P R A C E O R Y G I N A L N E
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"Internal coasting" for prevention of ovarian hyperstimulation syndrome (OHSS) in IVF/ICSI

„Internal coasting" – zapobieganie zespołowi hiperstymulacji w przebiegu IVF/ICSI

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Abstract

Objectives: *To prevent OHSS by interruption of the early stage of stimulation ("internal coasting").*
Design: *Prospective, randomized study.*
Material and Methods: *139 women who had unsuccessfully undergone standard long protocol ICSI procedure, complicated by OHSS of moderate or severe degree. The women were randomized to two groups – 68 undergoing stimulation in which, after 2 days of 225 IU hMG there were 2 days without hMG, and then, for the remainder of the stimulation period, 150 IU hMG. The control group (71 women) received standard doses of hMG, as in the first ICSI cycle. The main outcome measures was the prevalence and severity of OHSS, implantation and pregnancy rates.*
Results: *There were 39 cases of OHSS of moderate (32) and severe (7) degree in the control group and 7 (moderate) cases in the investigated group (p = 0.05).*
No differences were found in the implantation rate and pregnancy rate, the mean number of oocytes fertilized, fertilization rate and the mean number of embryos transferred.
Conclusion: *Stimulation with internal coasting is safe for women at a high risk of OHSS. It does not negatively influence fertilization, implantation or pregnancy rates.*

Key words:: **internal coasting** / **ovarian hyperstimulation syndrome** / **ovarian stimulation** / / **in vitro fertilization** / **embryo transfer** /

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Streszczenie

Stymulacja hormonalna u pacjentek z obrazem policystycznych jajników, poddawanych leczeniu za pomocą technik wspomaganego rozrodu, prowadzić może do rozwoju zespołu hiperstymulacji. Proponowany przez nas "Internal coasting" pozwala na zminimalizowanie ryzyka hiperstymulacji.

Materiały i Metody: *Badaniu poddano 139 kobiet, przygotowywanych do procedury IVF-ICSI z udziałem standardowego długiego protokołu stymulacji, u których wcześniej miały miejsce postaci średniego lub ciężkiego zespołu hiperstymulacji w przebiegu w/w leczenia. W celu wyodrębnienia badanych grup zastosowano proces randomizacji. Grupę badaną stanowiło 68 pacjentek, u których zastosowano następujący protokół stymulacji: 2 dni 225 IU hMG, 2 dni bez podawania hMG, a następnie przez kolejne dni 150 IU hMG. Grupę kontrolną (71 kobiet) stanowiły pacjentki otrzymujące standardowe dawki hMG tak, jak to miało miejsce w poprzednim cyklu leczenia IVF-ICSI.*

Wyniki: *W grupie kontrolnej stwierdzono ponowienie 39 przypadków OHSS (32 – postać umiarkowana, 7 – postać ciężka), natomiast w grupie badanej, podlegającej redukcji dawki hMG jedynie u 7 pacjentek zaobserwowano umiarkowaną postać zespołu hiperstymulacji (p=0,05). Nie stwierdzono znamiennie statystycznych różnic pomiędzy analizowanymi grupami w odniesieniu do ilości zapładnianych komórek jajowych, uzyskanych zapłodnień, ilości transferowanych zarodków, odsetka implantacji czy obecności ciąż.*

Wnioski:: *Stymulacja z zastosowaniem „internal coasting" jest bezpieczną metodą dla kobiet z ryzykiem wystąpienia OHSS. Nie ma ona negatywnego wpływu na zapłodnienie, implantację oraz odsetek ciąż.*

Słowa kluczowe: **zespół hiperstymulacji** / **stymulacja jajników** / / **zapłodnienie pozaustrojowe** / **transfer zarodka** /

Introduction

Ovarian hyperstimulation syndrome (OHSS) is one of the most dangerous complications of induction of ovulation. In some cases (less than 2%) it can result in a potentially life-threatening situation [1].

The pathophysiology of OHSS is still under investigation [2]. Loss of integrity of the mesothelium and loss of fluid from the vessels cause an increase in hematocrit, with consequences as regards clotting [3]. The triggering role of hCG in women with a high level of estradiol (E2) is commonly accepted [4]. Hence it is proposed that the maximal effect of stimulation should not result in more than 15 follicles or an E2 level exceeding 3000 pg/mL [5]. It is also possible to trigger the ovulation by GnRH agonist in the antagonists cycles. To prevent OHSS the following measures are proposed: lowering the gonadotropins doses, H antagonist protocol, early follicular aspiration, "coasting", cancellation of pick-up, reduction of the hCG priming dose, cancellation of embryo transfer and embryo cryopreservation and albumin administration and dopamine agonists administration [6, 7, 8, 9, 10, 11]. According to metaanalysis by Venetis, albumin administration in high-risk patients does not appear to reduce the occurrence of severe OHSS [12].

Aim

We tried to prevent OHSS by interruption of the early stage of stimulation ("internal coasting"). We investigated estradiol levels, numbers of mature follicles, fertilization rate, implantation and pregnancy rates, and OHSS of moderate or severe degree.

Materials and methods

Selection of subjects and stimulation

We chose 139 women who had unsuccessfully undergone our standard long protocol ICSI procedure, complicated by OHSS of moderate or severe degree.

At first, all the women were treated according to our standard long protocol of pituitary suppression with gonadotropin-releasing hormone (GnRH) agonist (Decapeptyl, Ferring GmBH, Germany) from day 14 of the cycle. Fourteen days later, administration of urinary gonadotropin (Menogon, Ferring USA) for ovarian stimulation was started according to the "step down" protocol (225 IU for 3 days and 150 IU in the following days), independently of the woman's age, basal serum FSH concentration and presence or absence of in ultrasonography assessment. Monitoring of follicular growth was carried out by means of a day 8 ultrasound scan and assay of the level of serum E2. Ovum pick-up was performed 35 hours after administration of 7500 or 5000 IU (for patients with Estradiol level above 3000 pg/ml) hCG (Choragon, Ferring USA).

For the next long protocol ICSI procedure the women were randomized to two groups – 68 undergoing stimulation in which, after 2 days of 225 IU hMG there were 2 days without hMG, and then, for the remainder of the stimulation period, 150 IU hMG.

The control group (71 women) received standard doses of hMG, as in the first ICSI cycle. Randomization was based on the generated table of random numbers known only to the administrative staff. They produced the classified file to which the recruited patient was added according to the time of recruitment. The medical staff was informed about the treatment group assignment on the day of the beginning of the stimulation protocol (http://www.randomization.com/).

We perform ICSI for all our patients because, in our hands, this procedure is more effective than IVF. Because in vitro fertilization is totally paid privately we decided not to propose classical IVF for patients. A maximum of two embryos was transferred on day 3 for women younger than 36, and three embryos for older women. Embryo transfer was performed atraumatically using a Wallace catheter under ultrasound guidance with a full bladder.

All subjects received luteal phase support with natural micronized progesterone (Utrogestan; Laboratoires Besins-Iscovesco, Paris, France), 600 mg per day vaginally in three divided dosages, starting on the pick-up day. All women were given 6 mg of estradiol daily for the whole of the luteal phase in accordance with our standard protocol [13].

Verification of pregnancy status and quality was performed on the 16th day after egg collection by assay of serum hCG, progesterone (P) and E2. Clinical pregnancies were defined as the presence of gestational sacs recorded by ultrasonography at 5 weeks and 1 day of gestation. The fetal heart was evaluated at 6 weeks and 1 day. Each time, progesterone levels were checked and progesterone supplementation was regulated accordingly.

OHSS evaluation

For evaluation of the degree of OHSS we followed the criteria described by Rizk and Aboulghar for classification of OHSS [9, 14]. According to these authors OHSS is divided into a moderate category and three categories of severity.

Specimen collection and preparation. Hormone analysis

Fasting venous blood samples (7 mL) were collected aseptically without any additives between 8:00 a.m. and noon on the days required. The blood was allowed to clot at room temperature and the serum was separated by centrifugation. The samples were stored at -20 °C until analyzed. Estradiol, progesterone and hCG levels were determined by chemiluminescence immunoassays (Immulite, DPC, Los Angeles, CA), carried out according to the manufacturer's recommendations. The sensitivities were: E2, 15 pg/mL; P, 0.2 ng/mL; hCG, 1.1 mIU/mL. The intra-assay and interassay coefficients of variation were less than 10% in all assays. Additional blood samples were collected in heparinized tubes for morphological analysis. This was performed immediately after collection by flow cytometry (Micros 60, ABX Diagnostics, Poland).

Table I. Characteristics of the treatment groups.

Variable	Internal coasting group	Control group	p value
No. of subjects = No. of cycles	68	71	NS
Mean (± SD) age (years)	31.3 ± 3.6	31.6 ± 2.5	NS
Mean (± SD) day 3 FSH level (IU/L)	6.2 ± 1.5	5.9 ± 1.5	NS
Mean (± SD) day 3 LH level (IU/L)	6.01 ± 3.7	6.2 ± 2.6	NS
Mean (± SD) BMI (kg/m^2)	20.3 ± 1.5	20.7 ± 2.3	NS
Mean (± SD) duration of infertility (y)	6.3 ± 3.1	5.7 ± 2.4	NS
No. of subjects with the following causes of infertility (%)			NS
Tubal factor	6 (8.8)	5 (7)	
Male factor	19 (28)	17 (24)	
Endometriosis	0 (0)	1 (1.4)	
Anovulation	6 (8.8)	8 (11.3)	
Immunological factor	0 (0)	0 (0)	
Unexplained	30 (44.1)	35 (49.3)	
Mixed factor	7 (10.3)	5 (7)	

NS – non significant
SD – standard deviation
BMI – body mass index

Statistical Analysis

The statistical package STATISTICA StatSoft, Inc. (2010) STATISTICA (data analysis software system), version 9.1. (www.statsoft.com) was used for data analysis. Clinical characteristics were analyzed by using Student's unpaired *t* test. Values are reported as mean ±SD. The χ^2 test was used to assess differences between groups with regard to different rates of development. A value of $p<0.05$ was considered statistically significant.

Results

Patient characteristics are shown in Table I.

No differences were found with regard to mean age, mean day 3 FSH and LH levels, mean BMI, cause of infertility, duration of infertility or presence of primary or secondary infertility.

Table II presents the characteristics of the ICSI cycles of investigated group.

The "internal coasting" group needed a similar dose of hMG as the control group. The serum estradiol level in the investigated group was 2759.8 ± 1445.7 (SD) pg/ml. The control group estradiol level was 4319.3 ± 1099.1, which is statistically significantly higher ($p<0.001$). In addition, the number of follicles ≥14mm in diameter was higher in the control group (22.1 ± 3.9 *vs.* 13.5 ± 6.6; p<0.001). The number of small follicles did not differ between the groups. There was a higher mean number of MII oocytes retrieved in the control group (13.8 ± 4.2 *vs.* 10.5 ± 5.6; p=0.03). No differences were found in the implantation rate and pregnancy rate, the mean number of oocytes fertilized, fertilization rate and the mean number of embryos transferred.

There were 39 cases of OHSS of moderate (32) and severe (7) degree in the control group and 7 (moderate) cases in the investigated group ($p = 0.05$).

Discussion

Coasting is a widely used procedure that significantly decreases the incidence of OHSS. Cancellation of the cycle is also an easy and very safe method to prevent OHSS, but it leads to a need to freeze the embryos, which significantly lowers the cumulative pregnancy rate [15, 16].

In the present investigation we altered stimulation among women at an elevated risk of OHSS. One of the problems of stimulation is that we have to choose between stopping preparation of the endometrium and follicles, and increasing the risk of hyperstimulation. In our new protocol we were not forced to stop stimulation because of the estradiol level. We obtained a lower number of follicles than in the control group, but this did not influence the quality of transferred embryos.

Table II. In vitro fertilization cycles in the "internal coasting" group (ICG) versus their previous cycles and control group (CG) cycles.

Variable	*p* value; ICG cycles/ previous cycles	Previous cycles of the "internal coasting" group	**"Internal coasting" group (ICG)**	Control group (CG)	*p* value; ICG cycles/ CG cycles
No. of cycles		68	**68**	71	
No. of transfers		68	**68**	71	
Mean (± SD) hMG dose (IU)	NS	1605.4 ± 255.2	**1636.4 ± 452.2**	1605.7 ± 295.2	NS
Mean (± SD) day of hCG priming	<0.001	9.4 ± 1.1	**11.9 ± 1.3**	9.8 ± 1.0	<0.001
Mean (± SD) E2 level on the day of hCG priming	<0.001	4086 ± 678.4	**2759.8 ± 1445.7**	4319.3 ± 1099.1	<0.001
No. of subjects with OHSS (%)	<0.001				0.055
moderate		56 (82.3)	**7 (10.3)**	32 (45.1)	
severe A		10 (14.7)	**0 (0)**	7 (10)	
severe B		2 (3)	**0 (0)**	0 (0)	
Mean (± SD) no. of follicles ≥14 mm in diameter	<0.001	24.0 ± 3.2	**13.5 ± 6.6**	22.1 ± 3.9	<0.001
Mean (± SD) endometrial thickness (mm)	NS	11.4 ± 2.7	**12.1 ± 2.5**	11.2 ± 1.3	NS
Mean (± SD) no. of MII oocytes retrieved	<0.001	15.3 ± 2.7	**10.5 ± 5.6**	13.8 ± 4.2	0.03
Mean (± SD) no. of non-matured oocytes retrieved	NS	4.5 ± 2.4	**3.5 ± 2.0**	3.9 ± 3.8	NS
Mean (± SD) fertilization rate (%)	NS	76.2 ± 19.2	**70.6 ± 21.1**	71.8 ± 18.4	NS
Mean (± SD) no. of embryos transferred	0.02	2.0 ± 0.0	**2.3 ± 0.5**	2.4 ± 0.6	NS
No. of pregnancies	-	0	**27**	29	NS
Pregnancy rate (%)	-	0	**39.7**	40.8	NS
Implantation rate (%)	-	0	**22**	28	NS
Multiple pregnancy rate – n (%)	-	0	**7 (25)**	19 (66)	0.06
Ectopic pregnancy (%)	-	0	**0**	0	-
Spontaneous abortion rate – n (%)	-	0	**3 (11.1)**	3 (10.3)	NS

SD – standard deviation

NS – no significant

The aim is to start stimulation effectively. Stimulation with 150 IU is not always effective. On the other hand in very sensitive patients it does not protect against hyperstimulation. With internal coasting we do not have a problem with very long and unsuccessful stimulation. The aim of interruption of HMG dosage is to perform atresia of most of reacting follicules.

Despite the fact that stimulation with internal coasting lasts longer, overall, the same dose of hMG was used as in the control group. The longer stimulation time allows the endometrium to reach a sufficient thickness without a risk of hyperstimulation. The thickness of the endometrium and its time under estradiol influence are probably associated with the "implantation window".

One of the problems regarding coasting is that the lack of FSH influence can cause atresia of the eggs. This is why we did not obtain a good number of mature eggs. Our results indicated that atresia is "digital" in that it is either "on" or "off". Even though there was atresia of some follicles, the remaining ones matured and were fertilized normally. They did not differ from those in the control group and were associated with good implantation and pregnancy rates.

Because the result of our procedure is the atresia of most of reacting follicles but not all we can call it coasting. If it is not effective we could call them 2-day temporary ineffective withholding stimulation.

The investigated group was not greatly afflicted with OHSS. There were only seven cases of (moderate) OHSS in this group (10.3%), compared with 39 cases of moderate or severe OHSS in the control group (54.9%). On the other hand, we transferred higher amount of embryos for susceptible to OHSS patients than

normally. We did it for obtaining right model. This caused the extremely high rate of multiple pregnancies (66%), what could increase the OHSS prevalence in this group.

We did not find the statistical difference in quality of transferred embryos between control and investigated group. We transferred minimum 1 3-days embryo class A or B according to Cummins classification. We could not explain the difference (not significant) between multiple pregnancies ratios. It could be correlated to possible changes in oocytes' genes expressions during internal coasting.

The internal coasting protocol does not fit all of treated patients equally. The duration of the coasting could be probably optimized for different patients.

Because the groups did not differ as regards the implantation rate and pregnancy rate and the mean number of oocytes fertilized, we can affirm that coasting does not negatively influence the most important aspects of infertility treatment.

Conclusion

Stimulation with internal coasting is safe for women at a high risk of OHSS. It does not negatively influence fertilization, implantation or pregnancy rates.

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References

1. Mathur R, Hayman G, Bansal A, Jenkins J. Serum vascular endothelial growth factor levels are poorly predictive of subsequent ovarian hyperstimulation syndrome in highly responsive women undergoing assisted conception. *Fertil Steril.* 2002, 78, 1154-1158.
2. Delbaere A, Smits G, Olatunbosun O, [et al.]. New insights into the pathophysiology of ovarian hyperstimulation syndrome. What makes the difference between spontaneous and iatrogenic syndrome? *Hum Reprod.* 2004, 19, 486-489.
3. Navot D, Bergh P, Laufer N. The ovarian hyperstimulation syndrome. In: Reproductive Endocrinology, Surgery, and Technology. Eds. Adashi E, Rock J, Rosenwaks Z. Philadelphia: *Lippincott–Raven Publishers.* 1996, 2215–2232.
4. Delbaere A, Bergmann P, Gervy-Decoster C, [et al.]. Increased angiotensin II in ascites during severe ovarian hyperstimulation syndrome: role of early pregnancy and ovarian gonadotropin stimulation. *Fertil Steril.* 1997, 67, 1038-1045.
5. Levinsohn-Tavor O, Friedler S, Schachter M, [et al.]. Coasting-what is the best formula? *Hum Reprod.* 2003, 18, 937-940.
6. Homburg R, Insler V. Ovulation induction in perspective. *Hum Reprod Update.* 2002, 8, 449-462.
7. Humaidan P, Quartarolo J, Papanikolaou E. Preventing ovarian hyperstimulation syndrome: guidance for the clinician. *Fertil Steril.* 2010, 94, 389-400.
8. Grochowski D, Wolczynski S, Kuczynski W, [et al.]. Correctly timed coasting reduces the risk of ovarian hyperstimulation syndrome and gives good cycle outcome in an in vitro fertilization program. *Gynecol Endocrinol.* 2001, 15, 234-238.
9. Rizk, B, Aboulghar M. Modern management of ovarian hyperstimulation syndrome. *Hum Reprod.* 1991, 6, 1082-1087.
10. Ben-Chetrit A, Eldar-Geva T, Gal M, [et al.]. The questionable use of albumin for the prevention of ovarian hyperstimulation syndrome in an IVF programme: a randomized placebo-controlled trial. *Hum Reprod.* 2001, 16, 1880-1884.
11. Busso C, Fernández-Sánchez M, García-Velasco J, [et al.]. The non-ergot derived dopamine agonist quinagolide in prevention of early ovarian hyperstimulation syndrome in IVF patients: a randomized, double-blind, placebo-controlled trial. *Hum Reprod.* 2010, 25, 995-1004.
12. Venetis C, Kolibianakis E, Toulis K, [et al.]. Intravenous albumin administration for the prevention of severe ovarian hyperstimulation syndrome: a systematic review and metaanalysis. *Fertil Steril.* 2011, 95, 188-196.
13. Lukaszuk K, Liss J, Lukaszuk M, Maj B. Optimization of estradiol supplementation during the luteal phase improves the pregnancy rate in women undergoing in vitro fertilization-embryo transfer cycles. *Fertil Steril.* 2005, 83, 1372-1376.
14. Rizk B, Aboulghar M. Classification, pathophysiology and management of ovarian hyperstimulation syndrome. In: In-Vitro Fertilization and Assisted Reproduction. Ed. Brinsden P. New York –London: *The Parthenon Publishing Group.* 1999,131-155.
15. Endo T, Honnma H, Hayashi T, [et al.]. Continuation of GnRH agonist administration for 1 week, after hCG injection, prevents ovarian hyperstimulation syndrome following elective cryopreservation of all pronucleate embryos. *Hum Reprod.* 2002, 17, 2548-2551.
16. D'Angelo A, Amso N. Embryo freezing for preventing Ovarian Hyperstimulation Syndrome. *Hum Reprod.* 2002, 17, 2787-2794.