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Risk Factors And Method For Predicting Hyperstimulation Syndrome Ovaries In The In Vitro Fertilization Program

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Abstract.

Ovarian hyperstimulation syndrome (OHSS) is the most severe and life-threatening complication of assisted reproductive technologies. OHSS is based on an excessive ovarian response to ovarian induction; however, the pathogenesis has not been fully understood yet. This occurs under exogenous administration of only chorionic gonadotropin, which serves as a trigger. The most serious complications of OHSS are thromboembolic complications and ovarian torsion. This article describes the risk factors for the development of ovarian hyperstimulation syndrome and proposes a method for individual prediction of the syndrome.

Keywords: in vitro fertilization, infertility, ovarian hyperstimulation syndrome, pregnancy.

Introduction. OHSS is a heterogeneous iatrogenic syndrome that occurs during ovarian induction, when the equilibrium established by feedback mechanisms, which is observed in the natural menstrual cycle, is disturbed by exogenous administration of gonadotropins followed by the administration of chorionic gonadotropin (HCG). HCG as an ovulation trigger plays a key role in the pathogenesis of this complication. Regardless of the level of ovarian response to gonadal stimulation, OHSS does not develop unless an ovulatory dose of HCG is administered [1]. Also, OHSS does not develop in women who got pregnant with a donor egg, despite the high VEGF [3].

During the stimulation of ovulation, many follicles mature. At the final stage of follicular maturation, HCG is administered, which causes massive luteinization of granulosa cells, which, in turn, leads to the production of vasoactive substances such as endothelial vascular growth factor (VEGF). VEGF belongs to the family of heparin-binding proteins that act directly on vascular endothelial cells, cause their proliferation, and ultimately lead to endothelial dysfunction. All these changes are associated with an increase in vascular permeability and the release of fluid from the vascular bed into the third space (abdominal cavity, less

often into the pleural and pericardial cavities). Studies of ascitic fluid in patients with severe OHSS have shown VEGF to be the main agent of vascular permeability.

OHSS independent risk factors.

History of OHSS [6]; polycystic ovary syndrome [6]; anti-Mullerian hormone >3.3 ng/ml and the number of antral follicles >8 [4].

Ovarian response-dependent risk factors.

Number of follicles >20, diameter >10 mm; fast-growing blood estradiol during ovulation stimulation (>3500 pg/ml); a large number of obtained oocytes; the use of CHG as a trigger; pregnancy [8].

OHSS classification

This syndrome has an early and a late form; each of them is HCG-dependent. The early form develops within the first 9 days and is associated with the introduction of exogenous CHG, if pregnancy does not occur, the symptoms rarely progress and spontaneous recovery is observed. In case of pregnancy, the patient's condition may worsen. The late form develops after 9 days and is associated with the onset of pregnancy and the production of natural endogenous CHG.

The classification can also be based on the severity of the clinical signs of the syndrome. There are mild, moderate, severe and critical forms. Table 1.

Table 1. OHSS classification.

Severity	Clinical signs	Biochemical markers
Mild	Abdominal discomfort Mild nausea/vomiting Diarrhea Enlarged ovaries	No clinically significant laboratory changes observed
Moderate	Sonographic signs of ascites	Hemoconcentration (hematocrit >41%) Leukocytosis (>15,000/ml) Hypoproteinemia
Severe	Ascites Severe abdominal pain Severe nausea and vomiting Rapid weight gain (1 kg or more in 24 hours) Pleural effusion Severe shortness of breath Oliguria/anuria	Hemoconcentration (Ht>55%) Leukocytosis >25,000/ml Serum creatinine >1.6 mg/dL Creatinine clearance <50 ml/min Hyponatremia (<135 meq/l) Hyperkalemia (>5 meq/l) Elevated liver enzymes

	Hypotension/low central venous pressure Fainting Venous thrombosis	
Critical	Anuria/acute renal failure Arrhythmia Pericardial effusion Massive hydrothorax Thromboembolism Arterial thrombosis Acute respiratory distress syndrome Sepsis	Deterioration of biochemical parameters

Methods of OHSS prevention.

One of the ways to prevent OHSS may be withdrawal of gonadotropin while continuing suppressing the pituitary gland until serum E2 levels fall within the acceptable range for CHG administration. Replacing the ovulation trigger can also reduce the likelihood of OHSS. Gonadotropin-releasing hormone agonists or a lower dose of CHG may be used as a trigger replacement. With the use of gonadotropin-releasing hormone agonists, this massive luteinization is usually not observed [2]. Such a pronounced effect of CHG is associated with its longer half-life and high biological activity, which is 6-7 times higher than those of endogenous LH.

While the use of recombinant CHG instead of the usual one has not delivered positive results [5]. Cryopreservation of embryos is increasingly considered in cycles with a high risk of OHSS; if the following situations arise, it is worth considering cryopreservation of germ cells or embryos:

1.Patients at risk of OHSS (>20 follicles larger than 10 mm) who had received a GRH agonist as a trigger. These patients have an extremely low risk of moderate or severe OHSS, but the implantation rate is lower due to impaired endometrial receptivity [8].

2. Patients at high risk of OHSS who had been prescribed CHG as a trigger. Such patients are more expedient to undergo cryopreservation of oocytes/embryos to avoid pregnancy and late OHSS, however, such patients still have a high risk of early OHSS.

According to the largest recent study, women with POS have lower OHSS rates (1 versus 7) when transferring frozen embryos compared to fresh embryos [6]. Also, the use of metformin in women with POS may reduce the likelihood of OHSS.

Supporting the luteinization phase with progesterone from the day of oocyte collection or during embryo transfer is associated with lower OHSS levels compared to the alternative approach of intermittent low-dose CHG [7].

The use of dopamine agonists may also be associated with a lower risk of OHSS, which is due to the ability of dopamine agonists to inhibit the phosphorylation of the VEGF receptor and thereby reduce vascular permeability [8].

The main key to preventing this complication is to identify the potential risk in each individual patient and then plan strategies to prevent OHSS. The main steps are to identify risk factors, use individual modes of stimulation of ovulation with the minimum dose and duration of gonadotropin therapy.

Materials and Methods.

During this study, we analyzed 671 treatment cycles in the IVF program for 2009-2018. All patients were divided into 2 groups. Group 1 (N=56) included women who developed OHSS during IVF procedure. Group 2 (N=615) consisted of women who did not have this complication during the IVF procedure. The study was carried out in the ART department of St. Joasaph Belgorod Regional Clinical Hospital. The study used the data of a standard examination before the IVF protocol in compliance with the order of the Ministry of Health of the Russian Federation dated August 30, 2012 No. 107n "On the procedure for using assisted reproductive technologies, contraindications and restrictions on their use", as well as anamnestic data and data of IVF procedure (ovulation stimulation protocol, ultrasound examination data, the number of oocytes obtained). All the observation and examination results were entered into a specially developed questionnaire, and then into a MS Excel spreadsheet. The material was processed by variable statistics using Statistica 10.0. According to the processing results, the values at the level of $p \leq 0.05$ were considered statistically significant. After that, we took only statistically significant indicators and, using the method of discriminant analysis, made a prognosis of OHSS.

Results.

The analysis showed that the incidence of ovarian hyperstimulation syndrome was higher in the group of younger women, 30.76 ± 3.67 years, in comparison with 32.78 ± 4.40 years in the group of patients without OHSS ($p<0.05$).

The analysis of the initial state of the reproductive system has shown that the group of patients with OHSS had a higher level of prolactin: 462.84 ± 191.56 mIU/L in comparison with 363.43 ± 187.84 mIU/L, which corresponded to the group of women without OHSS ($p <0.05$).

Patients with OHSS significantly less often had obesity, in 7.15 ± 1.04% of cases, while none of patients from the group without OHSS suffered from it ($p<0.05$). The study group of patients significantly less often had regular menstrual cycles (83.93 ± 4.91% of cases, in comparison with 93.82 ± 0.97% of cases),

($p<0.05$). The indication for IVF in the group of women with OHSS was more often endocrine infertility (28.57 ± 6.04 cases) in comparison with 15.45 ± 1.46 in the control group; statistically more often the group of patients with OHSS had male factor infertility (48.21 ± 6.68 cases), while in the control group this indicator was found in 33.17 ± 1.90 cases ($p<0.05$). The analysis showed that the group of women with OHSS had an earlier onset of stimulation of ovulation compared with the group of healthy women. Thus, stimulation of ovulation in the study group of patients with OHSS was started with gonadotropin-releasing hormone antagonists on the 8.37 ± 2.13 day of the cycle, while the control group was prescribed gonadotropin-releasing hormone antagonists on the 10.52 ± 5.72 day of the menstrual cycle ($p<0.05$).

During ovulation stimulation, the number of follicles in the group of patients with OHSS was significantly higher: on days 9-10 of the menstrual cycle, on average, there were 7.85 ± 3.89 and 2.6 ± 1.47 follicles in the ovaries in the study and in the control groups, respectively ($p<0.05$). When assessing the number of oocytes obtained by transvaginal ovarian puncture, a higher response to stimulation of ovulation was noted; in the group of patients with OHSS, 22.34 ± 8.10 follicles were obtained, in comparison with 7.31 ± 5.49 follicles in the control group ($p<0.05$).

The next stage of our study was a discriminant analysis for individual prediction of OHSS.

Table 2 presents informative indicators obtained from discriminant analysis according to the severity of the Fisher test (F-test), which exceeds the level of reliability (2.0) and the p-level. Also, Table 2 shows the coefficients of these signs for the possible reference of the studied women to a certain group.

Table 2 Informative signs and their coefficients of discriminant comparative analysis of women with OHSS and control women. F (16.653)=5.5831 p< 0.0000

	F-test	p	Control	OHSS
	(1.654)		p=0.91791	p=0.08209
Number of sampled oocytes	105.54	0.00	0.08	0.47
Number of follicles in the left ovary on the 6th day of the menstrual cycle	36.20	0.00	-0.27	0.66
Number of follicles in the right ovary on the 16th day of the menstrual cycle	30.94	0.00	0.30	0.91
Duration of the menstrual cycle, days	14.69	0.00	0.27	0.36
Endometrium on the 16th day of the menstrual cycle, mm	16.01	0.00	0.60	1.18
Gonadotropins, first day	11.28	0.00	0.16	0.04
ALT, U/l	16.56	0.00	0.33	0.12
Rod neutrophils, %	12.57	0.00	3.90	5.01

AST, U/l	6.00	0.01	1.00	1.13
Leukocytes, $*10^9$/l	5.99	0.01	0.00	0.00
The number of follicles in the left ovary on the 10th day of the menstrual cycle	6.20	0.01	0.27	-0.01
The number of follicles in the left ovary on the 16th day of the menstrual cycle	6.14	0.01	1.17	1.61
Follicle diameter in the left ovary on the 16th day of the menstrual cycle	4.30	0.04	2.58	2.75
Endometrium on the 10th day of the menstrual cycle, mm	3.01	0.05	1.60	1.33
Duration of menstruation, days	1.52	0.02	3.71	3.93
Constant			-59.23	-83.20

For individual prediction of OHSS, we used the following discriminant equation:

$$\mathbf{Y=a_1x_1+a_2x_2+a_3x_3+\ldots+a_nx_n+C,} \qquad \mathbf{(1)}$$

Where:a is the coefficient from Table 1

x is the value of the sign for a particular woman,

C is a constant

Solving this equation with the coefficients for groups with and without OHSS will provide two Y values (for each specific group). If, as a result of solving the above equation, Y in the study group is higher than in the control group, this means that a particular woman has a high risk of OHSS; if Y is less than in the control group, then the risk of OHSS is low.

The total probability of the presented model was 95.97%.

The next step was to study the effectiveness of the presented model.

We have conducted a retrospective study of the data of 250 women, patients of the ART department of St. Joasaph Belgorod Regional Clinical Hospital at the stage of preparation and IVF procedure. According to our data, 15 patients had a high risk of OHSS, and 14 of them had OHSS during the stimulation of ovulation. Thus, the probability of our model turned out to be 93.3%.

Conclusion.

OHSS is the most severe iatrogenic complication of assisted reproductive technologies, therefore it is extremely important to consider risk factors and take timely preventive measures.

Due to our study, we have established a high relationship between the above risk factors and ovarian hyperstimulation syndrome, and proposed a model for predicting this syndrome.

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