Int J Clin Exp Med 2016;9(3):6777-6782
www.ijcem.com /ISSN:1940-5901/IJCEM0017740

Original Article

Risk factors, clinical manifestation and therapy strategy for ovarian hyperstimulation syndrome-a retrospective study of 358 patients

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Received October 12, 2015; Accepted January 27, 2016; Epub March 15, 2016; Published March 30, 2016

Abstract: This study aims to investigate the high risk factors, clinical manifestation and therapy strategy of ovarian hyperstimulation syndrome (OHSS) in patients who received ovulation induction. Clinical data of 358 cycles of OHSS patients who received ovulation induction from January 2003 to December 2013, were analyzed retrospectively. The median recovery time of pregnant OHSS patients was 6.54 days longer than that of non-pregnant patients (P<0.001). Patients with hemocrit (Hct) greater than 40% were 2.76 times more likely to experience more serious OHSS than people with Hct less than 40%. The use of human chorionic gonadotrophin (HCG) was not a risk factor in the median recovery time and the severity of OHSS. Plasma expanders such as hydroxyethyl starch, low-molecular dextran and human serum albumin through restoration of effective blood volume were the most successful treatment. Paracentesis was necessary for critical OHSS patients with severe ascites and hydrothorax. Diuretic therapy should be cautiously used in OHSS patients. The most serious complication of OHSS was thromboembolism. The use of HCG may not be a trigger factor of OHSS. Pregnancy and the level of Hct were risk factors of the recovery time and the severity of OHSS. Anticoagulant therapy is critical given the hypercoagulatory state of OHSS. In summary,.....

Keywords: Ovarian hyperstimulation syndrome, risk factor, clinical manifestation, therapy

Introduction

Ovarian hyperstimulation syndrome (OHSS) being an iatrogenic complication resulting from ovulation induction in assisted reproduction technology (ART) treatment, is characterized by marked ovarian enlargement and acute third space fluid sequestration that almost always develops after HCG administration or in early pregnancy. The incidence of moderate OHSS is estimated to be between 3 and 6%, while the severe disease occurs in 0.1-3% of all cycles [1, 2]. It may result in a potentially life-threatening situation. The mortality risk is estimated to be 1 in 450000 to 500000 cases [3]. The pathogenesis of OHSS is complex and its etiology is still unclear. It has been recognized that either exogenous or endogenous HCG may be one of the triggering factors [4].

It has been demonstrated that there are two clear patterns in the onset of OHSS. Early OHSS is correlated to ovarian response to stimulation and is an acute effect of exogenous HCG administration, usually occurring within 9 days after oocyte retrieval. In contrast, late OHSS occurs after the initial 10-days period and is only poorly correlated to the ovarian response and is rather more correlated to the endogenous HCG produced by and implanting embryo or to the administration of HCG for luteal phase support (LPS) [5]. The two patterns of OHSS may be different in the course and severity of disease. In our paper, we retrospectively analysed 358 patients diagnosed with OHSS and admitted to our hospital aimed to investigate the clinical characteristics and treatment of OHSS.

Materials and methods

Patients

During January 2003 and December 2013, a total of 358 patients were admitted to depart-

Table 1. Patient clinical characteristics

Number of patients	358
Age (years)	29.9±3.2
Body mass index	21.3±3.5
Tubal factor	127 (35.5%)
Male factor	14 (3.9%)
Ovulatory factor	201 (56.1%)
Idiopathic infertility	20 (5.5%)
Use of HCG for ovulation induction	307 (85.75%)
Intrauterine pregnancy	129 (36%)
Ectopic pregnancy	5 (1.39%)
Bloating	355 (99.17%)
Abdominal pain	55 (15.36%)
Gastrointestinal symptoms	63 (17.6%)
Oliguria	153 (42.73%)
Electrolyte imbalance	18 (5%)
Elevation of liver enzyme	14 (3.9%)
Renal impairment	11 (3.07%)

ment of gynecology, Obstetrics and Gynecology Hospital of Fudan University for treatment of OHSS. All of these patients were infertility, the mean age was (29.9±3.2, from 21 to 40 years old. Among these patients, 206 (56.9%) were primary infertility, diagnosed as the inability to conceive after 12 months of frequent coitus and the patient had never conceived before, 152 (43.1%) were secondary infertility diagnosed as the inability to conceive after 12 months of frequent coitus and the patient had been pregnant before. Mean BMI were (21.3±3.5 kg/m^2) (18-24 kg/m^2). The cause of infertility was as follows: tubal (35.3%), male factor (3.9%), ovulatory (56.2%), unexplained (4.6%). The clinical characteristics of patients were shown in **Table 1**.

Classification of OHSS

The criteria by Golan et al were used to assess the severity of OHSS [6]. Moderate OHSS is characterized by abdominal distension and discomfort, nausea, vomiting or diarrhea, enlarged ovarian size (5-12 cm), and ultrasound evidence of ascites. Severe OHSS is characterized by variable ovarian enlargement; massive ascites ± hydrothorax; hemocrit >45%; white blood count >15,000/Ul; oliguria; creatinine 1.0-1.5 mg/dl; liver dysfunction; and anasarca. Once there was hemocrit >55%, renal failure, thromboembolic phenomena, or acute respiratory distress syndrome (ARDS), critical OHSS was diagnosed. In our study, 2 patients diagnosed as mild OHSS, 154 were moderate OHSS, 198 were severe OHSS and 4 were critical OHSS.

Ovulation induction protocol

4 patients used only clomiphene citrate; 3 patients used only human menopausal gonadotropin (HMG); 1 patient administrated bromocriptine; 6 patients used only HCG; 7 patients used clomiphene citrate plus HMG; 17 patients used clomiphene citrate-HMG-HCG regimen; 1 patient used letrozole-HMG-HCG regimen; 50 patients treated by HMG-HCG protocol; 4 patients used HMG-LHRH (luteinizing hormone-releasing hormone) regimen; 1 patient received donated ovum; 264 patients received controlled ovarian stimulation (COH) using gonadotropin-releasing hormone (GnRH) agonists (long protocol). 264 OHSS occurred 1-9 days after HCG administration and 43 OHSS occurred longer than 10 days after HCG administration. And 51 OHSS occurred without HCG administration.

Pregnancy outcomes

Among all these patients, 129 patients were diagnosed as intrauterine pregnancy, and 12 were twin pregnancy, 3 were multiple pregnancy. 5 patients diagnosed as ectopic pregnancy, and 1 patient received emergency surgery due to heavy internal hemorrhage. 12 patients were naturally aborted, 3 patients received therapeutic abortion.

Clinical manifestation

355 patients complained of bloating abdomen, 55 patients presented as abdominal pain, 63 complicated gastrointestinal symptoms, 153 patients characterized as oliguria, 356 patients had ultrasonic evidence of ascites, 194 patients presented as massive ascites + hydrothorax. All of these patients characterized by variable ovarian enlargement as the diameter of ovary larger than 5 centimeters.

Laboratory tests

109 patients with hematocrit 40-45%, 29 patients hematocrit 45-50%, and 10 patients with hematocrit >50%. 18 patients showed water and electrolyte disturbance: hypokalemia 4, hyperkalemia 2, hyponatremia 12, hypochloremia 3 and hypernatremia 1. 14 patients complicated liver dysfunction, 11 patients with creatinine >1.0 mg/dL.

Complication

1 patient had acute pulmonary edema, 1 subject received emergency surgery due to internal hemorrhage diagnosed as ectopic pregnancy, 1 patient diagnosed as coagulopathy, 1 subject suffered from deep venous thrombosis and 1 patient died from cerebral embolism.

Statistical analysis

Data was analyzed using SAS 9.4 statistical software (SAS Institute Inc., Cary, North Carolina, USA) and results for normally distributed continuous variables were expressed as mean ± SD and continuous variables with non-normal distribution were presented as median (interquartile range). Categorical variables were expressed as frequency and percentage.

The outcome variables of interest were recovery time, duration of hospitalization and severity of OHSS. The independent variables of interest were whether administration of HCG, the pattern of OHSS (early or late OHSS), outcome of pregnancy and the level of Hct. Linear regression models were used for continuous variables recovery time, duration of hospitalization and expressed as coefficient and odds ratio with corresponding 95% confidence interval. Logistic regression models were used for categorical variable severity of OHSS and expressed as odds ratio with corresponding 95% confidence interval. Univariate linear regression and univariate logistic regression were used to examine the effect of whether administration of HCG, the pattern of OHSS, outcome of pregnancy and the level of Hct on remission time of disease and severity of OHSS. After including whether administration of HCG, the pattern of OHSS (early or late OHSS), outcome of pregnancy Hct without adjustment for other variables. Multiple linear regression and multiple logistic regression were also used to investigate the independent effect of each variable on remission time of recovery time, duration of hospitalization severity of OHSS with adjustment for other variables. $P<0.05$ was considered significant.

Results

Monitoring indicators

The amount of excreted urine, body weight and abdominal circumference were monitored every 24 hours. A complete blood count with hematocrit, liver and renal function parameters, coagulation tests and level of D-dimer were measured on 2-3 days basis in all patients. Ultrasound evidence of ascites and hydrothorax were evaluated every 2-3 days.

Expansion treatment

356 subjects received plasma volume expansion once daily, mainly with hydroxyethyl starch solution and dextran. Dextran was administrated in 183 patients, 97 subjects administrated with dextran plus albumin. 24 patients received hydroxyethyl starch solution and dextran combined with albumin. 5 subjects administrated hydroxyethyl starch solution only. 2 patients used dextran and plasma, 5 patients received dextran, albumin and plasma, 5 subjects administrated hydroxyethyl starch solution combined with plasma, 37 patients used hydroxyethyl starch solution and dextran. Dextran and hydroxyethyl starch solution were administrated intravenously 500-1000 ml once daily, albumin was given 20-30 g once daily in case of hypoproteinemia and plasma was given 200 ml once when all those above agents not work. Plasma volume expansion was continued until 1-3 days after recovery of the hemoconcentration (hematocrit <40%). It took 3-43 days for the use of expansion treatment in all these subjects.

Paracentesis

Pracentesis of ascitic fluid was indicated in patients with severe discomfort or compromised pulmonary function (eg tachypnea, hypoxia, hydrothorax) and in those who remain oliguria despite adequate rehydration. A transabdominal approach was used. 1500-2500 ascitic fluid was drained once according to patient's complaints. The procedure can be repeated every 3-5 days. Total of 39 patients received paracentesis, among them 21 were pregnant and 18 were non-pregnant, 7 subjects drained ascitic fluid more than 5000 ml altogether.

Diuretic therapy

Diuretic therapy was cautiously used only after having started with the correction of intravascular volume and rehydration of the OHSS patients complained of oliguria/anuria with the hematocrit level less than 38%. Low-dose of

Table 2. Risk factors predictive to the recovery time of OHSS

	Univariate		Multivariate	
	β	*P*	β	*P*
HCG	1.02 (-0.89-2.94)	0.295	1.30 (-0.26-2.85)	0.102
Pregnancy	6.54 (5.33-7.76)	0.000	6.08 (4.93-7.23)	0.000
Age	0.05 (-0.12-0.22)	0.535	0.04 (-0.10-0.17)	0.601
Hct level	1.75 (0.35-3.16)	0.015	1.26 (0.10-2.43)	0.034

Table 3. Risk factors predictive to the severity of OHSS

	Univariate OR (95% CI)	Multivariate OR (95% CI)
HCG	0.79 (0.43-1.45)	0.77 (0.39-1.49)
Pregnancy	1.78 (1.14-2.79)	1.63 (0.99-2.67)
Age	1.03 (0.98-1.09)	1.03 (0.97-1.09)
Hct level	2.99 (1.84-4.83)	2.76 (1.65-4.61)

furosemide (5-10 mg) or mannitol (250 ml) was used in 36 severe OHSS patients.

The recovery time

2 mild OHSS patients naturally relieved in 3 days after admission. 201 patients relieved in 7 days after treatment, 113 patients relieved in 7-15 days, 42 subjects relieved more than 15 days, one patient died from cerebral embolism, one patient entered into ICU because of acute pulmonary edema. The length of stay ranged from 2 to 66 days.

Parameters predictive for the recovery time

The median recovery time was 8 days. We analyzed whether pregnancy, use of HCG for ovulation induction, level of hematocrit and age was predictive factor of recovery time (**Table 2**). Univariate analysis showed pregnant patients (n=134, 37.4%) revealed a significantly longer median recovery time than non-pregnant patients (n=224, 62.6%, regression coefficients 6.75, P<0.001). Multivariate analysis verified these results. It means the mean recovery time of pregnant patients was 6.54 days longer than that of non-pregnant patients (**Table 2**). Whether the use of HCG and age was not a risk factor in the median recovery time (P>0.05).

Parameters predictive for the severity of OHSS

In the univariate logistic regression, pregnancy and the level of hematocrit were associated with severity of OHSS (**Table 3**). The results of multiple logistic regression reported similar results. Patients with Hct great than 40% were 2.76 times (**Table 3**) more likely to experience more serious OHSS than people with Hct less than 40%. However, the effect of pregnancy on severity of OHSS revealed a marginal trend toward significance (P= 0.051) after adjusting for other variables.

Discussion

It has been known that HCG stimulates final follicular maturation, induces luteinization, and may stimulate the ovarian secretion of vasoactive substances that cause increased papillary permeability. It is accepted that either exogenous or endogenous HCG is one of the trigger factors in the development of OHSS [7]. However, in this retrospective study, use of HCG for ovulation induction was found not a predictive factor of the recovery time and the severity of OHSS. This result was contradictory to the accepted view [8]. In our data, the median recovery time was eight days. Our data demonstrated that 51 OHSS patients did not receive administration of HCG and one patient developed into critical OHSS and died of cerebral thrombosis. Compare to the patients using HCG, the pregnancy rate was higher in patients without using HCG, but difference was not significantly. Endogenous HCG production by pregnancy may be the trigger factor of development of OHSS; however, it could not identify the reason for those non-pregnant patients without using HCG. The reason why without using HCG could not prevent the development of OHSS may be that many oocytes produced high levels of estrogen by hyperstimulation of gonadotropin which could induce endogenous LH surge resulted in spontaneous ovulation without exogenous administration of HCG. Spontaneous ovulation resulted in luteinization of granulosa cells. Ovarian factors include vasoactive cytokines and proinflammation cytokines secreted by hyperstimulated ovaries may be involved in the increase of capillary permeability and pathophysiology of OHSS. This may be the reason why OHSS cannot be totally prevented by withholding HCG.

As recently reviewed, pregnancy substantially increases the risk for OHSS and this is thought to be due to an increase in endogenous HCG. Our study demonstrated that pregnancy and the level of hematocrit were independent risk

factor of the severity of OHSS. The recovery time in pregnant patients was 6.54 days longer than that of non-pregnant patients. Where pregnancy occurs, the course may be more prolonged and there is a risk of increased severity due to endogenous HCG stimulation.

Hemoconcentration was a major clinical manifestation of OHSS due to the extravasation of fluid from the vessels into the third space. Patients with hemoconcentration were in danger of thromboembolic phenomena which was deadly complication of OHSS. It is reported that hemoconcentration established by an increase of hematocrit of more than 35% on the day of oocyt pick-up was more likely to result in OHSS [9]. Our study confirmed that the level of hematocrit was a risk factor in the severity of OHSS, and the patients with Hct great than 40% were 2.76 times more likely to experience more serious OHSS than people with Hct less than 40%.

Since the precise pathogenesis of OHSS has not been fully understood, treatment is largely empirical. Once OHSS is diagnosed, patients should be treated symptomatically and be carefully monitored, the second complications especially thrombosis should be avoided.

Conventional management of OHSS is focused on supportive until the spontaneous resolution of the condition. The standard of care for treatment-monitoring of appropriate clinical parameters, fluid balance management, thrombosis prophylaxis and ascites treatment-should prevent severe morbidity in most cases.

Weight, abdominal girth recording and strict input/output recording which were the first signs of fluid retention should be monitored daily. Increasing weight and girth with output lagging behind intake are signs of worsening fluid retention. Conversely, an increased urine output and negative fluid balance is an early sign of recovering from OHSS. It is reported that most cases will resolve in two weeks. Our study demonstrated that the mean recovery time of non-pregnant patients was 5.62±3.1 days, among these patients 71.4% patients (170/238) resolved in one week, 25.6% patients (61/238) in 7-14 days and 3% patients (7/238) resolved in longer than 2 weeks.

Patients require intravenous fluid management to address the acute need for volume expansion while also considering the marked increase in vascular permeability. Correction of hypovolemia, hypotension and oliguria has highest priority, accepting that fluid administration may contribute to the accumulation of ascites. The administration of plasma volume expanders is the key treatment in OHSS patients. Colloid solution such as dextran, hydroxyethyl starch solution, albumin and fresh-frozen plasma was most commonly used. Dextran 40 is effective for antithrombotic infusion and is a good plasma expander with a strong hemodilution effect and is thought to be best for already-established OHSS. Hydroxyethyl starch which has a prolonged biological half-life is safe, biohazard free and cost-effective and is an efficient plasma expander which widely used in recent time. Albumin is expensive and as it is protein in-nature, anaphylactoid reactions with albumin have been reported. The ideal colloid solution for treatment of severe OHSS has not yet been determined. Our study demonstrated that 356 patients received plasma expander such as dextran 40, hydroxyethyl starch and albumin infusion. Hydroxyethyl starch solution combined with dextron 40 were the first choice for volume expansion. Albumin was preferred in patients who were hypoproteinemia and those who received paracentesis because of protein lost.

Tension ascites, resulting in respiratory distress, may be a life-threatening condition. Drainage of ascites has been shown to be symptomatically helpful. Ultrasonographically guided paracentesis is advisable to avoid the small risk of injury to ovaries and bowel. Current indications for paracentesis are based on symptomatic complaints of dyspnea, abdominal distension and pain, or oliguria. It should be aware that there are small risk of the abdominal infection and torsion of enlarged ovaries during paracentesis. Our experience showed that a marked relief of compression symptoms occurred after removing the first 1000-2500 ml of ascitic fluid. In our study, 36 patients received paracentesis to relieve symptom. The percentage of paracentesis is higher in pregnant patients than non-pregnant patients. And there was no significant difference in early OHSS and in late OHSS.

Diuretics therapy is usually contraindicated in patients with hemoconcentration as these patients are intravascular volume depleted secondary to capillary leak. After the patient is hemodynamically stable and their hemocon-

centration state has resolved (hematocrit <38%), low dosage of diuretics in combination with colloids may be considered to mobilize the third-space edema. Our study demonstrated that 153 patients complained of oliguria and after adequate infusion of colloid solution the urinary output of 36 patients (23.5%) were less than 500 ml 24 hours. And low dosage of diuretics (furosemide 5 mg I.V. and mannitol 250 ml I.V.) was administrated.

Thromboembolism prevention is critical given the hypercoagulatory state of OHSS. In our study, 1 patient died of cerebral embolism and we generally recommend anticoagulants such as heparin 5000 U subcutaneously once daily.

OHSS may be more unpredictable in severity and course in women who are pregnant. If an early pregnancy has been diagnosed in the patient with critical complications of OHSS such as embolism, acute pulmonary edema, the pregnancy may need to be terminated to prevent further deterioration of her condition. In our study, 3 critical patients received therapeutic abortion and resolved in 1 week.

Experience with ovulation induction therapy and knowledge OHSS pathophysiology and clinical features are key to prevent and managing OHSS. HCG may not be trigger factor in development of OHSS, and the patients without administration of HCG should also be respected for its potential to cause critical morbidity or even death. Pregnancy and the level hematocrit are independent risk factor of the severity and course of OHSS. Further prospective studies are needed to establish protocols for OHSS prevention and treatment.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (NSFC No. 81300466, Luo XZ) and Shanghai Municipal Science Foundation (Project No. 13ZR1404500, Luo XZ).

Disclosure of conflict of interest

None.

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