

## HEPATITIS B VIRUS AND PREGNANCY

Cionca Octavia, Hadnagy Z., Murariu A., Zahner Mihaela

*Collective for Research in Obstetrics – Gynecology and Neonatology, Emergency Municipal Clinical Hospital Timisoara, Romania*

### Abstract

*Globally, there are approximately 240 million people chronically infected with hepatitis B virus (HBV)—a major cause of liver cirrhosis and hepatocellular carcinoma. Pregnant women tested for HBsAg with a positive result, should be considered as a priority in order to reduce the risk of perinatal transmission.*

*Prevention is based on vaccination and implementation of safety strategies for parenteral treatment, blood transfusions and sexual behavior.*

### Rezumat: Virusul Hepatitei B și sarcina

*La nivel global, există aproximativ 240 de milioane de persoane infectate cronic cu virusul hepatitei B (VHB) - o cauză majoră a cirozei hepatice și carcinomului hepatocelular. Femeile gravide testate pentru AgHBs, cu rezultate pozitive considerate o prioritate, pentru a reduce riscul transmiterii perinatale.*

*Prevenția se bazează pe vaccinare și implementarea strategiilor de siguranță a tratamentului parenteral, transfuziilor de sânge și conduitei sexuale*

**Cuvinte cheie:** hepatita cronică B, prevenie, transmitere verticală

### Introduction

Recognition that hepatitis has an infectious etiology has been in the modern literature since early in this century, and the terms hepatitis A and B were first used in 1947. However, proof that viruses are responsible for this disease was first published in 1968 with the description of hepatitis B virus (HBV) particles in *Nature* (1).

Following acute HBV infection, the risk of progression to chronicity is age dependent with 5% of adults, and almost 95% of children born to chronically infected mothers, becoming chronic carriers (2).

Reflecting the special populations with substantive changes in management in recent years,

HBV-positive women in the context of pregnancy

CORRESPONDENCE: Octavia Cionca, e-mail: avia36ro@yahoo.com

KEY WORDS: chronic hepatitis B, prevention, vertical transmission

and post-partum requires consideration of risks to mother and fetus/infant, including the risk of mother-to-child transmission (3). Sustained activities of health promotion are required both in the general population and in the special groups (HIV positive, immunosuppressed patients, liver transplant recipients and pregnant women) (3, 4).

This paper provides an overview of the hepatitis B and pregnancy in the current context.

### Prevalence of viral hepatitis type B in the EU

In the WHO Europe region it is estimated that there are 14 million chronic hepatitis B carriers;

about an adult of 50 is infected with hepatitis B virus (4).

The downward trend in the number of cases of acute HBV is correlated with the global implementation of vaccination programs (4); while the prevalence of HBeAg negative CHB has been increasing over the last few decades probably reflecting the aging of existing HBV carriers and the effective prevention measures restricting new HBV infections. In a previous study from Italy, HBeAg negative CHB prevalence rose from 41% during the 1975-1985 period to 90% during the 1990s. The predominance of HBeAg negative CHB nowadays has also been supported by a French study (2).

In the EU in 2012, heterosexual transmission was on the first place (31.2%) followed by nosocomial (20.6%), among homosexuals (11.1%) and injecting drug users (8.7%). Perinatal transmission was the most frequent in the case of chronic hepatitis HBV (67.0%) (4).

The study made by the National Institute of Public Health Romania in 2013 showed a value of 4.2% for HBsAg in the study population. In women in the age group  $\geq 20$  years, the prevalence of this marker was 4.02%, and in those under the age of 20, the value was 1.37%.

Test results in the sero-epidemiological study of the prevalence of hepatitis B virus infection in pregnant women in 2016 will be evidence that can inform future public health strategies / interventions, and providing references to the improvement of HBV control strategy (5).

### **Hepatitis B virus (HBV): genetic variants and clinical significance**

There are ten HBV genotypes (A–J) classified by sequence divergence of at least 8% in the entire HBV genome. Genotypes A and D are prevalent in the European Union and in Central/South Asia; B and C in South/South East Asia and the Pacific region; E in West/Central Africa; F in South/Central America and Alaska; G and H in Europe and Japan; I in Vietnam and Laos; and J in Japan (6).

However, evidence suggests that HBV genotypes and subgenotypes play a critical role in

host–virus interactions. Knowledge of HBV genotype will enable clinicians to determine patients' response to treatment and their risk of future complications (6).

In the hepatitis B virus genome, naturally occurring mutations have been found in all viral genes, most notably in the genes coding for the structural envelope and nucleocapsid proteins. Viral variants may be associated with a specific clinical course of the infection, e.g., acute, fulminant or chronic hepatitis. Specific mutations may reduce viral clearance by immune mechanisms ('vaccine escape' and 'immune escape'), response to antiviral therapy ('therapy escape'), as well as detection ('diagnosis escape') (7). The identification of such immune escape variants may be important due to the risk of HBV vertical transmission despite complete passive-active immunoprophylaxis (8).

### **HBV Treatment and Diagnostic Assays**

The natural course of chronic hepatitis B virus (CHB) includes: i) An immunotolerance (IT) phase characterized by the presence of hepatitis B 'e' antigen (HBeAg), active HBV replication and normal levels of alanine aminotransferase (ALT), ii) an immunoclearance (IC) phase characterized by fluctuating or high serum HBV DNA and ALT levels, liver inflammation and HBeAg seroconversion, iii) a low replicative (LR) phase in which patients have undetectable levels of HBV DNA, are HBeAg-negative, anti-HBeAg positive and show minimal fibrosis and iv) HBeAg negative hepatitis (ENH) (9).

The annual incidence of HBeAg-negative immune-active hepatitis among inactive carriers is estimated to be 0.37%. Some patients do not fit into any of these conventional phases (10).

The HBV DNA levels in serum give important information on treatment monitoring, and HBV status. There is conflicting evidence regarding the variability of HBV DNA levels during pregnancy, as laboratory results obtained more distant from birth may not reflect the infant's true risk at the time of delivery (11).

There is limited data on HBV evolution and variants in the context of pregnancy, and the effect

of potent NA (nucleotide analogs) therapy, such as TDF (8). Tenofovir disoproxil fumarate (Tenofovir DF) is a nucleotide analogue. A multicenter study reports retrospectively the long-term efficacy and safety data with tenofovir DF treatment in nucleosid(t)e-naive, hepatitis B e antigen (HBeAg)-positive chronic hepatitis B patients. Tenofovir DF was well tolerated and produced potent, continuous viral suppression with increasing HBeAg loss (12)

### Interventions to prevent MTCT of HBV

The reported rates of VT range between 1% and 28%. Vertical transmission (VT) of HBV primarily occurs by intrauterine transmission (IUT), accounting for 13–44% of HBV transmission. Although technically not considered under the category of VT, sperm to ova transmission has been studied. None of their infants were infected with HBV, as determined by amniocentesis sampling for HBV seromarkers. In that study, infection occurred only in cases with HBV-positive mothers, regardless of paternal HBV status (13).

Perinatal transmission of HBV is strongly associated with HBeAg positivity in the mother and HBeAg seroconversion is considered as a marker for a sustained therapeutic response. HBeAg is an important early serum marker of HBV infection and correlates with high infectivity (9).

The ability of HBeAg to cross the placenta generates HBV specific T cell tolerance to the virus. This can ultimately lead to failure of immunoprophylaxis (13).

Studies have not shown a consistent relationship between perinatal transmission and other risk factors such as delivery mode, invasive procedures during pregnancy, or breastfeeding (11).

According to international guidelines, such as the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) guidelines, HBV-exposed infants should receive both hepatitis B immunoglobulin (HBIG) and HBV birth-dose vaccine to further reduce the risk of transmission. The World Health Organization (WHO) recommends administration of the first dose of the hepatitis B (HB)

vaccine within 24 hours of delivery (14). Children born from HBsAg-positive, and HBeAg(+)carrier mothers, should receive HIGB within the first 12 hours after birth (5).

International guidelines do not recommend treating women with HB viral loads lower than 200 000 IU/ml. Tenofovir (TDF), when administered around 28 to 32 weeks of gestation reduce maternal HB viral load during pregnancy and therefore the risk of mother-to-child transmission (MTCT) (14). In a recent, open-label, uncontrolled study, treatment with telbivudine started at the 20<sup>th</sup> to 32<sup>nd</sup> gestational weeks was not only safe, but also prevented all cases of HBV transmission in women with HBV DNA levels > 10<sup>7</sup> copies/mL (15).

When pregnancy is confirmed in women who are on IFN (interferon) or NA treatment other than TDF, treatment is discontinued if there is not advanced fibrosis or cirrhosis; if there is, it is continued with the substitution of current medication with TDF. Where medications are withheld during pregnancy, close monitoring is needed because of hepatic flare risk (15).

Reactivation of CHB occurs in up to 45% of HBsAg-positive mothers during the 6 months after delivery, probably because of restoration of the immune system. The outcome is worse in mothers with cirrhosis. Liver biochemistry and hepatitis B virus (HBV) DNA levels should be closely monitored after delivery (16).

Antiviral therapy for pregnant women with high HBV DNA levels has been proposed to reduce perinatal transmission, but its use is not yet standard of care. The exact viral load at which to initiate antivirals to prevent transmission has yet to be established. New guidelines are proposed to provide anti-viral therapy in pregnancy to prevent perinatal transmission. This requires both additional prenatal laboratory testing and a clear viral load threshold to offer therapy (11).

### Concluding remarks

Hepatitis B virus (HBV) remains a global health problem. Chronic infection with hepatitis B virus (HBV) greatly increases the risk for liver *cirrhosis*

and hepatocellular carcinoma (HCC). Our efforts to treat and prevent HBV infection are hampered by the emergence of drug resistant mutants and vaccine escape mutants (17). Pregnant women at high risk of perinatal transmission could be treated with lamivudine, telbivudine or TDF in the last trimester of pregnancy to reduce the risk of HBV transmission (15). Development of standardized assays for surrogate endpoints for HBV cure should occur in parallel with development of novel antiviral and immune modulatory therapies to expedite research (10).

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