

## Chronic HBV with pregnancy: Reactivation flare causing fulminant hepatic failure

Ashish Singhal,\* Rajesh Kanagala,\* Sajid Jalil,\* Harlan I. Wright,\* Vivek Kohli\*

\* Nazih Zuhdi, Transplant Institute, INTEGRIS Baptist Medical Center, 3300 NW Expressway, Oklahoma City, Oklahoma 73112, USA.

### ABSTRACT

Chronic HBV infection is a dynamic state of interaction between HBV, hepatocytes, and the immune system of the host. A series of reactivation flares and remissions may occur due to multiple causes. Among them, spontaneous reactivation and immunosuppressive drugs including steroids or cancer chemotherapy are well known. This is due to immune-mediated destruction of HBV-expressing cells following withdrawal of immunosuppressive effect. Few cases have been reported in females during postpartum period. We report a case of fulminant hepatic failure during pregnancy in a previously unrecognized hepatitis B positive female requiring emergent liver transplantation.

**Key words.** Hepatitis B virus. Flare. Reactivation. Pregnancy. Fulminant. Immunosuppression.

### INTRODUCTION

Reactivation of chronic hepatitis B (HBV) infection is a serious cause of morbidity and mortality in patients undergoing cytotoxic or immunosuppressive therapy or with AIDS.<sup>1,2</sup> Spontaneous reactivation has also been recognized.<sup>3,4</sup> Likewise, pregnancy being a relatively immunosuppressed state, few of the healthy hepatitis B carriers and those who have chronic hepatitis B may develop hepatitis flare or fulminant hepatic failure (FHF) after delivery;<sup>5-7</sup> however, it has been only anecdotally reported during the pregnancy.<sup>8</sup> Here, we present a case of formerly unrecognized hepatitis B positive female, who presented with FHF at 27-weeks of pregnancy requiring emergent liver transplantation.

### CASE REPORT

A 28-year-old Caucasian female, G<sub>1</sub>P<sub>0</sub>, was referred to our center in her 27<sup>th</sup> week of pregnancy with a diagnosis of fulminant hepatic failure. There

was no history of jaundice or abnormal liver function tests before or during pregnancy prior to this presentation. At presentation, she was icteric with grade III hepatic encephalopathy. Laboratory studies showed total leukocyte count- 22000/ cu.mm, AST- 1198 U/mL, ALT- 2010 U/mL, serum bilirubin- 12.9 mg/dL, and prothrombin time of 50 sec with INR of 4.9 (control- 10.5 sec). Viral serology was positive for HBs-Ag, Anti-HBc IgM, and HBe-Ag with HBV-DNA count of 3,700,000 IU/mL. Other relevant history includes death of her father due to liver failure (cause unknown).

Serological tests on acute sera for Epstein-Barr virus, Hepatitis A IgM, Hepatitis E IgM, Hepatitis D virus IgM, cytomegalovirus, herpes simplex virus, HIV, and antibody for hepatitis C and HCV-RNA were negative. Serum ceruloplasmin and urinary copper were within normal limits. Screening work-up for autoantibodies, acetaminophen, ethanol, and sepsis were negative. Abdominal ultrasonography showed fetal demise, enlarged liver with no signs of portal hypertension. Transjugular liver biopsy findings were consistent with submassive hepatic necrosis showing widespread loss of hepatic parenchyma and collapse of reticulin with inflammatory cell infiltrate including numerous macrophages and ductular proliferation. CT head showed cerebral edema with no midline shift or herniation. In view, she was listed for emergent liver transplantation.

Correspondence and reprint requests: Vivek Kohli, MD.  
Nazih Zuhdi Transplant Institute, INTEGRIS Baptist Medical Center, 3300 NW Expressway, Oklahoma City, Oklahoma 73112, USA  
Phone: 001-405-949-3349. Fax: 001-405-945-5844  
E-mail: vivek.kohli@integrisok.com

*Manuscript received: November 09, 2010.  
Manuscript accepted: December 28, 2010.*

She underwent dilatation and curettage and termination of pregnancy, and received deceased donor whole liver allograft. Intraoperative findings include shrunken, nodular liver with minimal ascites and enlarged uterus. Intraoperatively, she received hepatitis B immunoglobulin along with methylprednisone at induction. Hepatitis B immunoglobulin was continued for 6 days postoperatively. Her postoperative course was uneventful and she was discharged on 6<sup>th</sup> postoperative day on triple drug immunosuppression (tacrolimus, mycophenolate mofetil, and steroid) and antivirals (lamivudine and adefovir).

Histopathological examination of native liver showed submassive hepatic necrosis consistent with fulminant hepatic failure and a 7mm well differentiated hepatocellular carcinoma in right lobe of liver. Special staining showed positivity for HBs antigen and trichrome stain highlight the areas of bridging fibrosis. Presently, 2.5 years post-liver transplant, she is doing well and has remained negative for HBV DNA.

## DISCUSSION

Hepatitis due to reactivation of HBV is a well-recognized complication in patients with chronic HBV infection. Such exacerbations can occur spontaneously and may be mistaken for acute attacks of hepatitis B in patients not previously recognized to be hepatitis B surface antigen carriers and, in the absence of serial serologic data, are indistinguishable from superimposed non-A, non-B hepatitis.<sup>1-4</sup> The present patient presented with no prior history of hepatitis B seropositivity (past records were unavailable), which raised the suspicion for acute HBV infection. However, shrunken nodular liver, positivity for trichrome and HBs antigen, and presence of hepatocellular carcinoma on explanted liver were suggestive of unrecognized chronic infection. We are still missing some patients during the routine screening, which are potentially at risk for reactivation like patients who are HBsAg-negative and anti-HBc positive. A recent Denmark report showed that approximately 50% of infected pregnant women remained undetected using the routine screening strategy,<sup>9</sup> and a similar proportion was shown in a comparable study from an urban US hospital.<sup>10</sup> It may be wise to include anti-HBc and anti-HBs determinations in addition to HBsAg testing for screening.

Usually, pregnancy is well tolerated by healthy hepatitis B carriers and those who have chronic hepatitis B. One large study demonstrated

no differences in gestational age at delivery, birth weight, incidence of prematurity, neonatal jaundice, congenital anomalies or perinatal mortality comparing HBsAg-positive women with controls.<sup>11</sup> However, a proportion of HBsAg-positive mothers develop severe acute exacerbation, which may even lead to FHF.<sup>5-8</sup> The risk for FHF is higher in patients with unrecognized cirrhosis or advanced fibrosis.<sup>1,2</sup>

Reactivation of HBV has been identified as a two-staged process in patients undergoing cytotoxic or immunosuppressive therapy, comprising of stage of immunosuppression characterized by enhanced viral replication, as reflected by an increase in the serum levels of HBV-DNA, hepatitis Be antigen, HBV-DNA polymerase, and infection of naïve hepatocytes.<sup>1,2</sup> The second stage is related to restoration of immune function following withdrawal of immunosuppression effect, which causes rapid immune-mediated destruction of HBV-expressing cells. The consequences of sudden withdrawal and immune restoration are directly related to degree or potency of immunosuppression.<sup>12</sup> During pregnancy, this may be explained by an increased production of hormones such as adrenal corticosteroids, estrogen, and progesterone, which might have caused immunosuppressive effects leading to enhanced HBV DNA levels.<sup>13</sup> Estrogen has also been shown to suppress HBV expression;<sup>14</sup> however, one study has shown no significant differences in HBV viraemia.<sup>15</sup> The cortisol level has been seen to reach its peak at term and delivery, with serum levels during late pregnancy being comparable in activity to serum prednisolone levels in those on oral prednisolone for therapeutic purposes. Lin and colleagues suggested that a sudden decrease in cortisol level immediately after delivery could be analogous to that in steroid withdrawal therapy<sup>16</sup> causing the reactivation episode associated with or without HBeAg seroconversion.<sup>13</sup> Liver injury during these episodes mediate by HBcAg/HBeAg specific T-cells<sup>17</sup> and the severity of ensuing illness can vary from a mild, asymptomatic elevation of alanine aminotransferase (ALT) late in pregnancy or in the postpartum period<sup>15</sup> to fulminant liver failure.<sup>6</sup> There is small but definite risk in patients who have apparently cleared HBV infection (hepatitis B core antibody positivity (HBcAb+), hepatitis B surface antibody positivity (HBsAb+), and hepatitis B surface antigen negative (HBsAg-). This phenomenon is called as reverse seroconversion or seroreversion, which results in disappearance of hepatitis B surface antibody (HBsAb) and reappearance of he-

patitis B surface antigen (HBsAg), is thought to result from the persistence of replication-competent HBV in the liver, despite apparent serological clearance.<sup>1,2</sup>

Consistent with most published studies, the present patient had spontaneous intrauterine fetal death at presentation. Limited literature on liver transplantation in pregnant women with FHF showed excellent maternal outcomes using both cadaveric- and living-related grafts.<sup>18-21</sup> Unfortunately, fetal outcomes in all published reports have been poor with fetal survival in only 25%.<sup>21</sup> Reported causes of death ranged from spontaneous and artificial abortion to neonatal death.<sup>18</sup>

The interaction between chronic hepatitis B infection and pregnancy can present with unique set of issues. The relative lack of data makes this a critical medical challenge and leaves many questions unanswered. Why only some pregnant women with chronic hepatitis B develop flare during or after delivery? If immunological factors were involved, the same influences would apply to subsequent pregnancies, which may put these patients at risk of recurrent reactivation. Was there any cause-effect correlation between fulminant hepatic failure and intrauterine death? The role of antivirals in prophylaxis or treatment of acute flares during pregnancy is confusing. All these queries stimulated the need for more formal studies to understand this interaction.

## CONCLUSION

Multiple causes including pregnancy can cause a varying degree of immunologically directed acute exacerbations in healthy HBV carriers and those who have chronic hepatitis B infection. In the setting of pregnancy with HBV infection, aspects of care must consider the effects of pregnancy on the course of hepatitis B infection along with potential adverse effects of hepatitis B on maternal and fetal outcomes. Pregnancy may be a potential cause of acute exacerbation in patients with chronic HBV infection. The role of antiviral in prophylaxis or treatment of acute flares during pregnancy is yet to be established.

## ABBREVIATIONS

- **IRB approval:** Done
- **Acknowledgements:** None
- **Competing Interests:** None
- **Financial Disclosure:** None

## REFERENCES

1. Xunrong L, Yan AW, Liang R, Lau GK. Hepatitis B virus (HBV) reactivation after cytotoxic or immunosuppressive therapy- pathogenesis and management. *Rev Med Virol* 2001; 11: 287-99.
2. Lubel JS, Testro AG, Angus PW. Hepatitis B virus reactivation following immunosuppressive therapy: guidelines for prevention and management. *Int Med J* 2007; 37: 705-12.
3. Davis GL, Hoofnagle JH, Waggoner JG. Spontaneous reactivation of chronic hepatitis B virus infection. *Gastroenterology* 1984; 86: 230-5.
4. Lok ASF, Lai CL, Wu PC, Leung EKY, Lam TS. Spontaneous hepatitis Be antigen to antibody seroconversion and reversion in Chinese patients with chronic hepatitis B virus infection. *Gastroenterology* 1987; 92: 1839-43.
5. ter Borg MJ, Leemans WF, de Man RA, Janssen HLA. Exacerbation of chronic hepatitis B infection after delivery. *J Vir Hepat* 2008; 15: 37-41.
6. Yang Y-B, Li X-M, Shi Z-J, Ma L. Pregnant woman with fulminant hepatic failure caused by hepatitis B virus infection: a case report. *World J Gastroenterol* 2004; 10: 2305-6.
7. Jonas MM. Hepatitis B and Pregnancy: An underestimated issue. *Liver Intl* 2009; 29(s1): 133-9.
8. Rawal BK, Parida S, Watkins RPF, Ghosh P, Smith H. Symptomatic reactivation of hepatitis B during in Pregnancy. *Lancet* 1991; 337: 64.
9. Cowan SA, Bagdonaite J, Qureshi K. Universal hepatitis B screening of pregnant women in Denmark ascertains substantial additional infections: results from the first five months. *Eurosurveillance* 2006; 11: pii-2969
10. Jonas MM, Schiff ER, O'Sullivan MJ, et al. Failure of the centers for disease control criteria to identify hepatitis B infection in a large municipal obstetrical population. *Ann Intern Med* 1987; 107: 335-7.
11. Wong S, Chan LY, Yu V, et al. Hepatitis B carrier and perinatal outcome in singleton pregnancy. *Am J Perinatol* 1999; 16: 485-8.
12. Perrillo RP. Acute flares in chronic hepatitis B: the natural and unnatural history of an immunologically mediated liver disease. *Gastroenterology* 2001; 120: 1009-22.
13. Lin HH, Chen PJ, Chen DS, et al. Postpartum subsidence of hepatitis B viral replication in HBeAg-positive carrier mothers. *J Med Virol* 1989; 29: 1-6.
14. Almog Y, Klein A, Adler R, et al. Oestrogen suppresses hepatitis B virus expression in male athymic mice transplanted with HBV transfected Hep G-2 cells. *Antiviral Res* 1992; 19(4): 285-93.
15. Söderström A, Norkrans G, Lindh M. Hepatitis B virus DNA during pregnancy and post partum: aspects on vertical transmission. *Scand J Infect Dis* 2003; 35: 814-9.
16. Lin HH, Wu WY, Kao JH, et al. Hepatitis B post-partum e antigen clearance in hepatitis B carrier mothers: correlation with viral characteristics. *J Gastroenterol Hepatol* 2006; 21: 605-9.
17. Liaw YF. Hepatitis flares and hepatitis B e antigen seroconversion: Implication in anti-hepatitis B virus therapy. *J Gastro Hepatol* 2003; 18: 246-52.
18. Eguchi S, Yanaga K, Fujita F, et al. Living-related right lobe liver transplantation for a patient with fulminant hepatic failure during the second trimester of pregnancy: report of a case. *Transplantation* 2002; 73: 1970-1.

19. Merritt W T, Dickstein R, Beattie C, Burdick J, Klein A. Liver transplantation during pregnancy: anesthesia for two procedures in the same patient with successful outcome of pregnancy. *Transplant Proc* 1991; 23: 1996-7.
20. Moreno EG, Garcia GI, Gomez SR, et al. Fulminant hepatic failure during pregnancy successfully treated by orthotopic liver transplantation. *Transplantation* 1991; 52: 923-6.
21. Jarufe N, Soza A, Perez-Ayuso RM, et al. Successful liver transplantation and delivery in a woman with fulminant hepatic failure occurring during the second trimester of pregnancy. *Liver International* 2006; 26: 494-7.