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The effect of coasting on the outcome of intracytoplasmic sperm injection: comparable analysis of GnRH agonist and antagonist cycles

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Summary

Introduction: One of the preventive strategies in case of impeding ovarian hyperstimulation syndrome (OHSS) is coasting. The aim of this study was to compare the effect of coasting in high responder patients treated with gonadotropin-releasing hormone (GnRH) agonist or GnRH antagonist protocol for intracytoplasmic injection and embryo transfer. *Materials and Methods:* This retrospective study was conducted in the infertility unit in a private hospital. The study group included women who underwent an intra-cytoplasmic sperm injection (ICSI) cycle with a coasted period during ovulation induction from 2006 to 2013. The cycles outcome of cycles were compared between GnRH agonist (n=226) and GnRH antagonist (n=110) coasting cycles. *Results:* Women's age and other baseline characteristics of the groups were similar. Coasting was significantly more required in GnRH agonist cycles compared to GnRH antagonist cycles (11.8% *vs*. 4.5%, respectively, OR = 2.63, $p < 0.001$). Live birth rates after coasting were 41.5% in the GnRH agonist group and 40.9% in the GnRH antagonist group ($p = 0.903$). Moderate-severe OHSS occurred in 13 (5.7%) cases in the GnRH agonist group and three (2.7%) cases in the GnRH antagonist group ($p = 0.343$). In the GnRH agonist group, the longer duration of coasting (≥ four days) was associated with the lowest live birth rate (27.2%), but it did not reach a statistical significance. *Conclusions:* Live birth and moderate/severe OHSS rates are similar in the GnRH agonist and the GnRH antagonist cycles with coasting. Despite the lack of statistical significance, ≥ four days of coasting is related to the lowest live birth rate through ICSI compared to < four days of coasting in the GnRH agonist cycles.

Key words: Coasting; GnRH agonist; GnRH antagonist; OHSS; Intracytoplasmic sperm injection; In vitro fertilization.

Introduction

Ovarian hyperstimulation syndrome (OHSS) is a potentially life threatening iatrogenic complication of ovulation induction. The incidence has been estimated as 3–6% for moderate and 0.1–2% for severe OHSS [1]. It is characterized by cystic enlargement of the ovaries together with ascites following a vast number of follicles (≥ 20) and high E2 concentration.Human chorionic gonadotropin (hCG) stimulation seems the triggering factor for the development of OHSS [2].

One of the preventive strategies in case of impeding OHSS is coasting as defined as complete discontinuation of the exogenous gonadotropin administration and with holding hCG injection until serum estradiol (E2) level reaches a safer value. The rational behind coasting is apoptosis of the granulosa cells due to decreasing follicle stimulating hormone (FSH) concentrations and down-regulation of luteinizing hormone (LH) receptors, and consequently reduction in vasoactive substances considered to be initiators of the capillary permeability. However, there is no current consensus as to how coasting should be carried out. It is generally initiated when follicles are larger than 14 mm in diameter and serum E2 level exceeds 3,000 pg/ml [3, 4].

Gonadotropin-releasing hormone (GnRH) agonists and antagonists have been widely used to prevent premature LH surge during ovarian stimulation for in vitro fertilization (IVF). GnRH agonist suppresses gonadotropin secretion through pituitary desensitisation, whereas GnRH antagonist competes with endogenous GnRH for receptor binding and rapidly inhibits secretion of gonadotrophins. It has been suggested that the desensitisation by GnRH agonist has different effects on the intraovarian system than GnRH antagonist [5].

Many of the studies on the effect of coasting in GnRH agonist protocols presented convincing evidence for its application and the prediction of IVF outcome [6, 7]. However, the number of follicles and E2 level to initiate coasting, and the impact of prolonged coasting on oocyte quality and/or implantation potential of endometrium are yet to be established. Coasting was applied in the antagonist cycles with the same rational, but only a few studies are available regarding the impact of coasting in GnRH antagonist cycles [8-12].

This study aimed to compare the outcome of intra-cytoplasmic sperm injection (ICSI) cycle after coasting with a

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GnRH agonist protocol to GnRH antagonist protocol.

Material and Methods

The study was approved by the Institutional Review Board of Ota-Jinemed Hospital (Date of approval: January 16, 2015 and project approval no: 123/2015). The database of patients undergoing ovarian stimulation for ICSI in Infertility Unit of Ota-Jinemed Hospital between January 1, 2006 and January 1, 2013 was evaluated retrospectively. Patients in whom gonadotropins were withheld for at least one day prior to oocyte retrieval due to high response were enrolled. Inclusion criteria were the presence of normal uterine cavity confirmed with hysterosalphingography (HSG) and/or hysteroscopy, absence of any other hormonal disorder, and the use of ejaculated spermatozoa.

Findings were compared between GnRH agonist (n=226) and GnRH antagonist (n=110) coasting cycles. The main outcome measures were the number of retrieved oocytes, clinical pregnancy, miscarriage, live birth, and moderate/severe OHSS rates. Criteria suggested by Golan *et al.* were used for classification of OHSS [10].

In the GnRH agonist protocol, down-regulation was achieved with daily injections of leuprolide acetate 0.5 mg starting in the mid luteal phase. Ovarian stimulation with 150/225 IU recombinant FSH was initiated when serum E2 level fell below 50 pg/ml. The GnRH antagonist protocol used gonadotropin stimulation with the same dose as used for GnRH agonist protocol from day 3 followed by daily injections of 0.25 mg cetrorelix acetate on the sixth day of ovulation induction until the day of hCG injection. In both protocols, the initial dose of gonadotropins was selected according to the patient's weight and individual response to the previous stimulations, if available. Ovulation induction protocol was selected according to the patients' schedule or physicians' preference based on data in the previous cycle. Ovarian response was monitored by transvaginal ultrasound and serum E2 level everyone to three days, starting on the fifth day of stimulation, and the gonadotropin doses were adjusted accordingly.

Coasting was applied when the serum E2 concentration measured > 3,500 pg/ml in the presence of at least 20 follicles measuring > 12 mm in diameter. Same criteria were applied for both GnRH agonist and GnRH antagonist cycles. GnRH agonist or antagonist was continued when gonadotropins were withheld during coasting. Recombinant hCG was administered when at least three follicles measuring 17 mm were achieved and E2 level dropped below 3,500 pg/ml. Oocytes were retrieved transvaginally 35-36 hours after recombinant hCG administration and cultured in a medium supplemented with 10% HSA at 37°C under 6% CO2. Following cumulus-corona removal, ICSI was performed two hours after incubation as described elsewhere. Embryos were initially cultured in a culture medium G-1 PLUS until day 3, and then transferred to G-2 PLUS.

Blastocyst transfer was performed five days after oocyte retrieval under ultrasound guidance. A serum pregnancy test was performed 12 days after ET. Luteal phase was supported by either 50 mg of progesterone in oil IM or 90 mg progesterone vaginally and continued until fetal heart beat was detected. Clinical pregnancy was defined as the presence of fetal heart beat on ultrasound examination five weeks after oocyte retrieval. Implantation rate was calculated as the percentage of gestational sacs with fetal heart beat on the number of embryos transferred.

MedCalc Statistical Software Program version 15.8.0 was carried out. One-way analysis of variance (ANOVA), the log-transform method with Scheffe multiple comparison tests, the Kruskal-Wallis test, the Mann-Whitney test, and the χ^2 test were used, as appropriate. A p-value < 0.05 was accepted as statistical significant.

Table 1. — *Baseline characteristics of the two different groups with coasting.*

Characteristics	GnRH-agonist (n=226)	GnRH-antagonist (n=110)	p value
Female age (years)	30.9±4.0	31.6±4.4	0.134[a]
Baseline serum FSH level (IU/L)	6.3 ± 1.9	6.2 ± 1.8	0.746[a]
Duration of infertility (years)	5.7±3.3	5.5±3.6	0.543[a]
No. of previous attempts	1.6±1.0	1.8±1.2	0.234[a]
Etiology of infertility, n (%)			
Male factor	61 (27.0)	28 (25.5)	0.866[b]
Male factor + PCOS	20 (8.9)	17 (15.5)	0.103[b]
PCOS	91 (40.3)	35 (31.8)	0.167[b]
Unexplained	32 (14.2)	23 (20.9)	0.157[b]
Tubal factor	22 (9.7)	7 (6.4)	0.409[b]

Note: values are expressed as mean ± SD. *a: t*-test, *b:* χ^2 test.

Results

Of 4,379 IVF cycles performed during the study period, the GnRH agonist protocol was used in 1,918 cycles (43.8%) and the GnRH antagonist protocol in 2,461 cycles (56.2%). Coasting was applied in 226 (11.8%) cycles with the GnRH agonist protocol and in 110 (4.5%) cycles with the GnRH antagonist protocol (OR = 2.63, $p < 0.001$).

There were no significant differences in the baseline characteristics such as female age, baseline FSH level, number of previous attempts, duration, and etiology of infertility between the two groups (Table 1).

Cycle characteristics of the GnRH agonist and GnRH antagonist groups are shown in Table 2. Duration of ovarian stimulation (10.5 ± 2.1 *vs*. 10.9 ± 2.1 days), total dose of gonadotropins (1,968 ± 679 *vs*.1,843 ± 622 IU) used and E2 level (4,417 ± 605 *vs*. 4,304 ± 683 pg/ml) at the beginning of coasting were comparable between the two groups.Whereas, peak serum E2 level (4788 ± 849 *vs*. 5216 ± 605 pg/ml) during coasting, E2 level on the day of hCG administration (2961 ± 693 *vs*. 3418 ± 895 pg/ml) and the duration of coasting (1.5 ± 0.6 *vs*. 2.0 ± 1.0 days) were significantly lower in the GnRH antagonist group compared to the GnRH agonist group, respectively ($p < 0.001$). The number of oocytes retrieved (14.65 ± 6.41 *vs*. 15.58 ± 5.84), embryos transferred (2.1 ± 0.9 *vs*. 2.3 ± 0.8), and miscarriage rate (12.1% *vs*. 10.0%) were similar between the GnRH antagonist and the GnRH agonist groups, respectively. Live birth rate was 41.5% in GnRH agonist group and 40.9% in GnRH antagonist group ($p = 0.903$).

The rate of moderate/severe OHSS in the coasting cycles was 2.7% in the GnRH antagonist group and 5.7% in the GnRHagonist group ($p = 0.343$).

Association between the duration of coasting and the outcome of ICSI cycle was also evaluated. In the GnRH agonist group, the longer duration of coasting (four and more days compared to one to three days) was associated with

Table 2. — *Cycle characteristics in the GnRH agonist and GnRH antagonist groups with coasting.*

	GnRH agonist (n=226)	GnRH antagonist (n=110)	*p* value
Duration of gonadotropin stimulation (days)	10.5 ± 2.1	10.9 ± 2.1	0.071[a]
Total dose of gonodotropins (IU)	1968 ± 679	1843 ± 622	0.104[a]
Need for coasting of the cycles (%)	11.7	4.4	< 0.001[b]
E2 level at the beginning of coasting (pg/ml)	4417 ± 605	4,304 ± 683	0.125[a]
Peak serum E2 level (pg/ml)	5216 ± 878	4,788 ± 849	< 0.001[a]
Median duration of coasting (days)	2(2.0 ± 1.0)	1 (1.5 ± 0.6)	< 0.001[c]
E2 level on the day of hCG (pg/ml)	3418 ± 895	2961 ± 693	< 0.001[a]
No. of oocytes retrieved	15.5 ± 5.8	14.6 ± 6.4	0.184[a]
Fertilization rate (%)	60.2	64.5	0.905[a]
No. of embryos transferred	2.3 ± 0.8	2.1 ± 0.9	0.109[a]
Implantation rate, n (%)	141/522 (27.0)	62/236 (26.2)	0.492[a]
Clinical pregnancy rate, n (%)	107 (47.3)	50 (45.4)	0.834[b]
Miscarriage rate, n (%)	13 (12.1)	5 (10.0)	0.901[b]
Live birth rate, n (%)	94 (41.5)	45 (40.9)	0.903[b]
Moderate/severe OHSS, n (%)	13 (5.7)	3(2.7)	0.343[b]

Note: values are expressed as mean ±S D. *a: t*-test, *b:* χ^2 test, *c:* Mann-Whitney test.

Table 3. — *Association of duration of coasting with cycle outcomes in the GnRH agonist group.*

	Days of coasting				
No. of cycles (n)	Day 1 (n=77)	Day 2 (n=86)	Day 3 (n=41)	Day ≥4 (n=22)	*p* value
No. of oocytes retrieved (n)	15.8 ± 5.5	16.1 ± 6.0	15.8 ± 5.5	11.4 ± 5.0	0.005[d]
Fertilization rate (%)	61.4	59.3	59.8	60.3	0.094[d]
No. of embryos transferred (n)	2.1 ± 0.7	2.3 ± 0.9	2.2 ± 0.8	2.6 ± 0.9	0.128[d]
Implantation rate,n(%)	54/167 (32.3)	51/205 (24.8)	26/93 (27.9)	10/58 (17.2)	0.589[d]
Clinical pregnancy rate, n (%)	37(48.0)	44 (51.1)	20 (48.7)	6 (27.2)	0.250[b]
Live birth rate, n (%)	32(41.5)	39 (45.3)	17 (41.4)	6 (27.2)	0.502[b]

Note: values are expressed as mean ± SD. *b:* χ^2 test, *d:* ANOVA.

Table 4. — *Association of duration of coasting with cycle outcomes in the GnRH antagonist group.*

	Days of coasting				
No. of cycles (n)	Day 1 (n=59)	Day 2 (n=41)	Day 3 (n=10)	Day ≥4 (n=0)	*p* value
No. of oocytes retrieved (n)	14.2±6.7	14.8±5.5	16.±7.9	-	0.611[d]
Fertilization rate (%)	66.8	62.7	59.5	-	0.980[d]
No. of embryos transferred	2.1±0.9	2.2±0.9	2.0±1.0	-	0.672[d]
Implantation rate, n (%)	32/124 (25.8)	24/92 (26.0)	6/20(30.0)	-	0.536[d]
Clinical pregnancy rate, n (%)	26(44.0)	20 (48.7)	4(40.0)	-	0.840[b]
Live birth rate, n (%)	23(38.9)	18 (43.9)	4(40.0)	-	0.884[b]

Note: values are expressed as mean ± SD. *b:* χ^2 test, *d:* ANOVA.

the lowest live birth rate (27.2%) but it did not reach a statistical significance ($p = 0.502$) (Table 3).

In the antagonist group, there was no association between the cycle outcome and the duration of coasting up to three days (Table 4). None of the GnRH antagonist cycles required more than three days of coasting, whereas 9.7% of the agonist cycles needed four or more days of coasting.

Discussion

Withholding hCG administration until the peak E2 level has reached a safer level, namely coasting protocol, has been employed since the late 1980s [11]. This method was first used to prevent OHSS in GnRH agonist cycles; subsequently, it was applied in GnRH antagonist cycles. Following a case report of the use of coasting in a GnRH antagonist cycle [12], the first cohort was published in 2006 [13]. The number of studies on the effect of coasting in patients treated with GnRH antagonist protocol is limited in the literature [9, 11, 12].

In the present study, the authors compared the outcome of GnRH agonist with GnRH antagonist cycles, using the same criteria for the application of coasting, and detected similar live birth rates in high responders. There is no consensus on

the most suitable cases for coasting in the literature. In the present study, the authors included patients with the serum E2 concentration measured > 3,500 pg/ml in the presence of at least 20 follicles measuring > 12 mm in diameter. In a previous report, patients undergoing ovarian stimulation with a GnRH antagonist protocol and having E2 level > 5,000 pg/ml or > 18 follicles achieved an 83% sensitivity rate with a specificity of 84% for predicting severe OHSS [14]. Thus, patients included in the present study represent a high risk group for OHSS.

The present authors did not observe any difference in the number of oocytes collected, fertilization, clinical pregnancy, and live birth rate with ICSI in the antagonist group, as compared to the agonist group in the coasting cycles. These findings are similar with recent studies which reported no difference in the outcomes of IVF between agonist and antagonist cycles in the coasted patients [11, 12]. Dominant follicles can continue to grow even after withdrawal of gonadotropin injections, since FSH concentration may remain above a certain threshold level for a while. This level was found as 4.9 IU/L at hCG injection [17] with no live births when FSH dropped to 2.5 IU/L in down-regulated cycles [18]. Apparently, these levels cannot be applied to GnRH antagonist cycles but should be considered as a tool to optimize pregnancy rate in GnRH agonist cycles.

Chahvar *et al.* reported that ICSI had a negative impact on blastocyst development, theoretically due to the different location of spindle formation in the oocytes obtained from coasted patients [19]. Mansour *et al.* did not find any difference in the outcome of ICSI on the oocytes collected from patients with coasting of < three days [20]. Thus, present study provides additional information about the effect of coasting in ICSI cycles.

In the present study, coasting was applied in 11.7% of GnRH agonist cycles and 4.4% of GnRH antagonist cycles in high responders ($p < 0.001$). GnRH agonist triggering was not employed in antagonist cycles during the study period in the center. Thus, this difference cannot be attributed to the use of GnRH agonist triggering in GnRH antagonist cycles. Similarly, Farhi *et al.* observed a higher rate of the use of coasting in agonist cycles compared to antagonist cycles [15]. Desensitisation of the gonadotropic cells by GnRH agonist has different effects on the intraovarian system from GnRH antagonist which achieve suppression of gonadotropin secretion by the competitive blockade of the GnRH receptors in pituitary gland. Abrupt decline in gonadotropin levels may result in therapeutic effect within 24-72 hours and a drop in E2 level following antagonist administration. None of the patients required more than three days of coasting with GnRH antagonist protocol in the present study.

Also, GnRH antagonist cycles were characterized with significantly lower peak E2 level on the first day of coasting, shorter duration of coasting, and lower E2 level on the day of hCG administration compared to GnRH agonist cycles. These findings may be associated with the robust effect of GnRH antagonists following cessation of gonadotropins.

The moderate-severe OHSS rate in the present study population was similar in the GnRH antagonist and GnRH agonist coasting cycles (2.7% *vs*. 5.7%, $p = 343$, respectively). Farhi *et al.* reported moderate/severe OHSS rate in coasting cycles as 4.6% in the agonist group and 4.4% in the antagonist group [15]. The observed rate of severe OHSS in GnRH agonist coasting cycles ranged from 0 to 3.9% in different studies [4, 20].

Al-Inany *et al.* published an update, including 45 trials, demonstrated that OHSS rate in women treated with GnRH antagonist protocol is significantly lower compared to GnRH agonist protocol [21]. Furthermore, in a recent meta-analysis, it was stated that there was no benefit of coasting to prevent OHSS compared with no coasting [22].

Coasting might affect the outcome of an IVF/ICSI cycle through oocyte quality and/or endometrial receptivity. In many studies, short term coasting (particularly ≤ three days) was not found to compromise the outcome [6, 19, 23-25].

Elter *et al.* found that duration of coasting was shorter in antagonist cycles compared to agonist cycles [16]. The present findings are in parallel with this result that the duration of coasting is shorter in antagonist cycles compared with agonist cycles. Apparently, only 9.1% of GnRH antagonist cycles required more than two days of coasting whereas coasting lasted three or more days in 27.3% of GnRH agonist cycles.

Regarding the association between duration of coasting and cycle outcome, number of oocytes collected was the lowest in patients with ≥ four days of coasting in the GnRH agonist group in the present study. An impairment in oocyte number with prolonged coasting was previously reported [15, 21, 22]. Mansour *et al.* conducted a study to evaluate the effect of coasting duration on the outcome of IVF and concluded that coasting for > three days is associated with a moderate decrease in the pregnancy rate [15]. The fact that fewer oocytes were retrieved after three days of coasting may indicate a higher rate of atresia of oocytes in GnRH agonist cycles with prolonged coasting. This may be supported with the different effects of duration of coasting on oocyte survival and steroidogenesis which might be associated with irregular development of the endometrium. Implantation rate was found to be significantly impaired in recipients with coasting > four days in donor oocyte cycles [26]. On the contrary, Abdalla *et al.* reported that coasting for up to eight days does not impair live birth rate in a study in 1,068 coasted cycles [27]. Also, E2 level at trigger and E2 drop did not affect the outcome in 1068 coasted cycles.

The present authors are not able to comment on the effect of the prolonged coasting in GnRH antagonist cycles since none of the patients required more than three days of coasting in this group. Likewise, no study is present regarding

the impact of prolonged coasting in GnRH antagonist cycles in the literature. Two reasons can be proposed; first, high E2 level drops fast and almost eliminates prolonged coasting, and second, GnRH agonist trigger has been commonly used in clinical practice, which lessens the need for coasting.

In conclusion, live birth and moderate/severe OHSS rates are similar in the GnRH agonist and the GnRH antagonist cycles with coasting. Despite the lack of statistical significance, ≥ four days of coasting is related to the lowest live-birth rate through ICSI compared to < four days of coasting in the GnRH agonist cycles.

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