OPEN

Hepatitis E Virus Infection in a Pregnant Liver Transplant Recipient Leading to Chronic Infection

Olivier Marion, MD, PhD,[1] Florence Abravanel, PharmD, PhD,[2,3,4] Laure Conan, MD,[5] Charlotte Dubucs, MD,[6] Marie Danjoux, MD,[6] Jacques Izopet, PharmD, PhD,[2,3,4] and Nassim Kamar, MD, PhD[1,3,4]

Hepatitis E virus (HEV) is an RNA virus with 1 serotype and 4 main genotypes.[1] Genotype 1 and 2 are transmitted via the fecal-oral route in developing countries. Genotype 3 or 4 infection is a zoonosis, mainly observed in developed countries.[1] In immunocompetent patients, it is mainly responsible for self-limiting infection. In immunocompromised patients, especially in transplant patients, it can lead to chronic hepatitis in up to 60% of patients.[1] Infection with HEV genotype 1 or 2 in pregnancy, especially in the third trimester, may lead to severe illness and fulminant liver failure. Poor maternal and fetal outcomes have been reported with up to 30% mortality.[2] Few cases of HEV genotype 3 infection during pregnancy were reported in immunocompetent patients.[3,4] No poor outcome was observed in this setting. Only 1 case of HEV genotype 3 infection that occurred during the first trimester in a kidney transplant patient was reported.[5] Herein, we report the case of a female liver transplant patient who developed an acute HEV genotype 3 infection 2 wk before delivery.

CASE REPORT

A 34-y-old non-HLA-sensitized woman had undergone a first orthotopic liver transplantation for autoimmune hepatitis. She was given induction therapy with basiliximab followed by a triple maintenance immunosuppression based on tacrolimus (target trough level of 5–6 ng/mL), mycophenolic acid (500 mg bid.), and low-dose steroids (5 mg/d). The posttransplant period was uneventful and her liver enzyme levels were always within the normal range. Eighteen months after transplantation, the mycophenolic acid was replaced by azathioprine (100 mg/d) because of her desire to have a child. At 26 mo posttransplant, she got pregnant. At 34 wk of gestation, systematic control of her blood parameters revealed a slight increase in liver enzyme levels. She was completely asymptomatic. No anti-HLA antibodies or autoimmune antibodies were detected. Nuclear acid tests for hepatitis B and C as well as cytomegalovirus were negative. Conversely, HEV RNA was positive in the serum (7.13 log IU/mL) and in the stools. Retrospective analysis of a serum obtained 1 mo earlier did not reveal the presence of HEV RNA. Phylogenetic analysis revealed that the strain belonged to genotype 3c. Anti-HEV IgG and IgM, which were negative at transplantation, were positive: IgG concentration was at 1.59 IU/mL (limit of detection at 0.3 IU/mL) and IgM index was at 20.05. Total lymphocyte, $CD4^+$ T-cell, and $CD8^+$ T-cell counts were 200, 75, and 64/mm^3, respectively. The prothrombin test was 100%. No liver biopsy was performed because autoimmune antibodies were negative and HEV RNA was detected. The cause of HEV infection was not clearly identified, but it was likely related to the consumption of pork products. She did not receive any blood product transfusion, did not travel abroad, and was not in contact with animals. After the HEV diagnosis, no modification in the immunosuppressive regimen was done because the tacrolimus trough level was already at 5 ng/mL and the patient had a history of autoimmune disease.

Despite the lack of fetal distress and growth retardation, the baby was delivered by cesarean section 2 wk later (at 36 wk of gestation) because of a persistent increase in liver enzyme levels and a decreased platelet count (from 105 000 to 55 000/mm^3; Figure 1). No obstetrical complications occurred. The placenta tested positive for HEV RNA. Anti-HEV staining was done and was strongly positive (Figure 2). The breast milk tested positive for HEV RNA at days 2 and 20 after delivery. Consequently, breastfeeding was contraindicated.

The newborn was a boy weighing 2885 g. The Apgar score was 10/10. He was tested for HEV RNA at days 1–5,

Received 17 October 2023. Revision received 19 December 2023.
Accepted 23 December 2023.

[1] Department of Nephrology and Organ Transplantation, Toulouse University Hospital, Toulouse, France.
[2] Virology Laboratory, Toulouse University Hospital, Toulouse, France.
[3] INSERM UMR1291, CNRS UMR5051, Université Toulouse III, Toulouse Institute for Infectious and Inflammatory Diseases (Infinity), Toulouse, France.
[4] UMR 1291, CNRS UMR5051, Université Toulouse III Paul Sabatier, Toulouse, France.
[5] Department of Obstetrics, Paule de Viguier Hospital, Toulouse, France.
[6] Department of Pathology, Oncopole, Toulouse, France.
Correspondence: Nassim Kamar, MD, PhD, Department of Nephrology and Organ Transplantation, CHU Toulouse Rangueil, TSA 50032, 31059 Toulouse Cedex 9, France. (kamar.n@chu-toulouse.fr).

O.M. and N.K. conducted patient follow-up. L.C. did the obstetrical follow-up. F.A. and J.I. did the virological work-up. C.D. and M.D. did the pathological work-up. N.K. drafted the article and figures.
The authors declare no funding or conflicts of interest.

ISSN: 2373-8731
DOI: 10.1097/TXD.0000000000001634

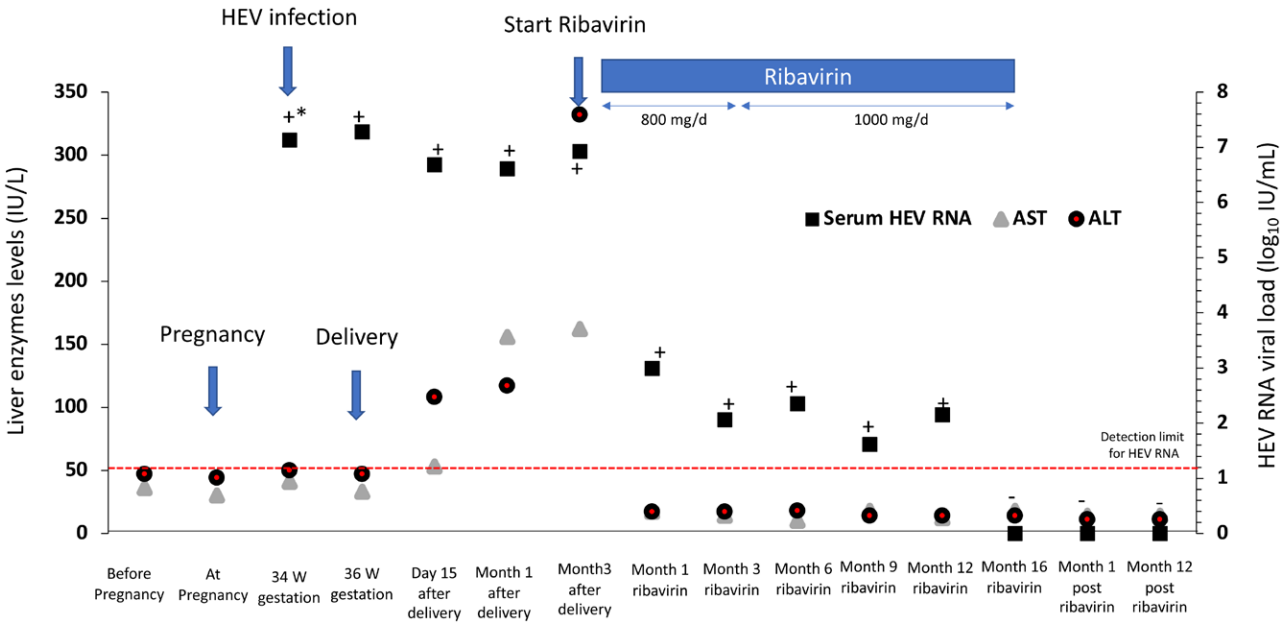

FIGURE 1. Outcome of liver enzyme and HEV RNA concentrations during and after pregnancy. *Superscripts correspond to HEV RNA in the stools. ALT, alanine transaminase; AST, aspartate transaminase; HEV, hepatitis E virus.

15 d, and 1 mo. All tests were negative. Liver enzyme levels remain within the normal ranges. Anti-HEV IgM was not detected. Conversely, anti-HEV IgG was positive (37 IU/mL).

Regarding the infected mother, tacrolimus level was maintained <5 ng/mL to obtain HEV clearance and azathioprine was stopped. Because of the lack of HEV clearance, ribavirin was started 3 mo after delivery at the initial dose of 800 mg/d, and the dose was then increased to 1000 mg/d because of the good hematological tolerance (estimated glomerular filtration rate according to the Chronic Kidney Disease-Epidemiology Collaboration formula was 63 mL/min). At the initiation of ribavirin, anti-HEV IgG concentration was 3.21 IU/mL and IgM index was 19.39. Liver enzyme levels returned to normal as soon as 1 mo after starting ribavirin and remained unchanged until the last follow-up (Figure 1). HEV RNA concentration also decreased rapidly. It remained detectable at very low levels for a long period. Ribavirin was stopped once HEV RNA was undetectable in the serum and the stools on 2 occasions at 1 mo apart. Thus, the total duration of ribavirin was 16 mo. At 1 y after ceasing ribavirin, HEV RNA is still undetectable in the serum and stools. Anti-HEV IgG concentration was 38 IU/mL and IgM index was 8. Hence, we can consider that she achieved a sustained virological response.

DISCUSSION

HEV genotype 1 infection during pregnancy, especially during the third trimester, is associated with a high viral load compared with acute hepatitis[6] and an increased risk of fulminant hepatic failure, which results in a high mortality rate ranging from 20% to 30%.[2] Miscarriage and stillbirths were also reported. In vitro data have shown that progesterone is crucial to maintaining HEV replication in human liver cells during pregnancy.[7] In pregnant Indian women infected by HEV, a reduction in the expression of progesterone receptor has been observed, leading to a predominance of T-helper type 1 lymphocytes. This immunologic shift results in an increase in the cytotoxic T-cell reaction responsible for fetal and maternal injury.[6]

Here, we report the case of a liver transplant patient who developed a genotype 3 HEV infection during the third trimester of pregnancy. In a large cohort from India, Patra et al[8]

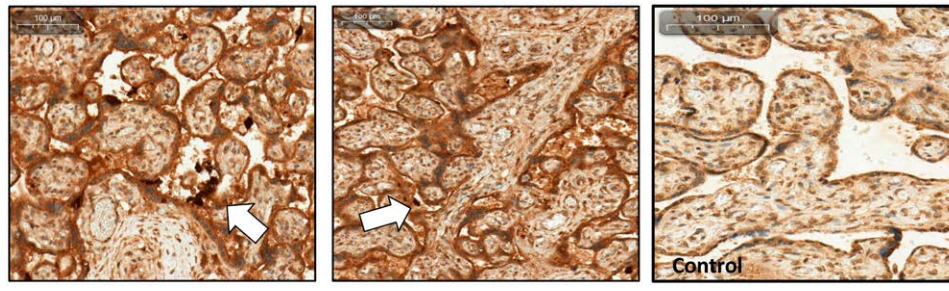

FIGURE 2. Anti-HEV staining of the placenta: positive cytoplasmic anti-HEV staining in trophoblastic cells. The control placenta was obtained from a woman not infected by HEV. The patient and control woman had given their informed consent to perform HEV staining on their placenta and tissue samples were stored in a biobank (CRB BB-0033-00014). HEV, hepatitis E virus. The arrow shows the positive staining.

reported that pregnant women with jaundice and acute viral hepatitis caused by HEV infection had a higher maternal mortality rate and worse obstetric and fetal outcomes than pregnant women with jaundice and acute viral hepatitis caused by other types of viral hepatitis. Elective preterm delivery is historically reserved for HEV-positive pregnant patients if obstetric complications occur. In the present case, because the patient was already at 36 wk of amenorrhea, had a persistent increase in liver enzyme levels, and a decreased platelet count, her baby was delivered by cesarean section despite the lack of fetal distress and growth retardation. Interestingly, although the HEV RNA viral load was high in the mother and HEV was detected in high levels in the placenta, the newborn was not infected. The anti-HEV IgG detected in the baby was probably transmitted by his mother. The lack of transmission of genotype 3 HEV infection from mother to child is in line with previous small case series and case reports. In a study from Vietnam, no transmission to children from 4 immunocompetent pregnant women with HEV genotype 3a replication at delivery was observed.[4] To our knowledge, no delivery with replication HEV has been reported in solid organ transplant patients. Mallet et al[5] reported the case of a kidney transplant patient who was infected by HEV (unknown genotype) at 8 wk of gestation. She cleared the virus after the reduction of immunosuppression at the beginning of the third trimester and had no replication at delivery.[5] The newborn was not infected. The risk of vertical transmission that can influence the decision for early fetal delivery still needs to be studied.

Bertuzzo et al[9] reported the case of an Asian nontransplant pregnant woman who was infected by HEV (unknown genotype) and developed acute hepatic failure. After delivery, she required a liver transplantation.[9] In the present case, liver enzyme tests increased after delivery. The reasons for a delayed increase in transaminases are unclear because of the lack of published data in this setting. This may be related to the changes in the hormonal or immunological status. After delivery, she developed chronic hepatitis that required long-term ribavirin therapy to obtain viral clearance both in the serum and stools. We observed that the detection of HEV RNA in the stools when stopping ribavirin is associated with an increased risk of relapse, even if HEV RNA is not detected in the serum.[10] Prolonging ribavirin therapy enables a sustained virological response.[11]

In summary, this case report highlights that despite HEV genotype 3 infection in the third trimester of pregnancy, the outcome was good and the newborn infection was not systematic. Although HEV genotype 1, which occurs during pregnancy, can induce acute liver injury and is associated with an increased risk of mother and child mortality, it does not seem to be the case for HEV genotype 3 infection. In this setting, there is a risk of developing chronic hepatitis.

REFERENCES

1. Kamar N, Bendall R, Legrand-Abravanel F, et al. Hepatitis E. *Lancet*. 2012;379:2477–2488.
2. Sooryanarain H, Meng XJ. Hepatitis E virus: reasons for emergence in humans. *Curr Opin Virol*. 2019;34:10–17.
3. Anty R, Ollier L, Peron JM, et al. First case report of an acute genotype 3 hepatitis E infected pregnant woman living in South-Eastern France. *J Clin Virol*. 2012;54:76–78.
4. Huy PX, Chung DT, Linh DT, et al. Low prevalence of HEV infection and no associated risk of HEV transmission from mother to child among pregnant women in Vietnam. *Pathogens*. 2021;10:1340.
5. Mallet V, Le Mener S, Roque-Afonso AM, et al. Chronic hepatitis E infection cured by pregnancy. *J Clin Virol*. 2013;58:745–747.
6. Bose PD, Das BC, Kumar A, et al. High viral load and deregulation of the progesterone receptor signaling pathway: association with hepatitis E-related poor pregnancy outcome. *J Hepatol*. 2011;54:1107–1113.
7. Sooryanarain H, Ahmed SA, Meng XJ. Progesterone-mediated enhancement of hepatitis E virus replication in human liver cells. *mBio*. 2021;12:e0143421.
8. Patra S, Kumar A, Trivedi SS, et al. Maternal and fetal outcomes in pregnant women with acute hepatitis E virus infection. *Ann Intern Med*. 2007;147:28–33.
9. Bertuzzo VR, Ravaioli M, Morelli MC, et al. Pregnant woman saved with liver transplantation from acute liver failure due to hepatitis E virus. *Transpl Int*. 2014;27:e87–e89.
10. Abravanel F, Lhomme S, Rostaing L, et al. Protracted fecal shedding of HEV during ribavirin therapy predicts treatment relapse. *Clin Infect Dis*. 2015;60:96–99.
11. Marion O, Lhomme S, Del Bello A, et al. Monitoring hepatitis E virus fecal shedding to optimize ribavirin treatment duration in chronically infected transplant patients. *J Hepatol*. 2019;70:206–209.