HEPATITIS EVIRUS INFECTION DURING PREGNANCY: WHY IS THE DISEASE STORMY?

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INTRODUCTION
Acute viral hepatitis (AVH) is a systemic infection affecting the liver predominantly. It is caused by six distinct types of viruses A, B, C, D, E and G. Acute viral hepatitis is defined as those cases which have acute self limited disease and a serum aspartate aminotransferase elevation of at least five fold or clinical jaundice or both. Acute liver failure (ALF) is considered when the patient after having a typical acute hepatitis, develops hepatic encephalopathy within four weeks. It is characterized by mental changes progressing from confusion to stupor and coma as a result of severe impairment of hepatic function, without any history of pre-existing liver disease. Viral hepatitis in pregnancy has been a subject of continuing interest and controversy. Reports from Europe and United States and a recent report from India have shown the course of viral hepatitis during pregnancy to be in no way different from non pregnant women. However, studies carried out in India, Iran, Africa and Middle East have found the incidence of fulminant hepatitis to be higher in pregnancy. Malnutrition superimposed on the normal demands of pregnancy and inversion of T and B lymphocytes in early pregnancy have been postulated to be the contributing factors.

In India viral hepatitis is a major public health problem. Acute viral hepatitis (AVH) continues to be a public health problem in India despite improving sanitation, health awareness and socio-economic conditions. AVH is also a serious health problem in lots of countries and is one of the most important infectious diseases to which man is prone. In India, Hepatitis E is the commonest cause of acute hepatitis in adults and hepatitis A is the commonest cause in pediatric age group. India is hyper-endemic for Hepatitis A and E.

Hepatitis E virus (HEV), a member of the genus Hepevirus in the family Hepeviridae is a major cause of enterically transmitted non A non B hepatitis in many developing countries with large epidemics already being reported in Asia, Africa and Latin America. Most importantly, high mortality rates have been reported for HEV related infection during pregnancy.

HEPATITIS AND PREGNANCY
Pregnancy appears to be a potential risk factor for viral replication and leads extreme low immune status of Indian/Asian pregnant women. Mortality rates among pregnant women, especially those infected in the 3rd trimester, have ranged between 5% and 25%, much higher that men and non-pregnant women. It has been reported that a significant proportion of pregnant women with acute hepatitis E (up to 70%) progress to acute liver failure with a short pre-encephalopathy period, rapid development of cerebral edema and high occurrence of disseminated intravascular coagulation. Vertical transmission of HEV infection from mother to infant, although rare, has been reported. Babies born to HEV-RNA positive mother had evidence of hepatitis E infection. Fulminant HEV infection in pregnancy contributes to highest mortality rate of the fetus and mother. The fatality rate among pregnant women with ALF is reported to be high in India at 22.2%, with the maximum severity occurring during the third trimester (44.4%). Hepatitis E in pregnancy is also associated with high rates of spontaneous abortion, intrauterine death, and preterm labour. Worse maternal and fetal outcome of Hepatitis E compared to other types of viral hepatitis has been observed in
pregnant women with HEV infection.\textsuperscript{23} Greater morbidity and mortality, particularly during epidemics of hepatitis, has been noted among pregnant females in developing countries.

Association of HEV and viral hepatitis with pregnancy has been reported earlier in many studies, Jaiswal and colleagues\textsuperscript{24} in central India and Aziz and associates\textsuperscript{25} in Pakistan have reported that HEV is responsible for 58% and 62% of cases of acute viral hepatitis in pregnant women, respectively. Two studies from New Delhi\textsuperscript{20,21} reported slightly lower prevalence (45% and 37%), and a study of sporadic HEV infection in the context of multiple HEV epidemics in Kashmir reported a prevalence of 86% among pregnant patients with acute viral hepatitis.\textsuperscript{18} Patra and colleagues in a study on pregnant women with jaundice and acute viral hepatitis caused by HEV infection concluded that, they had a higher maternal mortality rate and worse obstetric and fetal outcomes than did pregnant women with jaundice and acute viral hepatitis caused by other types of viral hepatitis.\textsuperscript{23}

Hepatitis E virus (HEV) infection during pregnancy leads to severe complications which may result in fetal and/or maternal mortality, abortion, premature delivery, or death of a live-born baby soon after birth depending on the severity of the infection which is stratified as AVH or ALF (most severe form of AVH). HEV infection is one of the predominant causes of pregnancy related complications in the developing countries including India.\textsuperscript{14,15}

HEV infection accounts for 50-70% of all patients with sporadic viral hepatitis in India.\textsuperscript{1} The reason for it may be that pregnancy is associated with high levels of steroid hormones. These steroid hormones may promote viral replication. It also has a direct inhibition on hepatic cells, which may predispose to hepatic dysfunction/failure when exposed to infectious pathogens.\textsuperscript{26} Steroid hormones are immunosuppressive\textsuperscript{27} and mediate lymphocyte apoptosis through NF-κB. NF-κB is a eukaryotic dimeric transcription factor which has a multiple cellular effects, including liver development and regeneration and its implications on the immune response.\textsuperscript{28} Jilani et al found that HEV infected pregnant women with fulminant hepatic failure had lower CD4 count and higher CD8 counts, they also observed that the levels of estrogens, progesterone and beta-HCG were significantly higher in the above-mentioned group when compared to HEV negative patients or control healthy pregnant females.\textsuperscript{29} Although the levels of hormones were physiologically high in the normal control population; patients with HEV infection seemed to have significantly higher levels than controls, which probably explain the direct interaction of HEV with the immune system. In another interesting study, Pal et al studied the cellular immune response in both pregnant and non pregnant women with acute hepatitis E and the control population\textsuperscript{30} they found that pregnant women with HEV had generalized immune suppression characterized by decrease in lymphocyte response to phytohemagglutinin (PHA) with a predominant Th2 bias as compared to non pregnant women with hepatitis E and normal healthy controls. This was contradictory to the earlier hypothesis that normal pregnancy is associated with systemic immune suppression with an increased risk of infections.\textsuperscript{31-34}

Higher viral load of HEV has been reported to be associated with FHF during pregnancy; this was reported in a study by Kar et al., where a comparatively higher HEV viral load was observed in FHF patients (139994.0±103104.17 copies/ml) than AVH patients (768.92±1105.40 copies/ml). However, HEV genotype could not be correlated with the disease outcome as only single genotype (genotype1) was detected in both the disease groups.\textsuperscript{35} High fetal mortality has been explained in AVH and FHF cases which showed vertical transmission of HEV from HEV infected mothers to their infants.\textsuperscript{39}

In a recent study by Deka et al., 2010 it was shown that PROGINS carriers and lower expression of PR and PIBF, as well as high viral load influences the Hepatitis E disease severity and outcome in pregnancy. Higher IL-12 to IL-10 ratio (Th1 bias) in FHF indicates, that after crossing the period when there was a lower IL-12 to IL-10 ratio and after the completion of HEV incubation period (i.e. 15-64 days), when the virus has started causing damage to the cells, cytotoxic immunity rises (Th1 immunological state) up to a particular level where body can fight against the virus infected cells but in the due process, lower PIBF expression and higher NK cell activity results in reduced fetal protection and eventually fetal death occurs because of immunological injury.\textsuperscript{36}

**HEV GENOTYPES AND SEVERITY OF HEPATITIS E DURING PREGNANCY**

There are 4 mammalian genotypes of HEV found to have unique geographic distributions. Genotype 1 includes Asian and African HEV strains, genotype 2 includes the single Mexican HEV strain and few variants identified from industrialized countries and genotype 4 includes human and sune HEV strains from Asia, particularly China, Taiwan and Japan. Hepatitis E virus with genotype 1 is most frequently recovered from patients in developing countries (Asia, North Africa). This genotype and genotype 2 appear to be more virulent than genotypes 3 and 4.\textsuperscript{37} It has been discussed earlier that the course and severity of hepatitis E in pregnant women is not different from that in non pregnant women in Europe and United States. This can be explained by the viral genotypes with lesser virulence found in those areas. In the United Kingdom. HEV genotype 3 is most common, like genotype 4 in China.\textsuperscript{18,39}

When HEV infection occurs, a cytotoxic immune response (Th1) is likely to be elicited in the Th2 biased pregnant women. FHF is always associated with high HEV load. For that a strong
Th1 response is required. This elevated Th1 immune response if still remains insufficient to fight with such a high HEV load, there is a possibility that Th1 response goes on increasing but in the due process, the cytotoxic immune response may result in reduced fetal protection and eventually fetal death.

Opinions differ over the maternal and fetal outcome of pregnancies associated with viral hepatitis. The studies from west opinions differ over the maternal and fetal outcome of pregnancies associated with viral hepatitis. The studies from the developed countries conclude that the pregnancy state, perse, has no adverse effect on the course of hepatitis, provided the nutrition is adequate. However, increased maternal and fetal mortality has been reported by many groups, mainly from the developing countries. Poor prenatal care and maternal nutrition appear to have contributed significantly to the increased severity of infection.

**CONCLUSION**

HEV infection in pregnancy leads to poor maternal and fetal outcome. FHF patients show Th1 biasness in terms of higher IL-12/IL-10 ratio. Thus, this shift of Th2 biasness, which is a characteristic of normal pregnancy, in the HEV infected pregnant women, is suggestive of the role of immunological shift during hepatitis E related FHF in pregnancy. This immune alteration in turn may lead to reduced fetal protection which is probably due to higher activity of NK cells leading to fetal death. Viral load is comparatively higher in FHF than AVH and also higher in patients with fetal morality in both AVH and FHF, suggesting its role with the disease severity. High viral load and Th1 immunological state together may attribute to the poor pregnancy outcome in hepatitis E.

**REFERENCES**


