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Case of the Successful Treatment of the Severe Form of the Ovarian Hyperstimulation

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Abstract

Introduction: The use of gonadotropic stimulation in assisted reproductive technology programs increases the risk of developing the ovarian hyperstimulation syndrome (OHSS), which is considered as a loss of control over the ongoing ovarian stimulation. The severe forms of OHSS lead to the severe complications that threaten the patient's life.

Methodology: A case of the successful treatment of the severe form of the ovarian hyperstimulation with ovarian apoplexy of patient was presented. It was developed on the background of the early pregnancy after the carried out low-dose hormonal stimulation (900 IU of gonadotropins). The number of follicles (14 -19 mm) is 15, the level of estradiol on the day of the appointment of the ovulation trigger is 1837 pg / ml, 13 oocytes were extracted, 1 embryo was transferred to the uterine cavity.

Results: Correction of hypovolemia, hypoproteinemia, hemoconcentration, hypercoagulation, anuria, respiratory failure, evacuation of ascitic fluid from the abdominal cavity was carried out. Deterioration of the patient's state, progressive ovarian enlargement up to 22 cm and the lack of the effect from the therapy determined the indications for pregnancy termination. Further deterioration of the patient's state, the appearance of signs of the intra-abdominal bleeding, determined the indications for laparoscopy, during which the ovarian apoplexy was diagnosed, and an organ-saving operation was carried out. During the postoperative period, stabilization of the patient's state, normalization of hemodynamics, hemostasis and other laboratory parameters were marked. On day 17, the patient in satisfactory condition was discharged from the hospital.

Conclusion: Severe forms of OHSS may develop in patients with ART programs even after low-dose hormonal stimulation and moderate ovarian response, are characterized by a complex wave-like course with the development of multiple organ dysfunctions and require the use of low molecular weight heparins in the maximum therapeutic dose for the prevention of thromboembolic complications.

Keywords: Ovarian Hyperstimulation Syndrome; Ovarian Apoplexy; Gonadotropic Stimulation; Assisted Reproductive Technologies

Introduction

Ovarian hyperstimulation syndrome (OHSS) is an iatrogenic systemic disease, which is based on the neurophysiological reaction of the ovaries against the background of stimulation of superovulation. Intensive development of new assisted reproductive technologies using modern superovulation protocols increases the risk of OHS development, which is considered as a loss of control over the carried out ovarian hyperstimulation [1-4]. Controlled ovarian hyperstimulation, characterized by some increase in ovarian size and changes in blood biochemical parameters, and not requiring intensive treatment, observed in the vast majority of cycles of gonadotropic stimulation and is a natural consequence of changes in the physiological parameters of folliculogenesis in the ovaries [1-8]. However, in 0.2 – 14% of cases there are cases of severe OHSS. Stimulation of ovulation leads to a state of hyperestrogenia, an increase in the levels of some blood clotting factors (factor V, fibrinogen, Willebrand factor) [5-7,9]. Therefore, OHS syndrome is accompanied by an increase in the level of fibrinogen, D-dimer, thrombin-antithrombin complexes, a decrease in the level of precallycrein and tissue factor [10]. It should be noted that elevated levels of D-dimer and thrombin-antithrombin complexes are associated with IVF failures [11]. The main characteristic feature found in OHSS is bilateral ovarian enlargement due to multiple cysts, morphological studies of which reveal numerous yellow bodies, follicular cysts and severe swelling of the ovarian stroma [1-5,15]. The effect of human chorionic gonadotropin (HCG) or luteinizing hormone (LH) on the ovaries after controlled

ovarian stimulation with follicle stimulating hormone (FSH) is at the heart of most OHS cases. The effect of HCG on the ovary after hyperstimulation leads to the production of proinflammatory mediators. The main one is the vascular endothelial growth factor (E), but probably the pathogenesis and clinical features of OHS are due to various cytokines. These metabolic products have a powerful vasoactive effect on vascular permeability, and play a leading role in the development of the phenomenon of vascular permeability, leading to a massive output of fluid into the "third space" with the formation of ascites, hydrothorax, hydropericardium, etc. [3-5,8,14-20]. Severe forms of OHSS are characterized by a wide range of laboratory manifestations, the degree of deviation from the norm, indicates the enhancement of the process (hemoconcentration, hypercoagulation, leukocytosis, hypoproteinemia, increased liver enzymes, electrolyte imbalance, etc.) [1-4,6,8-10,14-16]. The influence of products of metabolism changes the functioning of physiological processes and the pathogenesis of major disorders in OHSS is reduced to the following main points:

1. Violation of vascular permeability leads to a systemic redistribution of fluid in the body. A characteristic feature of this syndrome is the absence of interstitial edema, and the fluid accumulates selectively in the cavities (abdominal, pleural, pericardium) with the development of hypovolemia, hemoconcentration, hypoproteinemia, hypercoagulation.
2. Hypovolemia causes a decrease in renal perfusion with the development of oliguria, a violation of water-electrolyte balance, excessive accumulation of metabolic products, a violation of the function of natural anticoagulants.
3. Under the action of anti-inflammatory cytokines there is a systemic activation of the inflammatory response with the massive damage of the vascular endothelium and the development of endotoxicosis, increased intra-abdominal hypertension with the development of abdominal compartment syndrome.
4. Further deterioration of renal perfusion is accompanied by the development of a whole range of metabolic disorders: increased endotoxicosis, increased hypercoagulation, hypoproteinemia, hemoconcentration and water-electrolyte disorders, and as a result – the development of the most dangerous complications of OHSS – pulmonary embolism and respiratory distress syndrome.

Treatment of the severe form of OHS is carried out according to the international and domestic recommendations [3-5,7,8,14-16,19,20]- infusion therapy (crystalloids, colloids), hypoproteinemia (total protein less than 45 g\l and albumin less than 20 g\l) – albumin, hypercoagulation - therapeutic doses of low– molecular weight heparins (HMG) - sodium enoxaparin (Enoxaparin sodium), calcium nadroparin (Nadroparin calcium). The volume of intensive therapy, and primarily infusion, depends on the severity of the condition, the severity of hypovolemia, hemoconcentration, hypercoagulation, CVD level, the magnitude of hourly diuresis. Large volumes of injected fluid and aggressive infusion therapy can provoke an increase in the amount of fluid in the abdominal and pleural cavities and contribute to the development and progression of the abdominal compartment syndrome (intraperitoneal hypertension syndrome) [16,19,20].

Literature data and our own experience evidence that the most optimal electrolyte infusion solutions are balanced solutions based on malate and acetate. To this end, we use a solution of sterofundin (V. V, Germany) and plasmalite (Vah, the USA) in our practice. It should be noted that against the background of the use of these balanced solutions we have not noted expressed violations of electrolyte and acid-base balance. In addition, it should be noted that in patients with the severe OHS strategically and tactically correctly conducted infusion therapy, especially in conditions of evident hypercoagulation, when it is necessary to correct hemodynamic and volemic disorders, has the significant meaning to achieve the results of treatment. So, if the volume of infusions is insufficient for the correction of homeostasis disorders, it leads to increased phenomena of hypovolemia, and if the infusion therapy is excessive, it leads to hyperhydration phenomena, and eventually to such dangerous complications as pulmonary edema and brain edema [3-5,8,14-16,19,20].

The course of a severe form of OHS syndrome can occur both gradually with an increase in symptoms, and suddenly, acutely, when there is a sharp deterioration due to a sharp redistribution of fluid in the body with the formation of polyserosis. Massive exudative extracellular fluid accumulation in combination with hypovolemia and hemoconcentration eventually lead to multi-organ failure [16,19,20].

Indications for laparocentesis are:
1. Progressive tense ascites.
2. Oliguria.
3. Increasing hypoproteinemia and hypercoagulation.
4. Increased creatinine, lanine aminotransferase, aminotransferase.
5. Hemoconcentration, not amenable to correction.

Case presentation

Patient's identification

In this article we report a case of ovarian hyperstimulation with severe development of a 27-year-old patient. Upon admission of patient K. into the Center, 27 years old, she was diagnosed the severe hyperstimulation, which developed during early pregnancy (7 days after embryo transfer, according to HCG), after moderate hormonal stimulation (taking into account the level of AMG 6.33 ng\ml (1-12,6 ng\ml). According to the ultrasound at the beginning of the stimulation 6-7 antral follicles were recorded in each ovary. The total dose of gonadotropins was 900 IU, with ultrasound monitoring on the background of hormonal stimulation,

the total number of follicles with a diameter of 14-19 mm was 15. The level of estradiol on the day of the appointment of the ovulation trigger was 1837 PG\ml, which allowed the appointment of choriogonadotropin alpha at a dose of 250 μg (6500 IU). 13 oocytes were obtained by transvaginal puncture of follicles. On the day of the alleged transfer of embryos into the uterine cavity during ultrasound examination, the size of the right ovary was 45x35x38 mm, the left 48x40x42 mm, free fluid in the abdominal cavity and the posterior arch was not visualized. As a result, it was decided to transfer 1 embryo into the uterine cavity. The patient was discharged after embryo transfer in a satisfactory condition. When re-treatment in the clinic (7 days after discharge) it was clinically established: increased and tense abdomen, abdominal circumference 84 cm, in the lungs on both sides with auscultation moderate weakening of vesicular respiration in the posterior parts, respiration rate 22 per minute, BP 95\60, pulse 102 beats per minute. According to laboratory tests: hemoconcentration (hemoglobin 174 g\l, hematocrit 50.9%, leukocytosis 20,5x10^9\l), hypoproteinemia (total protein – 49 g\l, albumin – 30 g\l), hypercoagulation (fibrinogen – 6.6 g\l, soluble fibrin monometric complex – 7.0 mg, D-dimer - 2413 ng\ml), creatinine - 99.4 μmol\l, level platelets-301x10^9 \l, APTT - 32.8 sec, antitrombin III 70%, the level of estradiol -7826 PG\ml. Violations of braids and electrolytes were not noted. According to ultrasound an increase in the ovarian size was recorded (left 13.7 x 4.8 x 3.9 cm; right 12.3 x 5.8 x 3.2 cm).

Materials and methods

During hospitalization, complex intensive therapy was initiated to correct metabolic disorders according to clinical recommendations and treatment standards [13-16]: infusion therapy (crystalloids, colloids), low molecular weight heparins (LMH)- calcium nadroparin 0.9 ml, cabergoline 0.5 mg, nutritional support with enteral protein preparations, evacuation of ascitic fluid with laparocentesis by transvaginal access under ultrasound control. The choice of the transvaginal access was justified by the deformation of the anterior abdominal wall by postoperative scars (after previous surgical interventions for intestinal obstruction). Against the background of the complex intensive therapy, the patient's condition and well-being improved, but already on the 3rd day of stay in the clinic, deterioration, increased ascites (abdominal circumference + 6 cm), decreased diuresis (up to 550 ml per day), changes in laboratory parameters: hemoglobin 149 g\l, hematocrit 42.7%, total protein 47 g\l, albumin 23 g\l, creatinine 84.8 μmol\l, fibrinogen 5.4 g\l, APTT 37.2 sec, antitrombin III 58%, D-dimer 1609 ng\ml in the absence of violations of braids and electrolytes were revealed. In the consideration of the deterioration, the buildup of ascites and hypovolemia, increased hypercoagulability, an increase of hypoproteinemia, decreased urine output, it was decided to re-laparocentesis with the evacuation of intra-abdominal fluid. To correct the growing hypoproteinemia (total protein 47 g / l, albumin 23 g / l) in the composition of infusion therapy was added albumin 20% in the amount of 200 ml, because only hydroxide ethyl starch drugs were not able to hold adequate colloid oncotic pressure. In addition, persistent hypercoagulation has led to the need to introduce a maximum daily doses of HMG (nadroparin calcium 0.6 ml 2 times a day), but even against this background, hypercoagulation persisted throughout the treatment period. In order to prevent thromboembolic complications, intermittent pneumocompression of the lower extremities was used with the help of the "Kendall" apparatus (USA).

Results and Discussion

It is necessary to note the wave-like course of OHS syndrome in this patient, so after each evacuation of peritoneal exudate, the patient's condition and well-being improved, which was due to a decrease in intra-abdominal pressure and improved blood flow in the renal vessels. Thus, during the day after the evacuation of intraperitoneal contents there was an evident efficiency of the intensive therapy, then the condition deteriorated sharply, there was a progressive and intense ascites, increased hemoconcentration, hypercoagulation, hypoproteinemia and again there was a need to continue the correction of metabolism and evacuation of ascitic fluid from the abdominal cavity. Thus, during the first puncture (14.11.15), 2.2 l were simultaneously evacuated, the second (16.11.15) – 2.6 l, the third (18.11.15) – 1.8 l, the fourth (20.11.15) – 2.6 l and the fifth (24.11.15) – 3.0 l. Despite the correction of hypovolemia, hypoproteinemia, hemoconcentration, hypercoagulation, the patient's condition did not improve, and the size of the ovaries reached the left 22 x 16 x 10 cm, right 14 x 12 x 9 cm. On day 7, according to ultrasound, there was the appearance of free fluid in moderate amounts in the left and right pleural sinuses, and on day 9 – a small amount of free fluid in the pericardium. During laparocentesis there were technical difficulties associated with enlarged ovaries, therefore, to exclude the risk of injury to the ovaries and the development of intra-abdominal bleeding, ultrasound control was used. In connection with absence of the effect from the ongoing comprehensive intensive care and the continuing deterioration of produced termination of pregnancy for medical reasons (20.11.15) and adding antagonist gonadotropin releasing hormone to the treatment of OHSS. However, the stabilization of the condition did not occur, there was a further deterioration of clinical and laboratory parameters and the patient's health. During the 5th abdominal puncture, peritoneal fluid was stained with hemorrhagic contents, and after receiving the results of laboratory examination of the patient (hemoglobin-66 g\l,erythrocytes – 2, 2x10^{12} \l, hematocrit – 20%), laparoscopy was performed (24.11.15), during which intraperitoneal bleeding in the volume of 2 l was revealed, due to ovarian apoplexy, as evidenced by linear ruptures on the surface of the ovaries, on the background of severe hyperstimulation.

The postoperative period was characterized by stabilization of clinical and laboratory parameters, improving the condition and well-being, reducing ascites and abdominal circumference, normalization of diuresis were noted. Laboratory control: hemoglobin 117 g\l, erythrocytes 3,8h10^{12} \l, hematocrit 35%, platelets 252x10^9\l, leukocytes 12x10^9\l, total protein 62 g\l, albumin 37 g\l. Dynamic improvement of hemostatic parameters was noted. In the future, the stabilization of the patient's condition and well-being and the positive dynamics of laboratory indicators continued. On day 17, the patient was discharged for outpatient observation in a satisfactory condition.

Conclusion

The analysis of the presented case of hyperstimulation allows us to draw the following conclusions:
1) Severe forms of OHS are characterized by unpredictable wave-like course with the development of organ and/or multi-organ dysfunction.
2) Prolonged ineffective therapy of the OHS syndrome is severe, even with the full complex of treatment activities increases the likelihood of developing serious complications, including ovarian apoplexy.
3) Decision to replace the ovulation trigger and cancel embryo transfer may be difficult, in the absence of clinical and ultrasound signs of the threat of ovarian hyperstimulation at the stage of completion of stimulation, in the preparation of no more than 14 eggs (with a total number of all follicles with a diameter of more than 11 mm, not exceeding 19), with a concentration of estradiol on the day of the trigger less than 2500 PG\ml.
4) Changes in the composition of ascitic fluid aspirated from the abdominal cavity, and the appearance of hemorrhagic contents in the aspirate, indicates intra-abdominal bleeding and requires immediate surgical treatment.
5) Use of LMH in the maximum therapeutic dose does not allow to achieve the absolute effect of normalization of hemostatic parameters, but prevents the development of more severe complications - pulmonary embolism.
6) Rcommended therapy with solutions of hydroxyethylated starch and albumin does not always lead to the expected effect [21], therefore, it is necessary to recalculate the water balance every 8-12 hours to prevent hyperhydration and timely correction of hypovolemia.

Competing interests

The authors declare no competing financial interests. The study was conducted in the Center of Human Reproduction and IVF, Rostov-on-Don, Russia.

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