Peculiarities of the Pregnancy in Women with Hepatobiliary System Pathology

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Abstract

During pregnancy, there is a significant restructuring of various organs and systems, including liver functions. Due to the increase in circulating blood volume, most indicators of liver function may differ from their level in non-pregnant women. In the liver of pregnant women, the synthesis of a large class of proteins (excluding immunoglobulins), fibrinogen, prothrombin, blood coagulation factors (V, VII, X, XI, XII, XIII), fibrinolytic factors (antithrombin III, proteins C and S) increases. Hepatic enzymes (serum transaminases, γ-glutamyltranspeptidase), as well as the bilirubin content do not change during the physiological course of pregnancy[1].

Keywords: *Pregnancy, cholestasis, syndrome, acid, intrahepatic, preeclampsia.*

Introduction

Alpha-fetoprotein (AFP) is produced by the fetal liver and usually its level in the blood increases[2]. Alkaline phosphatase can be increased in the third trimester, due to its production by the placenta and the development of bone tissue of the fetus[3].

At the end of II and III trimesters, 50% of pregnant women may experience clinically insignificant varicose veins of the esophagus, resulting from compression of the inferior vena cava by the enlarging uterus and a decrease in venous return[4].

Altered hepatic tests are found in 3-8% of all pregnancies [5]. The main causes of liver pathology are very diverse. Traditionally, they are divided into related and not related to pregnancy [6]. The liver pathology that developed during pregnancy includes indomitable (excessive) vomiting of pregnant women, acute fatty hepatosis, pregnant HELLP syndrome, and intrahepatic cholestasis of pregnant women.

Non-pregnancy related liver pathology is represented by acute viral hepatitis, cirrhosis and portal hypertension, liver tumors, bile duct diseases, etc.

A mortality rate of 0 to 25% has been reported among mothers with liver diseases associated with pregnancy. According to Carmen S. G. et al., Liver diseases that occur during pregnancy were observed in 11.24% of pregnant women attending the National Institute of Perinatology in Mexico City over a three-year period. Concomitant liver diseases were found in 10.8% of patients, mainly associated with preeclampsia (9.9%). Only in 0.56%, preeclampsia was caused by a liver disease that existed earlier: acute or chronic HCV detected in this group (0.12%) [7].

Indomitable pregnant vomiting (hyperemesis gravidarum) is the most severe form of nausea and vomiting in pregnant women, leading to dehydration, ketosis and weight loss of over 5%. indomitable pregnant vomiting complicates 0.3–2% of pregnancies[8, 9].

Indomitable pregnant vomiting is not considered a true liver disease, but it is associated with an abnormal functional liver test (FPP) in approximately half of patients, while the increase in serum aminotransferases reaches 200 U/L. Other biochemical abnormalities may also be observed, such as an increase in serum amylase and lipase [10]. The standard of definition is the occurrence of more than three episodes of vomiting per day with ketonuria and weight loss of more than 3 kg or 5% of body weight, the diagnosis is usually made clinically after excluding other causes. Clinical studies of indomitable pregnant vomiting reveal dehydration, acidosis due to malnutrition, alkalosis due to loss of hydrochloride and hypokalemia [11].

Risk factors for developing indomitable pregnant vomiting include hyperthyroidism, psychiatric illness, cystic skidding, pre-existing diabetes, pregnancy in a pregnant woman, multiple pregnancy, increased body mass index[12], and high daily intake of saturated fat before pregnancy[15]. One study also identified female fetus as a risk factor[14]. According to Saad A., Jaquelyn F (2019) in the history of gastrointestinal disorders and asthma play a significant role in the development of indomitable pregnant vomiting[16].

According to other authors, the exact etiology of indomitable pregnant vomiting is unknown. Apparently, there is a direct correlation between the severity and the level of human chorionic gonadotropin (hCG), which reaches a maximum at 10 weeks of gestation. indomitable pregnant vomiting is more often observed in trophoblastic tumors and multiple pregnancy, i.e. with an abnormally high level of hCG. The latter activates the thyroid stimulating hormone receptor (TSR), which leads to the suppression of TSR and an increase in the level of thyroxine (T4). A positive correlation was found between the level of hCG, T4 and severity of indomitable pregnant vomiting[17]

Pregnant Intrahepatic Cholestasis (ChB) is the most common liver related pregnancy disorder. This is a reversible form of cholestasis, which is characterized by itching and an increase in the level of bile acids in serum on an empty stomach or after eating. Intrahepatic cholestasis of pregnant women is spontaneously resolved in the first 6 weeks. after childbirth, but often recurs during subsequent pregnancies [18]. The frequency is 0.2–2%. The highest incidence was recorded in South America and Europe. The incidence of intrahepatic cholestasis in pregnant women is more common among pregnant women infected with hepatitis C virus [19].

The incidence of intrahepatic cholestasis in pregnant women varies depending on geographic location and ethnicity: 3–5% of pregnant women in Chile, 1% in Europe, 0.7% in the UK, 0.3–1.0% in the United States and are rare in African countries. Seasonality indicates a higher incidence in the winter months in some countries. If jaundice is the initial symptom, then a further examination of the pregnant woman is necessary. It has been found that serum autotoxin, lysophospholipase D necessary for angiogenesis and neuronal development during embryogenesis, is a highly sensitive and specific diagnostic marker that distinguishes pregnant intrahepatic cholestasis from other itchy pregnancy disorders and liver diseases associated with pregnancy. Ultrasonography of the liver is necessary to exclude gallstone disease [20].

Kremer et al. A 2010 animal study found that autotoxin, a serum enzyme that converts lysophosphatidylcholine to LPA (lysophosphatidic acid), which causes itching, increased markedly in patients with spoils compared to pregnant women and patients with cholestasis compared to pregnant women without itching. Kremer et al. In another 2015 study in which 145 women participated, it was also reported that increased serum autotoxin activity is a highly sensitive, specific and reliable diagnostic marker for pregnant intrahepatic cholestasis, distinguishing pregnant intrahepatic cholestasis from other itchy pregnancy disorders and liver diseases associated with pregnancy. According to the authors, pregnancy and oral contraception increase serum autotoxin to a much lesser extent than intrahepatic cholestasis in pregnant women. [21].

Intrahepatic cholestasis of pregnancy affects 0.1–2% of pregnant women; in 1–4 women, gestation can be complicated by premature birth, fetal asphyxia, meconium staining of amniotic fluid, and stillbirth. The results of a large Swedish cohort study showed that pregnancy, in which the concentration of bile acid in maternal serum is 40 μmol/L or more, can be complicated by spontaneous preterm delivery[23], the presence of meconium in the amniotic fluid and fetal asphyxia. Another UK cohort study confirms these findings and showed that pregnancy outcomes[22] in women with intrahepatic cholestasis in pregnant women and a serum bile acid concentration of 40 μmol/L or more often lead to fetal death compared to 2205 women with uncomplicated pregnancy [25].

A differential diagnosis of intrahepatic cholestasis in pregnant women is carried out with viral hepatitis, autoimmune hepatitis, primary biliary cholangitis and gallstone disease [26]. pregnant intrahepatic cholestasis first appears at 28-30 weeks of pregnancy in the form of itching, especially pronounced at night. Almost half of patients develop jaundice[27].

Itching of the palms and soles is a key symptom. Skin rash is absent. Jaundice is rarely observed in patients with intrahepatic cholestasis in pregnant women. Serious adverse effects on the fetus are fetal distress, premature birth, prematurity, and fetal death. An increase in serum bile acids to 100 μmol/L or higher is associated with an increased risk of fetal death. Most societies recommend delivering a pregnant woman at 37 weeks because there is an increased risk of fetal death in the last 4 weeks of pregnancy. The risk of relapse in subsequent pregnancy is high and can reach 90% [28].

Intrahepatic cholestasis of pregnant women is more often observed with multiple pregnancy and in women who have previously been treated for infertility. In the etiology of intrahepatic cholestasis of pregnant women, genetic, endocrine and environmental factors[29] play a role. Apparently, an increase in estrogen and progesterone levels due to pregnancy can contribute to the development of this pathology [30].

Additional risk factors include maternal old age, multiple pregnancies, a personal or family history of the disease, preexisting liver disease, and a history of cholestasis when taking oral contraceptives.

Exogenous progesterone also plays a role in pregnant intrahepatic cholestasis. The study showed that 64% of patients who developed intrahepatic cholestasis in pregnant women took orally micronized progesterone to reduce the risk of premature birth. 70% of patients after progesterone withdrawal and 10% of patients after progesterone dose reduction experienced relief of pruritus before childbirth[31].

Many studies have shown that high estrogen levels are associated with the development of intrahepatic cholestasis in pregnant women, such as multiple pregnancies, the effect of ovarian hyperstimulation, and second trimester gestation[32]. pregnant intrahepatic cholestasis shows similar characteristics as in women taking high estrogen birth control pills. High levels of circulating estrogen can cause cholestasis in genetically predisposed women with intrahepatic cholestasis in pregnant women. Several animal studies have shown that sulfate metabolites of progesterone are partial agonists of the farnesoid X FXR receptor (bile acid receptor). Progesterone sulfate metabolites alter the hepatobiliary transport system, disrupting the functioning of the main bile acid receptor in the liver[33].

Multidrug Resistance Protein 3 (MDRP3) is a key carrier of phospholipids across the tubular membrane. A mutation of this gene leads to a loss of function and, consequently, an increase in serum bile acids. The MDRP -3 mutation is located on chromosome 7q 21.1 and was identified in 15% of cases of intrahepatic cholestasis in pregnant women. Altogether, ten different mutations were identified. Heterozygous mutations cause transport dysfunction, while a complete lack of transport function is associated with severe liver disease. The genetic tendency to intrahepatic cholestasis of pregnant women has been proved and there is information about pedigrees in which inheritance is of a limited type by gender of the dominant system.

Some environmental factors also play a role in the etiology of intrahepatic cholestasis in pregnant women, including the level of selenium in the region [34].

Immunological dysfunction also plays an important role in the pathogenesis of intrahepatic cholestasis in pregnant women. Thus, an increase in serum bile acid level causes a change in the immune system from a TH2-mediated response to TH1. As pregnancy proceeds to TH1, the immune response has more adverse outcomes, many risks of pregnant intrahepatic cholestasis are associated with the immune system.

Ovadia et al. conducted a comprehensive meta-analysis including 23 studies that compared perinatal outcomes in women with intrahepatic cholestasis of pregnancy (n = 5557) and healthy control group (n = 165136). The results of meta-analysis demonstrate the relationship of intrahepatic cholestasis of pregnancy with an increase in fetal complications, as described below[35]. Sudden intrauterine death of a fetus, meconium-stained amniotic fluid, spontaneous preterm birth, iatrogenic preterm birth, fetal distress. Maternal bile acids are transported through the placenta to the fetus and accumulate in the amniotic fluid, causing complications. The cause of preterm birth is unknown, but is possibly related to the accumulation of bile acid in the uterine myometrium, which causes increased uterine activity. Sudden death of the fetus is the most

serious complication of IVB; the cause of fetal death is not entirely understood; possibly associated with the toxic effect of bile acids on the fetal heart, causing arrhythmias and chorionic spasm, causing a decrease in the supply of maternal oxygenated blood to the fetus, causing asphyxiation [36].

Acute fatty hepatosis of pregnant women. Acute fatty hepatosis of pregnant women (AHFS), first described by Shihan, is a rare but serious disease, with a frequency of 1 to 7,000 per 16,000 pregnant women [37].

The accumulation of fatty acids in hepatocytes caused by various pathophysiological mechanisms is known as fatty liver disease. For example, metabolic syndrome or obesity, in which lipolysis is suppressed as a result of hyperinsulinemia, therefore, can provoke non-alcoholic fatty liver disease (NAFLD) or more severe non-alcoholic steatohepatitis (NASH). With a prolonged course of the disease, this condition can lead to cirrhosis of the liver. However, when this occurs during the gestational period, it is called acute pregnant fatty hepatosis (AHFS). AHFS is a devastating condition that can rapidly progress to fulminant liver failure with associated coagulopathy or hepatic encephalopathy[38].

The prevalence of acute fatty liver disease is 1 in 10,000-15,000 pregnancies. This life-threatening condition often develops in the second half of pregnancy (range: 27–40 weeks of pregnancy), usually close to delivery. The differential diagnosis is carried out with fulminant viral hepatitis, drug-induced hepatitis, idiopathic pregnancy cholestasis, with Reye syndrome in adults, as well as with hemolysis syndrome and an increase in liver enzymes and a decrease in platelets (HELLP syndrome)[39]. In the UK, it occurs at a rate of 1 in 20,000 pregnancies [40].

The etiology of AHL is completely unknown, and the connection with geographical or ethnic characteristics is also unknown[41].

Risk factors for the development of AHFS include congenital LCHAD deficiency, 1st pregnancy, multiple pregnancy (in patients with AHFS up to 25%), preeclampsia (in patients with AHFS up to 50%) and male fetus (3 times more often), underweight newborns, history of AHLH [42].

Chen et al. Indicated that twin pregnancy can be a protective factor for maternal outcome. Conversely, Knight et al. Came to the conclusion that double pregnancy is at a higher risk of AHL, similar to Davidson et al., Who have demonstrated this condition may increase the risk of AHL [43].

Maternal mortality reached 70%, but more recent estimates range from 7% to 18%, which is secondary to advances in the supportive care of these patients. Maternal complications include postpartum hemorrhage, renal failure, hypoglycemia, disseminated intravascular coagulation (DIC), pancreatitis, and pulmonary edema.

Perinatal mortality reaches 85%, and in more recent data, rates range from 9% to 23%. Due to urgent need, approximately 75% of the births are premature, and the average gestational age at birth is 34 weeks. All infants of mothers with AHFS are tested for defects in the FAO (fatty acid oxidation), because rapid detection and treatment can reduce mortality and morbidity. Relapse of AHB during subsequent pregnancies is rare, but often occurs in carriers of LCHAD mutations[40].

Fat accumulates in the liver due to the excess intake of free fatty acids (FFAs) in the liver, a decrease in the rate of β-oxidation of FFAs in the mitochondria of hepatocytes, excessive formation and absorption of FFAs in the intestines, a decrease in the synthesis of lipoproteins of different densities in the liver itself and a functional liver test caused by liver disease . The normal fat content in the liver does not exceed 5%, and with AGB, it rises to 13-19%. Of great importance for the development of steatohepatosis is insulin resistance [44].

Prevention by prenatal diagnosis after mutations in the family are possible by selecting chorionic villi at 11 weeks of gestation.

Maternal and antenatal fetal death in pregnant women with AHFS are 10% and 45%, respectively [45].

Biochemical signs of LCHAD deficiency are the accumulation of long chain 3-hydroxy fatty acids, such as 3-hydroxylauric acid, 3-hydroxymyristic acid, 3-hydroxypalmitic acid and 3-hydroxy dicarboxylic acid in the systemic circulation and increased excretion of 3-hydroxy dicarboxylic acids in the urine.

It is reported that children with LCHAD deficiency develop sudden death with hypoglycemia, cardio-respiratory failure, acute heart failure, severe neonatal cardiomyopathy, hepatic dysfunction and acute liver failure, skeleton myopathy with rhabdomyolysis. Next, 34% of children with disabilities die between four days

and 10 years after birth. In addition, mental disorders, retardation, developmental disorders, eye abnormalities, and sudden infant death may develop. It is believed that such damage to many organs is associated with the lipotoxicity of the intermediate accumulation of toxic 3-hydroxy fatty acid.

In the medical history of pregnant women with severe AHFS, placental abruption, premature birth, and fetal death were noted.

For the diagnosis of AHFS, the Swansea Criteria have been proposed and validated in large cohort studies in the United Kingdom. These criteria include symptoms and laboratory findings. Six or more of the following criteria are needed to establish a diagnosis of AHFS according to Swansea criteria[46].

1. Vomiting;
2. Encephalopathy;
3. Polydipsia and polyuria;
4. Abdominal pain;
5. An increase in the content of bilirubin (more than 0.8 mg/dl or 14 μmol/l);
6. Hypoglycemia (less than 72 mg/dl or 4 mmol/l);
7. Leukocytosis (more than 11 · 109/l; often 20-30 · 10 * 9/l);
8. Increased levels of transaminases (often 3-10 times higher than normal - more than 42 IU/l);
9. Renal dysfunction (creatinine content of more than 150 μmol/l);
10. An increase in the level of ammonia (more than 47 μmol/l);
11. An increase in the level of uric acid salts (more than 340 μmol/l);
12. Coagulopathy (prothrombin time more than 14 s; APTT more than 34 s);
13. Ascites or hyperechoic structure of the liver during ultrasound examination (ultrasound);
14. Microvesicular steatosis with liver biopsy and histological examination[31]. In the future, jaundice (more than 70% of cases), ascites (40%), fever (45%), headache (10%) and such severe complications as gastrointestinal bleeding (20-60%), PP (50%) develop), DIC (55%), hepatic encephalopathy (60-80%) and acute pancreatitis[5].

Symptoms of liver damage include epigastric pain or pain in the upper right quadrant, probably from hepatomegaly as a result of a stretching of the Glisson capsule. An increase in hepatic enzymes to double normal values classifies severe preeclampsia. Typically, coagulation rates remain normal until the progression of liver failure or placental abruption. Liver damage is a consequence of vasoconstriction, a decrease in hepatic blood flow, leading to hepatic ischemia, periportal hemorrhage, endothelial damage and fibrin deposition in the liver[47].

Recommendations of the American College of Gastroenterology (ACG)[33]:

- Women with AHFS must be delivered promptly; observation tactics are not suitable
- all women with AHFS and their children must undergo molecular testing for LCHAD,
- Children of women affected by AHL should be carefully monitored for the presence of LCHAD, including hypokinetic hypoglycemia and liver enlargement[8].

In a study by Meng et al. involving 43 patients[26] at the center of tertiary levels, prothrombin time, plasma fibrinogen, and platelet counts correlated with recovery time, while white blood cell count, blood glucose, and liver aminotransferase showed no significance in predicting. Transfusion of fresh frozen plasma (FFP), cryoprecipitate, or platelet concentrates in the case of abnormal standard tests such as prothrombin time (PT), activated partial thromboplastin time (APTT), or fibrinogen can prevent further bleeding complications. However, relative fluid overload can lead to acute lung damage and infection resulting from the use of these drugs. In addition, current standard coagulation tests are considered only weak predictors of bleeding in critically ill patients; Therefore, additional method such as thromboelastometry can be used. Thromboelastometry was used in the early prediction of bleeding complications in seriously ill patients. In a report by Crochemore et al., It was found that this method effectively detects a hypocoagulable condition and reduced quality of fibrinogen function at the beginning of an operation. Fibrinogen and prothrombin complex concentrates were administered to the patient and a cesarean section was performed without any major bleeding. Recombinant

factor 7 injection is also recommended along with supportive care in the intensive care unit [26].

Another important point concerns the deficiency of vitamin K, which is observed in newborns born to women with AGB. Cases of severe intracranial hemorrhage due to an early deficiency of vitamin K in a newborn whose mother has been diagnosed with GBV have been reported .

A recent multicenter retrospective study in China shows that male fetal sex, postpartum diagnosis of AHF, intrauterine fetal death, DIC, altered prothrombin time (PT), and activated partial thromboplastin time (APTT) can be potential factors that affect maternal complications [34].

Currently, artificial liver support therapy (ALST), which includes plasma exchange (PE) and molecular adsorbent of the recirculation system (MARS), is relevant. It is believed that the effect of ALST occurs due to the removal of circulating endotoxins, replacement of normal coagulation factors and proteins, stopping coagulopathy and, finally, improving liver function [25].

N-acetylcysteine (NAC), a precursor of glutathione, has some success in patients with Non Acetaminophen-induced acute liver failure, due to its anti-inflammatory, antioxidant, inotropic and vasodilator effects, which contribute to the improvement of vital microcirculation and oxygenation survival, as reported by Mumtaz K. Et al.[34].

A prospective study of 47 patients with this disease showed that new treatments such as plasmapheresis and the use of activated protein C were practiced in specialized centers, with variable results. Plasmapheresis, apparently, can be a promising treatment option for patients with AHFS, since it partially replaces liver function by removing ammonia, endotoxins, bilirubin, and inflammatory cytokines from maternal circulation .

Preeclampsia Preeclampsia is a multisystem disorder that affects 5 to 10% of all pregnant women, in some cases it develops multiple organ dysfunction syndrome, causing impaired renal and central nervous system function, hematological and liver dysfunctions. The disease can progress, causing microangiopathy, which mainly affects the kidneys, liver and brain. Thrombocytopenia, liver dysfunction, microangiopathic hemolytic anemia, acute renal failure, placental abruption, visual impairment, stroke, convulsions and maternal mortality are serious consequences of preeclampsia[7].

Preeclampsia is a complication of pregnancy, characterized by a deep violation of the functions of vital organs and systems, including the liver, which, depleting its reserve capacity as pregnancy progresses, becomes more vulnerable. The liver is a target organ in severe forms of preeclampsia. Preeclampsia is accompanied by severe dyslipidemia: the content of triglycerides of unesterified fatty acids (NEFA), total cholesterol, very low density lipoproteins (VLDL), low density lipoproteins (LDL) is much higher, and the level of high density lipoproteins (HDL) is lower than in uncomplicated pregnancy. Preeclampsia is characterized by a more pronounced than with a normally developing pregnancy, the appearance of unique, different from VLDL, lipoproteins loaded with triglycerides. Perhaps such an overload is associated with an increase in insulin resistance, a decrease in the intensity of β-oxidation in the liver, or a decrease in the activity of triglyceride catabolism due to inhibition of LP-lipase by cytokines.

Dyslipidemia, against the background of a decrease in the content of antioxidants in the blood, predisposes to the development of endothelial dysfunction. NEZHK, having high toxicity, contribute to the formation of free oxygen radicals. A possible mechanism explaining a significant increase in the level of NEFA during preeclampsia is an increase in the content of lipophospholipase in maternal blood flow. Its source in violation of trophoblast invasion is microvillosis membrane. [4].

Angiogenic markers have been identified and can confirm the diagnosis of PE in women without hypertension or proteinuria. These include a decrease in placental growth factor, an increase in serum soluble endoglin, and an increase in the soluble VEGF receptor[35].

However, the identified biomarkers and risk factors for the development of PE are only modestly predictive.

In PE, a generalized spasm of the vessels is observed, which leads to an increase in systemic vascular resistance and a pressor reaction to endogenous vasoconstrictors. Damage to vascular endothelium leads to the deposition of platelets and fibrin in the sinusoids, causing hepatocellular necrosis and hemorrhage in zone 1. Detection of necrosis and hemorrhage in zone 3 is associated with shock in severe preeclampsia. In mild cases of preeclampsia, a moderate increase in serum

AST/ALT/alkaline phosphatase is observed, as well as minor signs of DIC with thrombocytopenia. Jaundice is rare, but in its presence it manifests itself as a terminal and hemolytic reaction in its etiology, and the total serum bilirubin often does not exceed 6 mg/dl[33,37,38].

Conjugated bilirubin, albumin, and PT tend to remain normal. Liver damage, consisting of spasm of capillaries of liver tissue and fibrin deposition within the portal and periportal regions of the liver lobules, can lead to lobular ischemia and necrosis of hepatocytes.[6].

In earlier studies, it was shown that LCHAD mRNA, protein expression, and enzyme activity were reduced in the placenta of pre-eclampic patients. In addition, a decrease was found in mitochondrial oxidation of long chain fatty acids in the placenta obtained in patients with preeclampsia compared with the control group, which indicates that a decrease in the oxidation or defect of placental fatty acid in LCHAD may contribute to the pathogenesis of preeclampsia. Maternal AFLP is highly associated with fetal transfer and LCHAD enzyme deficiency [30].

Since one of the leading values in the pathogenesis of preeclampsia is given to microcirculatory disorders, which, in turn, lead to multiple organ failure, the liver, as an organ with a developed capillary system, is always more or less involved in the process of tissue hypoxia and microcirculatory disorders, the degree of which Depends on the severity of preeclampsia. Currently, impedance hepatography is one of the most sensitive functional method for examining the liver, revealing a violation of microcirculation, which occurs even before the increase of biochemical parameters. This method gives information about blood supply and microcirculation in the liver, about sinusoidal blood flow, the indicators of which correlate with data on morphological changes in liver tissue and its functional disorders. Of course, laparoscopy and puncture biopsy of the liver are invasive and unsafe diagnostic method for pregnant women with preeclampsia. In addition to impedance hepatography, there are also other non-invasive, safe method - such as ultrasound, dynamic hepatobiloscintigraphy and the study of the reticuloendothelial system (RES). The ultrasonic method allows you to evaluate the size of the liver, gall bladder, the presence of obvious pathological conditions - subcapsular hematoma of the liver, and also using echodsitometry it is possible to determine different sections of the density in the liver tissue, which is a criterion for fatty hepatosis. Dynamic hepatobyl scintigraphy is a functional morphological radionuclide study of the liver using a 99mTc-HIDA radionuclide. A feature of the drug is a low radiation load on the patient (0.2 m), which does not limit its use even in pediatric practice. This method allows a comprehensive assessment of both the functional and morphological state of the hepatobiliary system. The most diagnostically difficult cases are severe liver pathology during pregnancy, which are manifested by hepatocellular insufficiency syndrome and in which there is no correlation with the severity of preeclampsia. So, in 40-60% of cases of severe forms of liver pathology associated with pregnancy, there was no classical triad of symptoms characteristic of preeclampsia. So, with HELLP syndrome, an increase in blood pressure up to 160/100 mm. Hg. Art. met from 26-56% of cases, edema was recorded in 55% of patients, pronounced proteinuria - 85% of cases, in some cases, manifestation of preeclampsia occurs in childbirth, followed by rapid progression of clinical symptoms, the development of DIC and severe liver pathology. The manifestation of the complete HELLP syndrome against the background of severe preeclampsia and eclampsia was established in 53.5% of cases [39].

Finally, PE has been recognized as a marker for future cardiovascular disease, given the common risk factors, persistent endothelial dysfunction, and damage to the target organ. In the examined cohort, women with liver dysfunction due to PE and HELLP had a previous history of hypertension and diabetes mellitus, and were more prone to the subsequent development of metabolic disturbances [18].

Obstetric complications in PE include fetal growth restriction syndrome (10–25%), placental abruption, premature birth (15–65%), and fetal death. The condition of the maternal liver associated with preeclampsia/ eclampsia does not require special treatment, and the medical approach is based on the regulation of blood pressure, the reduction of concomitant symptoms and the timely treatment of seizures. After 37 weeks, women with preeclampsia should give birth. If in severe cases a deterioration of the fetus or mother is observed, childbirth should be taken in a period of 24–34 weeks [6].

HELLP syndrome: The term HELLP syndrome was first proposed in 1982 by L. Weinstein. This acronym includes: Hemolysis - the appearance of free hemoglobin in serum and urine; Elevated Liver enzimes - increased levels of AST, ALT; Low Platelets - Thrombocytopenia.

HELLP syndrome occurs in less than 1% of all pregnancies, but in 20% of pregnancies complicated by severe symptoms of PE. HELLP syndrome can occur during urgent delivery (18%), premature birth (53%) or after childbirth (30%). Risk factors include a family history of HELLP syndrome and preeclampsia or HELLP in previous pregnancies, occurring in 10–20% of patients.

Laboratory data are important for determining intravascular hemolysis, peripheral smear schistocytes, elevated FPP (usually ALT), and low platelet counts. All three HELLP elements must be observed in a pregnant patient before they are diagnosed. The level of serum aminotransferases can be increased by more than ten times. At the same time, unconjugated hyperbilirubinemia due to hemolysis may be present.

The pathogenesis of the HELLP syndrome is not entirely clear, but there is probably an abnormal development of the vascular system of the placenta and new defects in the endothelial cells of the mother's blood vessels, which leads to poor perfusion in various organs. Less commonly, LCHAD deficiency in the fetus is involved in its pathogenesis .

Insufficient immune tolerance leading to fetal trophoblast damage in early pregnancy is probably the initial sign of HELLP. Endothelial trauma and fibrin deposition may cause the HELLP microangiopathic process. As a result, hemorrhage and liver necrosis may develop. Maternal risk factors include a high body mass index, treatment for infertility, a history of preeclampsia or HELLP. HELLP syndrome may be the initial manifestation of antiphospholipid syndrome [9]. The main pathophysiological changes in HELLP syndrome occur mainly in the liver. The main link in the development of the syndrome are disorders in the hemostatic system due to damage to the endothelium and intravascular activation of the coagulation system. Deposition of fibrin in the sinusoidal capillaries of the liver leads to central necrosis with the formation of stasis and tension of the glisson capsule. Further progression of the process can lead to rupture of the liver. Subcapsular hematomas and liver ruptures more often occur with prenatal manifestations of the HELLP syndrome. Spontaneous liver ruptures are characterized by high maternal mortality (over 50%). If this vicious circle is not interrupted in time, then within a few hours, DIC develops with fatal bleeding.

Immunohistochemical analysis of the liver with HELLP syndrome showed the presence of large amounts of leukocyte elastase and TNF-α in the area of hepatocyte necrosis, which indicates the role of these factors in liver damage[4].

In approximately 65% of cases, pain is observed in the right upper quadrant of the abdomen or epigastrium, in 35% - nausea and vomiting, in 30% - headache, less often - bleeding and jaundice. In a significant number of cases of HELLP syndrome, pregnant women have no complaints. 85% of patients have an increase in blood pressure. Proteinuria is often found [3]. Excessive weight gain and edema precede the development of HELLP syndrome in 50% of cases.

The pathogenesis of HELLP syndrome has much in common with the pathogenesis of preeclampsia, DIC, and AHFS, which is reflected both in clinical manifestations and laboratory signs, as well as in the morphological picture of liver damage. Such mechanisms include impaired tone and vascular permeability (vasospasm); neutrophil activation, cytokine imbalance (increased levels of interleukin IL-10, IL-6 receptor and transforming growth factor β3 (TGF β3), and the concentration of CCL18, CXCL5 and IL-16 is significantly reduced); fibrin deposition and microthrombosis in microcirculation vessels; increased activity of plasminogen activation inhibitors (PAI-1); violation of the metabolism of fatty acids (long-chain deficiency of 3-hydroxyacylCoAdehydrogenase long chain 3-hydroxyacyl dehydrogenase) (LCHAD), characteristic for fatty hepatosis. Antiphospholipid syndrome and other variants of thrombophilia, various genetic abnormalities that play a role in the development of preeclampsia are of great importance in the development of HELLP syndrome. These anomalies are associated with the presence of polymorphism of genes encoding components of the lipid metabolism system (LPL, ApoE, LCHAD), antioxidant protection (EPHX, LPL, CYP1A1, SOD), immunological protection (HLA-G, TNFα (TNFα), IL-1, IL-10, CD14 receptor, CTLA-4), hemostatic systems (FVL, MTHFR, prothrombin, CBS, PAI-1, GP-IIIA, FXIII, FXVII, fibrinogen), placental factors (STOX1, SERPINA3, ACVR2, IGF- I, IGF-II), and factors involved in the regulation of vascular tone (AGT, ACE, AT1R, REN, PRCP, eNOS, ET-1, ER, Flt-1, ENG, VEGF, PIGF) .

HELLP syndrome usually develops in the third trimester or after childbirth and is associated with increased complications: as maternal (placental abruption, disseminated intravascular coagulation, hematoma and rupture, and acute kidney damage) and newborns (prematurity and low birth weight).

The clinical picture of HELLP syndrome varies greatly. The clinic may be asymptomatic or may appear with symptoms such as pain in the upper right quadrant of the abdominal cavity, enlarged liver, nausea, vomiting, jaundice, or confusion.[41].

Although the etiopathogenesis of this condition remains unclear, histopathological findings in the liver show intravascular deposition of fibrin, which is likely to result in hepatic sinusoidal obstruction, increased intrahepatic pressure followed by liver necrosis, intraparenchymal and subcapsular hemorrhage, and, ultimately, capsule rupture.

In a large retrospective cohort study involving 442 pregnancies complicated by HELLP syndrome, maternal mortality was 1.1%. The clinic is similar to VCB (intrahepatic cholestasis of pregnant women), prematurity remains the most common risk associated with complications from the fetus. According to Gul et al., 72 cases of perinatal mortality accounted for 34% before the 32-week gestation period and 8% after 32 weeks [29].

Cholelithiasis: Gallstone disease (cholelithiasis) is the second most common indication for surgery during pregnancy. Acute cholecystitis can occur in 20% of women under 40 years of age [43].

Risk factors for gallstone disease include an increased body mass index (BMI) (> 25 kg/m2), it is confirmed that 2.7% of women with normal BMI developed gallbladder disease before pregnancy, compared with 11% in women with obesity.

Gallstones are more common during pregnancy because the secretion of cholesterol increases compared with bile acid and phospholipids, thereby causing supersaturated bile. In addition, the volume of the gallbladder increases and emptying decreases, thus leaving an oversaturated bile in the gallbladder with the possible formation of gallstone [8].

Another mechanism suggests that while estrogens increase cholesterol secretion, progesterone decreases the secretion of soluble bile acids, and this contributes to the accumulation of insoluble bile acids predisposing to stone formation [44].

Biliary sludge and gallstones are diagnosed using ultrasound. Biliary sludge, also known as microlithiasis, is described as low-level echoes that shift when position changes and do not have an acoustic shadow, while gallstones have high-level echoes larger than 2 mm in size after postacousticshading[8, 45].

Symptomatic cholelithiasis may have typical signs of biliary colic in the upper right quadrant or epigastrium, abdominal discomfort, bloating, nausea.

Asymptomatic gallstones are found in 3.5% of pregnant women, and in 90% of cases they caused cholecystitis during pregnancy. Despite the predisposition to the formation of bile sludge and stones during pregnancy, cholecystitis occurs in only 1% of pregnant women [46]. Adverse obstetric outcomes include spontaneous abortion and premature birth.

Serious complications are cholangitis, sepsis, jaundice, cholelithiasis, pancreatitis, perforation and the formation of an abscess. In the absence of serious complications, conservative treatment is the initial option with normalization of bowel function, analgesics (opioids or non-steroidal anti-inflammatory drugs) and broad-spectrum antibiotics.

Nonsteroidal anti-inflammatory drugs should be used with caution after 32 weeks because of the risk of developing oligohydramnios and narrowing of the ductus arteriosus. Preferred antibiotics include cephalosporins and clindamycin. However, some researchers believe that a conservative approach is associated with higher relapse rates from 40% to 70%.

A study performed by Jelin shows a higher risk of fetal death (7%) was observed among patients who underwent conservative treatment, compared with patients who underwent laparoscopic cholecystectomy (2.2%).

In case of complications due to common bile duct stones, such as cholangitis or pancreatitis, endoscopic retrograde cholangiopancreatography with sphincterotomy and stone removal is a safe method with minimal risk of exposure to fetal ionizing radiation. Optional cholecystectomy can be performed after childbirth.

A review comparing conservative and surgical treatment for gallstone disease showed multiple remissions in the group that received non-surgical treatment, with 27% of them eventually having surgery, 19% in the first, 60% in the second and 10% in the third trimester. The frequency of preterm birth (3.5% and 6%) and fetal death were 2.2% and 1.2%, respectively. Cholecystectomy is recommended in the second trimester, due to the risk of termination of pregnancy in the first trimester and the risk of premature birth in the third trimester [48].

Cholecystitis: Diseases of the biliary system occupy one of the leading places among diseases of the digestive system and are found mainly in young people[3]. Chronic cholecystitis is one of the most common human diseases, takes third place after cardiovascular disease and diabetes. According to the VI World Congress of Gastroenterologists, 10% of the world's population suffers from chronic cholecystitis. In developed countries, the frequency of the disease is 10-15% and doubles for every decade [49]. During pregnancy, conditions arise that impair the function of the liver and biliary tract, which is associated with an increase in the load on the liver due to the neutralization of the vital products of the fetus, the mobilization of energy resources, and the need to strengthen metabolic processes. Pregnancy becomes a provoking factor contributing to the development of the disease[3].

The main role in the development of chronic cholecystitis is played by two factors: infection and stagnation of bile due to dyskinetic disorders. The latter, as a rule, determines the clinical manifestations of the disease. Hypomotor dyskinesia is characterized by a flaccid contractile ability of the gallbladder and ducts, as a result of which an insufficient, very small amount of bile enters the duodenum. Pregnant women are characterized by hypomotor disorders, since the main hormone prevailing in the second half of pregnancy is progesterone, which relaxes all smooth muscle organs (the main physiological meaning of its action in the pregnant woman is relaxation of the uterus, obstruction of premature birth, miscarriage). The basis of hypomotor dyskinesia is insufficient, weak emptying of the gallbladder. It is motor disorders that determine the clinical manifestations of chronic cholecystitis in pregnant women, and not inflammation.

Chronic cholecystitis (XX) worsens during pregnancy in 30-35% of women, and in most cases in the third trimester of pregnancy. In 88% of cases, the disease manifests itself in pain. Depending on the gallbladder dysfunction, pregnant women complain of dull, aching, bursting or sharp pains in the right hypochondrium, radiating to the right shoulder blade, shoulder or collarbone. Along with the pain of patients, feelings of nausea, bitterness in the mouth, vomiting, heartburn, bloating, and unstable stools are disturbing. In the second half of pregnancy, 25% of women associate the appearance of pain with fetal movement[3].

Clinical and biochemical blood tests should be evaluated in pregnant women with caution, since neutrophilic leukocytosis can only be a leukemoid reaction to pregnancy[50]. Peripheral blood tests usually do not show abnormalities. In some cases, moderate leukocytosis with a shift in the leukocyte formula to the left and an increase in ESR are noted. An increase in the activity of transaminases (ALT and AST), alkaline phosphatase and g-glutamyl transpeptidase (GGT), hyperbilirubinemia, and hypercholesterolemia is sometimes found in a biochemical blood test [61].

Buddy Chiari Syndrome. Baddi-Chiari syndrome (BCS) is defined as obstruction of the outflow of hepatic veins and is sometimes associated with myeloproliferative disorders. Up to 20% of cases of BCS occur in women who took oral contraceptives, were pregnant or gave birth in the previous two months. Because pregnancy alone is a prothrombotic condition; a physiological decrease in protein S concentration may explain the increased incidence of BCS during pregnancy. These patients have a risk of exacerbation during pregnancy due to an increased concentration of female sex hormones. Clinical signs include pain in the upper right quadrant, jaundice, and ascites. Dopplerography is very important for diagnosis. Treatment includes anticoagulation at the beginning, identifying the causes of the procoagulant, and bypass or liver transplantation in extreme cases[8].

Risk factors for developing BCS include injuries, hypercoagulant conditions, myeloproliferative disorders, oral contraceptives, and pregnancy. With BCS, abdominal pain, hepatomegaly and ascites are usually observed. Doppler sonography in most cases is enough to establish a diagnosis[2].

Thus, a review of recent literature in recent years on the pathology of the hepatobiliary system in pregnant women has shown that this problem is relevant and requires further study. The development of medical

science and practice today allows you to correctly establish the type of liver pathology by applying modern research method, although some of them are invasive. However, very often the pathology of the hepatobiliary system can first manifest itself during pregnancy, which limits both diagnostic and therapeutic options. Given the importance of this problem, the influence of the pathology of the hepatobiliary system on pregnancy and perinatal outcomes, and further studies to better understand the mechanism of development of these complications are relevant.

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