Case Report

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Severe hepatitis E infection in pregnancy: a case report

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Introduction and importance: Hepatitis E virus causes self limiting hepatitis most of the times but, during pregnancy it can lead to severe hepatitis along with various complications thereby increasing the mortality.

Case presentation: A 27-year-old woman gravida two, para one at 38 weeks and 6 days of gestation presented with multiple episodes of nonbilious vomiting, severe dehydration, and later developed right upper quadrant abdominal pain. The patient had a positive serological test for the hepatitis E virus, and liver enzymes were severely elevated. Under supportive treatment she delivered a healthy baby, and her liver enzymes returned to normal levels after 2 weeks of delivery.

Clinical discussion: Although the hepatitis E virus usually causes self-limiting hepatitis, it can quickly progress to severe hepatitis, liver failure, and even death during pregnancy. Immunological change with a Th2 biased response and increased hormonal levels during pregnancy could possibly facilitate the development of severe liver damage. No particular drug has been approved for the treatment of hepatitis E viral infection in pregnant women, and the commonly used drugs are contraindicated due to the risk of teratogenicity. Supportive therapy and intensive monitoring are the core management techniques for hepatitis E virus infection in pregnant women.

Conclusion: Due to the high mortality risk, pregnant women should try to avoid possible exposure to the hepatitis E virus, but once infected, symptomatic therapy is the mainstay.

Keywords: case report, hepatitis E, pregnancy, severe hepatitis

Introduction

Hepatitis E virus (HEV) is a hepatotropic, single-stranded, positive-sense ribonucleic acid virus belonging to the family *Hepeviridae* and is the only member of the genus *Orthohepevirus*, and can subsist in both enveloped and nonenveloped forms[1,2]. Predominantly affecting young adults, HEV has an incubation period ranging from 2 to 9 weeks and an all-inclusive mortality of 0.4–4%[3]. In pregnant women, HEV can cause severe hepatitis, especially in the third trimester, with mortality reaching up to 20%[3,4].

Here, we report the first case of severe HEV infection in pregnancy diagnosed at 38 weeks and 6 days of gestation from Nepal. This case has been reported in line with Surgical CAse REport (SCARE) criteria[5].

HIGHLIGHTS

- Hepatitis E viral infection in pregnancy can quickly progress to fulminant hepatitis.
- Can be associated with cerebral edema, encephalopathy, and disseminated intravascular coagulation.
- The mortality rate is very high with hepatitis E infection during pregnancy, especially in the third trimester.
- A possible change in immunogenicity and increase in hormonal status in pregnancy could result in increased severity of hepatitis E infection in pregnant women.
- Once diagnosed, the primary treatment modality is supportive therapy.
- No specific drug have been yet approved to be used during pregnancy for hepatitis E infection.

Presentation of case

A 27-year-old woman gravida two, para one at 38 weeks and 6 days of gestation presented to our center with complaints of vomiting for one day. She had multiple episodes of vomiting which was nonbilious, containing food particles. She had no history of pain in the abdomen, jaundice, passage of loose stool, and fever. She had no history of similar vomiting episodes throughout her first and second trimesters. Her previous obstetric history included a male child born through normal vaginal delivery 7 years back without any similar history and peripartum complications. Her past medical and family history is nonsignificant.

On examination, she was afebrile with presence of dehydration, pulse rate of 130 beats/min, blood pressure of 110/80 mmHg, and

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oxygen saturation of 96% in room air. There was no stigmata of chronic liver disease and she was not encephalopathic. An abdominal examination showed a term size uterus with a longitudinal lie and cephalic presentation. The fetal heart rate on auscultation was 142 beats/minute. Liver function tests (LFT) were deranged with raised total bilirubin of 100 micromol/l, direct bilirubin of 29 micromol/l, aspartate transaminase (AST) raised by 22 times (742 U/l, normal: 0–35 U/l), and alanine transaminase (ALT) raised by 17 times (622 U/l, normal: 0–35 U/l) the upper limit of normal. Urinary acetone was positive. Hemoglobin was 14.1 g/dl, white blood cell count 10 600/cumm , platelets 116 000/cumm, urea 4.5 mmol/l, creatinine 48 micromol/l, sodium 137 mEq/l, potassium 3.9 mEq/l, prothrombin time (PT) 12 s and international normalized ratio 1. There was no evidence of intravascular hemolysis or disseminated intravascular coagulation (DIC). She tested negative for HBsAg, hepatitis A virus IgM, and anti-HCV antibody and positive for HEV IgM. On ultrasound, hepatosplenomegaly was seen and an obstetric scan revealed a single live fetus weighing 3 kg with amniotic fluid index of 6.6 cm. She was admitted, maintained at nil per oral, and given intravenous fluid and antiemetics. Ursodeoxycholic acid 300 mg oral twice daily was also started. The number of episodes of vomiting decreased on the second day but she developed pain over the right upper abdomen. Liver enzymes were still increased in repeat LFT. Vomiting subsided on the third day but she had persistent mild right upper abdominal pain. LFT on the third day showed total bilirubin of 75 micromol/l, direct bilirubin 31 micromol/l; AST 386 U/L and ALT 428 U/L. Next day on repeat investigation, AST was 207 U/L and ALT 368 U/L. She was then planned for termination of pregnancy by induction with one tablet mifepristone 200 mg orally. She delivered a single male child of 3.74 kg at 39 weeks and 3 days of gestation with a good APGAR score. Baby was admitted to the neonatal unit for tachypnea and was handed over to the mother after 2 days with an uncomplicated course. Blood in the umbilical cord was negative for anti-HEV IgM, anti-HEV IgG, and HEV ribonucleic acid. The liver enzymes of the newborn were normal. She was discharged on her third postpartum day on 300 mg ursodeoxycholic acid twice daily. Her LFT was repeated after one week, which showed 2–3 times raised liver enzymes, which eventually normalized after 2 weeks postpartum. No further investigations of the baby were done.

Discussion

HEV is categorized into eight chief genotypes and most of the human infections are caused by genotypes 1–4[1,6]. Because of impoverished sanitation and hygiene in developing countries, HEV 1 and 2 are predominant in these areas causing epidemics as they are transmitted via the fecal-oral route, whereas HEV 3 and 4, which are zoonotic and transmitted through the consumption of undercooked pork and boar meat, are prevalent in developed countries, leading to sporadic and clustered cases[1,6,7]. Currently, HEV is being acknowledged as a global health problem in both developed and developing nations[1].

Similar to hepatitis A virus infection, HEV also usually causes acute self-limiting hepatitis[3]. Clinical symptoms when compared between pregnant and nonpregnant cases are almost similar, but the number of patients presenting with jaundice are much lower in pregnancy[8]. Our patient presented with multiple episodes of vomiting and abdominal pain, but without any jaundice. During pregnancy, HEV infection can, however, quickly lead to severe acute hepatitis, liver failure, and even death[9]. Further, complications like DIC, cerebral edema, and encephalopathy tend to develop at a higher rate[10]. Our patient had severe acute hepatitis as evidenced by very high transaminase levels, but did not have any features of fulminant liver failure and other above mentioned complications. A prospective field study by Khuroo *et al.*[4] showed that the incidence of HEV infection and fulminant rates were higher in pregnant women as compared to nonpregnant women and men. The exact reasons regarding severe liver damage due to HEV during pregnancy still remain unsolved with many hypotheses being proposed. A decrease in number of natural killer cells and T-lymphocytes with an increase in granulocytes, monocytes, and dendritic cells, and a shift to Th2-controlled immune response from Th1-dominated response during pregnancy; leading to weakened adaptive immunity with a comparatively strong innate response causing an initial decrease in susceptibility to infection but failing to clear the pathogen once infected has been highlighted for increased severity[10,11]. Similarly, increasing levels of estrogen, progesterone, and human chorionic gonadotropin as the pregnancy progresses is also implicated, as the levels of these hormones were found to be considerably higher in HEV positive pregnant women with liver failure as compared to HEV negative and controls[12,13]. Estrogen changes B cell survival and activation, and also subdues CD8 T cell cytotoxicity, whereas progesterone inhibits natural killer cells by imparting anti abortive action through progesterone-induced blocking factor; both hormonal activity influencing cellular and humoral immune response thereby altering the course of HEV in pregnancy[13,14].

The diagnosis of HEV infection in our case was done by the detection of IgM anti-HEV antibodies using an enzyme immunoassay with recombinant hepatitis E viral antigens. However, in recent times, a number of diagnostic tests for HEV have been developed. Aggregates of hepatitis E viral particles in stool can be detected with the help of immune electron microscopy using serum taken after acute HEV infection, and HEV antigens can be detected using a fluorescent antibody blocking assay in specimens obtained through liver biopsy[15].

Acute fatty liver of pregnancy or hemolysis, elevated liver enzymes, and low platelets were the foremost differential diagnosis in our case. But, these syndromes are characterized by hypercoagulability and DIC with thrombocytopenia and intravascular hemolysis in case of hemolysis, elevated liver enzymes, and low platelets, which were not seen in our case[10]. Hence, we proceeded with the primary diagnosis of acute HEV infection supported by a positive serological test.

Ribavirin, a nucleoside analog, and interferon-α are the primary therapeutics used to treat HEV infection currently[16]. However, these are contraindicated in pregnancy due to the risk of teratogenicity[17]. Further, no other definite straight-acting antiviral drugs against HEV have been recommended in pregnancy[1]. Hence, supportive treatment, concerted care, and industrious monitoring forms the basis of management of HEV infection during pregnancy[1]. Our patient was managed conservatively for the HEV infection with close monitoring of both mother and fetus, which ultimately led to a normal vaginal delivery without any peripartum complications, and the liver enzymes of the mother returned to normal after 2 weeks postpartum with the baby testing negative for hepatitis E viral serology. With various studies going on, sofosbuvir might be a

future drug after showing in-vivo and in-vitro antiviral activity[18]. Other potential antiviral candidates are antisense peptide-conjugated morpholino oligomers HP1, interferon λ1–3, nucleoside analogs NITD008, 2′-C-methylguanosine, and the non-nucleoside inhibitor GPC-N114; all of which have shown anti-HEV action by either by halting HEV replication or reducing transcription and translation of the viral genome[19–21].

Conclusion

HEV infection in pregnancy, especially in the third trimester, carries a high risk of mortality because of the tendency of rapid progression to fulminant hepatitis. Once hepatitis develops, the primary management consists of supportive therapy and intensive monitoring of the mother and baby. In order to prevent likely HEV exposure, pregnant women can be counseled to avoid possible feco-oral contact, and proper screening and monitoring of HEV infection during early pregnancy should be concentrated.

Ethical approval

Not required.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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Author contribution

K.J., A.T., P.S., S.B., and K.D.B.: study concept, data collection, and counseling and surgical therapy for the patient; K.J. and R. A.: writing-original draft preparation and literature review; K.J., R.A., and A.T.: editing and writing; P.S., S.B., and K.D.B.: senior author and manuscript reviewer. All the authors read and approved the final manuscript.

Conflict of interest disclosure

The authors have no competing interests to declare.

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