

**Original Article**

# Serum Oestradiol Pattern during Coasting is Different in Antagonist Cycles Compared with Long Agonist Cycles in *In Vitro* Fertilisation

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**ABSTRACT**

**Background:** GnRH agonists and antagonists have different mechanism of action, and therefore serum estradiol levels might differ during coasting in IVF.

**Aims:** To compare the change in serum oestradiol levels after withholding the gonadotropins for coasting between long agonist and antagonist cycles.

**Study Design:** Retrospective study.

**Methods:** Antagonist and long agonist cycles, in which coasting was performed, were analysed in this retrospective analysis. Antagonist cycles (n=50) were compared with long agonist cycles (n=52) with respect to daily serum oestradiol levels following withholding of gonadotropins.

**Results:** The pattern of change in serum oestradiol was different between groups; it increased on the first day by 11.2% and decreased thereafter on the second and third days in the agonist group. However, it began to decrease from the first day in the antagonist group. Therefore, peak serum oestradiol levels were significantly higher in the agonist group than in the antagonist group (mean±standard deviation; 5798±1748 vs 5104±1351 pg/mL). The duration of coasting was shorter in the antagonist group compared with that in the agonist group (mean±standard deviation; 2.60±1.40 vs 1.96±0.88 days).

**Conclusion:** Serum oestradiol pattern during coasting is different in antagonist cycles compared with long agonist cycles in *in vitro* fertilisation.

**Key Words:** Ovarian Hyperstimulation Syndrome, Estradiol, coasting, GnRH antagonists

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**Introduction**

Gonadotrophin-releasing hormone (GnRH) agonists and antagonists have been widely used to prevent premature LH surge during ovarian stimulation for *in vitro* fertilisation (IVF) and embryo transfer (1-3). GnRH agonist suppresses gonadotrophin secretion through both pituitary desensitisation and GnRH receptor down-regulation, whereas GnRH antagonist competes with endogenous GnRH for receptor binding and therefore rapidly inhibits secretion of gonadotrophin (1). It has been suggested that the desensitisation by GnRH agonist has different effects on the intraovarian system than GnRH antagonist (4). Also, GnRH antagonist-treated women showed lower serum and follicular oestradiol concentrations on the day of human chorionic gonadotrophin (HCG) administration during IVF (5-8). This suggests a difference in ovarian oestradiol metabolism between the two protocols.

Coasting, i.e., withholding gonadotropin stimulation whilst continuing pituitary desensitisation for a variable number of days is the most popular strategy for the prevention of ovarian hyperstimulation syndrome (OHSS) during ovarian stimulation (9). The above-mentioned differences between agonists and antagonists suggest different effects on serum oestradiol levels during coasting. Therefore, in this retrospective analysis, we aimed to compare the change in serum oes-

tradiol levels after withholding the gonadotropins for coasting between long agonist and antagonist cycles.

**Material and Methods**

Antagonist and long luteal agonist cycles, in which coasting was performed, were analysed in this retrospective analysis. Among 4220 cycles between 2001 and 2006, coasting was performed in 115 cycles. Coasting was performed for the indications of: [1] presence of >20 follicles, which were >10 mm in diameter; and/or [2] presence of high (>4000 pg/mL) serum oestradiol level. In all of these cycles, the follicular diameter for the smallest of the three leading follicles was 15 mm. Serum oestradiol levels were determined daily or every other day during coasting until serum oestradiol levels decreased to <4000 pg/mL. Only women between the ages of 21 and 39 years (n=102) were included in the analysis, to match the groups by age. Antagonist cycles (n=50) were compared with long agonist cycles (n=52) with respect to the duration of coasting and the serum oestradiol levels following withholding of gonadotropins. Pregnancy and implantation rates and the rate and severity of OHSS were also compared. The severity of OHSS was determined according to the Golan criteria (10). Cycle characteristics were compared by using the Student's t-test and chi-square test, where appropriate. Continu-



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**Table 1. Age and cycle characteristics in the long agonist and antagonist groups (NS = not significant)**

|   | Agonist cycles<br>(n=52) | Antagonist cycles<br>(n=50) | p     |
|---|--------------------------|-----------------------------|-------|
| Age (years)   | 29.00±3.23               | 30.58±4.85                  | NS    |
| Cause of infertility (n)  |                          |                             |       |
| Male factor   | 11                       | 15                          |       |
| Tubal factor  | 4                        | 2                           |       |
| Ovulatory dysfunction (PCOS)                                    | 8                        | 7                           |       |
| Male and Female (PCOS) factor                                   | 11                       | 9                           |       |
| Male and Female (other than PCOS) factor                        | 3                        | 4                           |       |
| Endometriosis   | 7                        | 3                           |       |
| Unexplained   | 7                        | 8                           |       |
| Other   | 1                        | 2                           | NS    |
| Duration of gonadotropin stimulation (days)                     | 9.21±1.81                | 9.60±3.15                   | NS    |
| Total dose of recFSH (IU)                                       | 1890±662                 | 2010±770                    | NS    |
| Serum E <sub>2</sub> level at the beginning of coasting (pg/mL) | 4521±698                 | 4588±658                    | NS    |
| Peak serum E <sub>2</sub> level (pg/mL)                         | 5798±1748                | 5104±1351                   | 0.03  |
| Duration of coasting (days)                                     | 2.60±1.40                | 1.96±0.88                   | 0.007 |
| Serum E <sub>2</sub> level on the day of hCG (pg/mL)            | 3211±942                 | 2966±972                    | NS    |
| Number of total oocytes   | 15.25±7.61               | 19.78±9.39                  | 0.009 |
| Fertilization rate (%)  | 59.9                     | 61.5                        | NS    |
| Number of embryos transferred (n)                               | 3.4                      | 3.5                         | NS    |
| Pregnancy rate (%/ET)   | 51.0                     | 43.8                        | NS    |
| Implantation rate (%)   | 21.5                     | 19.2                        | NS    |

**Table 2. Daily serum oestradiol (E) levels (pg/mL; mean±standard deviation) in antagonist and long agonist cycles**

|            | n  | Day 1    | Day 2     | Day 3     | Day 4     | Δ (%) | p     |
|------------|----|----------|-----------|-----------|-----------|-------|-------|
| Agonist    | 41 | 4533±742 | 5048±1728 | NA        | NA        | +11.2 | 0.036 |
|            | 25 | NA       | 5811±1596 | 5169±2163 | NA        | -7.7  | 0.196 |
|            | 17 | NA       | NA        | 6261±1336 | 4628±2462 | -25.0 | 0.144 |
| Antagonist | 36 | 4629±706 | 4342±1356 | NA        | NA        | -4.8  | 0.233 |
|            | 18 | NA       | 5374±853  | 3922±2145 | NA        | -29.3 | 0.003 |
|            | 12 | NA       | NA        | 6004±1560 | 4068±1715 | -32.5 | 0.001 |

Note: Each row indicates the results of two successive days only. (Δ = Mean for [ELater day – EEarlier day] / EEarlier day; NA = not applicable)

ous variables were compared using the former test, and rates were compared using the latter test. Each successive day was compared with each other by using Wilcoxon signed-rank test or paired t-test, where appropriate. The difference between the first and second days was compared using the paired t-test. The paired differences for the 2<sup>nd</sup> day-3<sup>rd</sup> day pair and the 3<sup>rd</sup> day-4<sup>th</sup> day pair were analysed using the Wilcoxon signed-rank test, due to the nonparametric nature of these data. Analysis of variance for repeated measures was not used since the number of subjects decreased with increasing number of successive days due to different durations of coasting. A further minor reason for analysing days separately was that serum levels had not been determined on weekends, i.e., daily, for every subject. The study was approved by the Institutional review board.

## Results

Cycle characteristics and pregnancy rates are shown in Table 1. Age, total dose of gonadotropins, and serum oestradiol level at the beginning of coasting were comparable between groups (Table 1). Serum oestradiol levels had been determined both on the first day and on the second day only in 41 cycles in the agonist group (n=52) and in 36 cycles in the antagonist group (n=50). Serum oestradiol level had been determined the day after in the remaining cycles due to intervening weekend days. The number of available samples for the other pair of successive days is shown in Table 2. The pattern of serum oestradiol change was different between groups; it increased on the first day by 11.2% (mean±standard deviation [SD], from 4533±742 pg/mL to 5048±1728 pg/mL)

and decreased thereafter, by 7.7% and 25.0% on the second and third days, respectively, in the agonist group (Table 2). However, it began to decrease from the first day, by 4.8% (mean $\pm$ SD, from 4629 $\pm$ 706 pg/mL to 4342 $\pm$ 1356 pg/mL) on the first day, and by 29.3% and 32.5% on the second and third days, respectively, in the antagonist group (Table 2). Therefore, peak serum oestradiol levels were significantly higher in the agonist group than in the antagonist group (Table 1). Serum oestradiol levels decreased to acceptable levels (<4000 pg/mL) in a shorter duration of time in the antagonist group compared with that in the agonist group (Table 1). A significantly higher number of oocytes were retrieved in the antagonist group than in the agonist group (Table 1). However, pregnancy and implantation rates were comparable between groups (Table 1).

Moderate and severe OHSS developed in seven and three women, respectively, in the agonist group. Corresponding values in the antagonist group were four and four. These rates were comparable between groups ( $p>0.05$ )

## Discussion

Serum oestradiol level follows a different course during coasting in antagonist cycles compared with long agonist cycles. This causes a shorter duration of coasting in these cycles compared with long agonist cycles. This seems to be due to the initial decrease in serum oestradiol level during coasting in the antagonist group, in contrast to the initial increase in the agonist group. In the present study, age was comparable between groups. Previously, we analysed a larger group in a similar study design (11). However, age was significantly different between groups in that study. Although we believe that the differences we observed in that study were not due to the difference in age, we analysed age-matched groups in the present study, and found similar results. To our knowledge, the effects of agonists and antagonists on serum oestradiol levels during coasting have not been compared previously in an IVF programme.

Egbase et al. (12) have examined serum oestradiol and progesterone concentrations after stopping gonadotrophins in a long down-regulation protocol in 15 women for OHSS prevention. Similar to the results in the present study, the authors reported that serum oestradiol concentrations increased on the first day of coasting in 13 of the 15 women before falling in the following days (12). In addition, Sullivan et al. (13) observed an initial increase in serum oestradiol level on day one following withholding of gonadotropin stimulation during IVF in long agonist cycles. Gustofson et al. (14) analysed 12 women who were treated with a standard microdose lupron protocol and subsequently experienced ovarian hyperresponse with a markedly elevated oestradiol level inadequate for hCG injection. Lupron was discontinued and ganirelix was initiated. Gonadotropins had not been withheld. The authors observed that serum oestradiol levels decreased by 40% and 35% on the first and second days, respectively. In a similar study design, Gustofson et al. (15, 16) reported that women who had been switched from a GnRH agonist in a down-regulation protocol to a GnRH antagonist for the prevention of OHSS had a significant decrease in serum E2 levels

within 24 hours of starting the antagonist, without coasting.

Our results suggest that the duration of coasting is shorter in antagonist cycles compared with agonist cycles. A shorter duration of coasting is also an advantage for the monitoring and cost of the cycle, i.e., a reduced number of visits and blood samples with a shorter duration of coasting. Although the effect of duration of coasting on IVF outcome, i.e., pregnancy and birth rates, is controversial, a significant impairment with a longer duration of coasting cannot be excluded with the available data (17-22). In the present study, the number of oocytes retrieved was significantly higher in the antagonist group compared with the agonist group; however, pregnancy rates were comparable between groups. An impairment in oocyte number with prolonged coasting was also previously reported (19, 20, 22). Therefore, the shorter duration of coasting in antagonist cycles appears to be an advantage for both the burden and the success of IVF in women at serious risk of OHSS.

Major weaknesses of the present study are the retrospective design and that there were missing serum oestradiol values. Despite these missing values, the data for the first day of coasting appear sufficient to draw a reliable conclusion for the relevant day. The results in the present study need to be confirmed by a prospective study, which will allow daily serum oestradiol determinations.

In conclusion, the pattern of serum oestradiol during coasting is different in antagonist cycles compared with long agonist cycles in IVF. In antagonist cycles, the decline in serum oestradiol level following cessation of gonadotropin stimulation begins earlier than that in agonist cycles. This causes a shorter duration of coasting in antagonist cycles.

**Ethics Committee Approval:** Ethics committee approval was received from Trakya University Faculty of Medicine Medical Ethics Committee (2013).

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