

# Coasting Versus GnRH Antagonist Salvage for the Prevention of Ovarian Hyperstimulation Syndrome

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**OBJECTIVE:** The purpose of the present study is to compare the use of GnRH antagonist salvage versus coasting for the prevention of OHSS in patients undergoing IVF/ICSI cycles with long GnRH agonist protocol.

**STUDY DESIGN:** Medical records of 91 patients (41 in coasting and 49 in GnRH antagonist group) identified as at high risk of developing OHSS were reviewed retrospectively. Groups were compared for occurrence of moderate and severe OHSS, serum estradiol on the day of HCG and IVF outcomes.

**RESULTS:** There were no differences between the groups in terms of moderate and severe OHSS and clinical pregnancy rates. Serum estradiol levels were decreased significantly in GnRH antagonist group. Quality of the transferred embryos was better in the coasting group.

**CONCLUSION:** Our results represent that both coasting and GnRH antagonist salvage are effective strategies to prevent OHSS in women undergoing long GnRH agonist IVF/ICSI cycles.

**Key Words:** OHSS, Coasting, GnRH antagonist

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## Introduction

In the recent years, increasing number of couples is seeking infertility treatment with assisted reproductive techniques (ART).<sup>1</sup> However, ovarian hyperstimulation syndrome (OHSS), an iatrogenic complication of controlled ovarian stimulation (COS), has been the most serious and distressing complication of ART. Although it is rare, it may be life threatening in 0.1-2% of assisted ART cycles and the mortality risk is estimated to be 1 in 450.000 to 500.000 cases.<sup>2,3</sup>

Several strategies for the prevention of OHSS have been employed including, minimizing the dose of HMG, reducing the dose of HCG for triggering ovulation, cryopreservation of the embryos and administration of iv albumin however, complete prevention was never achieved.<sup>4</sup> Coasting is defined as withholding exogenous gonadotropins and postponing the HCG trigger until estradiol (E<sub>2</sub>) levels have declined to a safer level, usually <3000 pg/ml. Coasting is believed to starve smaller follicles, induce apoptosis, and decrease the potential of follicles to elaborate vascular endothelial growth factor, a

well-recognized mediator of OHSS.<sup>5</sup> This procedure has been the first choice for the prevention of OHSS.<sup>6</sup> Prolonged coasting, on the other hand, is reported to be associated with reduced pregnancy rates.<sup>4</sup>

The events that take place in the development of OHSS are always associated with elevated E<sub>2</sub> levels. Although the exact role of E<sub>2</sub> is unclear, elevated levels are identified as a risk for the development of OHSS.<sup>7</sup> GnRH antagonist administration has been shown to result in a rapid reduction of E<sub>2</sub> in patients receiving GnRH agonist treatment and prevent OHSS while avoiding the drawbacks of prolonged coasting.<sup>8,9</sup>

The aim of the present study is to compare IVF-ICSI outcomes of hyperresponsive patients treated by GnRH antagonist salvage and coasting.

## Material and Method

Records of the patients undergoing IVF-ICSI cycles in years 2011 and 2012 were retrospectively reviewed. The study was approved by the Institutional Review Board and Women who have E<sub>2</sub> levels ≥3000 pg/ml and subjected to either coasting (n=41) or GnRH antagonist (n=49) injection until the day of HCG were recruited in the study. In the coasting group; gonadotropin injections were stopped completely and GnRH agonist continued until serum E<sub>2</sub> levels were ≥ 3000 pg/ml and HCG was administered. No patients in the coasting group were subjected to coasting more than two days. In the GnRH antagonist group, Cetrotide (0.25 mg, S.C., Serono, Germany)

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was given subcutaneously until the day of HCG when serum E2 levels of  $\geq 3000$  pg/ml were achieved. Oocytes were retrieved 36 hrs. after the injection of 10.000 IU of HCG (Ovitrelle 250 mcg, S.C., Serono, Italy).

Embryo transfers (ET) were performed on day 2, 3 or 5 depending on embryo quality. According to Turkish legislative law, single embryo was transferred in patients younger than 35 years and two in older women. A Wallace catheter (HG Wallace Ltd, West Sussex, and UK) was used with ultrasound guidance for all transfers, and difficult transfers were managed by after loading procedure.

Luteal phase was supported by vaginal progesterone (Crinone Gel 0.8%) twice daily and a serum pregnancy test was done 14 days after the ET. Clinical pregnancy was defined as the presence fetal cardiac activity on ultrasound.

Serum E2 on day of HCG, number of oocyte retrieved, fertilization rate, implantation rate, clinical pregnancy rates, moderate and severe OHSS as defined by Golan et al.<sup>10</sup> were compared between the groups.

For statistical analysis, Statistical Package for the Social Sciences version 15.0 for Windows was used (SPSS Inc., Chicago, IL, USA). Results are expressed as mean  $\pm$  standard deviation (SD). Groups were compared by Student's t test or Mann Whitney U test according to distribution characteristics. Categorical variables were tested by chi-square test. A p value of  $>0.05$  was considered statistically significant.

## Results

There were 41 women in coasting and 49 in the antagonist group. In the coasting group, there were 14 (34.1%) women with unexplained infertility and 21 (42.9%) in the antagonist group. Male infertility was the cause of infertility in 21 (51.2%) couples in the coasting and 21 (42.9%) in the antagonist group. Tubal infertility was present in 4 (9.8%) in coasting and 1 (2.0%) women in the antagonist group. Endometriosis was documented in 1 (2.4%) women in the coasting and 5 (10.2%) women in the antagonist group. There were 1 cases of hypogonadotropic hypogonadism in both groups (2.4% and 2.0% respectively). Distribution of indications for IVF\_ICS is represented in table 1.

Ages of the patients were similar in two groups (28.17 $\pm$ 4.61 years vs. 29.94 $\pm$ 5.31,  $p=0.082$ ). There were no differences between the groups with regards to basal FSH (6.11 $\pm$ 1.32  $\mu$ IU/ml vs. 6.19 $\pm$ 2.10  $\mu$ IU/ml,  $p=0.743$ ). Serum E2 on the day of HCG was significantly elevated in coasting group (2930.59 pg/ml $\pm$ 1242.13 vs. 2451 pg/ml $\pm$ 1565.16,  $p=0.011$ ). Number of oocytes retrieved and fertilization rates were similar between the groups (13.22 $\pm$ 5.41 vs. 11.94 $\pm$ 5.90,  $p=0.131$  and 46.68% $\pm$ 29.69 vs. 55.68% $\pm$ 30.38,  $p=0.160$ , respectively). Number of embryos transferred were also similar in both groups (1 $\pm$ 0.45 vs. 1.082 $\pm$ 0.64,  $p=0.319$ ). However, grades of the transferred embryos were significantly higher in the antagonist group (1.31 $\pm$ 0.56 vs. 1.52 $\pm$ 0.56,  $p=0.045$ ).

There were five (12%) cases of moderate OHSS in the coasting group and three (6.1%) in the antagonist group. Severe OHSS occurred in two cases (5%) in coasting and two (4.1%) in the antagonist group. There were no differences between the groups in regard to occurrence of moderate or severe OHSS (12.2% vs. 6.1%,  $p=0.857$  and 4.9% vs. 4.1%,  $p=0.316$ , respectively).

Clinical pregnancy rate was also similar between the groups (46.3% vs. 39%,  $p=0.475$ ). Baseline and clinical outcomes of the patients are represented in table 2.

Table 1: Distribution of IVF indications in coasting and GnRHant agonist groups

Cause of Infertility	Coasting Group		Antagonist Group	
	N	%	N	%
Tubal infertility	4	9.8	1	2.0
Male infertility	21	51.2	21	42.9
Endometriosis	1	2.4	5	10.2
Unexplained infertility	14	34.1	21	42.9
Hypogonadotropic	1	2.4	1	2.0
Hypogonadism				

Table 2: Baseline and clinical outcomes of the participants

	Coasting (n=41)	Antagonist (n=49)	p
Age	28.17 $\pm$ 4.61	29.94 $\pm$ 5.31	0.082
Basal FSH (uIU/ml)	6.11 $\pm$ 1.32	6.19 $\pm$ 2.1	0.743
E2 on day of HCG (pg/ml)	<b>2930.59<math>\pm</math>1242.13</b>	<b>2451.94<math>\pm</math>1565.16</b>	<b>0.011*</b>
No. of oocytes retrieved	13.22 $\pm$ 5.41	11.94 $\pm$ 5.90	0.131
Fertilization rate (%)	46.68 $\pm$ 29.69	55.69 $\pm$ 30.38	0.160
No. of embryos transferred	1 $\pm$ 0.45	1.082 $\pm$ 0.64	0.319
No. of high quality embryos	<b>1.31<math>\pm</math>0.56</b>	<b>1.52<math>\pm</math>0.56</b>	<b>0.045*</b>
Clinical pregnancy rate (%)	46.3	(22)39	0.475
Moderate OHSS (%)	12.2	6.1	0.316
Severe OHSS (%)	4.9	4.1	0.857

Values are expressed as mean  $\pm$  standard deviation and (%). \*  $p < 0.05$

FSH: Follicle stimulating hormone, HCG: Human chorionic gonadotropin, E2: Estradiol, OHSS: Ovarian hyperstimulation syndrome

## Discussion

Our results represent that both coasting and GnRH antagonist salvage are effective strategies to prevent OHSS in women undergoing long GnRH agonist IVF/ICSI cycles. Although GnRH antagonist administration resulted in lower E<sub>2</sub> on the day of HCG, we observed similar rates of moderate and severe OHSS in both groups. Number of oocytes retrieved and fertilization rates were not different between the groups. Clinical pregnancy rates were also similar, however, embryo grade was significantly higher in the GnRH antagonist group.

Although the exact role of E<sub>2</sub> in OHSS has not been confirmed, women with significantly elevated or rapidly rising E<sub>2</sub> levels are at an increased risk of developing OHSS.<sup>6,11</sup> By what mechanism the GnRH antagonist lowers the E<sub>2</sub> level is not yet clear. There are sufficient data in the literature that GnRH antagonist has an effect at the cellular level in extra pituitary tissues, including the ovaries. It is suggested to inhibit the synthesis of growth factors and thus the cell cycle.<sup>12</sup> An interaction of the GnRH antagonist and the GnRH receptor has also been reported.<sup>13</sup>

Gustafson et al.<sup>8</sup> have reported a rapid and significant reduction of E<sub>2</sub> levels with GnRH antagonist in hyperresponsive patients undergoing controlled ovarian hyperstimulation following pituitary down regulation by an agonist. Antagonist administration had no adverse effects on follicular growth, oocyte maturity, and fertilization rate and embryo quality.

In a recent study, Hill et al.<sup>9</sup> reported very favorable results with antagonist rescue in high responder women at risk of OHSS. They compared the outcomes of women who received antagonist rescue with the patients who did not. GnRH antagonist administration decreased the mean E<sub>2</sub> level by 35% on the first day of use. There were no difference in oocyte maturity, fertilization rate, and embryo grade. The live birth rate was 41.9% compared to 36.9% in the control group. They concluded that antagonist rescue reduced serum E<sub>2</sub> levels and enabled cycle completion high live birth rates in patients with high risk of OHSS.

Coasting has proven effective in reducing cycle cancellation while decreasing the risk for developing OHSS. However, prolonged coasting has been associated with poor IVF outcomes. When coasting was prolonged (>3 days), the number of oocytes retrieved, implantation and clinical pregnancy rates were significantly reduced.<sup>5</sup>

In a study by Yılmaz et al.<sup>14</sup> hyperresponsive women with E<sub>2</sub> levels >3000 pg/ml subjected to coasting were compared with who are not coasted and normoresponsive women. Implantation and pregnancy rates of women in coasting group were better than the group that was not coasted but similar

with the normoresponsive group. Thus, they concluded that coasting is a safe effective method for the prevention of OHSS without deteriorating IVF outcomes. Ulug et al.<sup>15</sup> have reported similar oocyte maturity, fertilization rate, and embryo cleavage rate in 207 patients with different durations of coasting (1,2,3 or >3 days). However, they found significantly reduced implantation and pregnancy rates when coasting was extended beyond 3 days.

Mansour et al.<sup>4</sup> have conducted first randomized study comparing the efficacy of coasting, the most common preventive measure employed so far, to antagonist administration together with a lower dose of gonadotropins. They found both strategies to be very effective in prevention of OHSS that there were no severe OHSS in either group. In this study, both coasting and GnRH antagonist administration achieved a sufficient reduction of E<sub>2</sub> levels, however, it took a longer duration in coasting group.

Aboulghar A. et al.<sup>7</sup> have also shown that both antagonist administration and coasting were effective for the prevention of OHSS, however they found higher quality embryos in the antagonist group even when compared to the group coast for two days. There were significant differences in the clinical pregnancy rate. Duration of coasting was restricted to two days in our study and we observed a better embryo quality in the coasting group.

Main limitations of our study are its retrospective nature and the relatively small sample size.

In conclusion, administration of GnRH antagonist and coasting in women at high risk of developing OHSS were equally effective in preventing OHSS. Prospective randomized trials with larger samples of patients are needed to elucidate the impact of both procedures on IVF outcomes.

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## Ovaryen Hiperstimülasyon Sendromunun Önlenmesinde GnRH Antagonist ve Coasting Uygulamalarının Karşılaştırılması

**AMAÇ:** Çalışmanın amacı, uzun GnRH agonist protokol ile IVF-ICSI uygulaması yapılan hastalarda coasting ve GnRH antagonist uygulamalarının OHSS'ü önlemede etkinliklerinin karşılaştırılmasıdır.

**GEREÇ VE YÖNTEM:** OHSS gelişme riski yüksek olan 91 hastanın kayıtları retrospektif olarak incelenerek, coasting (n=41) ve antagonist (n=49) uygulanan hastalar, orta ve ciddi OHSS gelişimi, HCG günü estradiol düzeyleri ve IVF sonuçları açısından karşılaştırıldı.

**BULGULAR:** Orta şiddette ve ciddi OHSS gelişimi açısından gruplar arasında farklılık izlenmedi. HCG günü estradiol düzeyleri antagonist uygulanan grupta daha düşük bulundu, an-

çak transfer edilen embriyoların kalitesinin coasting grubunda daha iyi olduğu gözlemlendi. Klinik gebelik oranları arasında fark yoktu.

**SONUÇ:** Sonuçlarımız, coasting ve GnRH antagonist uygulamalarının her ikisinin de OHSS'yi önlemede etkili olduğunu göstermiştir.

**Anahtar Kelimeler:** OHSS, Coasting, GnRH antagonist uygulaması

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