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OVARIAN HYPERSTIMULATION SYNDROME - AS A COMPLICATION OF OVULATION INDUCTION

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Resume

Despite such a well-developed medicine, the number of infertile couples increase every year and the problem of anovulation remains relevant. The solution to this problem is the induction of ovulation. Using of hormonal drugs, which stimulate ovulation, began in the second half of the 20th century. A serious complication of hormonal stimulation of the ovaries is hyperstimulated ovary syndrome (OHSS), which can be fatal. This syndrome was first described by Muller in the early 60s as a complication of ovulation stimulation using serum gonadotropins in mares in 1943 - as "massive ovarian hyperluteinization syndrome". The first lethal outcome from ovarian stimulation and such complication as OHSS was recorded in 1951 from renal failure.

Key words: ovulation induction, hyperstimulated ovary syndrome, hormonal drugs, follicles.

OVARIYA HIPERSTIMULATSIYASI TIZIMI - OVULATSIYA NAZORATINI QO'LLASH UChUN

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Rezyume,

Bunday rivojlangan tibbiyotga qaramasdan, har yili bepisht juftliklar soni ko'paymoqda va anovulyatsiya muammosi dolzarb bo'lib qolmoqda. Ushbu muammoning echimi ovulyatsiyani induksiya qilishdir. Ovulyatsiyani rag'batlantiruvchi gormonal dorilarni qo'llash XX asrning ikkinchi yarmida boshlangan. Tuxumdonlarning gormonal stimulyatsiyasining jiddiy asoratlari halokatli bo'lishi mumkin bo'lgan hiperstimulyatsiyalangan tuxumdon sindromidir (OHSS). Ushbu sindrom birinchi marta 60-yillarning boshlarida 1943 yilda maresdagi sarum gonadotropinlardan foydalangan holda ovulyatsiya stimulyatsiyasining asorati sifatida - "massiv tuxumdonlarning giperluteinizatsiya sindromi" sifatida tavsiflangan. Tuxumdonlarning stimulyatsiyasi va OHSS kabi asoratlarning birinchi halokatli natijasi buyrak etishmovchiligidan 1951 yilda qayd etilgan.

Kalit so'zlar: ovulyatsiya induksiyasi, giperstimulyatsiya qilingan tuxumdon sindromi, gormonal dorilar, follikulalar.

СИНДРОМ ГИПЕРСТИМУЛЯЦИИ ЯИЧНИКОВ – КАК ОСЛОЖНЕНИЕ ИНДУКЦИИ ОВУЛЯЦИИ

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Резюме,

Несмотря на столь развитую медицину, количество бесплодных пар с каждым годом возрастает и проблема ановуляции остаётся актуальным. Решение данной проблемы является индукция овуляции (ИО). Использование гормональных препаратов для стимуляции овуляции начато со второй половины XX века. Серьёзным осложнением гормональной стимуляции яичников является синдром гиперстимулированных яичников (СГЯ), который исход может быть и летальным. В первые данный синдром был описан Muller в начале 60-х годов как осложнение стимуляции овуляции с помощью сывороточного гонадотропинов жеребых кобыл в 1943 году - как "синдром массивной гиперлутеинизации яичников". Первый летальный исход от ИО и как его осложнение СГЯ зафиксировано в 1951 году от почечной недостаточности.

Ключевые слова: индукция овуляции, синдром гиперстимулированных яичников, гормональные препараты, фолликулы.

Relevance

Hyperstimulated ovary syndrome - occurs during the luteal phase or during pregnancy, which is a serious complication of ovulation induction. The occurrence of OHSS according to various sources varies from 2.5 to 44%. According to Shenker and Weinstein, the incidence of mild OHSS is 8-23%, moderate 0.005 to 7%, and severe from 0.008 to 10%. To date, there are reports in the literature on the development of OHSS using almost all known hormonal ovulation inducers: clomiphencitrate, chorionic gonatropin (CG), human menopausal gonatropin (hMG), and pure follicle-stimulating hormone [1,5,6]. And also, there is evidence of sporadic cases of signs of OHSS due to an increase in endogenous secretion of

gonadotropins, which was due to multiple pregnancy, cystic drift and the presence of luteal cysts[1].

Classification.

The first classification of OHSS, based mainly on the response of the ovaries, was proposed in 1967 by E. Rabau et al. In 1978, J. Schenker and Weinstein introduced changes in which the OHSS was divided into three categories and six degrees of severity (Table 1) [15].

Table 1. Classification of ovarian hyperstimulation syndrome.

Degree	Ovarian Diameter (cm)	Stage	The level of estrogen-E ₂ , PG / ml	Symptoms
Mild	<6	1	1500–2000	There are no clear symptoms
		2	1500-4000	Abdominal stress and discomfort
Moderate	6 - 12	3	> 4000	Mild + ultrasound signs of ascites
		4	4000-6000	Mild + vomiting, nausea, diarrhea
Severe	12	5	> 6000	Medium + clinical signs of ascites, pleural effusion, liver dysfunction
		6	> 6000	Medium + intense ascites, blood concentration (hematocrit > 45%), increased blood viscosity, decreased renal perfusion, oliguria, thromboembolism, RDSV, hypovolemic shock

In 1992, D. Navot et al. for the first time, severe and critical forms of ovarian hyperstimulation syndrome were identified (Table 2).

Table 2. Classification of severe and critical forms of OHSS.

Severe OHSS	Critical form of OHSS
Enlarged Ovaries	Enlarged Ovaries
Massive ascites ± hydrothorax	Stressed ascites ± hydrothorax
Hematocrit > 45%	Hematocrit > 55%
White blood cells > 15 10 ⁹ g / l	White blood cells > 35 10 ⁹ g / l
Oliguria	Oliguria
Creatinine 1–1.5 mg% (88–132 µmol / L)	Creatinine 1.6 mg% (141.3 µmol / L)
Liver dysfunction	Renal failure
Anasarca	Thromboembolism, RDS

Pathogenesis

Ovarian hyperstimulation syndrome develops against the background of abnormally high concentrations of steroid hormones in blood plasma. In this connection, there is a syndrome of

excessive vascular permeability with a massive exit of fluid, rich in proteins in the extravascular space - this is interstitium, and the formation of ascites, hydrothorax and anasarca [3,8]. Namely, “factor X” which is produced by hyperstimulated

ovaries and causes fluid transudation. The pathophysiology of hyperstimulated ovary syndrome is studied in three directions: the role of activation of the renin-angiotensin system, the relationship of the immune system and ovaries, the role of vascular endothelial growth factor. Under the influence of pro-inflammatory cytokines, systemic activation of coagulation processes occurs. Severe hypercoagulability is an integral part of the pathogenesis of the systemic inflammatory response syndrome. They discuss the role of the microbial factor in the development of OHSS - microorganisms that colonize the intestine, genitourinary tract, can penetrate beyond their environment and have an effect on the body similar to that in sepsis [9,12]. The pathophysiology of spontaneously occurring during pregnancy, as well as family recurring episodes of this syndrome in subsequent pregnancies that are not associated with the induction of ovulation, are associated with a FSH receptor mutation.

Under the influence of estrogens, the permeability of the vascular wall of the veins of the ovaries, vessels of the peritoneum, omentum and pleura increases. Rapid filtration of the liquid part of the blood into the abdominal and / or pleural cavity, pericardium leads to hypovolemia and hemoconcentration. Hypovolemia causes a decrease in renal perfusion with the development of oliguria, electrolyte imbalance, hyperkalemia and azotemia; there is hypotension, tachycardia, an increase in hematocrit, hypercoagulation. Angiotensins activate vasoconstriction, biosynthesis of aldosterone, prostaglandins, increase vascular permeability and neovascularization. Also, the role of the ovarian immune system in the induction of OHSS is very large: macrophages are located in the follicular fluid, which are the source of cytokines, play a role in steroidogenesis, luteinization of granulosa cells, and neovascularization of developing follicles[4].

Table 3. This table shows the risk factors for the development of OHSS.

Women at High Risk for OHSS	Women at Low Risk for OHSS
Young age (<35 years)	Age 36 and over
Polycystic Ovary Syndrome	“Calm” ovaries
Low Body Mass Index - Asthenic Body Type	Obesity
High serum estradiol (E2) activity	Low serum estradiol (E2)
An increase in the number of developing follicles	Several mature follicles
Pregnancy	Barren cycle
The introduction of high or repeated doses of exogenous Chorionic gonadotropin (CG) to support the luteal phase	Luteal phase support with progesterone
Allergic reactions	Lack of allergic reactions
History of OHSS	No history of OHSS
Ovarian stimulation with GnRH agonists	Stimulation with clomiphene citrate and / or hMG

Clinical and laboratory substantiation of intensive care:

- * hemoconcentration, hypovolemia, hypoproteinemia, electrolyte imbalance;
- * hematocrit exceeds 45%;
- * white blood cell count > 15 x 10⁹ / l;
- * signs of liver dysfunction - increased activity of transaminases (ALT, ACT), alkaline phosphatase, bilirubin content;
- * coagulation parameters of blood always change - a high level of fibrinogen, D-dimer, a decrease in the concentration of antithrombin III[9,13].

Antimüller hormone (AMH) is also being studied to study the ovarian response. It is

represented by granular cells of the preantral and small antral follicles and AMG is a measure of the ovarian reserve.

Treatment of mild OHSS is carried out on an outpatient basis. It includes a daily assessment of weight and urine output, limiting excessive physical activity and sexuality, drinking fluids as needed (only to quench thirst) [2,6].

In other degrees of severity, patients are hospitalized for treatment in a hospital.

With OHSS, hypovolemia always develops as a result of the movement of fluid into the extravascular space. During the “active phase” of OHSS, the reabsorbed fluid is transferred to the extravascular space. This enhances hypovolemic

disorders, contributes to the progression of ascites. Swelling slows down the delivery of oxygen and impairs the function of tissues and various organs. Long-term hypovolemia leads to a narrowing of the lumen of afferent arterioles, a decrease in the perfusion ability of the renal parenchyma, resulting in renal failure, which is one of the most serious complications of OHSS. In this regard, the intensive care program must necessarily include prosthetics of plasma oncotic insufficiency by prescribing solutions of colloids. The main purpose of colloid prescribing is to restore and maintain adequate perfusion and function of vital organs such as the kidneys. Ascites is the first manifestation of the phenomenon of increased vascular permeability (a characteristic feature of OHSS) and may be accompanied by pleural and / or pericardial effusions. The onset of ascitic fluid accumulation can only be detected by ultrasound[1,7]. Hydrothorax often acts as a result of the sweating of ascitic fluid through the diaphragmatic lymphatic vessels and more often occurs on the right side. Severe cases of OHSS have been repeatedly reported, in which the only sign, with the exception of enlarged ovaries, was extensive hydrothorax. This emphasizes that with the development of the syndrome, a combination of all clinical signs is completely optional.

High concentrations of sex steroid hormones and vascular endothelial damage cause hepatocellular and cholestatic changes. Laboratory signs of liver dysfunction are: increased levels of bilirubin, the activity of transaminases and alkaline phosphatase against hypoproteinemia. Cases of jaundice are described, which stopped within 4 weeks without special treatment. When examining patients with impaired liver function against a background of OHSS, it is necessary to exclude other possible causes of the identified disorders, including hepatitis A, B, C, cytomegalovirus infection, Epstein-Barr virus infection, and others. Ultrasound of the liver eliminates biliary tract pathology[3,10].

A high concentration of sex steroid hormones and damage to the endothelium of the vascular wall contribute to a change in blood coagulation parameters. The exact frequency of thromboembolism is not known. In the literature, it has been reported that approximately 10% of patients with severe OHSS have this complication. In the structure of thrombosis with the syndrome, venous prevail (75%). The most commonly diagnosed are deep vein thrombosis, jugular, subclavian and inferior vena cava. The

frequency of arterial thrombosis is about 25%. Cerebral, vertebral, subclavian arteries, lower carotid artery, femoral and mesenteric arteries, aorta can be affected[4,8].

Daily monitoring of clinical and laboratory parameters is required[1, 5]:

- Careful monitoring of changes in the severity of OHSS and the diagnosis of possible complications.
- Assessment of fluid balance - daily measurement of abdominal circumference, assessment of body weight and urine output.
- Hemodynamic parameters - blood pressure, pulse, heart rate, respiratory rate, ECG, CVP and echocardiography.
- Ultrasound - an assessment of the size and structure of the ovaries, the state of internal organs, the identification of polyserositis.
- Chest x-ray according to indications
- Blood tests must be taken at least 1 time per day - Ht, Hb, the content of red blood cells, platelets, white blood cells.
- Urinalysis - density, proteinuria.
- Biochemical blood test - protein level, ALT and AST activity, water-electrolyte state, creatinine clearance, plasma osmolarity.
- Determination of hCG in plasma for early diagnosis of pregnancy.
- Assessment of the blood coagulation system.
- There is no need for constant monitoring of the hemostasis system at normal rates.
- Many authors recommend controlling the activity of the kinin system of blood plasma, since its activation leads to thrombosis.

Signs of worsening conditions include increased pain, oliguria, increased body weight, difficulty breathing. In the acute stage of severe OHSS, patients may experience a 20% deficiency of bcc. However, in 1/3 of patients in the recovery stage, hypervolemia occurs[2]. In connection with the release of fluid into the extravascular space, hypovolemia is formed with a violation of the water-electrolyte state. A clinical sign reflecting these complex pathogenetic mechanisms is thirst. The drinking regimen of these patients should not be limited. Parenteral administration of antiemetics (metoclopramide) is necessary. While maintaining nausea and vomiting, infusion therapy is performed to correct dehydration and maintain fluid requirements with hydroxyethylated starch (HES) solutions in combination with crystalloid solutions. Criteria for the effectiveness of infusion therapy: blood pressure, heart rate, hourly rate of diuresis,

hematocrit, plasma oncotic pressure. In severe cases, with Ht > 45% and a serum albumin level of 20.0 g / l, human albumin (200 ml of a 20% solution) can be used. The binding of the drug to albumin is important for the delivery of the furosemide loop diuretic to its site of action in the kidneys, namely to the ascending knee of the Henle loop. Furosemide binds primarily to plasma albumin, and this furosemide-albumin complex interacts with the carrier of the tubule epithelial cell anion. Hypoalbuminemia reduces the delivery of furosemide bound to albumin. The following indications for the use of human albumin are currently agreed [2,3]:

- Hypoalbuminemia (plasma albumin concentration of 20.0 g / l).
- Intolerance to artificial colloids.
- Exceeding the maximum permissible dose of artificial colloid solutions.

Albumin has been used to maintain diuresis and resolve edema in patients with nephrotic syndrome since the 1940. There is evidence to suggest that colloids can better support kidney function than crystalloids. HES is synthesized by partial hydrolysis of corn starch from amylopectin [6].

If hemoconcentration and / or oliguria persist, despite these measures, it is necessary to remember about paracentesis. Despite the generally accepted use of dopamine in small doses in order to improve renal perfusion, its effect on increasing the rate of urine output and excretory function of the kidneys has not yet been determined from the standpoint of evidence-based medicine. For pain relief, paracetamol can be used [8]. With severe pain, parenteral administration of opioids. NSAIDs increase the risk of developing renal failure, and their use is not recommended. It must be remembered that pain can be associated with ectopic pregnancy or ovarian apoplexy. Surgical intervention should be performed only by an experienced surgeon, minimized, because hyperstimulated ovaries are easily injured[15].

OHSS is a risk factor for thrombosis. Activation of the plasma kinin system and leukocytosis > 22000 / ml are signs of inevitable thromboembolism. These complications can occur not only in the acute stage of the syndrome,

but also during an improvement in the course of this iatrogenic disease. The high-risk group for the development of thromboembolic complications includes patients with severe OHSS. This necessitates the appointment of low molecular weight heparin. Women with less severe forms of the syndrome, but having a history of a change in coagulation status, should also receive low molecular weight heparin for prophylactic purposes [10].

Paracentesis is indicated for severe ascites when it causes respiratory distress and pain. It is performed under the supervision of an ultrasound to prevent injury to the enlarged ovaries and the occurrence of bleeding. When removing a large amount of ascitic fluid, infusion therapy with colloids in combination with crystalloids is performed. Ascitic fluid with OHSS contains a large number of pro-inflammatory cytokines, and their excretion accelerates recovery[3].

At the same time, ascites contains a large amount of protein. To eliminate protein loss, reinfusion of ascitic fluid after filtering is proposed. It is possible to impose a peritoneal-venous shunt in severe or critical forms of OHSS. However, subject to all aseptic rules and reducing the risk of infection, there remains the risk of vasoactive mediators entering the bloodstream [4].

Not all syndrome prevention methods used earlier are effective and justified today. In 1993, it was suggested that the intravenous administration of 25% albumin at a dose of 50 g during follicular puncture would prevent the development of severe OHSS. The analysis of the accumulated data showed that in only one case for 18 patients this method of prevention was effective and therefore its introduction is considered unreasonable [8,12].

Conclusions

Unfortunately, an analysis of the studied literature shows that at present there are no absolutely reliable criteria, given that it would be possible to completely prevent the development of OHSS. In this regard, the continuation of the study of pathogenesis, the improvement of prevention methods, timely diagnosis, severity assessment and adequate intensive care are of particular importance.

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