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Hepatitis B in pregnancy – Review of literature and guideline proposal

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ABSTRACT

Vertical mother-to-fetus transmission of hepatitis B virus (HBV) is a concern of public health global policies. The transmission rate can be substantially influenced by the good function of the maternal screening programs and by the vaccination of newborns as well. Also, the appropriate treatment of pregnant women and the administration of anti-HBV immunoglobulin immediately after birth come up with the decrease of HBV transmission rate. Acute viral hepatitis during pregnancy constitutes the main cause of jaundice recognized in pregnant women. It has generally a mild course during pregnancy, without significantly influencing the health state of the mother. In the context of immunological adaptation in pregnancy, the condition of the pregnant woman with chronic HBV infection without notable hepatic dysfunction generally has a good evolution. However, there are some possible clinical consequences like hepatic flares and progression of liver disease. The paper presents a review of literature and guideline proposals to prevent vertical transmission of hepatitis B virus and to provide the best possible care for pregnant women with hepatitis B infection.

Keywords: hepatitis B, pregnancy, vertical transmission, anti-HBV immunoglobulin

INTRODUCTION

Hepatitis B virus (HBV) as a member of the *Hepadnaviridae* family is a small DNA microorganism with unusual features similar to retroviruses and it is a common cause of liver disease and also for liver cancer. Vertical mother-to-fetus transmission of hepatitis B virus (HBV) is a concern of public health policies worldwide. It has been established that it stands as the cause of almost half of chronic HBV infections, the chance of newborns to be chronically infected with hepatitis B from infected mothers achieve almost 90% in the absence of a correct vaccination at birth. The transmission rate can be significantly influenced by the good function of the maternal screening programs and by the vaccination of newborns as well (1). Also, the appropriate treatment of pregnant women and the administration of anti-HBV immunoglobulin instantly after birth are able to reduce the HBV transmission rate.

ACUTE AND CHRONIC INFECTION WITH HEPATITIS B VIRUS

The diagnosis of HBV infection and its associated disease is based on a constellation of clinical, biochemical, histological, and serologic analysis. Some

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viral antigens and their respective antibodies can be detected in serum after infection with HBV, and proper interpretation of the results (Table 1) is necessary for the correct diagnosis of the various clinical forms of HBV infection (2).

TABLE 1. The interpretation of hepatitis B virus serological and virological markers

Serological and virological marker	Clinical interpretation
HBsAg	HBV infection, both acute and chronic
HBeAg	High-level HBV replication and infectivity; a marker for treatment response
HBV DNA	Level of HBV replication is a primary virologic marker for treatment response
Anti- HBc IgM	Acute HBV infection, could be seen in the flare of chronic hepatitis B
Anti-HBc IgG	Recovered or chronic HBV infection
Anti-HBs	Recovered HBV infection or marker of HBV vaccination, immunity to HBV infection (titer can be measured to assess vaccine efficacy)
Anti-Hbe	Low-level HBV replication and infectivity, a marker for treatment response
Anti-HBc (IgG) and Anti-HBs	Past HBV infection, could lose anti-HBs
Anti-HBc (IgG) and HbsAg	Chronic HBV infection
Anti-HBc (IgG) and/ or anti-HBs and HBV DNA (PCR)	Latent or occult HBV infection

Acute HBV infection can be either asymptomatic or present with symptomatic acute hepatitis. Most adults infected with the virus recover, but 5-10% are unable to clear the virus and become chronically infected. Many chronically infected patients have a mild liver disease with little or no long-term mortality and morbidity. Other individuals with chronic HBV infection develop active disease, which can lead to liver cancer and cirrhosis.

The risk of developing a chronic hepatitis B infection is also directly related to the age at which one first becomes exposed to the hepatitis B virus: 90% of infected newborns and babies, up to 50% of infected children (1-5 years) and respective 5-10% of infected adults will develop a chronic hepatitis B infection.

People who test positive for the hepatitis B virus for more than six months after their first blood test result are diagnosed as having a chronic infection. Once the chronic infection is established within the host, the clinical course of HBV may fall into one of four phases like immune tolerance, immune clearance, inactive HBsAg carrier state, or reactivation. Immune tolerance is most frequently affiliated with younger individuals who likely acquired HBV infection perinatal through vertical or horizontal transmission. Very high serum HBV DNA levels, detectable HBeAg, normal serum alanine aminotransferase (ALT) levels, and minimal histologic activity on liver biopsy indicate this phase. In contrast, the immune clearance phase is associated with elevated ALT levels and significant HBV-associated disease on liver biopsy. In this phase, HBeAg is detectable and HBV DNA levels are typically elevated. The inactive HBsAg carrier state is remarkable for persistently detectable serum HBsAg, yet normal ALT levels, low or undetectable HBV DNA, and typically minimal disease on liver biopsy. This phase is also associated with seroconversion of HBeAg, defined by loss of HBeAg and emergence of antibody to HBeAg (anti-HBe). Some individuals may transition into an HBV reactivation phase also known as HBeAg-negative chronic HBV infection. Negative HBeAg, positive anti-HBe, persistently or intermittently elevated ALT levels and significant disease on liver biopsy characterize this phase. In the reactivation phase, HBV DNA may be elevated but typically not as elevated as noticed in HBeAg-positive infection. People who are in the immune clearance phase (HBeAg-positive) and the reactivation phase (HBeAg-negative) may candidate for antiviral therapy (2). Some groups have developed guidelines for the selection of appropriate candidates in whom therapy should be considered. Treatment of HBV infection is not indicated in the setting of immune tolerance or the inactive HBsAg carrier state; however, these patients should be constantly monitored as they may transition into a more active phase of infection.

HEPATITIS B VIRUS INFECTION DURING PREGNANCY

Acute viral hepatitis during pregnancy represents the principal cause of jaundice identified in pregnant women. It has generally a mild course, without significantly influencing the mother health state. Instead, there is a higher incidence of intrauterine growth restriction and prematurity. The rate of transmission of the infection to the fetus is higher as the birth term is approaching, varying between 10% in the first weeks of pregnancy and 60% around birth (3).

These are the management principles of pregnant women with acute viral hepatitis. Symptomatic-supportive treatment and monitoring coagulation tests and liver enzymes. In case there are severe forms (severe hepatitis or even acute liver failure) anti-viral treatments are recommended by a spe-

cialist in infectious diseases; because the treatment is in general short-term and the safety profile for pregnancy is good, tenofovir disoproxil fumarate (TDF) 300 mg daily or lamivudine (100 mg daily) are used. We will monitor the pregnant woman by periodic tests for HBs surface antigen and viral load (HBV DNA). If the antigen remains positive, the newborn is given in the first 12 hours postpartum the hepatitis B immunoglobulin in addition to the hepatitis B vaccine. If the viremia has a high level around the time of birth, it is considered appropriate to administer antivirals to the mother (3).

In the context of immunological adaptation in pregnancy, the condition of the pregnant woman with chronic HBV infection without significant hepatic dysfunction generally has a positive evolution. However, the following clinical outcomes are possible: hepatic flares and progression of liver disease.

Hepatic flares is represented by the reactivations of the infection, having the increase of the transaminases level (it doubles the pre-existing values, by exceeding the normal value by three to five times) as paraclinical expression. These flares can occur both during pregnancy and mostly postpartum. According to the prospective study conducted by Giles (4), which followed 126 pregnant women, two patients had a flare during pregnancy and 27 (25%) postpartum. The appearance of the flare is, according to the same author, determined by the positive value of HBeAg or its seroconversion (4).

Maternal adaptation in pregnancy can reveal or aggravate the evolution of liver damage, regarding to a potential progressive liver disease. Decompensated liver disease can occur as a result of a severe flare or less often, it can lead to cirrhosis. Laboratory diagnosis can be difficult to interpret, due to the decreased physiological albuminemia and hematocrit levels. We can also observe increased alkaline phosphatase and alpha-fetoprotein values. The clinical diagnosis may be laborious, as pregnant women may have spider angioma, palmar erythema and even edema of the lower limbs due to hyperestrogenemia. Quite unusual during pregnancy but also possible is an increased viremia.

Studies are showing a possible association between chronic viral hepatitis and gestational diabetes, increased risk of prematurity, low birth weight, and also antepartum hemorrhage (5-9).

In pregnant women with cirrhosis, the evolution of the disease can be burdened by maternal complications (esophageal varicose veins bleedings during the third trimester of pregnancy and in labor), pregnancy-induced hypertension (abruptio placentae, peripartum hemorrhages), and fetal distress (intrauterine growth restriction, intrauterine infections, premature birth or sudden intrauterine fetal death) (10,11). Pregnant women with cirrhosis and esophageal varicose veins will be monitored through endoscopic procedure; esophageal banding is also possible in pregnancy. Bleeding prophylaxis with beta-blocker may be performed, but we cannot administer octreotide due to the risk of uterine ischemia.

Some patients who have severe evolution of hepatitis B infection may ultimately receive liver transplantation. Patients may regain their fertility during their reproductive phase, but conception is best-delayed two years after the procedure, due to the time requested for stabilization of the immunosuppressive treatment. Both maternal-fetal medicine specialists from a high-risk obstetrics unit and specialists from the liver transplant center perform follow-up during pregnancy. These pregnancies are considered at high risk because of the high incidence of complications: gestational diabetes, pregnancy-induced hypertension, and early-onset preeclampsia, fetal growth restriction, premature birth, and higher incidence of fetal malformations. Pregnancy may impact the long-time survival of the mother; some studies suggest that about 15% of women die between 9 and 56 months postpartum (12). However, Bohiltea et al (13) report the 16 years experience of Romania in liver transplants, which included 29.6% women of fertile age (18-45 years); they also describe a case of 26 years old patient with liver transplant for cirrhosis of viral etiology (hepatitis B and D viruses) decompensated parenchymal and portal Child B stage, who gave birth by term-programmed caesarean section to a living normal weigh fetus, without negatively impact of the liver function during the pregnancy. The experience of pregnancy after liver transplant is still growing, but the most subtle complication of these cases remains cholestasis, which have a difficult differential diagnosis with graft failure (14).

Both the obstetrician and the hepatologist will observe pregnant women who have a chronic liver infection. To establish the therapeutic conduct, the risk of developing resistance to treatment, effects on the fetus, and the duration of treatment will be considered to stop the progressive evolution of the disease. In some patients only supervising the patient is possible. In other situations the antiviral treatment will be required. Some patients become pregnant while antiviral treatment is already administered (15). The criteria for administering antiviral therapy to pregnant women are similar to those of non-pregnant women. The antiviral therapy is usually indicated if ALT is maintained twice above the normal value or HVB DNA is over 20,000 IU/ml in HBeAg positive patients or over 2000 IU/ml in HBeAg negative patients. However, there are some situations that can bring concerns in pregnant

women; a patient may postpone or simply refuse the treatment in case of the levels of transaminases are above normal. Although, if a pregnant patient has a viral load of more than 20,000 IU/ml, but values of transaminases below the treatment criteria, principally in the third trimester, she has indication for antiviral treatment to minimize as much as possible the risk of transmission to the child (16). Also, if a patient gets pregnant in full antiviral treatment, she will continue the medication but is mandatory to change it with TDF, which is the best treatment option for this circumstance because it is effective and safe in pregnancy, and also develops lower treatment resistance (17,18). The patient should strictly monitored during the transition period between the two drugs, to confirm that viral suppression is achieved.

Laboratory tests will be constantly verified to be able to diagnose as soon as possible a disease reactivation in cases of pregnant women who do not receive treatment. The current recommendation is to check transaminases once in three months during pregnancy and then up to six months postpartum. Whenever increases in transaminases are detected, the viremia should be determined again. The viremia will also be determined at the end of the second trimester (26-28 weeks of pregnancy), to establish the necessity of possible antiviral treatment, with a preventive role in transmission from mother to child (19).

THE MECHANISM OF HVB TRANSMISSION FROM MOTHER TO CHILD

The usage of vaccination and active immunization with anti-hepatitis B immunoglobulin (IG HB) has markedly decreased the rate of vertical transmission of HBV infection from HBsAg-positive mothers. Consequently, a published data from United States revealed that from a cohort of 9252 children born by HBsAg-positive mothers, perinatal HBV infection was detected only on 1.1% of them. 95% of children received both the hepatitis B vaccine and the IG HB in the first 12 hours after birth. Most of those children received accurately all three doses of the HBV vaccine. In these cases, the risk factors for transmitting the infection were the HbeAg positivity and a viral load of more than 2000 IU/ml. Also, females aged less than 25 years or the administration of less than three recommended doses of vaccine may increase the transmission risk. It is interesting to note that generally younger women tend to be positive for HBeAg and have a higher viral load (possibly correlated with the immune tolerance phase) (20).

Regarding the principal modes of HBV transmission throughout pregnancy and postpartum, it is considered that the highest risk of transmission occurs at vaginal birth, due to prolonged contact between the fetal mucosa and the mother's secretions and blood. On the other hand, many studies have not been capable of proving the protective and limited role in the transmission of birth by cesarean section. For this purpose, the indication for cesarean delivery in HBsAg-positive women is not absolute (21-23).

The transplacental route of transmission has been vastly investigated, but it proves to be only a reduced route of infection transmission. However, HBV has been recognized in the villous endothelium and trophoblasts cells. Placental barrier discontinuities (for example increased contractility from the threat of premature birth or abortion) are thought to allow transfer from mother to fetus. Only one study had demonstrated the ability of HBV to translocate from mothers to trophoblasts. A high viral load may favor this transfer in case of premature birth (24).

Excepting the amniocentesis, the other invasive procedures (chorionic villus biopsy, cordocentesis, fetal interventions in utero) have been very slightly investigated from the perspective of maternal-fetal HBV transmission. Viral transmission can be possible during amniocentesis, but the risk is considered to be low, especially if risk factors do not exist (mother with no HBeAg, with low viral load). The procedure is allowed but must be done with a smaller needle, 22G (25-27). The available data provide conflicting conclusions about the rate of transmission of HBV infection in the case of PROM. In this kind of situation, there are no additional recommendations on obstetrical behavior.

The presence of HBV DNA was detected in the maternal colostrum. Nevertheless, studies do not show an obvious connection between breastfeeding and viral transmission, if there are no fissures or cracks in the nipple. Many studies confirm the safety of breastfeeding if the newborn follows the complete immunization schedule after birth.

GUIDELINE FOR PREVENTION OF VERTICAL TRANSMISSION OF HEPATITIS B VIRUS

The following methods have been demonstrated to be effective in preventing vertical transmission of HBV: active maternal screening, antiviral treatment in situations of clear indication (increased viremia), and complex immunization of the newborn.

At the first prenatal visit, which is desirable to be as early as possible, in the first trimester of pregnancy, any pregnant woman should be tested for the presence of HBsAg to assess the possible infection and the risk of vertical transmission. A particu-

lar category is that of pregnant women with risk behavior (those who use intravenous drugs, with a history of sexually transmitted diseases, with more than one sexual partner in the last six months), from disadvantaged socio-economic backgrounds, and also those who have a partner or other family member positive for HBsAg.

Pregnant women who are tested positive for HBsAg will be tested as well for HBeAg, anti-Hbe antibodies, viremia (HBV DNA) and level of transaminases. If there is an increased viremia, over 20,000 IU/ml, or the presence of HBsAg and/or an increase on transaminases level, the pregnant woman will be directed to a gastroenterologist/hepatologist, who will decide if there is a need for therapeutic intervention. Pregnant women who have low levels of viremia at the beginning of pregnancy should be retested at the end of the second trimester, for dynamic assessment and reassessment of behavior (treatment may be recommended if the risk of transmission becomes high). The high-risk pregnant women mentioned above should also be tested for anti-HBs and anti-HBc antibodies (those using intravenous drugs with a history of sexually transmitted diseases, with more than one sexual partner in the last six months), those from disadvantaged social-economic, those who have a partner or other family member positive for HBsAg). Pregnant women without antibodies will need to be vaccinated and retested for HBsAg at the beginning of the third trimester of pregnancy. Any pregnant woman who has not been tested during pregnancy must be tested when she arrives at the maternity hospital for the birth.

As mentioned earlier, in pregnant women without indication for therapy during the first months of pregnancy, it is recommended to re-check the viremia at the end of the second trimester to know if treatment is required during the last months of pregnancy (28). The treatment aims to reduce viremia, preventing transmission even if a premature birth occurs. Antiviral therapy is suggested when the viremia exceeds 20,000 IU/ml or 10^6 copies/ml and will be, of course, accompanied by active and passive immunization of the newborn. After about four weeks of treatment, the viremia will be verified again. The viremia decreases in most cases (29). In the main case of pregnant women taking antivirals only to reduce the risk of transmission to the fetus, it is considered safe to stop treatment after birth, which will also allow breastfeeding without additional risks (30). However, some authors recommend a continous treatment for four to twelve weeks postpartum, to reduce the incidence of flares (31). It is recommended to supervise these patients by serial determinations of transamination up to six months after the end of treatment, during the postpartum period (31).

Current immunization protocols are very clear in the recommendation of immunization as soon as possible after birth, preferably in the first 12 hours postpartum, regardless of the birth weight of the child or the antiviral treatment followed by the mother, the first dose of HB vaccine (intramuscular) and a dose of 0.5 ml of IG HB, also intramuscularly, in different anatomical areas. If the complex immunization is performed correctly, the newborn can be breastfed. This firm recommendation is based on data showing that in the absence of immunization, the perinatal transmission rate in children of AgHBs-positive mothers can reach 90% (32). The baby will follow the vaccination schedule according to its birth weight and will be tested for Ag HBs and anti-HBs antibodies at nine and twelve months of age (33).

CONCLUSIONS

Several publications are drawing attention to the fact that there is still an increased prevalence of HBs antigen in pregnant women, with consequent mother-child vertical transmission and also possible chronic infection transformation, if the newborn is not being treated properly or the infection is unknown. The correct treatment consists of vaccination of the newborn in the first 24 hours after birth with the first dose of hepatitis B vaccine and administration of hepatitis B immunoglobulin during the first 12 hours postpartum, regardless of birth weight. This is the standard of care in most European countries, the US and Australia, and, along with compulsory vaccination under the national vaccination program, allows for a decrease in the incidence of this infection.

Greater efforts are needed for pregnant women to come forward to highlight pregnancy (as much as possible during the first trimester), to be screened for hepatitis B virus (HBV), which means education, information, and even broad access to free/affordable health services.

Family physicians and pediatricians should be actively advised of those not at all rare situations in which either the first vaccination dose or the immunoglobulin prophylaxis were not performed, according to the standards of care. These infants represent a new pool for chronic B hepatitis and all potential later complications.

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