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Effect of Coasting on Success of In-Vitro Fertilization Cycles

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Introduction: "Coasting" is a method used in prevention of Ovarian Hyperstimulation Syndrome (OHSS) during In Vitro Fertilization (IVF) cycles. Coasting refers to witholding exogenous gonodotropine usage and delaying the administration of hCG in high risk cycles until serum estradiol levels falls into an acceptable range. The aim of our study is to evaluate coasting effect on IVF oucomes in patients with E_2 levels of 4000-5000 pikogram.

Method: This study was a single centered, retrospective and a case-control study. Study population were selected from women applied Zeynep Kamil Research Hospital IVF department between January 2003 and December 2013(n:7850). Patients were divided in 2 groups as conrol group (Group 1, n:48) and coasted group (Group 2, n:34) according to whether or not coasting performed.

Results: E_2 levels on the day of hCG in group 2 were significiantly lower than group 1 (4332.6±256.6 and 3180.8±702.9; $p<0.0001$, respectively). There were no statistically significiant difference in follicle count before oocyte pick up, collected M2 oocyte count, fertilized oocyte count, pregnancy rate and OHSS incidence in between groups.

Conclusion: Coasting is an effective method in high risk women to lower OHSS incidence. It can be appilied safely especially in patients having optimal follicular size and estradiol levels of 4000-5000

Keywords: Coasting, in-vitro fertilization, E_2 levels

Introduction

Controlled ovarian stimulation used in assisted reproductive techniques may cause ovarian hyperstimulation syndrome (OHSS). Exogenous human chorionic gonadotrophin (hCG) has a major role in OHSS development via increasing capillary permeability (1). There are many treatment varients such as cycle cancel, witholding HCG, coasting, intravenous albumin and dopamin agonist administration to reduce incidince and severity of OHSS in high risk patient (2). Coasting, one of the most used methods, refers to witholding exogenous gonodotropine usage and delaying the administration of hCG in high risk cycles until serum estradiol falls into an acceptable range (typically less than 2500 to 3000 pg/mL) (2-7). Coasting decreases FSH levels and causes

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granulosa cell apoptosis and inhibition of proliferation via luteinazition (2, 6). As a conse-quence, coasting prevent onset of OHSS (2, 8). Moreover it allows usage of embryos in that cycle instead of embryo freezing and it decreases patient anxiety and cost. Many studies demonstrated that coastıng reduced OHSS incidince effectively (7). Many studies have shown that pregnancy rate in coasted patients is similar to women with no coasting (9). In Cochrane systematic Reviews, only one study from 13 studies were evaluated and it was reported that coasting had similar incidence of OHSS and pregnancy rate compared to control group (2, 10). Some studies stated that coasting interval may change in vitro fertilization (IVF) outcomes (11). Coasting interval that will not change pregnancy rate adversely has not been explained yet (2, 7, 8, 12, 13).

There are controversies about coasting effects on IVF outcomes such as decreased picked oocyte, decreased implantation rate and decreased pregnancy rate (2). The aim of our study is to evaluate coasting effect on IVF oucomes in patients having E_2 levels of 4000-5000 pikogram.

Study Design

This study was a single centered, retros-pective and a case-control study. The study population was selected from infertile women applied Zeynep Kamil research hospital IVF department between January 2003 and December 2013 (n:7850). Patients, between 23 to 43 years and with a body mass index (BMI) of 23-28 kg/m^2, having normal serum hormone profile, regular menstrual cycle, first or second cycle of IVF were included. Male infertility was excluded according to World Health Organization (WHO) 2010 criteria (14). Women having uterine pathology were also excluded. There were 82 patients who fulfilled inclusion criteria. Patients were divided in 2 groups as conrol group (Group 1, n:48) and coasting group (Group 2, n:34) according to whether coasting performed or not. Medical history, gynecology examination and basic infertility tests had been performed all women.

All patients had venous blood sampling in early follicular period and on the day of HCG to detect FSH and estradiol (E_2) levels. Transvaginal ultrasonography had been performed to detect antral follicle count in early follicular phase.

Ovulation induction via agonist or antago-nist protocol, 100 mg aspirine and 400 mcg folic acide had been administered patients. GnRH agonist had been started in 21th Day of previous cycle and recombinant(rec) FSH [rec-FSH, Gonal-f® (Merck Serono, Turkey) or Puregon® (Shering Ploug)] had been added on third day of cycle in long agonist protocol. rec-FSH(150 IU, rec FSH) had been started on second or third day of cycle and GnRH antogonist had been added on the sixth day of cycle in antagonist protocol.Starting dosage of rec-FSH was made according to patients' age, BMI, antral follicle count and basal FSH levels. Following, in both protocols recFSH dosage had been arranged according to follicle diameter in TV USG and serum E_2 levels. When the leading follicle diameter reached to 18 mm or two follicle diameter were greater than 16 mm, 10,000 IU hCG (Pregnyl®, Shering Ploug) intramuscularly or 250 mcg rec-hCG subcutenously were enjected. Gonodotropines administration were stopped in women having peak E_2 levels greater than 4000 in group 2 and GnRH analogs were continued to administer.

Oocyte pick-up (OPU) were performed 35.5 hours after HCG administration under intra-venous (IV) sedation and with guidance of TV USG. Single dose Cefazolin sodyum (iv, 1 gram) were given all patients during OPU. Doxycycline (100 mg, two times daily,po) and methyl prednisolone (16 mg, one daily, po) were given patients for 4 days. Intravaginal 90 mg progesterone (%8 crinone gel, Serono) for luteal phase support were started all patients from OPU day. Oocyte maturation scoring were made according to Veeck`s classification as 0-4 (15). Pronuclear scoring was evaluated 16-18 hours after Intracytoplasmic Sperm Enjection (ICSI). Embryo quality was scored as 1-5 according to morphology of embryo splitting before ET (16).

Single Embryo transfer (ET) were performed via USG guidance after 2-5 days. After 12 days, serum Beta-HCG levels were measured for pregnancy detection. Beta-HCG levels >20 IU/l were named as biochemical pregnancy and fetal cardiac activity observed in USG after 6 weeks of ET was called as clinical pregnancy.

Statistical analyses were performed using the Statistical Package for the Social Sciences for Windows 15.0 software (SPSS, Chicago, IL., USA). Descriptive statistics were given as mean, standard deviation, frequency and per-centage. To compare parametric con-tinuous variables, the Student T-test was used; to compare nonparametric continuous variables, the Mann-Whitney U test was used; and to compare categorical variables, the chi-square test was used. P values <0.05 were considered to indicate statistical significance.

Results

In this study, 7850 patients were evaluated retrospectively. There were 173 patients to whom coasting was performed. 91 patients, who did not meet the inclusion criteria of the study, were left out and the study was completed with 82 patients. 82 patients were divided into two groupsaccording to whether coasting performed or not; 48 patients (58.5%) as study group (Group-1) and 34 patients (41.5%) as coasting group (Group-2).Mean age (30.8±4.9 vs 30.4±3.9, p:0.730, respectively) and BMI (24.85±1.5 vs 25.25±2.02, p:0.297, respectively) of control group and coasted group were similar.

Table-1. Baseline Characteristics and IVF Outcomes

Characteristics	Group 1 (n:48)	Group 2 (n:34)	P
Age, year	30.8±4.9	30.4±3.9	0.730[a]
Body mass index, kg/m^2	24.85±1.5	25.25±2.02	0.297[a]
Basal FSH, IU	6.9±1.6	5.9±1.3	**0.0002**[a]
İnfertility duration, year	7.6±5.4	8.3±4.5	0.547[a]
TP(Agonist/Antagonist), n	31/16	16/17	0.183[b]
Induction period (no coasting), day	9.2±1.2	8.7±1.4	0.105[a]
Total Gonadotrophine dosage, IU	2495±1006	1765±561	**0.0002**[a]
Peak E_2, pikogram	4333±257	4527±257	**0.0012**[a]
E_2 on HCG day, pikogram	4332±256	3180±702	**<0.0001**[a]
Follicle count before OPU	15±5.8	14.8±6.8	0.868[a]
Total M2 oocyte count	11.28±4.9	10.41±5.3	0.454[a]
Fertilization count	6.8±2.7	6.2±3.9	0.626[a]
Pregnancy rate, n (%)	16/48 (%33.3)	9/34 (%26.5)	0.673[b]
OHSS incidence, n (%)	5/48 (%10.4)	1/34 (%2.9)	**<0.0001**[b]

TP: Treatment protocol. Data are presented as mean±SD and number (percent). [a]Student t test. [b]χ2 test.

Basal FSH level of coasted group were lower than control group (5.9±1.3 vs 6.9±1.6,

p:0.0002, respectively) but it was not reached statistically significiance. The mean infertility duration and induction period except coasting duration were similar in between groups (9.2±1.2 vs 8.7±1.4 in days, p:0.105). Total Gonadotrophine dosage used were lower in coasted group compared to control group (1765.8±561.7 vs 2495.4±1006.1, p:0.0002, respectively). E_2 level on HCG day was lower in coasted group than control group (3180.8 ±702.9 vs 4332.6±256.6, p<0.0001, respectively). None of the patient had E_2 level lower than 2000 pikogram at the day of hcg injection in the coasting group.

The mean coasting day was 1.97±0.72 and only 2 patients had four days of coasting. There were no statistically significiant difference in groups according to Follicle count before OPU, total M2 oocyte count, fertilization rate and pregnancy rate. OHSS incidence was lower in coasted group than control (%2.08 vs %8.82,p<0,0001, respectively) (Table-1).

Discussion

Our study results revealed that Coasting in women with E_2 level of 4000-5000 pg/ml in IVF cycles. OHSS incidence reduced and IVF cycle results such as follicle count before oocyte pick up, collected M2 oocyte count, fertilized oocyte count and pregnancy rate.

OHSS is an important complication of ovulation induction. The incidece of OHSS is reported as 1-10% in IVF cycles (17). Etiopathogenesis of OHSS have not been completely understood yet. Human chorionic gonadotrophin (hCG) stimulation plays a key role in triggering syndrome (18). Younger patients are more likely to develop OHSS (1, 19, 20). This might be associated with higher response of the ovaries to exogenous gonadotrophins. The mean age of coasted patients in our study was similar to control group (30.4±3.9 vs 30.8±4.9, p:0.730, respectively). Many studies reported no correlation between BMI and OHSS (21, 22). In our study BMI was also similar in both groups. The data about the predictive value of maximum serum E_2 level on the development of OHSS is conflicting. D'Angelo et al. found a cut-off value of serum E_2 level (3346 pg/mL) on Day 11 of ovarian stimulation could detect 85% of women at risk for OHSS (10). In contrast to that Morris et al. reported that serum E_2 level is not an accurate predictive factor for OHSS development (23). Mathur et al. stated that different results between studies may be attributed to many factors such as variations in the methods of serum E_2 assays, the small number of patients involved in each of these studies, the biological variability of OHSS and occurrence of OHSS as early and late onset (24).

Cancellation of HCG injection prevent OHSS development but it is not cost effective and it may increse anxiety of infertile couples (7). Coasting another preventive method of OHSS does not require cycle cancellation but it can not completely prevent from cycle cancellation either. Firstly, Sher et al described coasting in IVF cycles (6). For More than 20 years, there are still no universal coasting guidelines. Coasting by decreasing FSH levels leads to the selective regression of smaller follicles which have lower density of FSH receptors and are more prone to changing FSH levels (25). In the literature there is no cut-off level of E_2 to perform coasting and E_2 levels ranges between 2500-6000 pg/ml in different clinics (26). In addition to, safe estradiol level to administer HCG after coasting may change in different clinics as<3000 pg/ml or <4000 pg/ml (27, 28).

It has been shown that the rate of decrease in E_2 levels during coasting does not affect the IVF outcomes (29). In the present study we performed coasting to patients having E_2 levels between 4000-5000 pg/ml in Goup-2 and HCG was administered after E_2 levels decreased to 3180.8±702.9 pg/ml as mean. In the present study decrese in E_2 level in coasting group also did not change IVF oucomes. Therefore, we suppose that coasting is an effective method to lower OHSS risk especially in patients having E_2 levels ranging 4000 to 5000 pg.

Prolonged coasting (more than 4 days) was found to related with reduced numbers or quality of oocytes (1, 13, 30). In our study mean coastig duration was less than 4 days and oocyte number in coasting group was similar to control group. Some studies reported that coasting does not reduce pregnancy rate (30).

In accordance with that, our study demonstrates an overall pregnancy rate of 26.5% in coasted patients which is similar to control group (33.3%). It was shown that coasting in GnRH agonist and antogonist protocol had similar IVF outcomes (31). Our study population consist of patients who take GnRH agonist or antogonist protocol.

Conclusion

Sometimes, ovaries are overstimulated by hormones and severe OHSS may be life threatening. In conclusion, coasting is a usable method in patients who have high risk to develop OHSS so it prevent cycle cancellation. Coasting can be performed safely before HCG administration in high risk patients who have optimal follicular size and E_2 levels ranging 4000 to 5000, until estradiol levels decrease to delicate levels. Although coasting could not increase pregnancy rate, it can decrease IVF complication risks.

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