

## EDITORIAL

## Hepatitis E Virus: Peril for Pregnancy

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According to World Health Organization (WHO) estimates, each year there are 20 million new cases of hepatitis E virus (HEV) infection globally, leading to more than 3 million cases of acute hepatitis and over 44,000 deaths, accounting for 3.3% of total mortality due to viral hepatitis.<sup>1</sup> In India infectious hepatitis due to HEV occurs both in epidemics and sporadic forms. It was suspected for first time in 1978 following an outbreak of acute hepatitis secondary to contamination of water supply in Kashmir.<sup>2</sup> It was only in 1991 that Tam et al sequenced the full length genome of 7.2 kb length and identified it as the causative RNA virus HEV. The virus has four genotypes causing disease in humans. Genotypes 1 and 2 mainly cause disease in humans in developing countries as outbreaks. Genotypes 3 and 4 infect humans as well as animals and have been responsible for sporadic cases globally. While adults and children both are affected, it causes clinically significant acute hepatitis more commonly in adults. HIV infected hosts and organ transplant recipients tend to develop chronic disease. It is a self-limiting disease in majority of patients with a case fatality rate of 0.5–3% in adults. However, in pregnant women risk of mortality is up to 30%, when acquired in the third trimester. Absence of specific anti-viral therapy that is safe and effective in pregnancy makes management even more challenging.

The exact reason, why pregnant women are at increased risk of HEV is unclear. Shift in the Th1:Th2 cell paradigm during pregnancy with definite skew towards Th2 cells, increased steroid hormone levels, and pre-existing micronutrient deficiencies in pregnancy may be responsible for increased incidence of HEV in pregnancy.<sup>3,4</sup> High concentrations of inflammatory cytokines (TNF- $\alpha$ , IL-6, IFN- $\gamma$  and TGF- $\beta$ 1) and reduced toll like receptor (TLR) expression may lead to adverse maternal outcome. Association of other host factors like nutritional

status and major histocompatibility complex or prior exposure to virus in childhood may explain the relatively benign outcome of HEV in pregnant women in Egypt. In endemic areas in developing countries HEV may present as asymptomatic infection, anicteric or icteric acute hepatitis, acute on chronic hepatitis and at times as fulminant hepatitis.<sup>5</sup> Aminotransferases are markedly elevated and may precede the onset of symptoms. In pregnant women with HEV there is high risk of acute liver failure (ALF) including fulminant hepatic failure (FHF) and coagulation failure, bacterial sepsis and death. Pregnancy is often complicated by preterm rupture of membranes, antepartum hemorrhage, IUGR and still birth. Even newborns are at increased risk of peri-natal mortality when infected by vertical transmission.

In the present issue of the journal Kashyap R et al have studied pregnancy and fetal outcomes amongst 30 obstetrics patients with HEV over two years from a hospital in Shimla, Himachal Pradesh.<sup>6</sup> Most of the patients were infected during second or third trimester or in the post-partum period. There were only two deaths, but outcome of 5 patients was not known. Twenty one patients had vaginal delivery and two required LSCS. Thirteen newborn were normal and there were 4 IUFDs. As this study is focused on obstetric outcome, it lacks clinical data on medical parameters like severity of jaundice, presence of encephalopathy, biochemical parameters and coagulation abnormalities in the mother. Also there is no information about transmission of HEV infection in newborn. However, the study re-confirms that even today HEV continues to contribute to maternal mortality and poor obstetric outcome in India. In a previously published article in the same journal hepatic encephalopathy, sepsis, acute

kidney injury, late presentation, and coagulopathy were found to be the risk factors for mortality amongst hospitalized pregnant patients with HEV in Himachal Pradesh.<sup>7</sup> While in South East Asian countries 25-30% of mortality is reported in HEV infected women with pregnancy, studies from intensive care unit have reported mortality approaching 50% amongst patients infected in third trimester and with higher grades of hepatic encephalopathy.<sup>8</sup>

Important question in front of physician today is whether anything can be done to improve the maternal and foetal outcomes in pregnant patients already infected with HEV. First of all, it is important to investigate for HEV in pregnant patient presenting with ALF.<sup>9</sup> Though HEV-RNA detection by polymerase chain reaction is gold standard, positive Anti-HEV IgM assay is suggestive of acute HEV infection in endemic area. All pregnant women developing symptomatic HEV hepatitis should be preferably admitted to hospital in view of anticipated risk of encephalopathy and adverse foetal outcome. Specific therapy with anti-viral drugs like ribavirin and pegylated interferon alpha have been used in patients with chronic HEV hepatitis of more than 3 months duration and in patients receiving immunosuppressive therapy.<sup>10</sup> But after the onset of FHF most patients have rapid deterioration over 5 to 6 days and anti-viral drugs are unlikely to be of any benefit.<sup>11</sup> Additionally, ribavirin is contra-indicated in pregnant women (category X drug) due to teratogenicity. Once FHF sets in, intensive supportive care, oxygenation and mechanical ventilation, correction of hypoglycaemia, prophylactic antibiotics for prevention of secondary infection, therapeutic trial with N-acetyl cysteine (NAC) and infusion

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of plasma factors for coagulation failure are the available supportive therapies. Early liver transplant should be considered in selected cases as an option but, its timing and indications are still unclear. Early termination of pregnancy has beneficial outcome in patients of ALF secondary to acute fatty liver of pregnancy (AFLP) or pre-eclampsia, but studies have not shown any survival benefit of early labour amongst pregnant patient of ALF due to HEV.<sup>12</sup> Hence, currently therapeutic termination of pregnancy or early induction of labour is not justified for improving maternal outcome in these patients. Vaginal delivery is safer and new-born should be monitored for possible vertical transmission. Breast feeding is considered unsafe for new-born only when mother has acute symptomatic hepatitis with high viral load as there is possibility of transmission of virus to infant through infected breast milk.<sup>13</sup>

At national level, every effort is being made to reduce maternal and infantile mortality rates but, HEV continues to be an important medical cause of maternal mortality. In the absence of availability of safe and effective definitive therapy, emphasis should be on preventive measures. Pregnant women residing in or visiting endemic areas should drink boiled or

chlorinated water, avoid adding ice cubes to beverages and wash fruits and vegetables thoroughly with safe water before consumption. Immune globulins are not recommended to prevent HEV in pregnant woman during sporadic outbreaks. Prevalence of hepatitis A virus infection has declined significantly since introduction of vaccine in 1995. Presently vaccine for prevention of HEV is licensed for use only in China, administered intra-muscularly at 0, 1 and 6 months interval.<sup>14</sup> It is effective against genotype 1 which is prevalent in India and has 94-100% efficacy. It was found safe when inadvertently administered to pregnant women and there were no foetal adverse effects. In near future, HEV vaccine should be evaluated in preventing severe infection and death in pregnant women and reducing risk of foetal loss and neonatal mortality and morbidity.

## References

- World Health Organization. Hepatitis E Fact sheet (updated 19<sup>th</sup> September 2018). <http://www.who.int/mediacentre/fact-sheets/fs280/en/> (Accessed on April 7, 2019).
- Khuroo M.S. Study of an epidemic of non-A, non-B hepatitis. Possibility of another human hepatitis virus distinct from post-transfusion non-A, non-B type. *Am J Med* 1980; 68:818-824.
- Navaneethan U, Al Mohajer M, Shata MT. Hepatitis E and pregnancy: understanding the pathogenesis. *Liver Int* 2008; 28:1190-1199.
- Kmush BL, Labrique A, Li W, et al. The Association of Cytokines and Micronutrients with Hepatitis E Virus Infection During Pregnancy and the Postpartum Period in Rural Bangladesh. *Am J Trop Med Hyg* 2016; 94:203-211.
- Agarwal R. Hepatitis E: clinical presentation in disease-endemic areas and diagnosis. *Semin Liver Dis* 2013; 33:30-40.
- Kashyap R, Joshi I, Gupta D, Prashar A, Minhas S. Characteristics and obstetric outcomes in pregnant women with Acute Hepatitis E Virus Infection in tertiary care hospital of Himachal Pradesh. *J Assoc Physicians India* 2019; 67:14-16.
- Ranjana A, Thakur S, Mokta J, Bhawani R, Ranjan V. Clinical Profile and Outcome of Pregnant Patients with Acute HEV Hepatitis During Water Borne Epidemic in Himachal Pradesh: A Hospital Based Study. *J Assoc Physicians India* 2017; 65:44-48.
- Kulkarni UP, Trivedi TH, Sonawane B S, Amladi AU, More AB, Moulick ND. Hepatitis E infection in pregnancy in an intensive care setting in Mumbai. Paper presented at APICON 2012; Kolkata; 2012; 12-15.
- Flamm SL, Yang YX, Singh S, Falck-Ytter YT. AGA Institute Clinical Guidelines Committee. American Gastroenterological Association Institute Guidelines for the Diagnosis and Management of Acute Liver Failure. *Gastroenterology* 2017; 152:644-647.
- Peron JM, Abravanel F, Guillaume M, Gerolami R, Nana J, Anty R, Pariente A, Renou C, Bureau C, Robic MA, et al. Treatment of autochthonous acute hepatitis E with short term ribavirin: A multicenter retrospective study. *Liver Int* 2015 doi: 10.1111/liv.12911.9.
- Shrestha A, P Gupta B, K Lama T. Current Treatment of Acute and Chronic Hepatitis E Virus Infection: Role of Antivirals. *Euroasian J Hepatogastroenterol* 2017; 7:73-77.
- Banait VS, Sandur V, Parikh F, Muruges M, Ranka P, Ramesh VS, et al. Outcome of acute liver failure due to acute hepatitis E in pregnant women. *Indian J Gastroenterol* 2007; 26:6-10.
- Chibber RM, Usmani MA, Al-Sibai MH. Should HEV infected mothers breast feed? *Arch Gynecol Obstet* 2004; 270:15-20.
- Zhu FC, Zhang J, Zhang XF, Zhou C, Wang ZZ, Huang SJ, Wang H, Yang CL, Jiang HM, Cai JP, et al. Efficacy and safety of a recombinant hepatitis E vaccine in healthy adults: A large-scale, randomized, double-blind placebo-controlled, phase 3 trial. *Lancet* 2010; 376:895-902. doi: 10.1016/S0140-6736(10)61030-6.