantly higher in the antagonist arm than in the coasting arm.

Statistical rates acquired of clinical pregnancy and multiple pregnancy displayed unremarkable dissimilarity between the two groups. On the other hand, resemblance of late severe OHSS was identified in both groups including two patients in each group. Early severe OHSS was not observed among patients without significant difference.

**Table 6:** Comparison between Coasting and Antagonist groups regarding the Pregnancy rates (PRs) and latesevere OHSS rate.

| | Coasting | Antagonist | P value |
|---|---|---|---|
| Clinical pregnancy (%) | 50(33.3%) | 54(36%) | 0.627 |
| Multiple pregnancy (%) | 14(9.3%) | 16(10.7%) | 0.874 |
| Severe OHSS (late) (%) | 2(1.3%) | 2(1.3%) | 1 |

## Discussion

Most of the previous studies on coasting are either observational or case-control trials. However, there is enough evidence in the literature that coasting is effective in reducing the incidence and severity of OHSS. (11). A demonstration of extended coasting of 4 days or further correlation to pregnancy rate expresses a low outcome (12). A substantial retrospective study that incorporated 1223 women disclosed the end-result of adopting coasting for excelled period of more than 3 days, that had diminishing consequences in terms of average number of oocytes retrieved, accomplishing implantation and successful clinical PRs (12).The follicular fluid was assessed in a programmed arrangement of coasting by two embryologists concurrently to point out the oocyte- cumulus complexes (OCC), an illustration of advanced research is necessary for gathering precise aspects of OCC, on account of negative impact of extended coasting to the number of granulosa cells neighboring the oocytes. (12). In addition to the effect of carrying out coasting for 4 days or more a study on egg donor cycles has described the counteraction to bring down the pregnancy rate. (13) This negative impact is assumingly affiliated to the poor quality of oocytes and embryos, as in traditional prolonged coasting IVF (regular-donor egg) cycles. Therefore, elimination of endometrial factor as a principal for lower pregnancy rates is crucial, a designated protocol was attained to halt the threatening disorders of prolonged coasting in women showing high risk of OHSS. The protocol hypothesis encourages the E2 concentration to drop down to a secure degree by the response of GnRH antagonist (8).

In our study on 300 women undergoing ovarian stimulation before ICSI; women were at high risk of developing OHSS, if they have a large number of follicles (>20) on both ovaries with 90% of the follicles being small (<14 mm in diameter), and E2 concentration ≥ 3500 pg/ml. They were divided into coasting group (150 patients) and antagonist group (150 patients) who received daily S.C injection of GnRH antagonist. When E2 concentration levels fell to < 3000 pg/ml all female patients subjected to HCG administration. None of them developed early onset severe OHSS. The mean number of oocytes gathered from the antagonist group had a considerable high difference from that of the coasting group by variance of 1.5±0.1 mean value. Finest embryo quality percentage was uplifted in the antagonist group with almost 30% better quality embryos that that of coasting group. Additional days were required in the coasting column. The primary approach applied in initial studies to weigh up the inhibitory practice for OHSS (coasting) (12) utilizing an original protocol of GnRH antagonist administration simultaneous to 75 IU of HMG in women at risk of OHSS. The central intention of averting severe OHSS in women at risk was established by coasting and administration of GnRH antagonist out of the 300 women in the study. The mode of action was achieved by minimizing the E2concentration to below 3000 pg/ml on the day of hCG administration. Nevertheless, timeframe accomplished to attain the desired concentration before administration of hCG, was brief ($P < 0.0001$) as stated in the antagonist arm with only 14.9% of patients that required ≥3 days of antagonist, while in comparison to the coasting group with 61.5% of patients that required protracted coasting of

≥3 days. Directing a small dose of HMG in a sustained manner, alongside the short intervention interval might be credible to unlikely nurturing granulosa cells and bearing a satisfactory classification of good quality oocytes and embryos. This study validated the hypothesis assumption of generating more oocytes (P = 0.0001) and high-quality embryos (P = 0.0001) in the antagonist arm. This relatively matches up with a study by Aboulghar et al. (9).

GnRH antagonist treatment of patients down-regulated with the long GnRH agonist protocol on patients with potential risk of OHSS prompted a significant drop in E2 concentration with avoidance of generating unfavorable results regarding assessment of oocyte maturation, evaluation of fertilization rate or embryo quality, the controlled non-randomized also supported a higher pregnancy rate in this group of women at risk of OHSS (8). The difference between PR in extended coasting and GnRH antagonist administration is not of a prime purpose in this study due to the extensive analytical requirements in each arm with a power of 80% and an alpha error of 0.05 presuming the pregnancy rate is 30%-35% which concludes a demand of 1307 women (9) Regardless of HMG suppression in the coasting group, E2 concentrations escalated within the first 24 hours with a later subsequent drop. Appropriately matching the work described by Isaza et al. (13). While the E2 concentration in the antagonist group fundamentally descended. E2 concentration dropped in coasting group following a cascade of events of follicular growth in lack of FSH stimulation to a point of apoptotic occurrence of granulosa cells (14). This clarifies the uprising concentrations of E2 prior to initiating coasting and elucidating the longer durations needed to drop below 3000 ml/pg. Allegedly this prohibits interchangeable reaction of chemical mediators from triggering OHSS (14). The sole machinery of antagonist that conducted an exclusive fall in E2 concentration explicitly not yet recognized. In a pilot retrospective study that conducted down-regulation with the long protocol (8 women) and flare-up protocol (39 women) Gustofson et al. (8) reported mild OHSS in a couple of patients and a single patient had to be treated of ascites as a result of severe OHSS. GnRH antagonist provided following a malfunction feedback of E2 concentration to a depletion of gonadotrophin dose. Controlled GnRH agonist has restorative ability towards the pituitary during directed administration with GnRH antagonist (15). Yet, the effect of GnRH antagonist to the pituitary after down-regulation by GnRH agonist was not anticipated (16).

In our study the mean drop in E2 concentration in 150 women after 1 day of antagonist administration was 34% in agreement with t Aboulghar et al. study in 2007;as the percentage of drop in E2 levels in 94 women after 1 day of antagonist administration was 36% .In Gustafson et al. study in 2006 the mean drop in E2 in 8 women was 49.5%.The riddle of sudden E2 level drop adherent to the effect of GnRH antagonist is yet incomprehensible. Although a substantiate amount of material was delivered proposing the action of GnRH antagonist at the cellular level in extra pituitary tissues, including physiological ovarian cycles. The synthesis of growth factors might be halted back due to the interference to the cell cycle (16). The likelihood of GnRH antagonist and the GnRH receptor interaction are of high chances as being reported (17). Mannaeils and Gordon. (18) opposed the fact of a direct extra pituitary tissues effect regulated by GnRH antagonist; claiming studies recited in this proposal are in-vitro studies, testing supra-pharmacological doses of GnRH antagonist in cancer cell lines.

Prolonged coasting represents a deficiency in oocytes, and specifically MII oocytes, which might potentially be refrained by the enrollment of GnRH antagonist as portrayed in the current study. The clinical PR in patients with prolonged coasting (4—8 days) was 27.7% in comparison with the preferable stats of 36% in the GnRH antagonist group, although a favorable percentage is not adequate against proportionally inconsiderable sample size. adversely, a committed approach nonrandomized large study from the present study proclaimed a feasible evaluation of pregnancy rate outcomes, in support of operating coasting for 3 days or less as compared with prolonged coasting. (12). Patients demanding extended coasting for more than 3 days took place in 24% of accumulative coasting patients. OHSS progress is usually bridged by uplifted levels of E2 concentrations that ambiguously has a parallel influence on complex evolvement of OHSS (19).

OHSS risk diminishing possibility is conditioned rationally by the potential depletion of E2 concentration. A study of categorized groups was executed to evaluate incidence of OHSS which represented 0.001 of the affected group from the study population and 0.01 concerning the women at risk (12). For an applicable, fitted study in a randomized clinical trial, the sustainable sample size acquired to minimize OHSS prevalence chances towards at risk population by 15 % is 17211 women in each treatment arm with an alpha error of 0.05 and 80% power. Manifestly this number would be immensely difficult to attain in a RCT.A conventional appropriate manner of managing coasting, as well as GnRH antagonist anticipated a constructive avoidance of OHSS development. None of the 300 patients at risk of OHSS elaborated early onset OHSS developments.

## Conclusion

Coasting alone and GnRH antagonist protocol are effective methods for prevention of OHSS. GnRH antagonist protocol was superior to coasting in producing more number of oocytes and more good quality embryos as well as reducing the time until hCG administration. There was no statistical significant difference in PR between the studied groups. No early onset OHSS developed in either group.

## Recommendation

GnRH antagonist administration during coasting is a valuable alternative protocol for prevention of OHSS during COH. We require to larger randomized studies compare coasting with or without GnRH antagonist to determine if there is any difference in PR and the incidence of OHSS between two protocols.

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