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PREGNANCY AND VIRAL HEPATITIS B

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Annotation: Based on the available literature and our own data on the vertical transmission of HBV, the features of the course of pregnancy on the background of HBV and the course of hepatitis B on the background of pregnancy, recommendations have been developed for the management of pregnant women with HBV.

Key words: viral hepatitis B, pregnancy, vertical transmission.

There are about 400 million people infected with hepatitis B virus (HBV) worldwide [1, 2, 27]. Almost half of them acquired it either through vertical transmission or in early childhood, especially in countries with a high or moderate degree of HBV infection in the population [2, 4,]. This is due to the high incidence of chronic viral hepatitis B (HCV). women of childbearing age in these countries and the possibility of transmission of infection from these women to their newborn children.

HBV immunoglobulin (HBIG) and HBV vaccines are known to be safe and effective means of preventing vertical transmission of the virus from mother to child, but they are used differently in different geographical regions. There are two approaches to screening women for HBsAg during pregnancy – universal (universal) and screening in risk groups. Universal screening means that all pregnant women are screened for HBV infection, while screening in risk groups is based on a history of "risk factors" (intravenous drug use, promiscuous sexual intercourse, commercial sex workers, sexual contact with HBsAg-positive individuals).

In the USA, testing for HBsAg is recommended for every pregnant woman, regardless of previous testing or a history of vaccination [12]. Other countries often lack consistent policies regarding screening women for HBV infection during pregnancy, and many countries rely on a "risk factor" strategy to determine screening indications. However, about 50% of infected pregnant women were not identified using this strategy [24].

In Russia, HBsAg screening is included in the plan for mandatory screening of pregnant women, however, due to the increasing migration of the population, including from regions highly endemic for HBV, despite the mandatory vaccination of newborns included in the National Vaccination Calendar, the problem of the spread of HBV remains relevant.

Prevalence of chronic HBV infection in pregnant women.

The prevalence of chronic HBV infection varies widely in different parts of the world. The percentage of the infected population can range from 0.1 to 20%. Regions with a high prevalence (8% or more of the HBsAg+ population) include Asia (except Japan), parts of the Middle East, sub-Saharan Africa, and the Amazon basin. Regions with an average prevalence rate (2-8% HBsAg+) include the Indian Subcontinent, parts of Central Asia and the Middle East, Eastern and Southern Europe, and parts of South America. Areas with low levels (less than 2% HBsAg+) include the USA, Northern Europe, Australia, and Japan. In

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Russia, the infection rate of the HBV population differs significantly depending on the region; among the practically healthy adult population, it ranges from 1.5 to 10%, which is at least 5 million people [6]. The prevalence of HBsAg+ among pregnant women varies in different European countries from <0.1% in Northwestern Europe to 1-4% in Southern Europe. The highest rates are observed in the south and east of Central Asia. A high percentage of the infected population was registered in the countries of Central and Eastern Europe: Bulgaria, Estonia, Latvia, Moldova, and the Russian Federation [7].

The effect of chronic HBV infection on pregnancy.

There is little data on the effect of maternal chronic HBV infection on pregnancy outcome. The results of published studies on this topic are contradictory. There are studies that have not revealed a link between adverse pregnancy outcomes and the presence of HBV in the mother[13]. At the same time, there are studies indicating a higher rate of maternal and neonatal morbidity in chronic HBV infection, in particular diseases such as fetal distress syndrome, premature birth and meconial peritonitis. A study conducted in Hong Kong demonstrated a link between gestational diabetes and the presence of HBsAg in the mother. It was also noted in this study that the frequency of bleeding during childbirth was higher among the "carriers" of HBsAg. This was associated with an increased frequency of placental presentation and premature detachment of the normally located placenta. HBsAg carriers also had an increased risk of premature birth (up to 34 weeks). It is believed that chronic HBV infection does not lead to negative perinatal outcomes, with the exception of lower indices on the Apgar scale [29].

Vertical transmission of HBV infection.

For a newborn whose mother has positive HBsAg and HBeAg, in the absence of immunoprophylaxis, the risk of developing chronic HBV infection is 70-90%. For children born to mothers who have HBsAg positive but HBeAg negative, the risk of vertical transmission is much lower: from 10 to 40% in the absence of immunoprophylaxis. 85-95% of infected infants develop chronic HBV [16]. Rare cases of fulminant hepatitis B among perinatally infected children have also been described [14]. Vertical transmission, mainly from HBeAg-negative HBsAg-positive mothers, is the most common cause of the development of acute or fulminant hepatitis B in infants [14]. Fulminant hepatitis B is more common in infancy than in other age groups. The incubation period from 6 weeks to 6 months usually precedes the manifestation of an acute or lightning-fast form of hepatitis B. HBV is not considered an etiological agent of viral hepatitis in newborns, the symptoms of which appear before the age of 1-2 months (as a rule, the cause of such hepatitis are rubella, herpes viruses, CMV, etc.). The lightning-fast form of acute hepatitis B is considered to be the form in which signs of liver failure, including coagulopathy, increased bilirubin levels with decreased aminotransferase levels, decreased liver size and manifestations of hepatic encephalopathy, occur within 8 weeks after the onset of symptoms of acute hepatitis without a history of chronic liver disease. Mortality from the fulminant form of hepatitis B in infants is very high (about 67%), but it is lower than with the development of this form in adults (about 90%).

There are three possible ways of transmission of hepatitis B virus from an infected mother to a child: prenatally (intrauterine or transplacental), intranatally (during childbirth) or

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postnatally (during child care or through breast milk). It is generally recognized that the most common transmission of the virus from mother to child occurs during or near the time of childbirth, which is why timely vaccination of newborns prevents infection in about 80-95% of cases. The risk of HBV transmission during childbirth depends on the duration and severity of the newborn's contact with cervical secretions and maternal blood.

Currently, the combination of hepatitis B vaccine and highly titrated HBIG immunoglobulin is quite effective in preventing mother-to-child transmission of HBV. Nevertheless, approximately 10% of newborns from mothers with HBV become infected, and timely vaccination is ineffective.

Currently, it is believed that the main cause of unsuccessful vaccination is prenatal or intrauterine transmission of HBV. The mechanism of such transmission remains unclear. Several possible mechanisms are being considered, which include:

1. Infection of the placenta and trans-placental transmission of HBV.

In the process of intrauterine transmission of infection, the condition of the placenta plays a very important role. Intrauterine HBV infection occurs mainly when the virus from the mother's blood enters the fetal blood through the placenta [58]. HBV can infect all types of cells in the placenta, however, HBV transmission occurs either from HBV-infected cells of the maternal decidual membrane to the villi of the capillary endothelium, or from HBV-infected trophoblast cells directly to the villi of mesenchymal cells and capillary endothelial cells [8]. A high level of viral DNA in the blood serum of pregnant women is one of the high risk factors for the occurrence of intrauterine HBV infection.

2. Trans-placental infusions of maternal blood.

The threat of premature birth or spontaneous abortion, with possible mixing of maternal and fetal blood, may increase the risk of HBV transmission [20].

3. Amniocentesis.

The amniocentesis procedure theoretically leads to maternal blood entering the uterine cavity, as the needle passes through the abdominal wall and the uterine wall. In fact, visible signs of intrauterine bleeding that are not related to the placenta can be seen in 38% of cases of amniocentesis [17]. However, cases of HBV transmission during amniocentesis are rare [19].

Breastfeeding.

HBsAg can be detected in breast milk in a significant proportion of women infected with HBV [15]. Following the availability of immunization, concerns have been raised that breastfeeding may contribute to mother-to-child transmission of the virus. However, the conducted studies did not reveal differences in the number of perinatally infected infants who were breastfed and artificially fed with timely vaccination [9]. Thus, HBV infection is not considered a contraindication to breastfeeding of children who receive HBIG and HBV

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vaccine. Breastfeeding also has no effect on the child's immune response to the HBV vaccine [19].

Genotype matching.

The current classification includes eight HBV genetic groups, designated as genotypes A – H. Different genotypes are distributed in different geographical areas. Genotypes A and D are usually found in Europe, while genotypes B and C are common in Asia. Among patients with hepatitis B genotype A, chronic hepatitis with high activity is more often diagnosed, there is a more severe course of the disease, a more pronounced necrotic-inflammatory syndrome, and there is a tendency to the earlier formation of liver cirrhosis. Patients infected with HBV genotype D show a weak response to interferon therapy. Genotype may be a factor related to the degree of viral load and the frequency of vertical transmission. For example, with a similar prevalence of HBV, the incidence of maternal-fetal transmission in East Asia, especially in China, is in the range of 10-88% [19, 23], compared with 8% or less in studies conducted in sub-Saharan Africa [25, 26]. This difference is largely explained by the natural history of HBV genotype B and C infection in Southeast Asia, where the majority of infected people have HBeAg and a high viral load in age groups that include most women of childbearing age. On the contrary, in sub-Saharan Africa, the majority of patients with HBV are infected with A1 or E genotypes, in which seroconversion with the appearance of anti-HBe occurs before the age of 15-16 years, therefore, most women of gestational age do not have HBeAg [11].

Latent HBV infection in pregnant women and its clinical manifestations. Chronic HBV infection is characterized by the persistence of HBsAg for more than 6 months. Previous studies have shown that the disappearance of HBsAg in patients with HBV is associated with the disappearance of viremia and the development of remission of the disease. However, low levels of hepatitis B virus DNA can still be detected in the blood serum and liver tissue of some patients who have lost HBsAg. Thus, the absence of HBsAg does not mean the complete eradication of HBV. In patients with the erased form of HBV, long-term preservation of viral genomes in liver tissue (and in some cases also in blood serum) can be observed even with negative HBsAg. With such erased forms of HBV infection, it can be transmitted through blood transfusion, hemodialysis, and organ transplantation. There may also be an exacerbation of HBV, up to the development of a lightning-fast form of hepatitis or the occurrence of hepatocellular carcinoma. Vertical transmission with the erased form of HBV from a pregnant woman to the fetus is also described. In a recent study conducted in Korea, HBV DNA was examined in 202 healthy pregnant women. The testing was performed using two specific quantitative tests with two independent sets of serum and cord blood. It was found that eight out of 202 (4%) using some test systems and 23 out of 202 (11.4%) using others were HBV DNA positive. Six (3%) patients were positive on both test systems. A study of HBV DNA in umbilical cord blood obtained from four out of six women who tested positive for HBV DNA gave a negative result [28]. Thus, the vertical transmission of erased forms of HBV infection through umbilical cord blood, although possible, is not so high as to be clinically significant.

Acute viral hepatitis B, acute liver failure and exacerbations of HBV due to pregnancy.

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Acute HBV is not more common in pregnant women than in the general population. In studies on acute viral hepatitis during pregnancy in Northern India, it was noted that HBV is the cause of acute hepatitis in 15-19% of pregnant women [18, 21]. Almost two thirds of acute hepatitis cases among pregnant women in Southeast Asia are associated with acute hepatitis B. It has been noted that acute HBV infection in pregnant women is no more severe than in non-pregnant women [18, 21]. The manifestations of acute hepatitis, as a rule, do not differ from those in non-pregnant women. Some pregnant women may develop a severe form of acute HBV, up to the development of acute liver failure, with symptoms of cerebral edema, coagulopathy and multiple organ failure. A recent report from India noted that 2.9% of pregnant patients with acute liver failure were caused by acute HBV infection [10]. Acute HBV, especially in late pregnancy, can cause premature birth. In addition, there is a risk of postpartum bleeding, especially in cases of blood clotting disorders due to the development of acute liver failure. Up to 10% of children whose mothers suffered acute HBV during the first trimester of pregnancy turn out to be HBsAg positive at the time of delivery. At the same time, 80-90% of newborns become HBsAg positive without specific prevention if an acute infection develops in the mother during the third trimester of pregnancy.

In countries with a high prevalence of HBsAg, perinatal transmission accounts for the majority of cases of HBV infection. Passive hepatitis B immunoprophylaxis immunoglobulin and hepatitis B vaccine at birth is 95% effective in reducing the risk of HBV transmission, but less effective in mothers with very high levels of serum hepatitis B DNA. Administration of lamivudine in the last 4 weeks of pregnancy may provide additional fetal protection in HIV-positive women with high levels of viremia. Further studies are needed to evaluate the use of nucleoside analogues for the treatment of chronic hepatitis B during pregnancy [25].

Recently, a randomized, double-blind, placebo-controlled trial was conducted to evaluate whether lamivudine administration in late pregnancy could reduce the risk of perinatal HBV transmission in mothers with a high viral load. Mothers received lamivudine 100 mg or placebo from the 32nd week of pregnancy to the 4th week after delivery. All children received recombinant HBV vaccine with or without HBIg at birth and were followed up to the 52nd week. 150 mothers with a gestational age of 26-30 weeks and a serum HBV DNA level > 1000 mg/ml were treated. The results of this study suggest that lamivudine administration reduces the risk of HBV transmission from a highly viremic mother to a child who has received passive-active immunization [14].

Conclusions.

1. In general, HBV has no significant effect on the course and outcome of pregnancy, although there is little evidence of a higher incidence of preterm birth, the birth of children with a lower weight and a more frequent development of diabetes mellitus in pregnant women.

1. The risk of vertical HBV transmission is low in the presence of timely active and passive immunization, but may increase with a high viral load in the mother.

2. The method of delivery, breastfeeding, and genotype do not affect the frequency of perinatal HBV infection in the presence of timely active and passive immunization. 4.

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Currently, there are no clear recommendations for the treatment of HBV during pregnancy and effective measures to reduce the incidence of perinatal infection, however, ALT monitoring at least once per trimester, as well as quantification of viral load at the 30th week of pregnancy, can be recommended to address the need for lamivudine administration at the end of pregnancy.

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