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Comparison of coasting with Cabergoline administration for prevention of early severe OHSS in ART cycles

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Abstract

Background: One of the major and life-threatening side effects of Assisted Reproductive Technique (ART) is ovarian hyperstimulation syndrome (OHSS). The available data however, have been showed that both Cabergoline (anti VEGF) and coasting reduce the severity of OHSS.

Objective: We aimed to compare coasting and Cabergoline administration in prevention of severe OHSS.

Materials and Methods: A total of 60 IVF/ICSI cycles were selected. Patients at risk of developing OHSS were divided into two groups as patient's convenience. For 30 patients in coasting group, exogenous gonadotropins were withheld to allow E_2 to decrease while GnRH-a was maintained. Then 10,000 unit hCG was administrated and oocyte retrieval was performed 36 hours later. In Cabergoline group, 30 patients were administered with 0.5mg Cabergoline tablet on day of hCG injection, continued for 8 days.

Results: The mean number of retrieved, good quality, mature oocytes and the mean number of embryos were significantly different in two groups ($p<0.05$). The clinical pregnancy rate was 13.3% in coasting and 26.7% in Cabergoline group that was not significantly different ($p>0.05$). The incidence of severe OHSS was similar in two groups.

Conclusion: The Cabergoline was as effective as coasting in the prevention of early severe OHSS in high risk patients, but yielded more retrieved oocytes.

Key words: *Cabergoline, Coasting, OHSS, ART.*

Introduction

The most serious and potentially life threatening iatrogenic complication of controlled ovarian hyperstimulation (COH) is a severe form of ovarian hyperstimulation syndrome (OHSS) (1, 2). It complicates less than 0.5-2% of In Vitro Fertilization (IVF) cycles (3) which cause mortality in 1/45000 – 1/50000 per infertile women receiving gonadotrophins (4). OHSS has been treated empirically over the years, because it is pathophysiology remained unknown.

The risk of OHSS increases with high serum E_2 levels and a large number of ovarian follicles, because the granulosa cells might secret not only sex steroids but also the vasoactive substances responsible for OHSS (1). Complications rarely manifest before the administration of human chorionic gonadotropin (hCG) to induce the final oocyte maturation .Vascular endothelial growth factor (VEGF) is the most important mediator of hCG dependent ovarian angiogenesis. VEGF not only stimulates new blood vessel development in ovary, but also induces vascular hyper permeability by interacting with VEGF receptor 2 (5, 6). Once the syndrome occurs, little can be done to change the course of events, only supportive measures can be performed, however the definite and useful method in this stage is cycle cancelling or preventing of hCG administration. Many methods have been tried to prevent the

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syndrome. The appropriate stimulation protocol and gonadotropin needs to be selected (7). Unilateral ovarian follicular aspiration prior to the administration of hCG was successful in some investigations (8). In our previous study, aspiration of half of follicles before hCG administration reduced the risk of severe OHSS (9). Cryopreservation of all embryos has no effect on the syndrome occurring in the days immediately following oocyte retrieval, but eliminates the risk of early pregnancy OHSS. It takes a good success rate at subsequent frozen – thawed transfers (10). Another method for preventing OHSS is coasting approach. Withholding gonadotropin administration has been employed in ovulation induction cycles to prevent excessive response (11-13). This was used in gonadotropin-releasing hormone analogue-treated patients (14). Recently a dopamine agonist, Cabergoline has been used successfully for prevention of severe OHSS (15).

The purpose of this prospective study was two folds: 1) to assess the effect of Cabergoline on cycle outcome and preventing severe OHSS and 2) to compare it with popular coasting method. To our knowledge, this is the first study which compares coasting with a pathophysiological approach.

Materials and methods

Patients

The study was approved by ethical committee of Research and Clinical Center for Infertility, Yazd University of Medical Sciences and it is was supported by a grant from the Research Deputy of Yazd University of Medical Sciences. The written informed consent was given from the patients. Among couples who underwent IVF or ICSI cycles because of tubal, male, ovarian, unexplained, endometriosis and both male and female factors, 60 women at risk of developing OHSS were included in this study. The definition of risk was: the presence of pre- ovulatory follicles ≥ 20 in both ovaries, most of follicles were > 15 mm and at least 3 follicles ≥ 18mm were present. The E_2 level was ≥ 2500 pg/ml.

Stimulation protocol

All women were down regulated according to the long protocol with Gonadotropin-releasing hormone analogue (GnRH-a) subcutaneously (Buserelin, Hoechst, Germany). Then, daily administration of human menopausal gonadotropin (hMG) (Menogon, Ferring, Germany) was added. Serum E_2 concentrations were measured with Enzyme-Linked Immunosorbent Assay (ELISA, DRG Instruments GmbH, Germany) at the Yazd Research and Clinical Center for Infertility. Patients at risk of developing OHSS, who did not have a tendency to cancel their cycle, were divided into two groups as patient's convenience. Group A (coasting group): gonadotropins were withheld (while GnRH–a was maintained), until the serum level of E_2 started to decline. In group B (Cabergoline group): hCG was administered and the patients received 0.5 mg per day Cabergoline orally from the day of hCG for 8 days. Luteal phase was supported by administration of progesterone in oil 100mg per day for 14 days and was continued if pregnancy occurred. Embryo culture and Embryo Transfer (ET) procedure were carried out in both groups in a similar fashion. Patients were monitored every 48 h from the day of hCG until the day 8 for the presence of symptoms and signs of severe OHSS and Hemoglobin (Hb) and Hematocrit (HCT) was measured. Clinical pregnancy was defined as the presence of gestational sac or cardiac activity 3 weeks after ET.

Statistical analysis

The Statistical Package for the Social Sciences 15.0 software was used to analyse data of all randomized patients. To control for the non-normal distribution of the data, Mann-whitney and X^2 tests were used when appropriate, for the small number of cases, Fisher’s exact test was used for the comparison of frequencies. A $p<0.05$ was considered statistically significant.

Results

Between July 2006 and July 2007, we studied 60 patients at Yazd Research and Clinical Center for Infertility which is a famous referral University center in Iran. In total, 30 patients in coasting and 30 patients in Cabergoline group were evaluated. The mean age was 28.37±3.2 years in coasting and 29.63±4.4 years in Cabergoline group (p=0.209). The mean duration of infertility was 8.66±3.55 years in coasting and 8.16±4.8 years in Cabergoline group (p=0.650). The mean serum E_2 level on day of hCG was 3035.40±1105 pg/ml in coasting and 3012.86 ± 512 pg /ml in Cabergoline group (p=0.232). There was no significant differences in etiology of infertility between two groups (p=0.542). The mean duration of coasting in coasting group was 3.20±0.76 days (2-5 days). One patient in coasting and one patient in Cabergoline group had very bad quality embryos and lead to cycle cancellation before ET. The mean number of retrieved oocytes (p=0.001), good quality oocytes (p=0.002), metaphase II oocytes (p=0.0001) and the mean number of embryos obtained was significantly higher in Cabergoline group than coasting group (p=0.020). The percentage of good quality oocytes (the number of good quality oocytes per number of oocytes retrieved ×100) was higher in coasting group (p=0.061). The percentage of metaphase II oocytes (the number of metaphase II oocytes per number of oocytes retrieved ×100) was significantly higher in coasting group (p=0.001). Fertilization rate was also significantly higher in coasting than Cabergoline group (p=0.001). One patient in coasting group had very bad oocytes and the cycle was cancelled. The quality of embryos was similar in both group (p=0.600). The clinical pregnancy rate per ovum pick–up was higher in Cabergoline than coasting group (p=0.285). A total of 4 pregnancies occurred in coasting group. All pregnancies were singleton and there were 2 early miscarriages in coasting group (before 8 week of gestation). Eight pregnancies occurred in Cabergoline group, 2 of these were twin pregnancies. Implantation rate was higher in Cabergoline than coasting group, but the difference was not significant (p=0.060). Four patients in coasting group and 5 patients in Cabergoline group developed severe OHSS and were hospitalized. One patient from each group required parasynthesis and for remaining patients infusion of normal saline was performed. The incidence of severe OHSS was similar in coasting (13.3%) and in Cabergoline (16.7%) group (p=0.100).

Table I. Basic characteristics and early results of patients at risk of OHSS in two groups.

	Coasting (n=30)	Cabergoline (n=30)	p-value
Age (years)	28.37(3.20)	29.63(4.42)	0. 209[a]
Duration of infertility (years)	8.60(3.50)	8.1(4.8)	0.650[a]
E_2 on day of hCG (pg/ml)	3035(1105.0)	3012(512)	0.232[b]
Number of retrieved oocytes	6.47(2.64)	12.60(5.26)	0.001[b]
Number of good quality oocytes	4.50(2.51)	7.27(3.76)	0.002[b]
Number of metaphase II oocytes	6.17(2.96)	10.17(4.06)	0.0001 [b]
Number of embryos obtained	5.07(2.44)	7.20(3.60)	0.020[b]
Number of embryos transferred	2.37(0.66)	2.30(0.83)	0.774 [b]
Score of embryos	17.23(3.52)	16.63(4.42)	0.600[b]
Percentage of good quality oocytes	66.98(23.34)	55.82(21.91)	0.061[a]
Percentage of metaphase II oocytes	95.00(20.12)	81.96(18.75)	0.001[b]

Data are presented as mean(SD); [a]using independent samples t-test; [b]using Mann- Whitney test.

Table II. Clinical outcomes of patients at risk of OHSS in two groups**.**

	Coasting (n=30)	Cabergoline (n=30)	p-value
Fertilization rate [a]	79.07(21.95)	59.94±18.03	0.001[b]
Implantation rate (%)[c]	4/71(5.6)	10/69(14.4)	0.060[d]
Clinical pregnancy rate (%)[c]	4/30(13.3)	8/30(26.7)	0.285[d]
Severe OHSS(%)[c]	4/30(13.3)	5/30(16.7)	0.100[d]

[a]Data are presented as mean(SD); [b]using independent samples t-test; [c]data are presented as n/N (%): n, number of patients with the quality, N, total number of the participants in this group; [d]using Pearson chi-square test with continuity correction.

Discussion

OHSS is the major complication of ovarian stimulation and its most severe form can even threaten the patient's life. Several strategies for preventing the syndrome have been described. The safest strategy is to cancel the cycle. However, it should be considered that any form of cancellation is associated with emotional and financial costs to the couple involved. It is also possible to avoid embryo transfer and freeze all embryos (16). Another approach for the prevention of OHSS is follicular aspiration prior to hCG administration (8). One popular method for reducing the risk of syndrome is withholding gonadotropin administration and postponing the hCG injection, while continuing GnRH agonists. This modality has been termed coasting (17). In our previous study, no significant difference was observed in terms of pregnancy rate and severe OHSS when coasting was compared with follicular aspiration (18).

Recently, Cabergoline has been successfully used for high risk patients and has reduced the severity of OHSS (19). It has been shown that Cabergoline could reverse increased vascular permeability in hyperstimulated animals by inhibition of $VEGFR_2$ phosphorylation. In animal studies, it has been shown that low dose Cabergoline blocked some specific $VEGFR_2$ phosphorylation sites. Therefore, changes in $VEGFR_2$ induced by low dose Cabergoline reversed the occurrence of increased vascular permeability without altering angiogenesis (20). The use of Cabergoline for prevention of OHSS neither reduced pregnancy nor implantation rate (19).

Coasting has proven to be an effective method to reduce the development of severe OHSS in high risk patients. It has been suggested that withholding gonadotropins may increase the rate of granulosa cell apoptosis (21). This may cause atresia of a large number of small follicles, thus leading to a reduction in serum E_2 concentration and vasoactive mediators (22). The decreased serum FSH concentrations down regulates the LH receptors of the follicles, thus making fewer oocytes available for maturation by hCG. At ovarian puncture, oocytes which fail to undergo the final maturation, stick to the follicle wall and are not retrieved. The end result is reduction of chemical mediators that cause hyperpermeability and a reduction in the number of oocytes retrieved (23).

In our study like the studies mentioned above, the number of retrieved oocytes, good quality and mature oocytes, were significantly lower in coasting group. But the percentage of mature oocytes and the fertilization rate were significantly higher in coasting than Cabergoline group. Clinical pregnancy and implantation rate were higher in Cabergoline group.

Since, oocyte quality was not affected by coasting; it seems that the receptivity of the endometrium was affected. Our results, like those of Tortoriello *et al* (1998) and Ulug *et al* (2002) suggest that coasting for > 3 days may reduces the implantation and pregnancy rates (21,24). However, Cabergoline has no teratogenic effects on fetus (25, 26).

In conclusion, coasting is a popular and effective method to reduce OHSS rates, but our study showed that this procedure appears to be associated with a reduced oocyte retrieval rate, and also reduced endometrial receptivity. Cabergoline administration was as effective as coasting for prevention of early severe OHSS. This method is a pathophysiological approach, time-saving and lead to higher pregnancy rate than coasting. However further studies with more cases are needed.

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