Case Report

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A Pregnant Case with Acute Hepatic Failure Treated with Tenofovir

Tenofovir ile Tedavi Edilen Bir Gebe Akut Karaciğer Yetmezliği Olgusu

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ABSTRACT

The acute flare of HBV infection in pregnancy has effects on two sides: the mother and the neonate. According to the recent reports, antiviral treatment has to be considered in mothers with high viral loads, particularly for reducing the risk of transmission-to baby. Here we report a case of pregnant patient treated with tenofovir for acute HBV infection. A 35 years old female patient, who was 32 weeks pregnant, had been hospitalized in another clinic with pre-diagnosis of hemolytic anemia, elevated liver enzymes, low platelet count (HELLP) syndrome, and then she was admitted to our hospital due to diagnosis of hepatitis B and decrease in her elevated liver enzyme levels. Her HBsAg status was unknown in her past pregnancies. Her laboratory results on admission were as follows: serum HBV-DNA level: 75 000 000 IU/mL, anti-HBc IgM: positive, anti-HBc IgG: positive, HBsAg: positive, anti-HBs: negative, HBeAg: positive and anti-HBe: negative. The patient was closely followed for the re-increasing liver enzymes and bilirubin levels. A probable acute liver failure was detected and supportive therapy was administered. Tenofovir treatment was also started in order to decrease HBV-DNA levels and to decrease the risk of perinatal transmission of the HBV to the upcoming fetus. On the 11th day of her admission she gave early birth to a 2010 grams baby-boy. The baby's APGAR score was 8/9 and had respiratory distress syndrome. No pathology was detected in baby except a minimal left peripheral pulmonary stenosis on echocardiogram examination. Tenofovir treatment of the mother continued. 12 weeks later the patient's liver enzymes were normal and her HBV-DNA was negative, HBeAg seroconversion was occurred. The baby was HBsAg negative, no side effects associated with tenofovir was detected. Acute HBV infection and hepatic failure in pregnancy requires a close follow-up. Antiviral treatment option should be considered especially in patients with high viral load, benefits and losses of the mother and the neonate should be considered for the treatment plan in each case. *(Viral Hepatitis Journal 2014; 20(1): 36-39)*

Key words: Pregnancy, antiviral treatment, hepatitis, tenofovir

ÖZET

Gebelikte geçirilen akut hepatit B virüsü (HBV) enfeksiyonu anne ve bebek olmak üzere iki kişiyi etkiler. Son bilgilere göre, yüksek viral yüke sahip annelerde özellikle bebeğe bulaşıyı da önlemek amacıyla antiviral tedavi düşünülmelidir. Bu çalışmada, akut HBV enfeksiyonu geçiren ve tenofovir tedavisi uygulanan bir gebe hasta sunulmuştur. Otuz beş yaşında, 32 haftalık gebe, başka bir merkezde "hemolytic anemia, elevated liver enzymes, low platelet count (HELLP)" sendromu ön tanısı ile izlenmiş, HBV enfeksiyonu saptanması ve yüksek olan karaciğer enzimlerinin nispeten gerilemesi üzerine ayaktan polikliniğimize yönlendirilmişti. Hastanın karaciğer enzimlerinde tekrar yükselme saptanması nedeni ile hasta hospitalize edildi. HBsAg değeri daha önceki gebeliklerinde bakılmamıştı. Laboratuvar sonuçları; HBV-DNA: 75 000 000 IU/mL, anti-HBc IgM pozitif, anti-HBc IgG pozitif, HBsAg pozitif, anti-HBs negatif, HBeAg pozitif ve anti-HBe negatif idi. Hastada akut karaciğer yetmezliği tablosuna gidiş görüldü ve destek tedavisi verildi. HBV-DNA düzeyini düşürmek ve perinatal bulaş riskini azaltmak amacıyla tenofovir tedavisi başlanan hastanın yatışının 11. gününde erken doğum oldu. Bebeğin ağırlığı 2010 g, APGAR skoru 8/9 idi ve Respiratuar Distress sendromu mevcuttu, ekokardiyografisinde minimal sol periferal pulmoner stenoz dışında herhangi bir patoloji saptanmadı. Hastanın tenofovir tedavisine devam edildi; 12 hafta sonra HBV-DNA düzeyi negatifleşti; HBeAg serokonversiyonu gerçekleşti. Bebek HBsAg negatif idi, tenofovire bağlı bir yan etki saptanmadı. Sonuç olarak, gebelerde akut karaciğer yetmezliği yakın takip gerektirmektedir. Özellikle yüksek viral yükü olan hastalarda antiviral tedavi seçeneği göz önünde bulundurulmalı, anne ve bebeğin yarar-zarar oranı değerlendirilerek her bir hasta bazında tedavi planı yapılmalıdır.*(Viral Hepatit Dergisi 2014; 20(1): 36-39)*

Anahtar Kelimeler: Gebelik, antiviral tedavi, hepatit, tenofovir

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Introduction

Hepatitis B virus (HBV) infection is endemic in our country and the sero-prevalence rates of the chronic HBV carriers differs from 5% to 10%, with higher rates in the East and lower rates in the South parts of the country. After routine vaccination program for HBV, which was established in 1998, the overall prevalence of HBV infections is decreasing. But still HBV remains the country's most significant cause of viral hepatitis and chronic liver disease (1). Although all infants are vaccinated and adults are usually recommended to check their hepatitis B surface antigen (HBsAg) and anti-HBs status in many occasions (like before marriage, before sports courses, etc.) there is no consistent legal policy on the maternal screening programs in Turkey. Along with horizontal transmission, perinatal transmission is the most common route of HBV transmission worldwide; it seems to be so in our country as well (1,2,3,4).

The HBV infection in pregnancy has effects on two sides: the mother and the neonate. It is known that chronic HBV infection is usually not effected from pregnancy but a flare may be seen after delivery (2). Clinical course of acute HBV infection is also similar to general population but if the viral load of the mother is high, the perinatal transmission is more likely (2,3,4). So the antiviral drug use is to be concerned. Lamivudine and tenofovir are seemed to be more experienced ones in human pregnancy comparing with the other antivirals. Lamivudine is in pregnancy category C and tenofovir is in category B. Telbivudine is also in category B but the data is usually based on animal studies and there are few reports on exposure in human pregnancy (3,5). Adefovir and entecavir are in pregnancy category C (6).

Although the management of chronic hepatitis patients is well known in routine clinical practice, experience in pregnancy, especially about the management of acute hepatic failure in pregnancy, is limited. Guidelines concerning the management of HBV infection underline the active and confirmation and recommended as B2 (6,7).

Here we report an acute HBV infection in a pregnant woman who presented with acute hepatic failure and treated with tenofovir.

Case

A thirty five years old female patient, who was 32 weeks pregnant, was referred from a gynecology & obstetrics hospital to the outpatient clinic of our infectious diseases and clinical microbiology department. She was HBsAg positive and had elevated liver enzymes. Her further anamnesis revealed that she had been admitted to that gynecology hospital with the pre-diagnosis of hemolytic anemia, elevated liver enzymes, Low Platelet Count (HELLP) syndrome. Then they realized that she did not have HELLP syndrome but acute hepatitis B. She was hospitalized there for ten days. After the patient's elevated liver enzymes decreased the patient was discharged. Then she was referred to our outpatient clinic of infectious diseases department for further follow-up for HBV infection. Since re-increasing in liver enzymes was detected, the patient was hospitalized immediately in our department. It was her 6th pregnancy, one was dead four were alive, and none of the siblings had hepatitis B. Her HBsAg status was not known in her past pregnancies. Her last pregnancy was 4 years before and she did not report any invasive procedure, blood transfusion or suspected sexual intercourse from that time till now. Her husband was anti-HBs Ag positive and did not report any hepatitis vaccination. On admission her all physical examination was normal except fatigue and icteric appearance. Her laboratory results were as follows: serum HBV-DNA level: 75 000 000 IU/mL, anti-HBc IgM: positive, anti-HBc IgG: positive, HBsAg: positive, anti-HBs: negative, HBeAg: positive and anti-HBe: negative. The other routine laboratory results on admission and follow-up during the hospitalization are given in Table 1. The patient was closely followed for the re-increasing liver enzymes and bilirubin levels. Although the patient seems to be always sleepy and her cognitive functions were slow, there was no significant shift in her mental status and all hemostasis parameters were within normal limits during her stay in the hospital. Her bilirubin levels and liver enzymes progressively increased. Because of the elevated liver enzymes and probable acute liver failure, hepatAmine (crystalline amino acids), ursodeoxycholic acid and acetylcysteine therapy and IV fluid as supportive therapy were administered. Tenofovir treatment was also started in order to decrease HBV-DNA levels and decrease the

Table 1. Laboratory findings of the patient during her hospital stay

Test*-unit (normal range)	1st day	2nd day	3rd day	5th day	10th day
Hb-g/dL (11.7-15.5)	11.5	-	10.8	8.1	10.1
Hct-% (34.5-46.3)	35.8	-	33.3	31.8	31.1
WBC-10^3/µL (4.5-11)	6.9	-	7.2	8.1	9.7
Plt-10^3/µL (150-450)	173	-	150	155	126
SGOT-U/L (0-35)	980	1325	1950	922	89
SGPT-U/L (0-35)	650	610	905	530	115
ALP-U/L (30-120)	147	150	153	136	98
GGT-U/L (0-38)	41	33	37	35	24
Total/direct bilirubin-mg/dL (0.3-1.3/0.00-0.20)	7.7/4.4	7.9/5.2	13.9/6.6	13.5/7.4	5.4/2.3
Ammonia (µg/dL) (45-80)	51	92	119	75	-

*Hb/Htc: Haemoglobin/hematocrite, WBC: white blood cell, Plt: platelets, SGOT: serum glutamic oxaloacetic transaminases, SGPT: serum glutamic pyruvic transaminase, ALP: alkalen phosphatase; GGT: gammaglutamile transferase, ID Bil/T Bil: indirect bilirubine/total bilirubine.

risk of perinatal transmission of the HBV to the upcoming fetus. On the 11th day of her admission she gave birth to a 2010 grams baby-boy. The baby's APGAR score was 8/9 and it had respiratory distress syndrome. A minimal left peripheral pulmonary stenosis on echocardiogram examination was found. No neonatal jaundice was seen. Baby was discharged from the pediatrics department in good condition after 2 weeks of therapy. The mother was in good condition too. Six weeks after the patients' discharge from the clinic her SGOT and SGPT levels were decreased to 43 IU/L and 44 IU/L respectively and her HBV-DNA level decreased to 117 IU/mL. 12 weeks later her liver enzymes were totally normal and her HBV-DNA was negative, anti-HBc IgM and IgG were still positive, HBeAg seroconversion was occurred and she was HBeAg negative and anti-HBe Ag positive. The baby was HBsAg negative; both baby and mother were healthy. On the 6th month, the mother's HBV-DNA was still negative, HBsAg was positive, HBeAg was negative and anti-HBe Ag was positive.

Discussion

Seroprevalence rates of acute hepatitis B in pregnancy differ from country to country. Unfortunately the studies on pregnancy and hepatitis usually focus on the HBsAg positivity and very few studies give the ratio of acute hepatitis case prevalence. In an Indian study of 4000 pregnant women, 37 (0.9%) were positive for HbsAg and 6 of them (16%) developed acute hepatitis B (8). The HBsAg positivity among pregnant women can be as high as 8.2% like in Nigeria and 6.71% in China (9,10). The ratio seems to be intermediate in our country. In two recent Turkish studies the HBsAg was found to be positive in 2.1% and 2.8% in 11 840 and 4700 pregnant women, respectively (11,12). Unfortunately we don't know the ratio of the acute cases among those positive patients.

Our patient was admitted as an acute case at the beginning. But since she was anti-HBc IgM and anti-HBc IgG positive we couldn't decide if it is an acute case or a chronic case with an acute flare. She had four more siblings and five pregnancy history, the last one was four years old and in none of her pregnancies she was shown to have HBsAg positivity, it was not checked at all. None of her children had HBsAg positivity as well. The reason of her second flare in the liver enzymes; (first was in the gynecology hospital and second was seen in our follow-up), remained unclear. Her records showed that she was well in the first ten days of her admission to that hospital and her liver enzymes were gradually decreasing. When we admitted the patient, the liver enzymes and bilirubin levels had started to increase again. No drug use or other herbal medication was detected. We suggested that the progress of the acute hepatitis in pregnancy could be unpredictable.

Management of HBV infection in pregnancy has many sides: follow-up of the mother, evaluating the effects of hepatitis on pregnancy and effects of pregnancy on hepatitis; protecting the perinatal transmission of HBV, concerning the antiviral therapy etc. Acute hepatitis B in pregnancy is reported to be associated with perinatal transmission risk and higher incidence of prematurity and low birth weight. Acute HBV infection in early pregnancy is associated with a 10% perinatal transmission rate, and the rate increases substantially with HBV infection in the third trimester (2,3). About chronic hepatitis B there are different studies with different outcomes. In a study by Tse et al, HBsAg carriers were found to have increased risk for gestational diabetes mellitus (GDM), antepartum hemorrhage and threatened preterm labor (before 34 weeks of pregnancy) and their infants found to have increased risk for lower APGAR scores and increased risk for intra-ventricular hemorrhage (13). In another recent study by Reddick et al., a nationwide study, they stated that mothers with hepatitis B had an increased risk for preterm labor. But there was no association with viral hepatitis and intrauterine growth restriction (14).

High maternal HBV-DNA levels correlates with perinatal transmission of hepatitis B (4). In the study of Wiseman et al., of 313 HBsAg-positive pregnant women, 213 (68%) were HBV-DNA-positive and 92 (29%) were positive for HBeAg; 138 babies born to HBV-DNA-positive mothers were tested for HBV infection at about 9 months of age. Four cases of transmission were identified. All four mothers had very high HBV-DNA levels (> 10^8 copies/mL) and were HBeAg-positive. Transmission rates were 3% in HBV-DNA-positive mothers overall, 7% in HBeAg-positive mothers, and 9% in mothers with very high HBV-DNA levels. HBV perinatal transmission was restricted to HBeAg-positive mothers with very high viral loads (4).

In a study by Canho et al. the rate of transmission among 705 infants born to HBsAg positive mothers was 1.1% (15). But the same rate was 23%-28% in different studies despite passive and active immunoprophylaxis. The possible explanation was made by Weisman et al. as the variation in HBIg efficacy, varying adherence to immunization protocols or possibly different prevalence of vaccine escape mutations (4). In Canho's study, antiviral therapy with lamivudine in third trimester of pregnancy, especially in the last month, perinatal transmission fell from historical controls (15).

All the data above suggest that perinatal transmission may still be occurring despite the use of active and passive prophylaxis. Since high maternal viremia seem to be the most important factor associated with failure of neonatal vaccination, antiviral treatment during pregnancy has been considered along with prophylaxis to reduce transmission. None of the mothers with low viremia showed perinatal transmission in the past studies. Reducing the maternal viremia will reduce the perinatal transmission. Our patient was HBeAg positive and had a very high viral load of HBV-DNA (7.5x10^7U/L). We decided to give our patient antiviral therapy to reduce the viral load. Our aim was to protect the child and to also have the benefit of antiviral therapy for decreasing the viral load in acute liver failure of the patient.

An algorithm for management for HBV infection during pregnancy was suggested by Tran (16). The treatment decisions are based on HBV-DNA levels, the viral load, at 28th week of pregnancy and presence or absence of a history of perinatal transmission. Among all, lamivudine is the most experienced antiviral used in pregnancy until now. Lamivudine is associated with a risk of birth defects of 2.2 to 2.4% and these rates were not higher than baseline birth defect rate (17). Tenofovir treatment experience is mainly based on HIV positive mothers rather than

hepatitis cases. Antiretroviral pregnancy registry (APR) began to collect data regarding tenofovir exposure in pregnancy since 2001. In their report 1547 pregnant mothers exposed to a tenofovir containing regimen and no specific patterns of birth defects was seen in the second and third trimester exposure. The rate of birth defects with tenofovir was 1.5% in second trimester use and 2.3% in first trimester use. These rates were similar to background rate and tenofovir was accepted as a safe drug (17,18).

Giving antiviral treatment in the third trimester may reduce the transmission to baby but the treatment after the delivery is not clear. The baby will get both passive and active immunization and there will be no need for continuing the antiviral therapy. On the other hand what will be about the mother? One may choose to stop the treatment after delivery and consider the treatment conditions after stopping the breastfeeding. Since our patient had acute liver failure and get benefit from the treatment we decided to continue the therapy. The delivery happened in the 34th week of pregnancy. Baby's peripheral pulmonary stenosis was minimal and suggested to be associated with the prematurity. The follow-up of the patient and the baby is still continuing and no other side effect was detected.

In conclusion we aimed to underline that acute hepatitis B in pregnancy could follow a different pattern, like biphasic flare in liver enzymes as it was seen in our patient and a close follow-up is needed. And also antiviral treatment should be considered for these patients.

Conflict of interest: None declared.

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