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Case Report

Acute hepatitis B in pregnancy with surprisingly rapid clearance of serum HBs antigen associated with a favourable outcome

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ABSTRACT

Acute hepatitis B (AHB) is usually asymptomatic, but it can progress to chronic hepatitis B (HB) defined by HB surface antigen (HBsAg) persisting beyond 6 months. Nevertheless, the delay of HBsAg seroclearance is not well-defined. During pregnancy, the immune system of the pregnant women is altered and delayed HBsAg loss can be observed, leading to chronic infection. Here, we present an uncommon case of AHB in a pregnant woman in whom rapid HBsAg seroclearance (52 days after AHB) was associated with a favourable outcome (no injury to liver). This patient received tenofovir disoproxil fumarate promptly after diagnosis. The case raises questions about the use of antiviral treatment in AHB. This is generally not recommended in AHB, but it would be potentially useful in pregnant women to reduce the risk of chronic HB infection and could also prevent the transmission of the maternal precore mutation, thus reducing the significant risk of fulminant hepatitis in the infant. This case also highlights the impact of the hepatitis B virus (HBV) genotype and precore/core mutations on the clinical course of the disease.

Introduction

Despite the availability of an effective vaccine and antiviral drugs, hepatitis B (HB) virus (HBV) infection remains a major health problem worldwide. HBV infection is characterised by acute HB (AHB), which is usually asymptomatic but can progress to chronic hepatitis and subsequent cirrhosis or hepatocellular carcinoma. The delay of HB surface (HBs) antigen (HBsAg) seroclearance is not well-defined. Nevertheless, chronic HB (CHB) is defined by HBsAg persisting beyond 6 months. The global incidence of AHB in pregnant mothers is unknown because of regional differences, and few data are available regarding this topic (Wong et al., 2020). According to a national prenatal survey undertaken in France, the prevalence of HBsAg in pregnant women was 0.84% in 2016, reaching 5.5% in mothers born in Sub-Saharan Africa or Asia, with both classed as high endemic areas (Brouard et al., 2020). Here, we present an uncommon case of AHB in a pregnant woman with a rapid clearance of serum HBsAg (52 days after AHB) associated with a favourable outcome.

Case report

On 10 January 2020, a 26-year-old pregnant woman (at 5 weeks' gestation), native of Guinea, was seen in the gynaecological emergency department because of several days of vomiting and asthenia. The interview revealed no recent travel, no drugs and no change of sexual partner within the past 2 years. Cholestasis and a high hepatic cytolysis (aspartate aminotransferases: 2,204 IU/L; alanine aminotransferases: 2,197 IU/L) were found, with a high risk of liver failure because prothrombin time and total bilirubin amount were 58% and 99 µmol/L, respectively. No hepatic encephalopathy was detected. On the basis of these results, an abdominal ultrasonography was performed, showing no liver abnormalities. Serological investigations revealed the presence of HBsAg (4,349 signal-to-cut-off [S/CO]) associated with HB core antibodies immunoglobulins M (40 S/CO) without HBs antibodies, thus suggesting an AHB. An additional check-up confirmed the presence of HBsAg with a high HBV viral load of 7.18 log IU/mL, and the pres-

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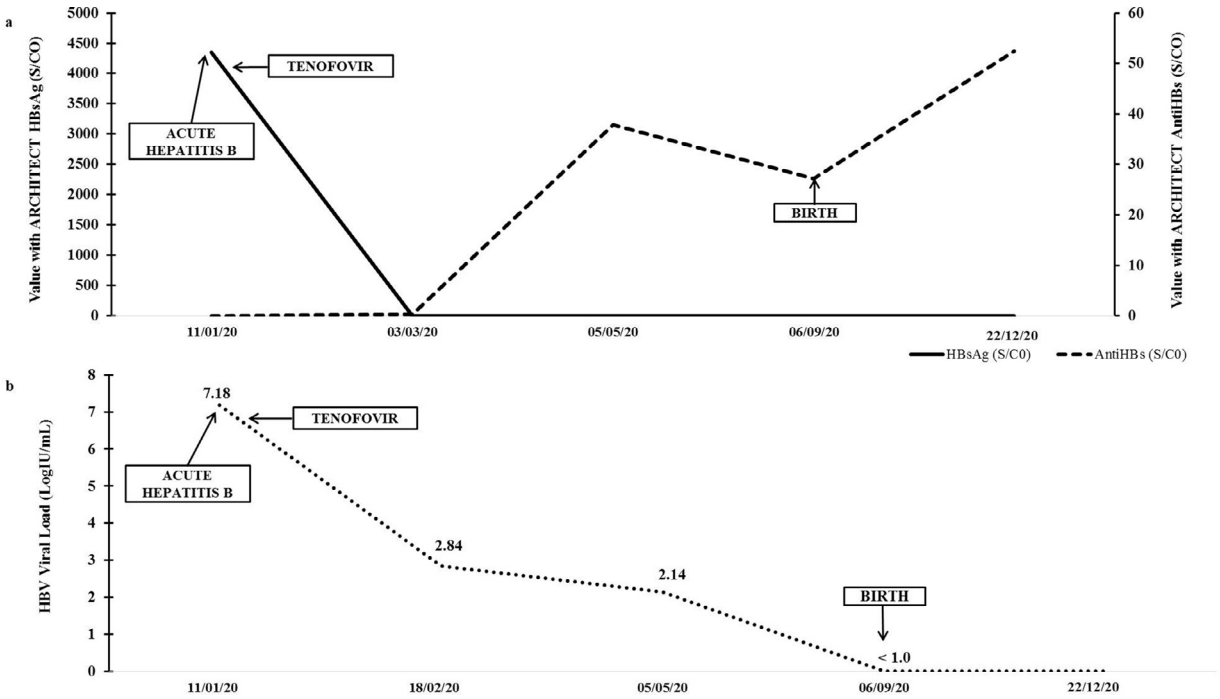

Figure 1. (A) Hepatitis B (HB) virus (HBV) serological course (HB surface [HBs] antigen and anti-HBs antibodies); (B) HBV viral load monitoring in pregnant woman. Tenofovir disoproxil fumarate was rapidly started on 11 January 2020. The birth of the newborn took place on 6 September 2020. S/CO, signal-to-cut-off.

ence of HB e (HBe) antibodies without HBe antigen (HBeAg). In the absence of a medical history of HBV, we suggested a probable AHB with precore/core (PC/C) mutations or reactivation of CHB related to pregnancy (with either seroconversion of HBeAg or PC/C mutations during CHB). During a renewed investigation, we found that the preconceptional serology was negative for HBsAg (August 2019) and her husband, who is a native of Africa, had only recently come to France. Taking these elements into account, we concluded that the patient had acute de novo HB. Partial genetic sequencing of HBV was undertaken as previously described (Ducancelle et al., 2013), which showed a G1896A mutation in the PC/C gene and highlighted a genotype E. Tenofovir disoproxil fumarate (TDF, 245 mg, daily) was rapidly started because of the severity of liver damage, which permitted a favourable outcome with full resolution of hepatic cytolysis and cholestasis, and a significant decrease of HBV viral load by May 2020 (Fig. 1). At the delivery, HBV DNA was undetectable. We also noted a rapid seroconversion and HBsAg seroclearance during pregnancy, 52 days after the first symptoms (Fig. 1). The newborn received 1 dose of HBV vaccine at birth, without HB immunoglobulins, considering the mother's HBV status (negative HBsAg). The HBsAg status and HBV viral load were not available in the newborn at birth. In January 2021, the liver function tests showed no liver injury and the absence of fibrosis (FibroScan®: 3 kPa; FibroMeter®: 0.03), and TDF was therefore stopped.

Discussion

Nowadays, AHB infection is uncommon in France because of a universal vaccination programme and of strong recommendations for HBsAg screening in the first trimester of pregnancy (Lampertico et al., 2017). Pregnant women are characterised by their specific susceptibility to some infectious diseases because their immune system is altered by significant hormonal changes. This may explain why the loss of HBsAg in pregnant women acutely infected with HBV is less likely than that observed in non-pregnant women. A study has shown HBsAg loss and seroconversion to be delayed in pregnant women when compared with non-pregnant women (145 versus 80 days) (Han et al., 2014). Therefore, pregnancy might be a risk factor for chronicity following acute HBV infection (Sirilert and Tongsong, 2021). Although an aggressive cytotoxic response seems to be required for rapid HBsAg clearance, with the drawback of a more intense (albeit transient) parenchymal damage, here we observed rapid HBsAg loss associated with a favourable outcome (no liver injury). Menzo et al. indicate that both HBsAg at day 28 and the kinetics of HBsAg in the first 4 weeks from admission are predictors of the chance of clearing HBsAg within 6 months (Menzo et al., 2018).

Moreover, we highlighted a genotype E, which is predominant in people from Sub-Saharan Africa. The previous comparative study (Han et al., 2014) does not specifically mention HBV genotypes, whereas many studies have shown clinical and biological variations according to the HBV genotype (Revill et al., 2020). For instance, patients infected by genotype D would experience the highest liver alterations and the lowest HBsAg titres (Menzo et al., 2018), but the impact of genotype E has never been investigated. Further studies are needed to investigate the evolution of HBsAg titre according to genotypes. The identified G1896A mutation seems to be associated with a shorter time to HBsAg clearance, extending the observation that this mutation, frequently selected during the immune-active phase of CHB, can also occur very early after infection or could indeed be transmitted (Mphahlele et al., 1997). The transmission of HBV without functional HBeAg is therefore not conducive to the establishment of CHB but predisposes patients to more severe clinical hepatitis. Likewise, HBeAg-negative status in mothers was more likely to be associated with fulminant hepatitis in their infants, whereas infants of HBeAg-positive mothers were more likely to have mild hepatitis followed by CHB (Tseng et al., 2014).

Antiviral treatment (AT) is generally not recommended in AHB because it has not been shown to have an impact on the course of the disease. It may, however, be considered in earlier stages of pregnancy with the hope of reducing pregnancy complications (Wong et al., 2020). To minimise mother-to-child transmission of

HBV, it is recommended that antiviral prophylaxis is administered to HBV-infected pregnant women with a high viral load in the third trimester (Lampertico et al., 2017).

This case raises questions regarding the early use of AT in cases of AHB at any stage of pregnancy to prevent progression to chronicity, transmission of the maternal precore mutation and fulminant hepatitis in the infant (Tseng et al., 2014).

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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Author contributions

Steven Roger: Investigation, Writing – Original draft; Julien Fontana: Investigation, Visualisation; Alexandra Ducancelle: Visualisation; Hélène Le Guillou-Guillemette: Visualisation; Clémence M Canivet: Investigation, Writing – Review and Editing; Caroline Lefeuvre: Supervision, Investigation, Writing – Original draft. All authors have approved the final draft submitted.

Ethical Approval statement

Ethical approval was not required.

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