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Is Coasting Valuable in All Patients with Any Cause of Infertility?

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ABSTRACT

Objectives: This study aimed to assess the influence of coasting duration on the number and quality of oocytes and fertilization rate in male factor infertile women and those with polycystic ovary syndrome (PCOS). ***Methods:*** In this prospective observational follow-up study, 114 patients undergoing coasting (53 women with male factor infertility and 61 women with PCOS) were evaluated at the Royan Institute Research Center, Iran, between 2010 and 2012. ***Results:*** The results were analyzed according to the coasting periods of 1–4 days. In normal females, the number of oocytes retrieved was significantly reduced after the second day ($p = 0.004$). In addition, a statistically significant drop was observed in the number of metaphase II oocytes and fertilization rate after the third day ($p = 0.006$ and $p = 0.006$, respectively). No significant differences were observed in the number and quality of oocytes retrieved and fertilization rate with regard to coasting days in PCOS patients. ***Conclusion:*** Coasting with duration of more than three days should be performed with caution in normal females who are at risk of developing ovarian hyperstimulation syndrome.

Despite major advances in assisted reproductive techniques (ART), there remains a considerable risk of developing life-threatening ovarian hyperstimulation syndrome (OHSS) as a result of supraphysiological stimulation of the ovaries.[1] OHSS has a reported incidence of 1 to 10% of all ART cycles.[2] Several preventive strategies have been introduced to avoid OHSS occurrence or to diminish its severity. Coasting is one of the most popular choices among physicians for the prevention of OHSS.[3–5] On the other hand, using a gonadotrophin-releasing hormone (GnRH) antagonist as an alternative method has been suggested as one of the preferred strategies to prevent OHSS in a long protocol.[1,6] However, there are some restrictions on the use of antagonist, for example in whose have had an inadequate response to the use of antagonists in the past, and the lack of accessibility to the antagonist in some countries. Accordingly, coasting has been advocated as an effective approach to avoid OHSS in polycystic ovary syndrome (PCOS) patients by several investigators.[1,7–9] The principle behind coasting is based on the phenomenon of apoptosis/necrosis. By withholding exogenous gonadotropins, mature follicles will survive for a few days, while the number of smaller follicles will reduce through atresia of granulosa cells during apoptosis.[9–11] Interestingly, there is insufficient evidence using identical criteria for the application of coasting, and many unknowns also remain regarding management of this treatment.[12] The debate on whether coasting has an effect on ART cycle outcomes, such as the number and quality of oocytes, is still ongoing.[13] However, the literature suggests that coasting does not exert a negative impact on in vitro fertilization (IVF) cycle outcome provided that its duration is not extended.[14–16]

The majority of studies have evaluated the impact of coasting on IVF outcome,[3] but the effect of coasting in patients with different infertility causes has not been previously explored. Therefore, our study was designed to determine the impact of coasting in women at risk of developing OHSS with

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male factor infertility (normal women) and women with PCOS.

METHODS

In this prospective observational follow-up study, we included 114 patients who showed a predisposition to developing OHSS during controlled ovarian stimulation before IVF/intracytoplasmic sperm injection (ICSI) and had undergone coasting at the Royan Institute Research Center, Iran, between June 2010 and December 2012.

Approval to conduct this study was obtained from the Institutional Review Board of the Royan Institute Research Center and the Royan Ethics Committee. All patients signed an informed consent authorizing the use of their information.

The patients were further subdivided into those with male factor infertility (n = 53) and PCOS (n = 61). The criteria for inclusion in the male infertility group were women with partners who had asthenospermia or who were candidates for percutaneous epididymal sperm aspiration (PESA) and those with 3–4 failed intrauterine insemination (IUI) cycles. Patients using sperm retrieved from testicular sperm aspiration (TESA) procedures and those using frozen sperm were excluded from the study. Women with PCOS who failed to have an adequate response to the antagonist in their previous induction ovulation were included in the study. PCOS was defined by the 2003 Rotterdam consensus criteria.[17]

All patients underwent conventional IVF/ICSI treatment with the standard long protocol using a GnRH agonist (Suprefact, Hoechst, Frankfurt, Germany) for pituitary suppression. In addition, a starting dose of 112.5 IU of recombinant human follicle-stimulating hormone (follitropin alfa pen; Gonal-F, Merck Serono S.A., Geneva) was used with or without Menopur (Ferring, Germany) to induce ovulation. Monitoring of cycles was performed by sonography and measurement of estradiol (E2) levels. Coasting started when serum E2 was more than 3000 pg/mL or there were at least 15 follicles with a size of 14–16 mm. During coasting, which was not more than four days, gonadotropin administration was withheld, whereas GnRH agonist was maintained. Furthermore, daily monitoring by sonography and serum E2 measurements was continued until E2 concentrations decreased by 50% of maximum rising. Ovarian puncture was performed 34–36 hours after human chorionic gonadotropin (hCG) administration.

The coasting duration was determined as the number of days from the last injection of gonadotropin to the hCG-day administration. The fertilization rate was calculated as the number of oocytes with two pronuclei divided by the number of injected oocytes when ICSI was performed and by all intact oocytes retrieved when IVF was performed. The results were analyzed according to the coasting periods for 1–4 days, separately in each group of infertile women with male factor and PCOS.

The statistical comparisons were performed using one-way analysis of variance (ANOVA), Kruskal-Wallis nonparametric analysis of variance and chi-square when appropriate. The results were reported as median (IQR; interquartile range). A p-value < 0.050 was considered statistically significant. Data analysis was performed using SPSS Statistics (SPSS Statistics Inc., Chicago, US) version 18.0.

RESULTS

In this study, the data of 114 women undergoing coasting were analyzed. Coasting was performed in 53 normal patients and 61 patients with PCOS. The demographic and hormonal levels compared with the duration of coasting by days (1–4) are presented separately in male factor infertile women and women with PCOS [Table 1]. There were no statistically significant differences between different days of coasting with regard to age, body mass index (BMI), and basal hormone levels. When comparing the E2 level at the start of coasting between coasting days, a statistically significant difference was observed in each group of normal women and women with PCOS ($p = 0.036$ and $p = 0.005$, respectively).

In normal females, the number of oocytes retrieved was significantly reduced after the second day of coasting ($p = 0.004$). Additionally, a statistically significant drop was observed in the number of metaphase II (MII) oocytes and fertilization rate after the third day ($p = 0.006$ and $p = 0.006$, respectively). On the other hand, in PCOS patients, no statistically significant differences were revealed between different days of coasting regarding the number and quality of oocytes retrieved and fertilization rate [Table 2].

Table 1: Comparison of age, BMI, basal hormone levels, and stimulation days of women with male infertility and PCOS according to the number of days coasting.

	Coasting, days				*p*-value
	1	2	3	4	
Male infertility					
Patients, n	10	16	19	8	
Age, years	28.5 (25.2–32.7)	26.0 (24.0–27.0)	30.0 (25.0–33.0)	28.0 (23.7–32.7)	0.260
BMI, kg/m^2	26.1 (23.6–28.8)	25.3 (21.7–27.0)	22.6 (19.3–25.4)	22.9 (19.2–25.2)	0.090
FSH, MIU/mL	4.3 (2.9–6.6)	6.0 (4.6–7.0)	6.6 (5.2–7.4)	5.6 (3.8–7.1)	0.311
LH, MIU/mL	2.9 (1.6–8.1)	6.1 (3.9–8.7)	5.0 (2.7–8.6)	5.1 (4.1–7.9)	0.396
TSH, MIU/mL	1.3 (0.7–1.8)	1.7 (1.1–2.4)	1.8 (1.3–3.8)	1.8 (0.5–3.6)	0.376
PRL, ng/mL	18.9 (14.6–566.2)	14.9 (9.5–28.0)	38.5 (15.2–247.0)	35.1 (11.0–320.2)	0.400
E2 at start of coasting, pg/mL	2639.0 (1036.0–4068.0)	4332.0 (4006.0–5164.0)	4856.0 (3919.0–6517.0)	5390.0 (4728.0–7809.0)	0.036
E2 at hCG day, pg/mL	2087.0 (1793.0–4434.0)	2925.0 (1663.0–4411.0)	3265.0 (2482.0–6581.0)	4204.0 (627.0–5682.0)	0.573
PCOS					
Patients, n	23	20	11	7	
Age, years	31.0 (25.7–35.2)	31.0 (28.0–33.0)	36.0 (29.0–38.0)	30 (29.0–32.0)	0.425
BMI, kg/m^2	24.8 (23.8–29.2)	24.4 (22.7–27.6)	25.3 (21.2–26.4)	25.5 (24.3–28.4)	0.583
FSH, MIU/mL	7.3 (4.5–8.0)	4.2 (3.7–6.7)	5.0 (2.6–6.6)	4.0 (2.9–4.4)	0.261
LH, MIU/mL	5.5 (4.0–9.8)	7.6 (2.1–10.6)	6.8 (3.0–18.0)	6.3 (3.3–9.0)	0.881
TSH, MIU/mL	1.8 (0.6–2.2)	2 (1.0–2.8)	1.8 (0.8–2.6)	1.5 (0.8–3.0)	0.756
PRL, ng/mL	22.9 (14–168)	15 (10.1–133.5)	20.1 (4.6–162.5)	19.9 (9.7–286.0)	0.774
E2 at start of coasting, pg/mL	3462.0 (3163.0–4336.0)	3353.0 (2059.0–4382.0)	5182.0 (4360.0–7632.0)	5358.0 (5263.0–6772.0)	0.005
E2 at hCG day, pg/mL	2501.0 (1774.0–4514.0)	3419.0 (2390.0–5551.0)	5061.0 (2549.0–6710.0)	2203.0 (1110.0–4324.0)	0.109

Values given as median (IQR). The statistical comparisons were performed by Kruskal-Wallis test. PCOS: polycystic ovarian syndrome; BMI: body mass index; FSH: follicle stimulating hormone; LH: luteinizing hormone; TSH: thyroid stimulating hormone; PRL: prolactin; E2: estradiol; hCG: human chorionic gonadotropin.

DISCUSSION

OHSS is a serious complication related to ovulation induction which is sometimes seen in low-risk patients, but it is more likely to occur in high-risk patients.[3] PCOS is a well-known risk factor for OHSS.[12,13,18] Despite the widespread use of coasting

Table 2: IVF outcome according to the duration of coasting in women with male infertility and PCOS.

	Coasting, days				*p*-value
	1	2	3	4	
Male infertility					
Patients, n	10	16	19	8	
Oocyte, mean±SD	18.6±2.4[a]	15.3±1.9[ab]	13.1±1.0[b]	7.1±1.3[c]	0.002
MII, mean±SD	16.1±2.2[a]	13.2±1.6 [a]	11.8±0.9 [a]	6.7±1.3[b]	0.006
Fertilization rate, % (n)	60.2 (97/161) [a]	63.0 (136/216) [a]	57.3 (129/225) [a]	37.0 (20/54)[b]	0.006
PCOS					
Patients, n	23	20	10	7	
Oocyte	14.0 (10.0–20.0)	14.5 (8.2–18.5)	10.5 (8.7–20.0)	9.0 (6.0–17.0)	0.433
MII	11.0 (8.0–16.0)	11.5 (4.5–15.0)	9.5 (6.0–19.2)	7.0 (6.0–16.0)	0.698
Fertilization rate, % (n)	63.7 (235/369)	56.5 (169/299)	65.2 (75/115)	63.2 (43/68)	0.202

Values given as median (IQR) unless otherwise stated; a, b, c: The same letter in each row indicates no significant difference between days at 0.050 level. IVF: in vitro fertilization; PCOS: polycystic ovarian syndrome; MII: metaphase II.

treatment by physicians,[3,4] our findings do not provide explicit evidence that coasting is useful in the prevention of OHSS in all patients undergoing controlled ovarian hyperstimulation with any cause of infertility.

Many studies have addressed the effect of coasting on controlled ovarian hyperstimulation (COH) cycles.[9,12,15,19,20] A large body of evidence has advocated coasting as an effective method for preventing OHSS in high-risk groups without compromising pregnancy outcome.[7–9] In contrast, others have shown a decline in the number of oocytes obtained and oocyte quality in coasted cycles.[19,21,22] A recent Cochrane review demonstrated that randomized controlled trials performed for the prevention of OHSS by coasting were not powerful enough to confirm the efficiency of this method.[3,20]

Based on clinician experience, E2 levels for initiation of coasting is varied.[3,5] A retrospective analysis of 608 patients demonstrated that the initial level of E2 to start coasting might have an impact on oocyte quality.[3] Furthermore, a recent review study emphasized that coasting should be initiated with a serum E2 level greater than 3000 pg/mL.[23]

Our study revealed that coasting treatment and success varies with cause of infertility. Accordingly, in normal females, coasting with duration of more than two days is likely to exert an adverse effect on the number of oocytes, and coasting for more than three days negatively affects oocyte quality and fertilization rate. However, in contrast, coasting can be safely applied to infertile PCOS women in light of OHSS potential risks without compromising the outcome. Many investigators have used different criteria to specify the time of starting and ending of coasting and they have reported different results for the effect of coasting period on the prevention of OHSS and reproductive outcomes.[1,8,16,19,24] Some authors believe that too short a period of coasting may not be effective in preventing OHSS, whereas too long a period may have a less satisfactory outcome in terms of oocyte quality and endometrial receptivity.[5,15,23] Despite the debate over the coasting effect, there has almost been an agreement among studies that oocyte quality and pregnancy outcome are adversely affected after four days of coasting.[11,16,19]

The observed differences between our study and previous studies could be due to our patient selection according to the cause of infertility. In general, physiological mechanisms are probably involved in the adverse effects of coasting on outcome of treatment cycle in normal women compared to women with PCOS. This, in turn, may indicate that PCOS patients show less sensitivity to the manipulation occurring during coasting. This may be explained by the critical role of luteinizing hormone (LH) in the final stages of follicular maturation. The LH receptors of the follicles decrease following the coasting process, and this reduction is expected to be severe with longer coasting periods. Consequently, these follicles with a low number of functional LH receptors have a poor response to exogenous hCG, and so, final maturation will not be obtained.[9,13] On the other hand, granulosa cells from polycystic ovaries contain higher number of LH receptors compared with normal granulosa cells.[25] Accordingly, despite the loss of receptors following coasting, in women with PCOS there are relatively adequate receptors for supporting final maturation, whereas in normal women these endocrine changes are not tolerable by follicles. As our study showed, in women with male factor infertility, there was a decreasing trend in the number of oocytes obtained, and oocyte quality and fertilization rate with regard to the coasting days (even with periods less than four days).

CONCLUSION

Our results indicate that before making important treatment decisions in infertile patients at risk of developing OHSS, the impact of an infertility diagnosis should be considered. Accordingly, coasting for more than three days should be performed with caution in normal women who are at risk of developing OHSS. In this respect, an attempt to determine a recommended protocol for normal women, coasting for one or two days combined with another preventive method appears to be the most desirable option for avoiding OHSS. Obviously, the lack of research in this area and the potentially sensitive nature of OHSS makes it difficult to draw definite conclusions and further studies with a larger population is suggested.

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