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Evaluation of polycystic ovary syndrome patients treated for OHSS

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Abstract

We aimed to present the management, hospitilization time, pregnancy rates and complications of our polycystic ovary syndrome (PCOS) patients that we treated for OHSS in our clinic. Therefore this study is designed by analyzing of retrospectively collected data of 31 PCOS patients who were treated for OHSS. Diagnosis of PCOS is based on Rotterdam criteria that is published in 2003 and OHSS diagnosis is based on classification that is formed by Golan et al. GnRH (Ovitrelle® 250 mcg subcutan) is used for final maturation of oocytes. Same protocol is used for all patients at hospitalization. Results showed that GnRH agonist protocol is used for 23 patients and GnRH antagonist protocol is used for 8 patients. 8 patients (%25) were mild, 19 patients (%61) were moderate and 4 patients (%1,2) were severe OHSS. 13 patients (%42) were early onset OHSS and 18 patients (%58) were late onset OHSS. Mean oocyte counting was 21±6,3. Total freezing is used for 13 patients (%42) pregnancy is resulted for 13 patients. Mean total transvaginal aspiration liquid volume was 4800cc ±1786 cc in hospitalization. Abortion is not induced for any patient. Require for intensive care or mortality is not resulted at any patient. Mean hospitalization time was 7±2,6 days. We concluded that altough a lot of strategies are performed recently to prevent OHSS, it is still a problem. Early diagnosis and prevention of severe OHSS is very important to prevent fatal complications.

Keywords: OHSS, PCOS, Dopamin agonist, Cabergoline, Assisted Reproductive Techniques

1. Introduction

Ovarian hyperstimulation syndrome (OHSS) is often an iatrogenic complication often assisted reproductive techniques (ART). It is characterized with ovarian cystic enlargement, fluid accumulation from intravasculer area to the third space due to increased capillary permeability and ovarian neo-angiogenesis (1). It occurs in approximately 1-14% of ART cycles and the mortality is reported as 3/100,000 (2). Despite the common use of antagonist cycles recently, OHSS still emerges as an important complication of ART. Polycystic ovary syndrome (PCOS) and age is a major risk factor for OHSS (3).

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Despite the long-term clinical experience, OHSS pathophysiology is still not fully understood (4). Beccause there is not a specific treatment of OHSS, treatment is based on the type and severity of symptoms and varies, in rare circumstances termination of pregnancy is needed. So the prevention of OHSS is more important than the treatment. Prevention of OHSS strategies include; preference of antagonist stimulation, coasting, triggering of oocyte maturation by gonadotropin-releasing hormone (GnRH), in vitro maturation (IVM), blastocyst single embryo transfer, dopamine agonists (cabergolin®), human albumin, total freezing and cycle cancellation (5). Management of patients who have risk for OHSS sometimes emerges as a diffucult problem for clinicians and patients. In this context, knowledge of the treatment and possible

complications in OHSS is important. In this study we aimed to present the management, hospitilization time, pregnancy rates and complications of our polycystic ovary syndrome (PCOS) patients that we treated for OHSS in our clinic.

2. Material and methods

This study is designed by analyzing of retrospectively collected data of 31 PCOS patients who were treated with controlled ovarian hyperstimulation(COH) and complicated OHSS, between December 2009 and September 2014. Diagnosis of PCOS is done according to the Rotterdam ESHRE / ASRM criteria that is published in 2003; Oligomenorrhea/ amenorrhea, proven by clinical or laboratory hyperandrogenism, polycystic ovaries (12 or more and antral follicle count in each ovary) at transvaginal ultrasonography (TV-USG).

Diagnosis is done with the presence of two or more criteria (6). 23 patients underwent GnRH agonist protocol and eight patients underwent GnRH antagonist protocol. GnRH (Ovitrelle® 250 mcg subcutan) is used for final maturation of oocytes. Al patients were informed about total freezing. Diagnosis of OHSS is done by the classification of Golan et al: mild OHSS Grade 1 (abdominal distantion and discomfort), Grade 2 (in addition to grade 1 nausea, vomiting or diarrhea, and 5 cm to 12 cm expansion of the ovarian volume), moderate OHSS Grade 3 (presence of ascites in the ultrasound findings, in addition to mild OHSS), severe OHSS grade 4 (in addition to moderate OHSS symptoms of dyspne or hydrothorax), grade 5 (in addition to the previous findings changes in blood volume, hemoconcentration due to increased blood viscosity, coagulation abnormalities, renal dysfunction)(7).

Early and late onset OHSS is described by the classification of Carizz et al. Early onset OHSS is defined as the OHSS developed in the first 10 days after oocyte pick-up and late OHSS is defined as OHSS developed 10 days after oocyte pick-up (8). Patients with mild OHSS was followed ambulatory by a two-day intervals. Patients with moderate and severe OHSS were hospitalized. After obtaining informed consent from patients enumerated below management protocol was applied.

1.Ringer lactat 1000cc twice a day
2.Input and output of fluid
3.Measurement of abdominal circumference
4. Weight measurement
5.Total blood count, albumin, blood urea and creatinin, liver function tests and coagulation tests
6. Diet rich in protein
7. Dopamine agonist cabergoline is started 1 mg/day to all patients at oocyte pick –up and is used for 10 days.
8. Enoxaparin sodyum0,4 mg/day subcutaneous is used in patients with moderate and severe OHSS during treatment. In pregnant patients it is continued until 12.gestational week.
9. Maximum 2000cc transvaginal fluid aspiration (TVFA) through the cul de sac with the ultrasound guidance was performed daily to symptomatic moderate and severe OHSS patients.
10.Cefazolin sodium 1gr/day is started at the day of TVFA.

Hospitalized patients were monitored daily. Discharge criteria were defined as hematocrit <40% two days apart and absence of any symptoms without any treatment. At the 14. day ß-hcG is tested to all patients. Statistical analysis was performed by MedCalc statistical software (MedCalc Software, Ostend, Belgium).

3. Results

Demographic data of the patients are summarized in table 1. 8 patients (%25) were mild, 19 patients (%61) were moderate and 4 patients (%1,2) were severe OHSS. 13 patients (%42) were early onset OHSS and 18 patients (%58) were late onset OHSS. Mean oocyte counting was 21±6,3 at oocyte pick-up. Embryo transfer was canceled and the total freezing was performed to 13 patients (42%) due to moderate or severe OHSS. Embryo transfer was performed to 18 patients (58%) of 31 patients who were incorporated to study. The average number of transferred embryos was 2 ± 0.48. Pregnancy is resulted at 13patients (%42). Pregnancy continued to birth at 10 patients (76,9%). Three patients (23,1%) had missed abortion in the first trimester. The most frequent symptom in patients with abdominal distension and pain.

Ascites is detected in 23 patients and pleural effusion is detected in 6 patients. The average hematocrit values of the patients was 42 ± 5.8%. 14 patients underwent TVFA during hospitalization. Total transvaginal liquid aspiration amount was average 4800cc±1786cc.

Human albumin is transfused to four patients(1.2%) due to low albumin levels. Mean albumin of all patients was 2,32. Thoracic fluid aspiration is not performed for any patient. Abortion is not induced for any patient. Require for intensive care or mortality is not resulted at any patient. Mean hospitalization time was 7±2,6 days.

Table 1. Demographic data of the patients

Age	29,29±3,9(23-37)
Infertility time	7,3±2,9(3-13) yıl
Body mass index (BMI)	27,5±3,4 (19-33) kg/m2
Etiology of infertility	Oligo-anovulation

4. Discussion

It is worth to say that protection is the most appropriate approach in the treatment of OHSS actually, in the prevention of it the patients must be strictly selected and individualized strategies should be used. Type of hyperstimulation and to avoid hCG for the final oocyte maturation are of the most important steps to prevent OHSS (9). Usage of GnRH agonist is related with increased risk for OHSS (10). The incidence of severe OHSS found to be significantly less frequent in antagonist protocol than agonist protocol in Cochrane review (11). In our study we used GnRH agonist protocol for 23 patients and used GnRH agonist protocol for 8 patients. GnRH(Ovitrelle® 250mcg, subcutane) is used for final oocyte maturation in all patients. It has been shown in several studies that cabergoline the dopamine agonist inhibits vascular endothelial growth factor fosforilation thus it reduces cyclus cancellation and prevents OHSS (12, 13). In a study by Alvarez et al on patients with risk for OHSS, it has been shown that use of cabergoline reduces OHSS incidence (14). However, cabergoline for the treatment of OHSS were less effective than the use for the prevention (15). In our study we used cabergoline for prevention. PCOS is one of the most important risk factors for OHSS. In a review by Tummon et al, designed in 2005 with the attribution of eight cohort and two case control studies; it is indicated that presence of PCOS results OHSS seven times more(OR:6,8 95% CI:4,9-9,6) (16). In ART cycles, excessive ovarian response such as PCOS does not only cause the life-threatening emergencies of OHSS, also due to high levels of sex steroids may be associated with decreased implantation rates (17). In addition, there are clinical studies about that it may have adverse effects on oocyte and embryo quality (18). In our study pregnancy is resulted at 13 patients (42%) and 10 patients (76,9%) had live babies. Three patients (23,1%) had spontan abortion. Recent studies have shown an increased risk of OHSS under 33 years of age (19). This may be due to the reduction at number of follicles decreased growth hormone reserve. In our study mean age of patients was 29. American Society for Reproductive Medicine (ASRM) 2008 Committee has also assessed a low BMI s a risk factor for OHSS (20). In our study mean BMI was 27,5±3,4 kg/m^2. In a study by Courbiere et al, 23% patient were early onset OHSS and 77% patients were late onset OHSS. In our study13 patients (42%) were early onset and 18 patients (58%) were late onset OHSS. Although OHSS is usually a self-limiting condition, rarely severe form that needs hospitilazition can be seen in 2% of ART cycles and most of them resolve with medical tr eatment (21). In a study at 2011 moderate and severe OHSS that needs hospitalization were 1,1% of3504 IVF cycles (22). In our study severe OHSS was 1,2% and it was consistent with the literature. Although reported criteria for hospitalazition is severe OHSS with hematocrit >45%, in our study we hospitalized moderate OHSS patients too. The protocol was the sam efor all hospitalized patients. Until now, the reason for accumulation of fluid in the third space (ascites) is not explained. The most widely accepted theory is the release of mediators from ovaries that is induced by human chorionic gonadotropin (hCG) (23). It has been shown in several studies that increased levels of CRP, leukocytes, endothelial selectins, and vascular endothelial growth factor (VEGF) is detected after administration of Hcg (24). Abdominal paracentesis is the most common performed operation for OHSS (25). In our study, intermittent TVFA was applied to all patients with moderate and severe OHSS. In a study that evaluated the clinical signs of OHSS; ascites was present in 92% of patients, dyspnea in 47% of patients and pleural effusion was detected in 21% of patients (26). In our study 74% of patients had ascites, 22% had dyspnea and 19% had pleural effusion. No patient needed thoracentesis. Definite improvement criteria of OHSS is not precisely defined in the literature. It is expressed as the provement of clinical and laboratory findings of OHSS, at ASRM committee in 2008. In our study, improvement criteria is defined as hematocrit <40% and asymptomatic patient, without treatment by two days apart. No patient needed intensive care unit and we did not encounter any mortality. In several studies it is reported that risk for thromboembolism is 4-12% (27). In our study we used enoxaparine sodium at prophylactic dose for 74% patients by considering the clinical risks and pulmonary embolism is not developed at any patient.

5. Conclusion

OHSS is an iatrogenic complication. The pathophysiology and management of OHSS is still unclear. In particular, the identification of patients at risk for OHSS and early diagnosis is extremely important in terms of potential complications. Despite all precautions taken to develop the OHSS; if

it is developed spontaneous improvement of the process should be waited with close monitoring and medical support should be continued.

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