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Diagnosing and management of iatrogenic moderate and severe ovarian hyperstymulation syndrome (OHSS) in clinical material

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Abstract: Severe ovarian hyperstymulation syndrome is a rare but potentially life-threatening complication in patients undergoing assisted reproductive techniques (ART). The pathogenesis of this condition is likely to be multifactorial. The aim of the retrospective study was to present management in moderate and severe iatrogenic ovarian hyperstymulation syndrome (OHSS) in clinical material. The study group was 19 women, admitted to the Department of Obstetrics and Gynecology in Central Clinical Hospital of Ministry of Interior and Administration in Warsaw from large outpatient infertility center "Novum" in Warsaw with moderate and severe OHSS between 14.07.2004 and 8.11.2005. Laboratory tests and ultrasound examination of the ovarian size and ascites were performed, abdominal circumference was measured. Patients were treated with rehydration with intravenous crystalloids and colloids, diuretics, antibiotics, anticoagulants and ultrasound-guided paracentesis if symptoms of ascites become severe (ascites causes pain and compromised pulmonary function). Oral intake of water was restricted, monitoring of fluid intake and output, and daily monitoring of body weight was performed. During treatment controlled laboratory tests were done. In one patient occurred intra-abdominal hemorrhage from ovarian rupture and laparotomy with oophorectomy was performed. The ovarian hyperstimulation syndrome is still a difficult diagnostic and therapeutic problem and more studies are required to elucidate pathophysiology of OHSS. Because of still unknown etiology treatment is empirical and in most of cases bases on experience of medical team. Thus, the management in individual patients varies according to the severity of ovarian hyperstymulation syndrome and its complications.

Key words: OHSS - ART - Ovulation induction - Infertility

Introduction

Ovarian hyperstymulation syndrome (OHSS) is rare but potentially dangerous complication of assisted reproductive techniques (ART). The iatrogenic form of syndrome is an exaggerated response to gonadotrophines used in ovulation induction. The use of the gonadotrophin releasing hormone (GnRH) agonist long down-regulation protocol is associated with the higher incidence of OHSS. The risk is increased in younger women with low body weight and in the presence of polycystic ovaries (PCO). Spontaneous forms of OHSS are very rare, always occur during pregnancy, and are reported to develop between 8 and 14 week of pregnancy when iatrogenic form usually starts earlier, between 3 and 5 weeks of amenorrhea [1-4].

The pathophysiology of this condition is characterized by ovarian enlargement, massive extravascular exudate accumulation in combination with profound intravascular volume depletion and haemoconcentration. The underlying cause of these pathophysiological changes remain unknown, but there are evidences that vascular endothelial growth factor (VEGF), tumor necrosis factor alpha (TNFα), interleukin 2 (IL-2) and interleukin 6 (IL-6) contribute to the development of syndrome [3,5,6].

The OHSS has traditionally been classified as mild, moderate or severe. Milder forms are usually self limited and requires usually no further therapy other then

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Table 1. Mean laboratory results, ovarian size in ultrasound examination, abdominal circumference, and amount of albumin and hydroxyethyl starch (HES) transfused to the patient.

	N	χ	SD
Haematocrit (%)	19	35,97	±3,99
C-reactive protein (mg/l)	19	11,90	±7,90
White blood count (x 10^3/ml)	19	11,37	±2,43
Serum protein (mg/dl)	19	6,25	±0,57
Serum albumin (mg/dl)	19	3,94	±0,34
Ovarian size in ultrasound examination (mm)	19	105,74	±23,55
Abdominal circumference (cm)	19	87,36	±6,35
Amount of albumin and hydroxyethyl starch (HES) transfused to the patient during therapy (ml)	19	11640	±9185

observation. The severe form occurs in approximately 1-2% of IVF cycles [3,7,8].

The aim of the retrospective study was to present management in moderate and severe iatrogenic ovarian hyperstymulation syndrome in Department of Obstetrics and Gynecology in Central Clinical Hospital of Ministry of Interior and Administration in Warsaw.

Materials and methods

The study was performed in Department of Obstetrics and Gynecology in Central Clinical Hospital of Ministry of Interior and Administration in Warsaw and large outpatient infertility center "Novum" in Warsaw between 14.07.2004 and 8.11.2005. Among 1306 consecutive cycles of ART performed, in 19 cases occur moderate or severe iatrogenic ovarian hyperstymulation syndrome and patients required hospitalization. As the result of total 1306 ovarian stimulation, 1281 ovarian punctures and 1237 intracytoplasmic sperm injections (ICSI) were done. Administration of intravenous 20% albumin at the time of oocyte retrieval to prevent OHSS was routine.

Subjects for the study were admitted to the Department of Obstetrics and Gynecology in Central Clinical Hospital of Ministry of Interior and Administration in Warsaw with moderate and severe OHSS, according to the Golan criteria [9].

Nineteen women were admitted with massive ovarian enlargement, ascites, oliguria, in 12 cases liver dysfunction and in 3 cases hydrothorax were present. No renal failure, hypovolemic shock, adult respiratory distress syndrome (ARDS) was observed. None of the patient died.

Laboratory tests (blood sample taken to measure complete blood count, serum protein, albumin, creatinine, urea, electrolytes, liver enzymes, C - reactive protein (CRP), β-hCG, progesterone, estradiol (E2), coagulation parameters; urine analysis) and ultrasound examination of the ovarian size and ascites was done, abdominal circumference and body weight was measured. Vital signs (pulse, blood pressure, temperature) were recorded every hour.

Patients were treated with rehydration with intravenous crystalloids and volume expander such as hydroxyethyl starch (HES) and albumin to achieve or maintain hemodynamic stability and adequate urine output. 16 patients receive 20% albumin, minimal dose was 100 ml and maximal was 4200 ml during hospitalization (mean 1423.68 ml SD ±1319.23) In 10 cases diuretics (furosemide 10mg intravenous daily) were used because of low urine output after adequate intravascular volume restoration. In case of suspicion of inflammatory state or after paracentesis patients were treated with antibiotics, usually semi-synthetic penicillin. Patients with past history or laboratory findings putting them at high risk of thrombosis also receive anticoagulants such as low molecular weight heparin and used elasticated tubular stockings. Ultrasound-guided paracentesis from transabdominal approach was performed when symptoms of ascites become severe (ascites causes pain and compromised pulmonary function). In 11 patients paracentesis was done, minimal volume of ascitic fluid removed daily was 500 ml, maximal 2500 ml, 9 of woman require serial paracentesis to maintain adequate renal and pulmonary function (mean volume of ascitic fluid removed during hospitalization was 2863, 15 ml, one patient during 9 cycles of paracentesis loss 18600 ml ascitic fluid).

In one patient occurred intra-abdominal hemorrhage from ovarian rupture and laparotomy with oophorectomy was performed.

Oral intake of water was restricted, monitoring of fluid intake and output, and daily monitoring of body weight was performed. During treatment controlled laboratory tests were done. All patients were followed by serial ultrasound examination.

Laboratory tests results and clinical findings were reported as mean and standard deviation. Statistical analysis was performed using SPSS software package (SPSS Inc., Chicago, IL).

Results

In our study 1.45% of patients undergoing assisted reproductive technology (ART) program develop moderate or severe ovarian hyperstymulation syndrome required hospitalization. The mean age of the patients admitted to the ward was 31.2 years (SD ±3.90), mean duration of hospitalization was 20.6 day (SD ±4.55).

Mean laboratory test results, ovarian size in ultrasound examination, abdominal circumference and amount of albumin and hydroxyethyl starch (HES) transfused to the patient are presented in Table 1.

Discussion

Severe ovarian hyperstymulation syndrome is a rare but potentially life-threatening complication of pharmacological ovarian stimulation. In the pathophysiology of this syndrome the main mechanism is an increase in capillary permeability of ovarian vessels

and other mesothelial surfaces resulting in fluid shift from intravascular space to the third space compartment. The pathogenesis of this condition is likely to be multifactorial [10-18].

This state is responsible for the development of symptoms of the syndrome such as ascites, pleural and pericardial effusion, oliguria, hypovolemia and as the result of haemoconcentration - thromboembolic events [3,7,19,20].

Until now the only method proven to be effective in prevention of OHSS is discontinuation of ovarian stimulation and hCG administration to trigger ovulation. There are suggestions about protective role of albumin in reducing the incidence of severe OHSS, by prevention the fluid shift to third space and binding factors responsible for development of this syndrome, but there is still debate on its value, because OHSS can occur despite the use of albumin. In Gockmen *et al.* study both HES and albumin significantly reduced the incidence of moderate, severe and overall incidence of OHSS. It is concluded that hydroxyethyl starch is a cheaper and safer alternative to Human Albumin in OHSS prevention. Albumin is also very useful in treatment of OHSS as volume expander in severe cases [3,8,21,22].

Continuous autotransfusion of ascitic fluid into the systemic circulation as peritoneovenous shunting (CATSA) in severe OHSS treatment was suggested by Koike *et al.* The aim of this method was transfusing to the patient her own proteins instead exogenous. However these may increase plasma levels of inflammatory cytokines, thereby increasing capillary hyperpermeability and aggravating the extravascular fluid shifts. Also risk of contamination during this procedure increase its usability [1,23].

In cases with risk factors for OHSS stimulation procedures can be modified and lutheal hCG exposure can be minimized by using lutheal support with progesterone in preference to hCG, or by freezing all embryos. However freezing all embryos increases the financial and emotional stress accompanying in vitro fertilization. Reducing only the number of embryos transferred to one, can be the way of preventing multiple pregnancy and by that way, especially in woman of high risk, incidence of severe ovarian hyperstymulation syndrome can also be decreased [1,3].

It's also very important to monitor patient condition to detect symptoms and signs of ovarian hyperstymulation syndrome in early state and identify worsening or complications during outpatient therapy. Frequent evaluation include frequent physical and ultrasound examination [3,24].

During treatment of severe OHSS careful and frequent re-evaluation of the hospitalized patient is essential, because pain and ascites can mask ovarian rupture, as it was in our case.

In case of severe OHSS required hospitalization apart from medical treatment we should give psychological support to the patient [3,20].

In conclusion, it is very important to identify high risk patients prior to assisted reproduction treatment and choose appropriate therapy. Identification of all risk factors and it's correlation with clinical features require more large randomized studies but can be key to preventing and managing this dangerous condition.

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