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Original Article

Risk Factors and Methods for Predicting Ovarian Hyperstimulation Syndrome (OHSS) in the in vitro Fertilization

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Abstract

Ovarian hyperstimulation syndrome (OHSS) is the most severe and life-threatening complication of assisted reproductive technologies (ART). OHSS is based on an excessive ovarian response to ovarian stimulation; however, the pathogenesis has not been fully understood yet. The most serious complications of OHSS are thromboembolic complications and ovarian torsion. The current study describes the risk factors for the development of ovarian hyperstimulation syndrome and proposes a method for specific prediction of this syndrome. This study was designed to investigate 671 therapeutic cycles in the IVF program during 2009-2018. All patients were divided into two groups. Group one (n=56) included women who developed OHSS during the IVF procedure. Group two (n=615) consisted of women who did not have this complication during the IVF procedure. All the observation and examination outcomes were entered into a specially developed questionnaire, and then into a Microsoft Excel spreadsheet. The data were processed by variable statistics using Statistica 10.0. Analyzing of the recorded data revealed that the rate of OHSS was higher in the group of younger women, aged 30.76±3.67 years, in comparison with those aged 32.78±4.40 years in the group of patients without OHSS ($p<0.05$). The analysis of the initial phase of the reproductive system has confirmed 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 ($p<0.05$). In our results, 7.15±1.04% of cases with OHSS had obesity, while of the patients from the group without OHSS suffered from it ($p<0.05$). OHSS is the most severe iatrogenic complication of ART, therefore it is extremely important to consider its risk factors and take timely preventive measures. This study has established a high relationship between the studied risk factors and ovarian hyperstimulation syndrome and proposed a model for predicting this syndrome.

Keywords: Hyperstimulation Syndrome, in Vitro Fertilization, Infertility, Pregnancy, Ovarian

1. Introduction

Among the causes of female infertility, about 40% are related to anovulation. It is defined as the disruption of secretion of hormones that cause a woman to ovulate and may be part of polycystic ovary syndrome (PCOS) (1). This syndrome, with a range of symptoms and metabolic disorders, affects women's health in the long run and the response of these ovaries in the treatment of infertility depends on weight loss and improvement of metabolic disorders and the type of stimulant drugs (2).

Ovarian hyperstimulation syndrome (OHSS) is a complication of ovulation stimulation in women taking hormonal drugs (3). In this condition, the ovary overreacts to excess hormones and becomes swollen

and painful (4). In most cases, this complication is mild and rarely becomes severe, leading to serious illness or death (5). In this syndrome, the ovaries become swollen and painful. A small number of women may develop severe OHSS.

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 human chorionic gonadotropin (hCG). HCG as an ovulation trigger playing a crucial 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 (6). Also, OHSS does not develop in women who got pregnant with a donor egg, despite the presence of high vascular endothelial growth factor (VEGF) (7).

The etiology of ovarian hypersympathy syndrome has not been fully elucidated (8). However, high levels of hCG, a hormone commonly produced during pregnancy, can be a cause (9). Ovarian blood vessels react abnormally to hCG and begin to leak fluid (10). This fluid stimulates the ovaries and sometimes a large amount of it is transferred to the abdomen (11). During treatment of infertility, hCG acts as a stimulant and causes the adult follicle to release an egg (12). OHSS usually develops within a week after injection of hCG (13). If the patient becomes pregnant during a course of infertility treatment, the OHSS may worsen. Because, the patient's body begins to produce hCG in following the occurrence of pregnancy (14).

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 VEGF. VEGF belongs to the family of heparin-binding proteins that act directly on vascular endothelial cells, causing their proliferation, and ultimately lead to endothelial dysfunction. All these changes are associated with an increment in vascular permeability and 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. Young age (15), low body weight (16), particular ovulation stimulation protocols (17), high estradiol levels (18), rapid elevation in estradiol levels (19), number of the stimulated follicles (20), number of the removed oocytes and the presence of polycystic ovaries are the known risk factors for OHSS (21).

OHSS independent risk factors include: history of OHSS, PCOS (22), anti-Mullerian hormone above 3.3 ng/ml, and the number of antral follicles more than 8 (23). Risk factors related to ovarian response are also included number of follicles >20, diameter >10 mm, fast-growing blood estradiol during ovulation stimulation (>3500 pg/ml), a large number of obtained oocytes, and the use of CHG as a trigger; pregnancy (24).

This syndrome has early and late forms; each of them is HCG-dependent. The early form develops within the first nine days and is associated with the introduction of exogenous CHG, if pregnancy does not occur, the symptoms rarely progress and spontaneous recovery is expected. In the case of pregnancy, the patient's condition may worsen. The late form develops after nine 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 this syndrome consisted of mild, moderate, severe and critical forms (Table 1).

One of the ways to prevent OHSS may be withdrawal of gonadotropins while continuous suppression 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 not commonly observed (7, 23). 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 (25). 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 (24).

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 (22). 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 (26).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 (24). The main key to preventing this complication is to identify the potential risk in each 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. This study aimed to investigate the risk factors and predictive methods of OHSS in the *in vitro* fertilization programs.

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

2. Materials and Methods

During this study, we studied 671 treatment cycles in IVF programs during 2009-2018. All patients were divided into two groups. Group one (n=56) included women who developed OHSS during theIVF procedure. Group two (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. In this study we collected data from standard examination before the IVF protocol in compliance protocols of 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 and IVF procedure data (ovulation stimulation protocol, ultrasound examination, the number of collected oocytes). All the observation and examination results were entered into a specially developed questionnaire, and then into Microsoft Excel spreadsheet.

The data was analyzed by Statistica version 10.0 and in all measurements p-value less than 0.05 was considered statistically significant. Afterwards, based on the statistically significant variables, by using discriminant analysis, the prognosis of OHSS was estimated. Prior to including the patients data in the study, a consent form was obtained.

3. Results

Our findings revealed that the mean age (30.76 ± 3.67) of women with OHSS was significantly less than the women without it (32.78 ± 4.40) (P<0.05). Analysis of the initial state of the reproductive system showed that the group of patients with OHSS had higher prolactin levels (462.84 ± 191.56 mIU/L) compared to 363.43 ± 187.84 mIU/L in the group of women without OHSS. (P<0.05).

Patients with OHSS significantly less often had obesity, (7.15±1.04% of cases), while none of the patients without OHSS suffered from it (P<0.05). The patients group 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 due to endocrine infertility (28.57±6.04 cases) in comparison with 15.45±1.46 casesin the control group. The frequency of male factor infertility (48.21±6.68 cases) in the patients with OHSS was statistically more than the control group that (33.17±1.90 cases) (P<0.05). The data analysis also 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 patients with OHSS was started with gonadotropin-releasing hormone antagonists on the 8.37±2.13 day of the cycle, while the control group the average day that the gonadotropin-releasing hormone antagonists (GRHA) was prescribed was 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 the control groups, respectively (P<0.05). A higher response to stimulation of ovulation was observed in the patients with OHSS, 22.34±8.10 follicles compared with 7.31±5.49 ones in the control group, when assessing the number of oocytes obtained by transvaginal ovarian puncture (P <0.05).

The next stage of the study was a discriminant analysis for individual prediction of OHSS. Table 2 presents the informative indicators obtained from discriminant analysis according to the severity of the Fisher's exact 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. Informative signs and their coefficients of discriminant comparative analysis of women with OHSS and control group demonstrated that F (16.653) equals 5.5831 (P <0.001).

Table 2. The coefficients of signs for the possible reference of the studied women

	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, the following discriminant equation was applied:

$Y=a_1x_1+a_2x_2+a_3x_3+\ldots+a_nx_n+C$, (1)

a is the coefficient from table 1, *x* is the value of the sign for a particular woman, and *C* is a constant.

Solving this equation with the coefficients for groups with and without OHSS provided two *Y* values (for each specific group). Regarding the above equation, *Y* in the study group was higher than in the control group, this means that a particular woman has a high risk of OHSS and if *Y* is less than the control group, meaning the risk of OHSS is low. The total probability of the presented model was calculated 95.97%.

The next step was to study the effectiveness of the presented model. A retrospective investigation on data of 250 women was conducted on the patients of ART department of St. Joasaph Belgorod Regional Clinical Hospital at the stages of preparation and IVF procedure. The findings of this study demonstrated that 15 patients had a high risk of OHSS, and 14 of them had a diagnosed OHSS during the stimulation of ovulation. Thus, the predictive ability of our model turned out to be about 93.3%.

4. Discussion

The demands for IVF is growing, and its challenges are also gradually known. OHSS is a clinical presentation identified by ovarian enlargement, an acute fluid shift from the intravascular space to the third space, thromboembolism, abdominal distention, breathing difficulties (27), *etc*.

Elevated prolactin is another factor associated with ailments classified in Group II of the World Health Organization (WHO) classification for ovulation disorders. This disorder is observed in one percent of female population and the most prevalence age for pituitary adenomas is 2-26 years old (28, 29). On the other hand, one-third of women with irregular menstruation experience hyperprolactinemia (30). Secretion of this hormone follow a rhythmic cycle and increases during sleep, stress, pregnancy, breast irritation, or breast trauma. The high levels of this hormone can also be due to repeated injections to stimulate the ovaries and the stress caused by them (31).

According to the initial concentration of gonadotropins in both groups and alterations in the

number and diameter of follicles, the positive effect of ovarian stimulation was determined. However, the use of gonadotropin-releasing hormone (GnRHa) analogues increases by body mass index (BMI), which may be due to the difference in the prevalence of obesity in the OHSS group compared to the controls (32).

Moreover, researchers have reported that weight gain is normal in postmenopausal women and menopause is associated with lipid profile variations and predominant abdominal fat accumulation (33). Observational studies and clinical trials have shown that estrogen deficiency is associated with increased fatty tissue (34), and low-dose estrogen therapy before 60s can reduce the accumulation of abdominal fat. Sex hormone-binding globulin levels increase the free testosterone level due to estrogen reduction (35). Ovulation-stimulating drugs cause OHSS, which is a potentially fatal disease (36). During this disease, we see symptoms such as incurable vomiting, intravenous rehydration, paracentesis, hypercatabolism, and Proteinuria leading to severe hypoalbuminemia and gradual deterioration of liver function (37, 38). Moreover, albumin level reduction and liver function abnormalities are also reported (37).

OHSS is the most severe iatrogenic complication of assisted reproductive technologies, therefore it is extremely important to consider the risk factors and take timely preventive measures. Our findings revealed a high relationship between the above risk factors and OHSS and it seems to be suggestive of the predicting factors for diagnosis of this syndrome. Thus, with the increased usage of in vitro fertilization techniques, the training programs for elevating the physicians' awareness about the clinical features, complications, and treatment of this disease should be held and it is suggested that in management of the patients with severe OHSS the obstetricians ask for internists consultation.

Authors' Contribution

Study concept and design: S. P. P.
Acquisition of data: V. S. O.
Analysis and interpretation of data: I. N. V.
Drafting of the manuscript: N. V. S.
Critical revision of the manuscript for important intellectual content: S. P. P. and A. V. M.
Statistical analysis: A. V. N.
Administrative, technical, and material support: S. P. P.

Ethics

All the procedures were approved by the Human Ethics Committee at the Belgorod State University, Belgorod, Russia.

Conflict of Interest

The authors declare that they have no conflict of interest.

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