Arch Gynecol Obstet (2015) 292:1145–1152
DOI 10.1007/s00404-015-3723-0

Predictive factors of early moderate/severe ovarian hyperstimulation syndrome in non-polycystic ovarian syndrome patients: a statistical model

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Received: 26 May 2013 / Accepted: 13 April 2015 / Published online: 29 April 2015

Abstract
Purpose To evaluate demographic, medical history and clinical cycle characteristics of infertile non-polycystic ovary syndrome (NPCOS) women with the purpose of investigating their associations with the prevalence of moderate-to-severe OHSS.
Methods In this retrospective study, among 7073 in vitro fertilization and/or intracytoplasmic sperm injection (IVF/ICSI) cycles, 86 cases of NPCO patients who developed moderate-to-severe OHSS while being treated with IVF/ICSI cycles were analyzed during the period of January 2008 to December 2010 at Royan Institute. To review the OHSS risk factors, 172 NPCOS patients without developing OHSS, treated at the same period of time, were selected randomly by computer as control group. We used multiple logistic regression in a backward manner to build a prediction model.
Results The regression analysis revealed that the variables, including age [odds ratio (OR) 0.9, confidence interval (CI) 0.81–0.99], antral follicles count (OR 4.3, CI 2.7–6.9), infertility cause (tubal factor, OR 11.5, CI 1.1–51.3), hypothyroidism (OR 3.8, CI 1.5–9.4) and positive history of ovarian surgery (OR 0.2, CI 0.05–0.9) were the most important predictors of OHSS. The regression model had an area under curve of 0.94, presenting an allowable discriminative performance that was equal with two strong predictive variables, including the number of follicles and serum estradiol level on human chorionic gonadotropin day.
Conclusion(s) The predictive regression model based on primary characteristics of NPCOS patients had equal specificity in comparison with two mentioned strong predictive variables. Therefore, it may be beneficial to apply this model before the beginning of ovarian stimulation protocol.

Keywords OHSS · Non-polycystic ovarian syndrome · Risk factors · Statistical model

Introduction

Ovarian hyperstimulation syndrome (OHSS) is a serious consequence of using hormones in ovulation induction in assisted reproduction techniques (ART). Mild forms of OHSS are common, affecting up to 33 % of in vitro fertilization (IVF) cycles, while the moderate and severe forms may occur in 3–8 and 0.1–5 % of IVF cycles, respectively [1, 2]. The characteristics of this syndrome are cystic enlargement of the ovaries and an acute intravascular fluid shift to the third space, which is caused by increased vascular permeability and ovarian neoangiogenesis triggered by human chorionic gonadotropin (hCG) administrations. Early OHSS (1–9 days after hCG) is related to gonadotropin administration, whereas the late form (10 days after hCG) is the result of placental hCG. The roles of estradiol, luteinizing hormone, hCG, inflammatory

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mediators, the renin–angiotensin system, vascular endothelial growth factor (VEGF), follicle stimulating hormone (FSH) receptor variability [3] and genetic predisposition [4] are already discussed in the pathophysiology of OHSS [3, 5, 6].

In order to prevent the risk of OHSS, it is important to identify the women who are at risk. Prevention of OHSS is a multi-step approach [7]. The new algorithm for prevention of OHSS is based on two decision-making time periods, including primary time period belonging to the follicular phase and the luteal phase, while the secondary time period occurring at four different points of time, like the final day of patient workup, the day of hCG triggering, 1 day after oocyte pick-up (OPU) and the 5 days after OPU [5]. However, the OHSS reducing strategy essentially begins when the physician evaluates the patient's ovarian reserve, as well as the risk for hyperstimulation prior to stimulation [4]. One of the best ways to prevent OHSS is the review of patient characteristics, workup during the follicular phase (baseline) and appropriate management until the ovulation triggering day. The most important keys for primary prevention of OHSS are identification of the risk factors of OHSS and individualization of controlled ovarian stimulation protocols, appropriately [7]. Identifying the OHSS risk factors not only could be useful for a better understanding of its pathophysiology, but also could be helpful for clarifying precautions to reduce the incidence of OHSS. Primary risk factors, including young age, low BMI, polycystic ovarian syndrome and a history of previous OHSS likely cause an increase in the response to ovarian stimulation [3, 8, 9]. Secondary risk factors are as follows: increasing levels of serum E2 (estradiol), number of medium/large follicles $\geq$13 follicles $\geq$11 mm in diameter, high number of oocytes retrieved [1, 3, 8, 9], elevated inhibin A and inhibin B [10], high basal anti-müllerian hormone level >3.36 ng/mL [11], total volume of the ovaries on hCG triggering day [12], history of allergies [2], hypothyroidism [8], hyperprolactinemia [8] and blood group A [13].

As reported, most studies have evaluated the risk factors and the predictive values of OHSS in Western population, but only one study by Rajesh et al. [14], have cited that risk factors of OHSS in Asian population are similar to those in the Western population [14]. So, we considered polycystic ovarian syndrome (PCOS) as well-known and proven risk factor of OHSS in all populations and conducted this study retrospectively to evaluate the variables associated to OHSS in non-PCOS (NPCOS) patients in order to improve preventive strategies in these population. In the present study, we evaluated demographic, medical history and clinical cycle characteristics of infertile NPCOS women with the purpose of investigating their associations with the prevalence of moderate-to-severe OHSS.

Materials and methods

This retrospective study analyzed 86 cases of NPCO patients who developed OHSS while being treated with in vitro fertilization and/or intracytoplasmic sperm injection (IVF/ICSI) cycles during the period of 2 years (January 2008 to December 2010) at Royan Institute. To review the OHSS risk factors, 172 NPCOS patients who were treated at the same period of time with IVF/ICSI or ICSI cycles without developing OHSS (no OHSS) were selected randomly by computer as the control group. The Rotterdam criteria were used for defining PCOS or non-PCOS patients [15]. The study population was limited to cycles of autologous and fresh embryo transfers. At first visit, the demographic, medical and clinical characteristics of patients, including age, BMI, gynecologic and obstetrics history (cause of infertility, ultrasonographic features of ovary, history of ovarian surgery, history of previous renal disease, preeclampsia, allergic diseases, etc.) and routine laboratory tests (FSH, LH, TSH, T4, blood group, etc.) were recorded. In addition, the data of current IVF/ICSI cycle (gonadotropin dose, antral follicle count, estradiol level on hCG day and pregnancy outcomes) of participants were collected. Then, the obtained data of the OHSS and non-OHSS groups were compared. Allergy is defined as the presence or history of any airborne, dermal and food allergies. Ovarian hyperstimulation is classified according to Golan's classification [5]. In our setting, moderate hyperstimulation is managed on an outpatient basis, while patients with severe hyperstimulation are admitted for treatment. We defined OHSS with an onset $\geq$10 days after oocyte retrieval as "late", whereas OHSS with earlier onset as "early" OHSS. Patients with standard long protocol were included. A team of IVF specialists decided the starting dose of gonadotropin for each patient, in non-PCOS patients with antral follicular count (AFC) greater than 12 and under 30 years or patients with previous history of OHSS, we started stimulation with low dose of gonadotropins (150 IU). AFC was evaluated using ultrasonography (US) between day three or five of natural cycle (follicular phase). The patients were monitored days five and seven after gonadotropin stimulation, while the clinician was at liberty to adjust the dose of rFSH according to ovarian response. In our institute in patients with serum E2 level greater than 3500 pg/ml, the half dose of hCG (5000 IU) was used for oocyte triggering. We used progesterone for luteal phase support in all patients. Normal value of serum thyrotropin hormone (TSH) was considered between 0.4 and 2.5 mIU/L [16]. All of hypothyroidism women in the present study were subclinical type with TSH level of 4.5–7 mIU/L, and hypothyroidism treatment were started simultaneously with infertility treatment cycle in

our institution. The clinician decided to freeze all embryos in the some cases of moderate or severe OHSS in order to prevent the further severe complications.

The demographic factors, medical and clinical characteristics of patient and ART cycle-specific parameters, as well as pregnancy outcomes were compared between the two groups using the following different methods: Chi-square test for categorical variables, Student's *t* test for continuous variables when data were normally distributed, and Mann–Whitney *U* test in abnormal cases. In order to build a prediction model, we used multiple logistic regression in a backward manner. Variables of history and basic features of patients, such as age, BMI, blood group, infertility cause, hypothyroidism history, allergy history, ovarian surgery history, and previous history of OHSS were used in construction of logistic regression model. We compared the different logistic regression models by area under the receiver operating characteristic (ROC) curve. An area under the curve (AUC) value of 0.5 indicates no discriminative performance, whereas an AUC value of 1.0 indicates perfect discrimination. Data were analyzed using the SPSS, version 16.0 (SPSS Inc., Chicago, IL, USA).

Results

Among 7073 IVF/ICSI cycles performed from 2008 to 2010 for NPCOS patients, a total of 86 NPCOS patients encountered with moderate-to-severe OHSS were evaluated and compared with 172 NPCOS patients without OHSS event as the control group (Fig. 1).

When clinical and laboratory follow-up of OHSS patients were compared with the control group, the results revealed that some variables, such as age ($p < 0.001$), TSH level ($p < 0.001$), infertility cause ($p = 0.01$), previous history of ovarian surgery ($p = 0.002$), previous history of OHSS ($p = 0.03$), previous history of preeclampsia ($p = 0.03$) and hypothyroidism ($p = 0.001$) have significant statistical differences between the two groups. There were no significant differences in terms of body mass index (BMI) and previous history of allergy between two groups (Table 1). However, after the classification of BMI (<25 and ≥25), there was significant difference in terms of BMI between the two groups, so that 65 % of OHSS patients versus 50 % of the control group had body mass index less than 25 ($p = 0.02$). As shown in Table 1, type and duration of infertility did not influence the OHSS incidence.

Despite the starting and total doses of gonadotropins in the OHSS group being significantly lower than control group, a greater number of follicles ≥12 mm and retrieved oocytes in OHSS group were observed [odds ratio (OR) 1.6, confidence interval (CI) 1.4–1.9, $p < 0.001$; OR 1.9, CI 1.5–2.3, $p < 0.001$; respectively] (Table 2). The mean esteradiol level on hCG day in OHSS group was higher than the control group (3606 ± 1089 vs. 1424 ± 692; OR 1.0, CI 0.9–1.1, $p < 0.001$).

ROC curve analysis revealed that the model based on the serum E_2 level on hCG day had an AUC value of 0.95. Also, logistic regression based on the number of follicles ≥12 mm on hCG day had an AUC value of 0.94, indicating acceptable discriminative performances (Fig. 2). After analysis of prediction of demographic factors only in patients with early-onset moderate-to-severe OHSS, we excluded all late OHSS cases (13 patients) due to twin pregnancy. In the multiple regression analysis based on primary demographic, medical history and clinical characteristics of the non-PCOS patients, some variables, such

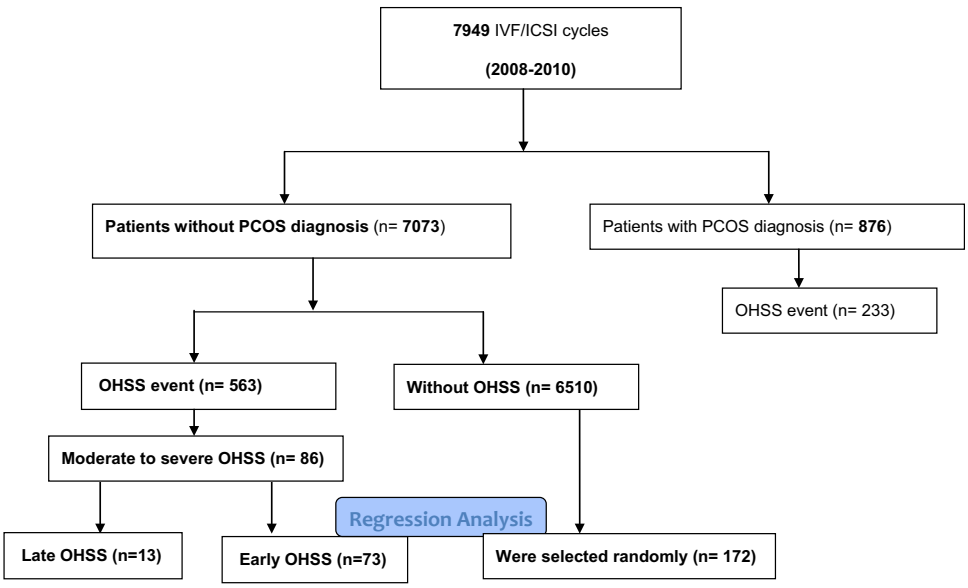

Fig. 1 Chart shows the distribution of patients

Table 1 Comparison of the demographic, medical history and clinical workup characteristics of the patients with OHSS and without OHSS

Variables	With OHSS ($n = 86$)	Without OHSS ($n = 172$)	Odds ratio (OR)	Confidence interval (CI)	p value
Age* (mean ± SD)	28.5 ± 3.9	31.0 ± 5.1	0.8	0.8–0.9	<0.001
BMI (kg/m^2) (mean ± SD)	24.4 ± 3.7	25.1 ± 3.6	0.9	0.8–1.0	0.13
BMI category*, *n* (%)					
<25	56 (65)	84 (49)	Reference group	0.2–0.9	0.02
≥25	30 (35)	88 (51)	0.5		
Basal serum FSH (mIU/ml) (mean ± SD)	5.9 ± 3.3	6.6 ± 3.0	0.9	0.8–1.0	0.08
Basal serum LH (mIU/ml) (mean ± SD)	5.7 ± 4.7	5.2 ± 3.4	1.0	0.9–1.1	0.14
Basal serum TSH* (mIU/l) (mean ± SD)	3.3 ± 2.0	2.2 ± 1.8	1.3	0.1–1.5	0.01
Antral follicles count* (mean ± SD)	14.2 ± 1.6	11.0 ± 1.7	4.0	2.7–5.9	<0.001
Infertility type, *n* (%)					
Primary	83 (96.5)	156 (90.7)	0.4	0.1–1.2	0.11
Secondary	3 (3.5)	16 (9.3)			
Infertility cause*, *n* (%)					
Unexplained	6 (7)	30 (17.4)	1.1	1.0–13.1	0.8
Male factor	59 (68.6)	91 (52.9)	3.6	0.2–5.0	0.04
Tubal factor	11 (12.5)	12 (7.0)	5.0	1.1–22.2	0.03
Ovulatory factor (except PCOS)	3 (3.5)	17 (9.9)	Reference group	–	0.02
Multiple factors	7 (8.1)	22 (12.8)	1.7	0.3–7.9	0.4
Infertility duration, years (mean ± SD)	6.9 ± 3.6	7.4 ± 4.8	0.8	0.9–1.0	0.43
Previous history of OHSS*, *n* (%)	9 (10.5)	6 (3.4)	3.4	1.1–10.7	0.03
Previous history of early OHSS*, *n* (%)	8 (9.3)	1 (0.5)	18.8	2.3–53	0.006
Previous history of ovarian surgery*, *n* (%)	9 (10.5)	48 (27.9)	0.3	0.1–0.6	0.002
Previous history of allergy	8 (9.3)	12 (7.0)	0.8	0.3–2.4	0.6
Previous history of preeclampsia, *n* (%)	3 (3.4)	1 (0.5)	0.1	0.01–1.2	0.07
Previous history of renal disease (%)	4 (4.7)	1 (0.5)	0.1	0.01–1.4	0.03
Hypothyroidism*, *n* (%)	47 (54.7)	38 (22.0)	4.2	2.4–7.5	0.001
Blood group, *n* (%)					0.37
O	28 (32.5)	55 (32)	Reference group	–	–
A	27 (31.5)	72 (42)	0.7	0.3–1.4	0.13
B	23 (26.7)	38 (22)	1.1	0.5–2.4	0.35
AB	8 (9.3)	7 (4.0)	0.5	0.5–5.9	0.28

* Significant differences ($p < 0.05$)

as age, infertility cause, antral follicles count, hypothyroidism, and positive history of ovarian surgery were the most important predictors of OHSS (Table 3). The regression model based on primary demographic, medical history and clinical characteristics of the non-PCOS patients with an AUC value of 0.94 presents an allowable discriminative performance in comparison with two strong predictive variables including the number of follicles and E_2 levels on hCG day, showing no significant differences ($p = 0.6$) (Fig. 2). A statistical formula for calculating the probability risk of OHSS in non-PCOS women was obtained based on the regression model; therefore, using the following model probability formula, we can predict the risk of OHSS in NPCOS women (Fig. 3).

In order to check the prediction capacity of OHSS in NPCOS patients based on the esteradiol level on HCG day; number of follicles ≥12 mm on HCG administration; and primary characteristics of patient, we fitted three logistic regression models to the data and compared them by area under ROC curve. The cut-off values for the serum E_2 level

Table 2 Comparison of ovarian stimulation and IVF/ICSI cycles outcomes in patients with and without OHSS

Variables[a]	With OHSS ($n = 86$)	Without OHSS ($n = 172$)	p value
No. of follicles ≥12 mm (mean ± SD)	24.4 ± 7.3	11.2 ± 3.8	<0.001
Serum E_2 on day of hCG (pg/mL) (mean ± SD)	3606 ± 1089	1424 ± 692	<0.001
No. of oocytes retrieved (mean ± SD)	22.2 ± 6.9	9.9 ± 3.4	<0.001
No. of MII oocytes (mean ± SD)	15.7 ± 7.2	8.4 ± 3.2	<0.001
No. of embryo transferred (mean ± SD)	2.1 ± 0.5	2.3 ± 0.6	0.1
Endometrial thickness at ET day (mean ± SD)	9.6 ± 1.4	10.1 ± 1.7	0.047
Pregnancy rate/ET, *n* (%)	34/64 (53.1)	58/172 (33.7)	0.007
Multiple pregnancy, *n* (%)	7 (10.9)	14 (8.1)	0.7
Live birth rate, *n* (%)	15 (23.4)	33 (19.1)	0.3

[a] Student's *t* test and Chi-square test were used respectively to compare the quantitative and qualitative variables between two groups

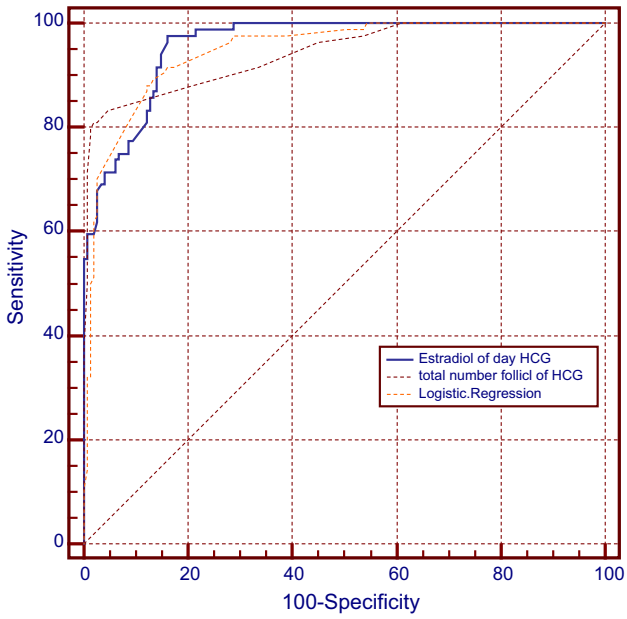

Fig. 2 Comparing the area under the *curves* shows that the predictive performance of the regression model is equal with two strong predictive variables including the total number of follicles and serum E_2 levels on HCG administration

and total number of follicles ≥12 mm on HCG day for OHSS risk were selected based upon each ROC curve, and the corresponding sensitivity and specificity for predicting OHSS are depicted in Table 4.

The overall pregnancy rate in OHSS group was about 53.1 %; this was in correlation with classification of OHSS, so the pregnancy rate in severe cases was higher than moderate OHSS cases (75 vs. 37.1 %) as shown in Table 5.

Discussion

The frequency of moderate-to-severe OHSS observed in this study in non-PCOS patients was 1.2 %. This study attempted to identify the important risk factors of OHSS with regard to non-PCOS patients, while to form a model for probability of OHSS from variables of patient history in the purpose of more accurate prediction. A logistic regression analysis produced four significant prognostic variables, like age, hypothyroidism, history of previous ovarian surgery and infertility cause. Previous history of OHSS and preeclampsia were also considered as significant variables, but were excluded from the model due to lack of significance in association with the other variables. The relationship found between previous history of renal disease and preeclampsia with ovarian hyperstimulation syndrome can indicate the likely impact of renin–angiotensin system activation on creating or accelerating of OHSS. Therefore, more studies with large sample size are required in this field.

Our findings in NPCOS population confirm what has been previously reported that OHSS is more likely among younger women [17–19]. Hypothyroidism is another postulated risk factor for the development of spontaneous OHSS [20–22], but the exact mechanism by which ovarian hyperstimulation syndrome might occur in hypothyroid patients is not clear. We found that hypothyroid NPCOS women are fivefold more at risk for developing OHSS. A possible elucidation suggested by Rotmensch and Scommegna (1989) is on the basis of preferential formation of estriol via the 16-hydroxylation pathway instead of normal 2-hydroxylation [23]. Substitution of estradiol by the less potent estriol leads to decrease feedback regulation, thus excessive gonadotropin released would result in excessive ovarian stimulation [24]. Another explanation suggests low levels of thyroid hormone possibly activate the release of FSH and LH besides the activation of TSH which diminishes FSH activity on FSH receptors, causing gonadal stimulation [23]. In ART cycles, despite levothyroxine treatment in these patients during ovulation induction, the mechanism of hypothyroidism on OHSS process is not clear and needs further large prospective studies.

Our data revealed significant reverse relationship between previous history of ovarian surgery and OHSS

Table 3 The backward logistic regression analysis for predicting the risk of early OHSS based on the primary demographic, medical and clinical characteristics of the non-PCOS patients

Variable	B*	OR[a]	CI[b]	*p*
Age	−0.11	0.9	0.81–0.99	0.007
Antral follicles count	1.4	4.3	2.7–6.9	0.02
Hypothyroidism	1.3	3.8	1.5–9.4	<0.001
Infertility etiology[c]				
Male factor	1.9	6.9	1.2–38.6	0.02
Unexplained	0.1	1.2	0.1–10.9	0.8
Tubal factor	2.4	11.5	1.1–51.3	0.03
Mix factor	1.0	2.8	(0.3–22.7)	0.3
Ovulatory factor	–	Reference group	–	–
Previous history of ovarian surgery	−1.4	0.2	0.05–0.9	0.01

* The beta regression coefficient

[a] Odds ratio

[b] Confidence interval

$$P(OHSS) = \frac{e^{Z}}{1+e^{Z}}$$

$e = 2.71$

$Z = \text{constant} - (B_1 \times VAR_1) + (B_2 \times VAR_2) + (B_3 \times VAR_3) + (B_4 \times VAR_4) + (B_5 \times VAR_5)$

$\text{Constant} = -21$

$Z = -21 + (20 \times 0.1) + (14 \times 1.4) + (2.4) + (1.3) + (0 \times 1.4) = 4.3$

$$P(OHSS) = \frac{2.71^{4.3}}{1+2.71^{4.3}}$$

$P(OHSS) = 0.98$

Fig. 3 A statistical formula for calculating the probability risk of OHSS in non-PCOS women; e.g., we calculated the risk of OHSS in hypothyroid 20-year-old woman with tubal factor infertility and 14 antral follicles count without previous ovarian surgery

occurrence; this may be due to diminished ovarian reserve resulting from surgery. We found that the NPCOS patients with infertility caused by ovulatory dysfunction (age factor, hypogonadotropic hypogonadism, and diminished ovarian reserve) showed the lowest risk for OHSS, and the NPCOS patients with tubal factor infertility revealed the highest risk for OHSS. The patients with male factor, mixed factors and unexplained cause for infertility were at next ranks, respectively.

We found no correlation between BMI and propensity for OHSS, which was in agreement with some previous studies [2, 3, 8, 9, 11] and in contrast to Navot et al. [17]. However, in our study, majority of OHSS patients had BMI less than 25 and this difference with control group was significant; it is possible that patients with BMI less than 25

Table 4 The predictability of regression model and two important OHSS risk factors on HCG day compared by means of ROC curve analysis

Variable	Area under ROC curve (95 % CI)	Cut-off value	Sensitivity (95 % CI)	Specificity (95 % CI)
Serum E_2 level on HCG day	0.95 (0.92–0.98)	2045	96.5 (90.1–99.3)	83.7 (77.0–89.2)
Total number of follicles ≥12 mm on HCG day	0.94 (0.90–0.96)	17	81.4 (71.6–89.0)	98 (94.4–99.6)
Regression model based on primary demographic, medical and clinical history of patients	0.94 (0.91–0.97)	–	88.1 (79.2–94.1)	87.9 (81.6–92.7)

Table 5 Ovarian hyperstimulation (OHSS) grading of non-PCOS patients treated at the Royan institute

OHSS type	No. of patients, *n* (%)	No. of pregnancies, *n* (%)	No. of embryo freeze, *n* (%)
Early onset	73 (84.9)	24 (45.2)	20 (27.3)
Late onset	13 (15.1)	10 (90.9)	2 (15.3)
Grade II	45 (52.4)	13 (37.1)	10 (22.2)
Grade III	41 (47.6)	21 (75)	12 (29.2)
All OHSS	86 (100)	34 (53.1)	22 (25.5)

are at greater risk for OHSS. It seems this subject needs to be further evaluated on large cohort studies.

It has been hypothesized by Enskog et al. (1999) that overactive inflammatory responses with participation of immunomodulatory cytokines are the same as the pathophysiological changes that occur in the ovaries during OHSS [19]. In addition, differences in the immunological sensitivity of patients may be a predictive sign of OHSS. In contrast to the study of Enskog et al. [19], we could not find a relationship between history of allergies and propensity for OHSS. This is probably due to different definitions of allergy in two studies. However, this observation should be examined through biological evaluation of a large cohort study.

Previous history of OHSS was reported as a risk factor for developing OHSS in previous studies. We found significant difference between two groups in this regard, but after adjustment, this difference did not remain significant. The history of moderate and severe OHSS, particularly those with hospitalization history is important and is likely to come back [7]. Unfortunately, we did not document the severity of previous OHSS in patients; it is likely that the severity of previous OHSS in our control group was mild or inappreciative.

Binder et al. (2008) expressed a novel hypothesis that the patients with blood group A may be exposed to a higher risk of OHSS than those with blood group O [13]. The authors hypothesized that this finding could be due to the 25 % reduction of Von Willebrand factor (VWF) and plasma concentrations of factor VIII among individuals with blood group O compared to those with blood group A [13]. In present study, we found no relationship between blood group A and moderate/severe OHSS occurrences in agreement with study of Bellver et al. [25]. In the mentioned study, the authors have indicated that the increase of some coagulation factors in women with OHSS is one of several complications associated with this condition, but it is not the main reason [25]. Further studies are needed to clarify this issue.

In our study, the cut-off levels of E2 level and observed number of follicles greater than 12 mm on hCG day for prediction of OHSS in non-PCOS were 2045 pg/ml and 17 follicles $\geq$12 mm. In a standard protocol for prediction of OHSS, the E2 level greater than 4000 pg/ml and observation of greater than 20 follicles $\geq$11 mm in hCG day were used [26]. However, Papanikolaou et al. [27] reported the number of the number of follicles on the day of HCG administration seems to be a better prognostic variable for the occurrence of severe OHSS than the estradiol values. AUC analysis for several E2 concentrations and number of follicles with a diameter of $\geq$11 mm showed that the predictive value of the optimal threshold of $\geq$13 follicles (85.5 % sensitivity; 69 % specificity) was statistically significantly superior to the optimal threshold of 2560 ng/L for E2 concentrations (53 % sensitivity, 77 % specificity) in identifying patients at risk for OHSS [28]. In this study, Papanikolaou et al. concluded that the combination of a threshold of $\geq$18 follicles and/or E2 of $\geq$5000 ng/L have 83 % sensitivity and 84 % specificity rates for prediction of severe OHSS cases [28]. In our study, the AUC analysis showed that the number of the number of follicles and The E2 concentration on the day of HCG had same predictive values with similar sensitivity and specificity for prediction of moderate-to-severe OHSS cases. It seems that the differences in the cut-off levels were due to differences in studied population, we specially evaluated the non-PCOS patients.

The perfect review of demographic characteristics, medical history and workup profile of non-PCOS patients can significantly predict the development of OHSS in these patients. We found that the advantage of logistic regression was to define the overall model based on primary demographic, medical and clinical history of patients prior to ovarian stimulation. In addition, it provided equally the specificity compared with the other risk factors for OHSS near the completion of controlled ovarian stimulation, namely the E2 levels and number of follicles on the day of hCG administration.

Conclusion

Based on our result, serum E_2 peak concentrations $\geq$2045 and total number of follicles >12 mm on hCG day $\geq$17 may be useful indicator for identifying patients at high risk for moderate–severe early OHSS in non-PCOS women. The performance value of predictive regression model based on primary demographic, medical and clinical history in NPCOS patients had equal specificity compared with serum E_2 level and the total number of follicles on the day of HCG injection. It may be more important to identify the high-risk non-PCO patients before the beginning of ovarian stimulation cycle because we can prevent of severe OHSS by determining the appropriate stimulation protocols [gonadotropin releasing hormone (GnRH) antagonist versus agonist], performing close monitoring, and using the preventive drugs in high-risk patients.

Acknowledgments We would like to extend our special thanks to Ms. Masoumeh Jodmardi for data entry and all participants involved in this study.

Conflict of interest The authors declare no conflict of interest in this article.

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