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PREGNANCY AND VIRAL HEPATITIS, AND THEIR LABORATORY DIAGNOSTICS

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Abstract: This review article examines data on the characteristics of the course of hepatitis of viral etiology in pregnant women, clinical and laboratory signs of extraheparal manifestations of chronic viral hepatitis. Diagnostic laboratory indicators of hemochromatosis, autoimmune hepatitis, intrahepatic cholestasis, acute fatty liver degeneration, and HELLP syndrome are quite significantly indicated here.

Key words: pregnancy, viral hepatitis, extrahepatic manifestations of hepatitis, autoimmune hepatitis, hemochromatosis, intrahepatic cholestasis, acute fatty liver, HELLP syndrome.

When preparing a woman for pregnancy, it is important to assess the state of her health, including the hepatobiliary system. Many pathological conditions of the liver can be corrected or cured before conceiving the unborn child.

The high prevalence of viral hepatitis B, C, D with a chronic, often anicteric course makes their screening diagnosis necessary in women at the preconceptional stage. With the onset of pregnancy, women with chronic viral hepatitis (CVH) not verified in a timely manner and practically asymptomatic liver cirrhosis (LC) may experience decompensation with the development of liver failure, bleeding from varicose veins, spontaneous miscarriages, postpartum hemorrhage and etc. For the laboratory diagnosis of chronic hepatitis, the following tests are used: HbsAg, anti-Hbcor IgG, anti-HCV IgG (total) and anti-HDV IgG (in the presence of positive markers of viral hepatitis B) [1].

In addition to the clinical manifestations of chronic liver pathology - severe pathological fatigue, asthenodepressive syndrome, darkening of morning urine, discoloration of stools, subicterricity of the mucous membranes and sclera, dyspepsia, bitter speech in the mouth and telangiectasia - extrahepatic manifestations of chronic hepatitis B (CHB) can first be diagnosed) and chronic hepatitis C (CHC). These include disorders of carbohydrate metabolism - impaired glucose tolerance test, insulin resistance and type 2 diabetes. Elimination of HBV and HCV leads to a significant improvement in carbohydrate control and is the prevention of clinical manifestations of diabetes in pregnant women [2].

The persistence of hepatitis B and C viruses in some patients induces the development of autoimmune Hashimoto's thyroiditis with lymphomonocytic infiltration of thyroid tissue (thyroid gland) and the development of hyper or hypothyroidism. Patients with long-term unverified increased thyroid function often turn to cardiologists and therapists about high blood pressure, hypertensive crises of the sympathicotonic type with high pulse pressure, tachycardia, and extrasystole. Also, thyrotoxic conditions contribute to women turning to obstetricians-gynecologists with dysamenorrhea, miscarriage, to gastroenterologists - with chronic diarrhea, to infectious disease specialists - with parainfluenza or fever of

unknown origin, to oncologists - with progressive loss of body weight, severe weakness, high ESR, to psychiatrists and neurologists - with anxiety, insomnia, hand tremors, asthenodepressive syndrome. All these clinical manifestations are an indication for studying the level of free T3, T4 (increased) and thyroid-stimulating hormone (TSH) in the blood serum (decreased), antibodies to TSH receptors (increased) in hyperthyroidism. In the presence of antibodies to thyroid tissue - antithyroid peroxidase, antithyroglobulin, antimicrosomal antibodies and a diagnosis of "autoimmune thyroiditis", verification of chronic hepatitis B and C virus (HbsAg and anti-HCV total (IgM + IgG)) is reasonable. [7].

Extrahepatic manifestations of CHB and CHC should also include many symptoms of somatic pathology. Hematological manifestations of chronic viral hepatitis include: mixed cryoglobulinemia, idiopathic thrombocytopenia, non-Hodgkin large B-cell lymphoma, Waldenström macroglobulinemia, aplastic anemia. Skin extrahepatic manifestations of chronic hepatitis include: porphyria cutanea tarda, cutaneous necrotizing vasculitis, lichen planus, erythema multiforme, erythema nodosum, urticaria. CVH negatively affects the renal parenchyma with the development of cryoglobulinemic glomerulonephritis with severe generalized edema. Neuromuscular and articular manifestations of chronic viral hepatitis B and C include: peripheral polyneuropathy, polyarthritis, arthralgia, Guillain-Barré syndrome [8].

In all these clinical situations, it would be reasonable to look for markers of CHB, and especially CHC, using screening laboratory tests. The triggering nature of the hepatitis C virus is due to the fact that, like HIV, the antigenic structure of HCV changes in the body of patients very quickly - within 20-30 minutes, and the synthesis of antibodies to the antigen occurs within several hours. Therefore, in the serum of these patients, antibodies to HCV accumulate in high concentrations, which do not have an antiviral effect, but induce the development of autoimmune and immune complex pathologies in the internal organs [9, 10].

When HbsAg is detected, to clarify the diagnosis, the amount of HBV in the blood serum is determined using polymerase chain reaction (PCR) (up to 500 thousand copies - low concentration, from 500 thousand to 2 million - medium, more than 2 million - high). The replicative variant of chronic viral hepatitis B is characterized by the presence of HbeAg in the blood serum, and when hepatitis is transformed into an integrative variant, the disappearance of HbeAg and the appearance of IgG antibodies to HbeAg. The body's serological response to HBV can be monitored in the laboratory using anti-Hbcor IgM, which can increase in the presence of acute hepatitis B or exacerbation of CHB if the patient simultaneously has anti-Hbcor IgG detected in the blood serum. With successful vaccination or a history of hepatitis B (including in the anicteric form), anti-Hbs IgG antibodies are detected in the serum of patients [11].

In clinical practice, it is important to exclude the presence of hepatitis D virus (HDV) in patients with chronic hepatitis B, which is always a coinfection with HBV, is difficult to eliminate and often contributes to the chronicity of the disease. These viral hepatitis B and C as potential triggers of autoimmune damage to the thyroid gland [6].

Patients with reduced thyroid function (hypothyroidism) can unsuccessfully consult many doctors for years, including obstetricians-gynecologists, with dysmenorrhea, miscarriage, and resistant iron deficiency. Memory impairment, asthenodepressive syndrome, and dizziness cause these patients to turn to psychiatrists and neurologists; hypotension, bradycardia - see cardiologists; persistent constipation - see a gastroenterologist; dry, hard skin, aggressive hair loss - see a dermatologist; pasty face, tendency to edema - see nephrologists. In all these clinical situations, laboratory verification of hypothyroidism (T3, T4 free are reduced, TSH is increased) against the background of autoimmune thyroiditis is advisable and examination of women for the presence of anicteric forms of the virus is verified by the presence of specific antibodies anti-HDV IgM and IgG, PCR for HDV [12].

When verifying CHC, in addition to quantitative assessment of the HCV virus in blood serum, the HCV genotype is examined. The most aggressive and rapidly progressing genotypes are 1a, 1b, the most

prognostically favorable is the 3rd HCV genotype. The importance of this test has decreased somewhat due to the introduction of pangenotypic treatment of CHC into clinical practice. The use of combinations of interferon-free therapy is contraindicated during pregnancy and breastfeeding, therefore early verification and treatment of CHC before conception prevents the progression of liver pathology during pregnancy [13].

In all these clinical situations, after verification of CHB and CHC, it is advisable to assess the intensity of cytolysis, cholestatic syndrome (GGTP, ALP), protein-synthetic liver function (albumin, globulins), blood coagulation factors (coagulogram), iron overload syndrome (ferritin). In addition to elastography, the most effective in assessing the severity of fibrosis, hepatitis activity, and steatosis of the liver parenchyma is FibroMax (Fig. 1). This is a complex biochemical method of performing a puncture-free biopsy, which allows one to assess the real condition of the liver tissue in a network of laboratories certified for this study, for example, Sinevo, without resorting to invasive technologies [14].

The group of patients most vulnerable to the development of autoimmune pathology are women aged 20 to 40 years. With long-term use (without immunological control) of immunocorrective drugs, biologically active additives, and many medications, the initiation of autoimmune and immune complex reactions in this group of patients is possible. With the development and progression of autoimmune hepatitis (AIH), rapidly progressing jaundice, fever, arthralgia, abdominal pain, itching, and hemorrhagic rashes occur. Systemic manifestations are also characteristic: pleurisy, pericarditis, myocarditis, ulcerative colitis. Lesions of the thyroid gland, polylymphadenopathy, hemolytic anemia, and diabetes occur less frequently [15].

Laboratory methods for verifying autoimmune hepatitis include the autoimmune liver panel, which includes 6 diagnostically important parameters. During serological verification of AIH type 1, anti-smooth muscle antibodies (SMA) and antinuclear antibodies (ANA) are found in the blood serum. SMA is detected in 60–80% of cases of AIH, in half of the cases of primary biliary cirrhosis and is not detected in systemic lupus erythematosus and extrahepatic lesions of the biliary tract. During immunosuppressive therapy of patients with type 1 AIH, the disappearance of SMA and/or ANA is observed, which is a criterion for serological remission of the disease [16].

Antibodies to liver and kidney microsomal antigen (LKM-1) serve as the main diagnostic marker of AIH type 2, which is observed mainly in young people and children. The production of antibodies to LKM-1 can be induced not only by autoimmune mechanisms, but also by certain drugs (phenobarbital, carbamazepine, halothane, phenytoin, etc.). This marker is used to diagnose AIH-2, as well as to monitor the effectiveness of immunosuppressive treatment [18].

Searching for a potential trigger for AIH is prognostically important. If the doctor finds and excludes from the prescription a specific drug that causes autoimmune liver damage, the prognosis of AIH improves significantly. So, if with drug-induced AIH the 5-year survival rate is more than 80%, then with cryptogenic it is less than 30% [11].

When pregnancy occurs, women suffering from AIH may experience improvement or sometimes remission of hepatitis. In these cases, pharmacotherapeutic titration of immunosuppressive treatment is performed. The postpartum period, when the physiological mechanisms of immunosuppression in pregnant women decrease, is dangerous in this group of patients. An increase in the level of gamma globulins and IgG, an increase in cytolysis, cholestasis, a secondary immunodeficiency state according to the relative hyposuppressive variant, an increase in the concentration of hepatic autoantibodies indicate the need to resume intensive immunosuppressive treatment [12].

The combination of cirrhosis and pregnancy is uncommon, since progressive fibrotic changes in the liver provoke dysamenorrhea and anovulation. If pregnancy occurs in patients with cirrhosis, maternal mortality increases, two thirds of which are caused by massive bleeding from the veins of the esophagus, and a third by liver failure syndrome. In women with cirrhosis, the number of spontaneous abortions, premature births,

postpartum hemorrhages significantly increases, and the level of perinatal mortality increases. It is important to verify CP and the level of its compensation using elastography, the FibroMax test, proteinogram, coagulogram, bilirubin level, severity of cytolytic and cholestatic syndromes. If it is impossible to perform fibrogastroduodenoscopy in a pregnant woman with cirrhosis, the thrombocytopenia indicator is used, which, if the value is less than 110 • 109/l, indicates the presence of varicose veins of the esophagus with high sensitivity and specificity [17].

During pregnancy, unvaccinated women (lack of anti-Hbs antibodies) may experience clinical manifestations of acute HBV or exacerbation of CHB. In addition to dyspeptic symptoms and jaundice syndrome, polyarthromyalgia and increasing fatigue are possible. To verify HBV, screening tests are used - HbsAg and anti-Hbcor IgG. If HbsAg is detected, the amount of HBV in the blood serum is determined using PCR to clarify the diagnosis. The replicative variant of CHB is characterized by the presence of HbeAg in the blood serum, and when hepatitis is transformed into an integrative variant, the disappearance of HbeAg and the appearance of antibodies to HbeAg IgG. With successful vaccination or a history of hepatitis B (including in the anicteric form), protective anti-Hbs IgG antibodies are detected in the serum of patients [14].

To prevent perinatal HBV infection, which occurs mainly during childbirth, a combination of passive and active immunization with specific immunoglobulin (HBIg) and the administration of an HBV vaccine are used. If the mother has a replicative variant of CHB (HbeAg+) with a high level of viremia - more than 200 thousand IU/ml or an HBsAg level of more than 4 log10 IU/ml, even with the use of specific immunoglobulin and vaccination, a high percentage of vertical transmission of the infection to the child is observed. Therefore, it is advisable to prescribe Tenofovir in the 3rd trimester of pregnancy with continued use for 3 months after birth under the control of quantitative HBV PCR, indicators of cytolytic syndrome (prescription of the only approved hepatoprotector during pregnancy - heptral), cholestasis, and study of the FibroMax test indicators. It should be noted that breastfeeding during treatment with Tenofovir is not a contraindication for HBsAg-positive women due to the low concentration of HBV in breast milk and the low bioavailability of this drug for the child [18].

Treatment of CHC in pregnant women does not allow the use of drugs from the group of interferons, ribavirin, as well as modern drugs for interferon-free pangenotypic therapy (sofosbuvir, velpatasvir, ledipasvir, etc.). If treatment for CHC occurred before pregnancy, then at least 3-4 months should pass between the last tablet of these drugs and the conception of the child, and to prevent possible adverse consequences for the fetus, a woman who is not planning a pregnancy should use reliable contraception [4].

When using even approved medications during pregnancy, drug-induced idiosyncratic hepatitis of autoimmune etiology may occur due to sensitization to haptens—complexes of the drug and blood proteins. This condition is accompanied by an increase in the activity of the cytolytic enzymes ALT, AST, markers of cholestasis GGTP, ALP and requires exclusion from the prescription of the maximum number of drugs, vitamins, dietary supplements and the prescription of hepatoprotective therapy and antioxidants.

Among the systemic metabolic changes, hemochromatosis (HC), or iron overload syndrome, which is accompanied by a significant increase in iron content in a woman's body, should be noted. In this disease, iron is redistributed from the blood serum into the blood transport protein (transferrin) and further into the liver tissue, pancreas, heart and skin, where it accumulates in the form of ferritin. HC is accompanied by cytolysis of hepatocytes, cholestasis, progression of liver fibrosis, diabetes mellitus, "rusty" color of the skin and mucous membranes, cardiomyopathy with arrhythmias, memory impairment and dizziness [5].

Asymptomatic hemochromatosis is most insidious in pregnant women with iron deficiency anemia. When studying in this group of patients only a clinical blood test and the level of free iron in the blood serum, anemia with low levels of red blood cells, hemoglobin, hematocrit, and a reduced level of free iron

concentration in the blood serum will be established. The natural desire of the doctor will be to prescribe iron supplements to compensate for anemia, but in the case of iron overload syndrome (hemochromatosis), all the iron received by the woman will be redistributed into the liver tissue with the accumulation of ferritin and will cause intense cytolysis of hepatocytes with frequent fetal loss. Therefore, in the presence of iron deficiency conditions, especially in pregnant women and patients with CHC, it is mandatory to study all three indicators of iron metabolism: free iron, transferrin saturation with iron and ferritin level.

The conditions described above in pregnant women are comorbid and are not caused specifically by the pathology of pregnancy. The second group includes diseases that are directly related to the course of pregnancy, and in some cases only immediate delivery saves the life of both mother and child [9].

In the first trimester, women often experience uncontrollable vomiting of pregnancy (UGP), which is predisposed to: hyperthyroidism, diabetes mellitus, obesity, age under 25 years, multiple pregnancy, mental disorders and a female fetus. This condition is accompanied by nausea, severe vomiting, sometimes leading to malnutrition, dehydration, electrolyte imbalance (hypokalemia, hyponatremia, hypomagnesemia), jaundice, decreased body mass index, ketoacidotic conditions and increased activity of serum transaminases (usually AST activity exceeds ALT) more than in half of the patients. Typically, NRP lasts until the 20–22nd week of pregnancy and can provoke late complications: placental insufficiency, premature birth, preeclampsia [1].

The most common problem in the second and third trimester (usually after the 30th week) associated with liver pathology is intrahepatic cholestasis of pregnancy (ICP). Pathogenetically, this condition is caused by the increased sensitivity of hepatocytes to sex hormones, hereditary disorders of the enzymes responsible for bile formation and bile outflow. ICP is accompanied by generalized skin itching (usually the soles and palms), worsening at night, jaundice, dark urine, discolored stool [2]. Risk factors for the development of ICP include long-term use of contraceptives, a history of frequent antibiotic therapy, family history, multiple pregnancies, cholelithiasis, and non-alcoholic steatohepatitis (NASH). This condition of the pregnant woman should stop after childbirth, but if laboratory indicators of cholestasis (bile acids, GGTP, ALP, cholesterol, triglycerides), cytolysis (ALAT, AST, especially with NASH) remain elevated after the birth of the child, it is necessary to conduct a comprehensive examination of the woman to exclude primary biliary cholangitis, AIH and primary sclerosing cholangitis. In these cases, ICP should be regarded as the onset of progressive chronic liver pathology [6].

In severe cases of ICP, the development of a stage of hypercoagulation is possible - disseminated intravascular coagulation syndrome (DIC) with an increase in thrombin levels, a decrease in the concentration of antithrombin, thrombocytopenia and the formation of multiple intravascular thrombi. After childbirth, women with ICP also have an increased risk of postpartum hemorrhage due to reduced levels of vitamin K, so intramuscular administration is recommended. [8].

The most dangerous conditions of pregnant women that require immediate delivery include acute fatty liver degeneration (AFLD). This condition occurs in the 3rd trimester with a peak at 36–37 weeks and is characterized by diffuse fatty degeneration of the liver parenchyma without inflammation and necrosis, with high mortality due to acute liver failure. Factors that provoke mitochondrial cytopathy in AFDP include: a genetic defect of enzymes that oxidize fatty acids (FA) (LCHAD deficiency) in the first-time mother; a male fetus with an acquired genetic defect in FA oxidation (LCHAD deficiency) or Reye's syndrome in a previous child; use of tetracyclines or valproic acid in high doses; recurrent vomiting leading to protein deficiency; low maternal body mass index; multiple pregnancy [5].

Clinically, ARDP begins with severe weakness, headache and dyspeptic symptoms - nausea, abdominal pain, vomiting, unbearable heartburn. Next comes the icteric stage of the disease: icterus and hemorrhagic rash on the skin and mucous membranes, generalized itching, wavy nature of the soporous state in hepatic

encephalopathy. Hepatosplenomegaly is rarely verified on ultrasound, but ascites, portal hypertension and swelling of the pancreatic parenchyma (acute pancreatitis) are characteristic. The blood reveals hypoproteinemia, hypoalbuminemia, hypoglycemia, a sharp decrease in blood coagulation factors (DIC - consumption coagulopathy), hyperleukocytosis more than 40 • 109/l; hyperbilirubinemia (15–20 times higher than normal), hypertransferasemia (AlAT, AST up to 300 U/l), high alkaline phosphatase activity (5–8-fold increase), decompensated metabolic acidosis. Progression of the condition is accompanied by arterial hypertension, edema, proteinuria, bleeding from the upper gastrointestinal tract, hepatic encephalopathy and acute renal failure with a significant increase in serum concentrations of cystatin C, creatinine, and urea. When a pregnant woman is diagnosed with AFDP, immediate delivery is indicated, preferably via cesarean section (if safe induction of labor cannot be carried out within 24 hours), against the background of compensatory pathogenetic treatment (correction of disseminated intravascular coagulation, hypoglycemia, arterial hypertension, renal failure). In women who have undergone AFDP, the condition of the liver after childbirth is quickly compensated with the normalization of biochemical markers of cytolysis and cholestasis [11].

A special place in the practice of obstetricians and gynecologists is occupied by HELLP syndrome, which includes: hemolysis, increased activity of liver enzymes, and a decrease in the number of platelets. This is a dangerous complication for the mother and fetus that occurs in the second or third trimester of pregnancy and sometimes in the postpartum period [13].

The maximum risk of developing HELLP syndrome is created by the first symptoms of progressive PE, which necessitates careful laboratory monitoring of the liver condition in these pregnant women. HELLP syndrome is accompanied by hemolysis, severe cytolytic syndrome with high activity of serum ALT, AST, severe thrombocytopenia, complicated by acute liver failure, DIC syndrome, multiple organ failure, liver ruptures and hematomas of various locations. Prognostically unfavorable blood parameters for the progression of HELLP syndrome are: more than a 4-fold increase in the concentration of indirect bilirubin; increased ALT activity more than 70 IU/l; thrombocytopenia less than 100,000/mm3; lactate dehydrogenase activity more than 600 IU/l; impaired coagulation (increased activated partial thromboplastin time, decreased prothrombin index, low fibrinogen level); severe proteinuria. If HELLP syndrome is suspected, immediate ultrasound of the abdominal organs is mandatory for early verification of hemorrhage in the liver, its rupture and infarction [9].

After emergency delivery, laboratory parameters in postpartum women with HELLP syndrome begin to improve within 2 days after birth [9].

Thus, before conceiving a child, at all stages of pregnancy, during the three trimesters and after delivery, women need laboratory monitoring of the condition of the liver for timely verification of its pathology and the prescription of pathogenetically based treatment.

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