

1. Introduction

Hepatitis B is caused by a virus that affects the liver, and when the infection progresses over time, it is called "chronic". This can lead to liver damage as well as cause hepatic failure and hepatic cancer. The high prevalence of hepatitis B during pregnancy makes it an urgent problem, and the treatment of chronic viral hepatitis B during pregnancy is a difficult task. Scientists have found that despite immunoprophylaxis, a significant proportion of children born of mothers with high viremia are infected with hepatitis B virus [1].

In the chronic viral hepatitis B (CVH B), the abortion in mild disease was noted in 7.7 %, in moderate – in 34.1 %, in severe – in 55.5 % of pregnant women. Pregnancy infertility is 15–20 %. In chronic viral hepatitis, the frequency of prematurity (miscarriage and premature birth) is significantly lower: 2 % and 10 %, respectively. Thus, chronic viral hepatitis B generally complicates the course of pregnancy, childbirth and the postpartum period: the frequency of preeclampsia increases (21.4 %), chronic fetoplacental insufficiency is more common (27.1 %), premature birth is more common (8.6 %), untimely discharge of amniotic fluid (16.8 %) and bleeding in the early postpartum period (5.7 %). The accumulated data make it possible to suggest that antiviral therapy in the III trimester of pregnancy is an effective measure [2].

Since liver damage in viral hepatitis B is predominantly immune-mediated, the activity of the hepatic process is often reduced in the second half of pregnancy due to hypercorticism. Risk factors for exacerbation or complications of liver disease in connection with pregnancy are the presence of signs of activity of the liver and cholestasis, the presence of cirrhosis stage of the liver with signs of portal hypertension.

2. Methods

Theoretical analysis of scientific literature; analysis and generalization. Statistics and comparisons. Classification of theoretical material and development of recommendations. The solution of the tasks set in the work was carried out using a systematic approach in the selection of material, methods of inductive and logical analysis, observation and statistical methods of analysis of data. Characterizing viral hepatitis B

THE TACTICS OF ANTIVIRAL THERAPY FOR CHRONIC VIRAL HEPATITIS B IN PREGNANT WOMEN

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Abstract: The aim of the study. Analysis of tactics of antiviral therapy for chronic viral hepatitis b in pregnant women.

Methods. Theoretical analysis of scientific literature; analysis and generalization. Statistics and comparisons. Classification of theoretical material and development of recommendations.

Research results. Today, there are about 2 billion people in the world ill with a chronic infection caused by the hepatitis B virus, 350 million of whom suffer from chronic hepatitis B, and most are asymptomatic carriers of the Australian antigen (HBsAg). Up to 50 % of all new cases of hepatitis B virus infection are due to vertical infection. Despite the lack of increase in viral load during pregnancy, alanine aminotransferase tends to increase in late pregnancy and in the postpartum period. A sharp drop in postpartum corticosteroids may create favourable conditions for hepatitis B virus activation. It is emphasized that the current treatment of hepatitis B virus includes the use of antiviral drugs, where Peg-IFN is absolutely contraindicated in pregnancy, lamivudine and entecavir are classified by the FDA as category C, and tenofovir and telbivudine are classified as category B. During pregnancy, it is recommended to use mainly category B drugs.

Conclusions. The use of antiviral therapy in combination with immunoprophylaxis of new-borns is the optimal strategy for implementation as a universal program, as the success of such an intervention can make a significant contribution to achieving the ultimate goal of global elimination of hepatitis B virus.

Keywords: hepatitis B, antiviral therapy, pregnancy, lamivudine, entecavir, tenofovir, telbivudine, HBsAg, immunoprophylaxis, effects on the fetus.

during pregnancy, it should be noted that the main route of perinatal infection with CVH B is intranatal, although the transplacental transmission of CVH B in the III trimester of pregnancy is also possible. The clinical picture of chronic viral hepatitis B during pregnancy is characterized as oligosymptomatic. However, the evidence-based symptoms of hepatitis B in pregnant women may be asthenoneurotic disorders (unmotivated fatigability, unmotivated weakness, irritability and poor sleep, pain in the right hypochondrium); dyspeptic disorders (vomiting, nausea, loss of appetite, stool disorders, increased flatulence); cholestatic disorders (the emergence of icterus as a result of impaired bile secretion, the presence of itching).

3. Results

The results of a previous study, which included 17,951 observations, showed that there is a linear correlation between failed immunoprophylaxis and the level of viremia in the mother [3]. This explained the increase in cases of ineffective preventive measures with increasing frequency of high viremia in the mother – more than 106 copies/ml. Experts of the First International Symposium on Hepatitis B Infection in Special Population (2009) recommended the use of antiviral medication to prevent the transmission of hepatitis B virus from mother [4].

Currently, the basis of modern treatment of viral hepatitis B is antiviral therapy (AT). At the same time, Peg-IFN is abso-

lutely contraindicated for pregnant women, lamivudine and entecavir are classified by the FDA as category C, and tenofovir and telbivudine are classified as category B (classification is based on teratogenicity data obtained in preclinical studies). During pregnancy, it is recommended to use mainly category B medications [5] (Table 1).

Regarding the achievement of the stable clinical-laboratory and virological remission of chronic hepatitis B, the effectiveness of interferon-alpha and nucleoside analogue lamivudine, tenofovir and telbivudine has been proven. Kipferon and suppositories for vaginal or rectal administration are used as immunocorrective treatment. Immunomodulatory and antiviral medication can provide a therapeutic effect up to eradication of the virus, but their use in pregnant women is contraindicated [6].

Table 1
Toxicity categories of antiviral therapy taken during pregnancy (FDA Classification)

Category	Effects on the fetus	Antiviral treatment
A	The results of controlled studies did not reveal a risk to the fetus in the first trimester of pregnancy; there is no evidence of risk in subsequent trimesters of pregnancy	–
B	The results of animal studies did not reveal a risk to the fetus; the results of controlled studies on pregnant women or animals did not reveal side effects of the medicament on the fetus; controlled studies on pregnant women found no risk to the fetus in any trimester of pregnancy	telbivudine, tenofovir
C	Animal studies have shown negative effects on the fetus; controlled human studies have not been conducted; the potential benefit of the medicament in pregnant women outweighs the potential risk to the fetus	kipferon, lamivudine, entecavir, adefovir
D	There are data on the negative effects of the treatment on the fetus, obtained in controlled and post-marketing studies, but the potential benefits of the medicament for pregnant women may outweigh the potential risk to the fetus	–
X	The results of controlled and post-marketing studies in animals and humans revealed abnormalities in fetal development; the risk associated with the use of the medicament in pregnant women far outweighs the potential benefits	interferon

4. Discussion

The meta-analysis in 2017, which included 15 studies, showed that treatment of infected women with lamivudine from 28 weeks of pregnancy significantly reduced the likelihood of vertical transmission of the infection (RR 0.33–0.43), and the effectiveness correlated with a reduction in viremia to 200,000 IU/ml [7]. The safety of lamivudine administration during pregnancy remains open – due to insufficient human studies, the FDA classifies it for pregnant women as a category C drug (data based on animal studies that have shown adverse effects on the fetus). Another disadvantage of lamivudine is the high frequency of drug resistance, which develops during the year in 15 % of patients treated [8].

It has also been established that mothers with baseline liver cirrhosis due to chronic hepatitis B have a high risk of perinatal complications. The results of a population-based study (observation period – from 1993 to 2005) showed that the risk of developing liver failure during pregnancy in women with cirrhosis is on average 15 %. Maternal mortality and perinatal fetal death in such cases are 1.8 and 5.2 %, respectively. These data serve as a good basis for earlier appointment of antiviral therapy during pregnancy or continuation of treatment already started before pregnancy. Although this tactic is associated with more frequent cases of prematurity and stunted children, it helps reduce the risk of gestational hypertension, placental abruption, bleeding during childbirth – complications that contribute significantly to maternal mortality. The drug of choice in this case is tenofovir.

Tenofovir, in comparison with lamivudine, has better efficacy and lower frequency of drug resistance, so in recent years this drug is recommended as the first line of chemoprophylaxis of perinatal infection in pregnant women [9]. Tenofovir for pregnant women according to the FDA classification belongs to category B, the absence of its teratogenic effect has been confirmed by several PCI. EASL (2015) recommends initiating tenofovir therapy in women with DNA CVH B levels above 200,000 IU/ml or HBsAg levels greater than 4 log₁₀ IU/ml from 24–28 weeks of pregnancy and continuing for 12 weeks after the act of delivery. Some researchers, addressing the question of initiating chemotherapy with tenofovir during pregnancy, recommend to focus on the level of AST or ALT, which exceeds the norm by 1.5–2 times as an additional criterion for assessing viremia.

Telbivudine for pregnant women according to the FDA classification belongs to category B and has shown efficacy in the prevention of perinatal infection when used in the second

or third trimester in HBsAg-positive mothers with viremia levels >200,000 IU/ml. In a study telbivudine at a dose of 600 mg/day was administered from 20 to 32 weeks of pregnancy to 135 women with high viremia, whose children were given a hepatitis B vaccine and a specific immunoglobulin after delivery. At 28 weeks postpartum, perinatal infection in children was found in 0 % of the women receiving telbivudine and in 8 % of the group of women not receiving chemotherapy.

High resistance to immunoprophylaxis occurs only in HBsAg-positive women with high levels of DNA CVH B (>200,000 IU/ml) and/or HBsAg levels above 4 log₁₀ IU/ml, so in the third trimester of pregnancy such women are recommended chemoprophylaxis with lamivudine, tenofovir and telbivudine, among which tenofovir is the most acceptable. The duration of chemoprophylaxis of nucleoside analogues (NA) is not precisely defined and can be stopped both before childbirth and 3 months after childbirth.

Due to the short duration of therapy with lamivudine and telbivudine (8–12 weeks) in the III trimester of pregnancy, resistance to these drugs in the treatment of pregnant women who have not previously received antiviral therapy, develops very rarely [10]. Tenofovir is recommended for the treatment of patients with appropriate indications due to its favourable safety profile and potentially high activity in suppressing viral replication. European Association for the Study of the Liver (EASL) [11] and the American Association for the Study of Liver Diseases (AASLD), classified the tenofovir therapy as first-line one [12]. In addition, the replacing of antiviral drug with tenofovir is recognized as a more effective tactic for the treatment of pregnant women with already developed resistance to nucleoside analogues.

Thus, the tactics in antiviral therapy of pregnant women with chronic HBV infection is the following:

- in the absence of indications for antiviral therapy and viral load of HBV DNA less than 1,000,000 IU/ml, the patient is subject to dynamic monitoring;
- in case of liver disease less than F3 and viral load of HBV DNA less than 1,000,000 IU/ml, therapy may be delayed until delivery [13];
- in the absence of active liver disease, stage less F3 and high viral load of HBV DNA (1,000,000 IU/ml and more), especially with HBeAg-positive status, there is a high risk of vertical infection (10 %), despite the active and passive immunization of the child. Such drugs (tenofovir or telbivudine or lamivudine)

are prescribed to women to prevent perinatal transmission throughout the 3rd trimester. Control determination of HBV DNA is performed after 8 weeks, and the drug is recommended to continue for 12 weeks after delivery. In the future, the need for AT is determined by general indicators;

– in the case of active liver disease with severe fibrosis or cirrhosis, standard AT is recommended using category B drugs, the most preferred of which is tenofovir.

Summing up, it can be stated that antiviral therapy in pregnant women remains a difficult task and requires individual and detailed assessment of the risks of medical exposure to the fetus in comparison with the benefits of treatment [13]. The positive effects of antiviral therapy include a significant reduction in the transmission of hepatitis B virus from mother to fetus in patients with high viremia, as well as the provision of therapeutic control of chronic hepatitis B as prevention of progression of liver fibrosis/cirrhosis. Finally, the use of antiviral therapy in combination with immunoprophylaxis of new-borns is the optimal strategy for implementation as a universal program, as the success of such an intervention can make a significant con-

tribution to achieving the ultimate goal of global elimination of hepatitis B virus.

5. Conclusions

In order to detect pregnant women infected with hepatitis B virus in a timely manner, it is necessary to examine women for hepatitis B virus antigen (HBsAg). It is necessary to conduct timely medical examination of pregnant women for early detection of pregnancy complications and threatening conditions in the fetus.

In addition, to minimize the effect of nucleotide and nucleoside analogues on the fetus, antiviral therapy during pregnancy should be prescribed to mothers at high risk of disease progression and decompensation of hepatitis B virus infection. The safety data suggest that telbivudine and tenofovir may be used during pregnancy. However, antiviral therapy requires careful risk and benefit assessment.

Conflict of interest

The authors declare that they have no conflicts of interest.

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