Development of a lymphoid variant of acute leukemia after five-fold treatments of ovulation induction

ABSTRACT

Ovarian hyperstimulation syndrome is a complication of IVF procedure. Describes the case of a 31-year-old patient with body mass index 22k/m2. After 5 IVF procedures with the previous stimulation of ovulation complaints of weakness, dyspnea, pain in the chest, unproductive cough, epigastric pain, fever, pain in the hip and spine, ascites, hydropericardium, hydrothorax, acute respiratory distress syndrome was appeared. "Ovarian hyperstimulation syndrome" was made. The treatment with glucocorticosteroids improved the condition of the patient. After a bone marrow puncture the diagnosis "lymphoid variant of acute leukemia" was confirmed.

Keywords: Ovarian hyperstimulation syndrome, lymphoid variant of acute leukemia

1. INTRODUCTION

In various regions of Russia infertility occurs from 7 to 18 % [3-5]. In vitro fertilization (IVF) is a technique of assisted reproductive technology. In any medical manipulation there is a risk of complications. One of them is ovarian hyperstimulation syndrome (OHS). OHS is an iatrogenic systemic disease that occurs in response to the introduction of drugs that stimulate ovulation by activating the production of vasoactive mediators by the ovaries. The incidence of this syndrome is from 0.5% to 33% [1]. According to literature sources, the probability of death in this pathology is estimated as extremely rare-1: 400000 cycles of ovarian stimulation. OHS is characterized by wide variability of symptoms from mild abdominal pain to severe homeostasis disorders, development of adult respiratory distress syndrome, thromboembolic complications, acute renal failure, ascites, and hydropericardium. Forecasting, prevention of the development of the syndrome are fundamental measures, but if the syndrome has already developed, early diagnosis and timely treatment are very important.

2. MATERIAL AND METHODS

A retrospective analysis of anamnestic data, the course of the disease, laboratory data, instrumental studies and the treatment of a patient with OHS in a therapeutic hospital was carried out

3. RESULTS AND DISCUSSION

The woman O., 31 years old, entered the therapeutic Department of the emergency Hospital on 27.08.2018 with complaints of increasing t^0C of the body to 37,8^{0}C, dyspnea, shortness of breath, unproductive cough, weakness, chest pain on inhalation, pain in the epigastric region, nausea, vomiting for 2 days, single liquid stool. In 2018, two in vitro fertilization procedures were carried out (30.05.2018 and 18.07.2018). 1 weeks ago, pain in the hip and spine began to disturb. 2 weeks ago pain in the throat, cough was appeared. The therapist in the outpatient clinic diagnosed pharyngitis and prescribed the antibiotic Cefotaxime. The patient took the drug for 10 days, but the cough did not pass, t ^{0}C of the body grew and the woman was hospitalized in an emergency hospital with a diagnosis of pneumonia.

Anamnesis vitae: A woman was treated for 10 years for endometriosis in a gynecologist. There were 5 laparoscopic operations, 5 IVF attempts for 6 years, but the pregnancy did not occur. 3 years ago for a short time she took Dostinex ½ tablet/day for medical hyperprolactinemia and levothyroxine for subclinical hypothyroidism and infertility. Thyroid ultrasound revealed 5.08.2018 G. nodes 6*4*4mm in the right lobe of the thyroid gland. Thyroid status was without pathology.

Objectively: state of moderate severity, consciousness is clear. The skin is clean, physiological color, moderate humidity. T= body 37,80 C. BMI of 22.5 kg/m2. The breathing is hard, dry rales are on both sides, RR- of 18 beats/min. Heart sounds are clear. Heart rhythm is regular. BP 110/70 mm of mercury. Pulse 78 beats/min. Tongue is moist with white bloom; abdomen is soft, painless. The liver is not palpated. Listened to peristalsis is active. The spleen is not enlarged. A symptom of a beating on the lower back is negative on both sides. Urination is free, painless. No peripheral edema.

Laboratory tests: General blood test: leukocytosis-15,4 *10*9/l; Coagulogram: PT-14.7 sec., inr-1,340, Fibrinogen-8,2 g/l. C-reactive protein - 162 mg/l.. ECG: sinus rhythm, tachycardia 120 beats / min. incomplete blockade of the right branch of the atrioventricular bundle. Myocardial hypoxia is moderate. Chest x-ray: pulmonary infiltration is not excluded in the S5 segment of the right lung. The root of the right lung is reactive, the root of the left lung is slightly structural. Conclusion: right-sided segmental pneumonia.

Diagnosis: right-sided segmental pneumonia. Respiratory failure of the 1st degree. Osteochondrosis of the cervical spine. Pain syndrome. 27.08.18 doctor prescribed 2 grams of Ceftriaxone intravenously; 30 ml Ketorolac intramuscularly, 0.9% NaCl 500 ml, intravenous drip.

Inspection 28.08.18: Complaints of cough with difficult sputum, shortness of breath, weakness, pain in both hypochondria continue to disturb. The state of moderate severity. In the lower parts of the right lung, wet scattered rales are heard. RR- 16 per minute, heart rate 88 beats per minute, blood pressure 100/60 mm Hg, the abdomen is soft, painless, palpation of intercostal spaces is painful on the left. Body temperature 37,2 ^{0} C. C-reactive protein 204 mg/l In the blood test contains 13,5*10*9/l of leukocytes.

Sputum examination: a significant amount of elastic fibers in the field of vision, leukocytes 12-15-18 in the field of vision, erythrocytes. Urine analysis according to Nechyporenko: leukocytes-2.500, erythrocytes-2300, cylinders-0. The General analysis of urine from 30.08.18: proteinuria-0,014 g/l. Consultation with a clinical pharmacologist 29.08.18: it is recommended to continue intravenous administration of Ceftriaxone 2 grams per day. Add Azithromycin 0.5 grams 1 time per day 3 days intravenously.

Inspection 31.08.18. Complaints of pain in the lower segments of the ribs. The state of moderate severity. In the lungs, breathing is vesicular, a few dry rales, RR- 15/min are heard, the heart Tones are clear, rhythmic. Heart rate 88 / min, blood pressure 100/60 mm Hg/ Thermometry: t 37,8^{0} C. Rheumatoid factor 6 IU/ml, The procalcitonin test is negative . Computed tomography of the chest: 31.08.18. Small bilateral hydrothorax, hydropericard. Consult a neurologist 29.08.18. Cervicobrachialgia right. Echocardiography 31.08.18. Typical echo characteristics of infective endocarditis was not detected. Blood count: leukocytes 12,0*10*9/l; C-reactive protein 189 mg / l.

Inspection 3.09.18: Thermometry t body 39 ^{0} C in the evening. Pain in the lower intercostal space on both sides, moderate General weakness persists. In the lungs vesicular breathing, wheezing no. Heart rate 88 / min, blood pressure 110/60 mm Hg. A Council of doctors was appointed prednisolone 50 mg per day. In the General analysis of leukocyte blood– 10,0 *10*9/l, platelets– 137 *10*9/l, total bilirubin-52.5 µmol / l: direct bilirubin-21.9 µmol/ l, indirect bilirubin-30.6 µmol/ l, AST 65.0 IU/l; C-reactive protein 24.0 mg/l. in the General analysis of urine: proteinuria 0.014 g / l. Coagulogram: PT-13,7 sec, fibrinogen-8,0 g/l.

Consultation of the gynecologist 03.09.18: Genital endometriosis. Infertility of 1 mixed genesis. There are no data for acute gynecological pathology at the time of examination. ULTRASONIC examination of abdominal organs 04.09.18: ULTRASONIC signs of cholecystitis, diffuse changes in the pancreas. 04.09.18: ultrasound of the pelvic organs: the Endometrium proliferative type. Ovaries are not increased in size (volume 4-5 ml, located in a typical place, the follicular apparatus is represented by follicles 4-6 mm in diameter, the number of follicles in one cut 4-5.. On the peritoneum and loops of the small intestine several anechogenic formations with uneven, fuzzy contours, 10*16mm in size are located. Conclusion: Ultrasound signs of endometrioid heterotopias of the abdominal cavity.
Inspection 5.09.18 1:00 complaints of continued pain in both subcostal areas. Ketorolac injections do not relieve pain. Sowing blood from 5.09.18 is sterile.
6.09.18: the patient complains of severe pain in the lumbar spine, cannot get up, sits in a forced position, night sleep is disturbed. Taking into account the remaining pronounced pain syndrome, tramadol 2.0 ml was administered intramuscularly once. MR is a picture of diffuse focal structural rearrangement of the thoracic and lumbar vertebral bodies. MR data confirming the presence of spondylodiscitis have not been obtained. Th 11-12 intervertebral disc protrusion. Immunological examination 6.09.18: p-ANCA-positive: +, C-ANCA - positive: +++. UAC: leukocytes 5.5 *10*9/l, thrombocytopenia 66*10*9/l.
Thyroid status: TSH 1,820 μm/ml, fT4 1,190 ng / DL. Coagulogram: normal. Biochemical blood test: C-reactive protein 58 mg / l. Prednisolone scheme: 5 tablets (5 mg) at 8:30 am, 4 tablets at 14:00, Sulfasalazine 500 mg* 4 times a day per os.
7.09.18: consilium of the Deputy chief physician for clinical and expert work, head of the therapeutic Department №2: taking into account the presence of the patient's symptoms of polymyositis, polyserositis, sacroiliitis, restrictions of lung excursion, the presence of pneumonia, positive antibodies C-ANCA (4+), it is impossible to exclude the presence of Bekhterev's disease in the patient.
Esophagogastroduodenoscopy 07.09.18: gastritis with focal atrophy of the gastric mucosa. Insufficiency of the pylorus. Signs of pathology of the pancreatobiliary system.
Examination 10.09.18: the patient complains of weakness. The state of moderate severity. Skin covers of physiological color, moderate humidity. In the lungs, breathing is vesicular, wheezing is absent BH 18 per minute, heart tones are muted, rhythmic, blood pressure 120/70 mm Hg, heart rate 76 per minute. Belly soft, painless.
Medical report of the rheumatologist 10.09.18: at the time of examination of convincing data for systemic connective tissue disease was not revealed. The patient needs to continue the diagnostic search, it is necessary to exclude collagenosis, purulent focal lesion of the abdominal cavity and retroperitoneal space.
Recommended cancel intramuscular injection of Dipyrone (as the patient lowers the number of white blood cells). Prednisolone scheme 45 mg (5 tablets in the morning, 4 tablets in the afternoon), reduce 2.5 mg 2 times a week to 15 mg (3 tablets in the morning). Continue antibiotic therapy. Preparations of calcium, vitamin D3. When pain Ketoprofen 2.0 ml intramuscularly, Omeprazole 20 mg on an empty stomach.
Hip MRI 13.09.18: Mr-signs of structural adjustment with fine-grained transformation in the area of the heads and trochanter major of both thighs, symmetrically on both sides. Laboratory: General blood test 14.09.18: leukocytosis– 12,9*10*9/l, thrombocytopenia 124 *10*9/l. Amitriptyline 25 mg* 2 tablets in the morning, 1 tablet at night, 5% Glucosae -25 ml, 5% Novocaini, 0.5% -40 ml intravenous drip, 1 tablet at night, 8 mg IV-slowly, e-4 ml/4000 IU subcutaneously, N8.
17.09.18: a Council consisting of the Deputy chief physician, head of therapeutic Department №2 head of the Department of radiation diagnostics, senior clinical pharmacologist, head of the neurological Department, traumatologist, surgeon, infectious diseases specialist: the condition of the patient heavy, moves with the aid of a cane due to pain in his right leg and sacral region of the spine. The skin is pale, with a gray tint, moderate humidity. Body temperature 37 degrees Celsius. Above the lungs breathing vesicular, no wheezing, RR -16

per minute. BP 110/70 mm Hg, heart sounds clear, rhythmic, heart rate 78 per minute. Tongue wet, is imposed. Belly soft, painless. The patient was examined by a neurologist and traumatologist, acute neurological and traumatological pathology was not revealed. Conclusion: Undifferentiated collagenosis. Genital endometriosis. Data for purulent focal formation of the abdominal cavity and retroperitoneal space, sepsis-were not revealed. Recommended: blood test for brucellosis, CT of the abdominal cavity, hip joints, consultation of a gynecologist, dentist, consultation of otorhinolaryngologist, re-examination of blood for procalcitonin test. C-reactive protein-74 mg / l.

Inspection 19.09.18: the patient complains of pain in the right thigh, on the front surface, radiating to the front surface of the lower third of the right Shin. Pain increases when walking. Pain in the lumbar region, migraine. General status: condition is satisfactory, consciousness clear. Skin covers of physiological color, moderate humidity. Heart sounds clear, rhythmic, blood pressure 120/80 mm Hg, heart rate 76 per minute. In the lungs vesicular breathing, no wheezing, respiratory rate 14 per minute. Belly soft, painless. No peripheral edema.

Local status: palpation, percussion, axial loads show moderate pain in the lumbosacral spine and in the hip area symmetrically on both sides. The pain radiates to the anterior surface of the tibia, more to the right. The movements in the right hip joint are moderately painful, the volume of movements is full. In the projection of the lateral cutaneous branch of the right femoral nerve moderately pronounced hyperesthesia. MRI examination: Mr signs of transient osteoporosis of the lumbar spine, hip joint, most likely occurred on the background of massive hormone therapy of infertility.

Based on complaints, data previously collected anamnesis of the disease, anamnesis of life, clinical examination, MRI study established clinical diagnosis: Endocrine arthropathy of the right hip joint. Neuropathy of the right femoral nerve. Recommended: protective regime, walking with a cane, NSAIDs in pain, chondroprotectors, consultation and treatment of a psychotherapist, consultation and treatment of neuropathy of the femoral nerve at the neurologist's place of residence.

The inspection of the Professor of the Department of endocrinology Ivanova L. A. 19.09.18:

The Professor was informed of the patient's complaints, anamnesis, clinical course of the disease, laboratory and instrumental studies. According to the anamnesis, over the past 6 years, 5 attempts of in vitro fertilization, stimulation by chorionic gonadotropin have been made. The fourth attempt was 30.05.18, and then came the pain in his leg, the fifth attempt carried out 18.07.18, after 2 weeks having a fever, signs of pharyngitis.

The patient's condition progressively worsened, there were pain in the chest, shortness of breath, cough, febrile temperature persisted, increased pain in the right leg, right hip joint, sacrum. The patient is examined. Moves within the Department with the help of a cane, sparing the right lower limb. The skin is moderately pale, with a gray tint. The temperature is 37 degrees Celsius. Above the lungs are vesicular respiration, no wheezing, RR- 16/min, BP 120 and 70mm Hg, heart Tones clear, rhythmic. Heart rate 98 per minute. The abdomen is soft, painless, the tongue moist, covered with gray bloom. No peripheral edema. The area of the right hip joint without hyperemia, no swelling.

Conclusion: Rheumatoid polyarthritis with lesions of large joints of the spine, developed as a result of five procedures of stimulation of the ovaries of HCG, with the development of ovarian hyperstimulation syndrome. Recommended: blood test for calcium content, glycemic profile, HbA1C. Add to the treatment regimen calcium, potassium, antispasmodics, antimycotic drugs. The treatment regimen added fluconazole, 50 mg in the morning, N7.

21.09.2018 consultation: as part of the Deputy chief physician, head of the therapeutic Department №2, resuscitator. Conclusion: Undifferentiated seronegative spondyloarthritis, chronic course with the defeat of all parts of the spine: spondylitis, defeat of the ligamentous apparatus-syndesmophytes, sacroiliac joints, radiological stage 1 (sacroiliitis), high degree of activity, with extra-articular manifestations: fever, anemia, functional insufficiency of joints of 1 degree. Community-acquired pneumonia in stage of resolution. Ovarian hyperstimulation

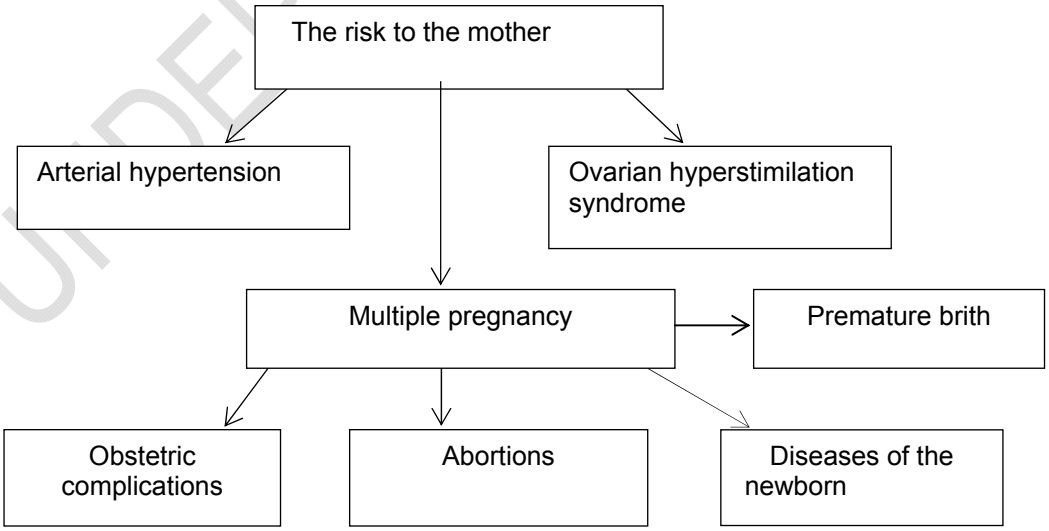
syndrome, polyserositis. Extragenital endometriosis. Infertility. Recommended: pelvic x-ray examination, blood test for vitamin D, Arcoxia 120 mg per day, 2 weeks, then 90 mg per day, 2 weeks, then 60 mg per day, long-term. Prednisolone is reduced by 2.5 mg (with a frequency of 1 every 3 days), with a decrease in the dose at lunchtime, to 25 mg per day. Calcium D3 in 22 h-1 tablet for the entire period of hormone therapy. Omeprazole 20 mg in the morning. Stop taking sulfasalazine. Iron preparations in combination with folic acid 1 time a day. The patient was discharged for further examination and treatment on an outpatient basis by a rheumatologist.

Laboratory 20.09.18: Glycemic profile: 3,7-6,2-5,8-5,47 mmol / L. 26.09.18: blood test for p-ANCA positive++, cANCA positive++, antibodies to DNA negative. The procalcitonin test is 0.6 (negative), HbA1C of 6.1%. Calcium total – 2,040 mg/DL. consult a hematologist 26.09.18: anemia normochromic, mild. In October 2018, at the Institute of rheumatology in Moscow, the patient underwent a bone marrow puncture and was diagnosed with a lymphoid variant of acute leukemia. Currently, the patient is being treated in the Hematology Department of the Regional Oncology center.

Dynamics of indicators Of C-reactive protein, dynamics of changes in the number of leukocytes		
	C-reactive protein, mg/l	leukocytes *10^9/l
27.08.18	162	15,4
28.08.18	204	13,5
31.08.18	189	12,0
3.09.18	24	10,0
6.09.18	58	5,5
13.09.18	-	12,9
17.09.18	74	-

4. DISCUSSION

Health risks associated with assisted reproductive technology



Ovarian hyperstimulation syndrome is a conscious violation of the physiological principle, aimed at the simultaneous maturation of 10-20 or more follicles to choose the best egg. As a result, multiple cysts are formed in the ovaries and the ovaries increase in volume. The

introduction of an ovulatory dose of chorionic gonadotropin increases the total volume inside the follicular fluid. It contains macrophages and cytokines involved in immune reactions. They are a trigger factor for the development of the disease.The blood receives abnormally high amounts of sex steroids and biologically active substances, vascular endothelial growth factor. Damaged endothelial cells of the inner shell of blood vessels. There is an activation of the renin-angiotensin-aldosterone system of the body, which is one of the links in the development of the pathological process. As a result of these mechanisms, the permeability of the walls of the capillary network of tissues of many organs to proteins that carry water increases. Hydrothorax, hydropericardium, ascites and, rarely, anasarca are formed. All symptoms of hyperstimulation syndrome occurred in our patient except for enlarged ovaries. We believe it was due to the hospitalization in critical condition 2 months after the onset of the disease. Moreover, the changes in blood, characteristic of leukemia, the patient was not. It may be a large number of macrophages and cytokines have led to a change in the immune system, and to a change in the epigenome. Insufficient methylation (hypomethylation) of the genome was one of the first identified epigenetic markers of cancer. Hypomethylation leads to the activation of genes, which normally should be silent. In the case of tumors, these are individual oncogenes that are in a healthy cell in a methylated (inactive) state. The decrease in the total level of genome methylation is expressed in the removal of natural repressive labels from oncogenes, which causes a cascade of destructive events. However, we must not forget that the lack of DNA methylation is as dangerous as its excess, and also causes a number of cancer pathology. For example, there is total demethylation of DNA in cancer cells against the background of high DNA-methyltransferase activity in chronic lymphocytic leukemia. Total removal of methyl labels has a significant destabilizing effect on the eukaryotic genome, changes the structure of chromatin, the degree of its condensation, the replication time, which can cause disturbances in the expression of various genes. We can not say why our woman developed lymphoblastic leukemia on the background of ovarian hyperstimulation syndrome. Moreover the patient had contraindications for ovulation induction procedure: the presence of polycystic ovaries syndrome and five-fold treatments of ovulation induction.

However, the consequences of this iatrogenic condition, its impact on the patient's health and on the subsequent course of pregnancy have not been studied.

Encouraging a woman or couple to perform artificial insemination is a manifestation of respect for their reproductive independence.

1.Reproductive independence is the right of a woman(or couple) to be independent(free) in controlling her Affairs and goals.

2.The right has always been presented as a negative right, that is, the right to non-interference in the reproductive decision and individual integrity.

On the other hand, this is a positive right. It means the right to help, that is, the obligation to help a woman (couple), if necessary.

But doctors are not allowed to help needy couples (women), if the health risk can not be minimized.

COMPETING INTERESTS

Authors have declared that no competing interests exist

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DEFINITIONS, ACRONYMS, ABBREVIATIONS

Here is the Definitions section. This is an optional section.

AST- aspartate aminotransferase
BP - blood pressure
CT - computer tomography
ECG – electrocardiogram
fT4 - free thyroxine
HbA1C - glycated hemoglobin
INR - international normalized ratio
HCG - Human chorionic gonadotropin
IVF - in vitro fertilization
NSAIDs - nonsteroidal anti-inflammatory drugs
OHS - ovarian hyperstimulation syndrome
PT - prothrombin time
RR - respiration rate
TSH - thyroid stimulating hormone