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NON-ALCOHOLIC FATTY LIVER DISEASE AND PREGNANCY

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НЕАЛКОГОЛЬНАЯ ЖИРОВАЯ БОЛЕЗНЬ ПЕЧЕНИ И БЕРЕМЕННОСТЬ

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The issues of epidemiology, risk factors, and pathogenetic mechanisms of non-alcoholic fatty liver disease during pregnancy are considered in the review. The impact of liver steatosis and obesity on the course and outcome of pregnancy, the perinatal state of the mother and fetus are described. Fluctuations in the hormonal spectrum, an increase in body weight, which can affect the development and progression of liver steatosis, occur during pregnancy. Women of reproductive age with metabolic syndrome, obesity require a thorough examination and, if it is necessary, optimization of metabolic health before planning pregnancy. Pregnant women with liver pathology need dynamic control and prevention of disease progression and associated obstetric complications.
Keywords. Liver, pregnancy, non-alcoholic fatty liver disease, obesity.

В обзоре рассмотрены вопросы эпидемиологии, факторов риска, патогенетических механизмов неалкогольной жировой болезни печени при беременности. Описано влияние стеатоза печени и ожирения на течение и исход беременности, перинатальное состояние матери и плода. При беременности происходят колебания гормонального спектра, увеличение массы тела, что может влиять на развитие и прогрессирование стеатоза печени.

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Женщинам репродуктивного возраста с метаболическим синдромом, ожирением до планируемой беременности требуется тщательное обследование и при необходимости оптимизация метаболического здоровья. Беременным женщинам с патологией печени показан динамический контроль и профилактика прогрессирования заболевания и ассоциированных с ним акушерских осложнений.
Ключевые слова. Печень, беременность, неалкогольная жировая болезнь печени, ожирение.

INTRODUCTION

Fatty liver disease is quite common during pregnancy and occurs in two completely different conditions: non-alcoholic fatty liver disease (NAFLD) and acute fatty liver disease across pregnancy. The prevalence of NAFLD increases every year and is registered in 10–20 % of women of childbearing age [1; 2], 10–15 % of pregnant women [3], which is associated with the obesity pandemic and the increasing age of pregnant women, especially in Western countries. The number of pregnant women with fatty liver disease is expected to increase in the coming years [4]. During pregnancy, there are fluctuations in the hormonal spectrum and an increase in body weight, which can affect the development and progression of liver steatosis [5]. The issues of diagnosis and principles of correction of NAFLD in pregnant women, the features of maternity care, childbirth and the postpartum period in these women are also discussed.

EPIDEMIOLOGY AND RISK FACTORS FOR NAFLD IN PREGNANCY

Recently, there has been an increase in obstetric and perinatal pathology caused by hepatocellular insufficiency. Pathology of the hepatobiliary system occurs in women 4.7 times more often than in men, which leads to an increase in the number of pregnant women with liver diseases [6; 7]. Liver pathology is registered in 3–5 % of pregnant women and is characterized by a variety of etiological forms, which are divided into two main groups: liver damage caused by pregnancy itself (with uncontrollable vomiting of pregnancy, intrahepatic cholestasis of pregnancy, acute fatty liver disease of pregnancy, liver damage in preeclampsia, eclampsia and HELLP syndrome), and liver diseases not directly caused by pregnancy (acute diseases that developed during pregnancy and chronic diseases that preceded pregnancy, including NAFLD) [8; 9]. Over the past 10 years, there has been a trend towards an increase in the prevalence of NAFLD among women [10], as well as a sharper increase in mortality compared to men [11].

NAFLD is associated with an increase in the prevalence of risk factors in the population, such as metabolic syndrome (MS), obesity, diabetes mellitus and dyslipidemia [5]. In women, MS develops 2.4 times more often than in men [12], in women of childbearing age, MS is recorded in 7.6–15.7 % [13; 14], the increase in the prevalence of MS among pregnant women, according to some data, over a period of 1988–2015 amounted to from 3 to 42 % [15].

Recently, the problem of obesity and overweight, according to WHO, has become a pandemic of global proportions. By 2025, the number of obese people worldwide is expected to reach approximately 300 million. Obesity has a detrimental effect on every aspect of reproductive health and during pregnancy can have enormous consequences and increase the risk of obstetric pathologies such as gestational hypertension, preeclampsia, gestational diabetes and preterm birth [16–18]. For one in five women of reproductive age, obesity has a high socioeconomic cost due to increased risk of maternal and neonatal complications [19]. It has been established that gestational diabetes mellitus occurs significantly more frequently in obese pregnant women, regardless of the type of fat deposition. The visceral type of fat tissue distribution is associated with an increased risk of gestational diabetes mellitus in women with normal and excess body weight [20; 21].

Dyslipidemia is diagnosed in 40–50 % of the population and is often asymptomatic [22]. Pregnancy changes lipid parameters as early as the 12th week, causing physiological hyperlipidemia, which can affect the outcome of pregnancy [23]. According to research, all obese pregnant women in the third trimester have dyslipidemia with a predominance of the atherogenic fraction of lipoproteins and hypertriglyceridemia, 12 % have hyperfermentemia, and 52 % have signs characteristic of liver steatosis according to ultrasound data. Moreover, premature and late births were significantly more common in the group of women with obesity compared to pregnant women with normal BMI [24]. Pregnancy alters lipid parameters from the 12th week of amenorrhea and causes physiological hyperlipidemia. The lipid profile of patients may influence obstetric outcome. There is an increased risk of gestational diabetes (33 %), preeclampsia (25 %) and gestational cholestasis [25–27].

The characteristics of MS make it difficult to conduct retrospective studies to determine the contribution of each metabolic risk factor to the development of NAFLD during pregnancy. Prospective studies are needed to clarify the association between NAFLD and pregnancy-specific features and to assess the actual impact of NAFLD on pregnancy outcomes [2].

Pathogenetic mechanisms linking NAFLD and pregnancy

The pathogenesis of NAFLD is currently considered as a complex multifactorial process of a combination of adipose tissue dysfunction with hyperproduction of proinflammatory cytokines, insulin resistance, activation of lipolysis, dyslipidemia, impaired hepatic lipid clearance, oxidative stress, mitochondrial and endothelial dysfunction, and intestinal microbiota disorders [2; 14; 28–33].

There is currently no evidence that pregnancy can provoke the development of NAFLD, but it has been proven that estrogen imbalance, weight gain and insulin

resistance (IR) due to pregnancy itself, as well as the result of obesity before and during pregnancy, are important in the pathogenesis of liver steatosis during pregnancy. Leptin and insulin levels directly correlate with gestational age [2; 34]. It has been established that IR in obese pregnant women is based on proinflammatory processes, since visceral adipose tissue synthesizes proinflammatory cytokines, which leads to the development of systemic inflammation and changes in endocrine and immune functions [35–37].

There is evidence that the production of proinflammatory cytokines in obese pregnant women may increase in adipose tissue, blood, placenta and mucous membranes, including the intestines, where an increase in the number of opportunistic microorganisms is recorded. Gut microbiota is involved in whole-body metabolism, influencing energy balance, glucose metabolism, and low-grade inflammation associated with obesity and associated metabolic disorders [38]. The number of microorganisms increases from the first to the third trimester of pregnancy. High concentrations of bacteroides are associated with excessive weight gain during pregnancy [39].

The mechanisms of pathogenesis of insulin resistance, endothelial dysfunction underlying the formation of placental insufficiency and preeclampsia, thrombophilia, against the background of a chronic inflammatory reaction in pregnant women with obesity have been described [37]. It has been established that clinical manifestation of previously asymptomatic NAFLD may occur during pregnancy [27].

Influence of NAFLD on the course and outcome of pregnancy

Obesity and NAFLD can affect the course of pregnancy, labor, and the postpartum period. Complications such as miscarriage, preeclampsia, premature birth, bleeding, infections are registered, and the risk of congenital anomalies and fetal death increases [14; 41–44].

A large meta-analysis involving patients of childbearing age showed an association of liver steatosis with the risk of developing miscarriage, preeclampsia and eclampsia, gestational hypertension and diabetes mellitus, premature birth, and bleeding in the postpartum period [45–48]. There is evidence that NAFLD is associated with an increased risk of low birth weight and more frequent Cesarean sections. The risk of developing preeclampsia and gestational diabetes is increased in pregnant women with NAFLD even in the absence of obesity or overweight [48]. There is also an increase in the incidence of rapid development of liver cirrhosis as an outcome of NAFLD [49] and a higher risk of developing this pathology in infants born to mothers with NAFLD [50; 51]. There is also an increase in the incidence of rapid development of liver cirrhosis as an outcome of NAFLD [49] and a higher risk of developing this pathology in infants born to mothers with NAFLD [50; 51].

The pathophysiological mechanisms of the influence of NAFLD on the perinatal state of the mother and fetus are not completely clear. There is an opinion that IR associated with NAFLD activates the sympathoadrenal and renin-angiotensin-aldosterone systems, leads to endothelial dysfunction, which can contribute to the development of hypertension [52]. The development of preeclampsia in NAFLD and obesity is associated with an imbalance of adipose tissue hormones [53–55].

Conclusions

Structural and functional changes in the liver affect the course of pregnancy and require timely adequate correction. Women of fertile age with MS and obesity require a thorough examination and, if necessary, optimization of metabolic health before the planned pregnancy.

Pregnant women with NAFLD require dynamic monitoring and prevention of disease progression and associated obstetric complications. The complex of preventive measures should include recommendations to prevent excessive weight gain during pregnancy (diet and exercise), as well as hepatotropic agents as indicated. Appropriate counseling and monitoring of patients with or at risk for hepatic steatosis during pregnancy may have significant health benefits for the mother and child.

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