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*Editorial*

# Hepatitis E Virus — A Potential Threat to Pregnancy

Hepatitis E virus has become the most frequent and leading cause of acute hepatitis in developing countries.[1] The disease was first recognized in the Indian subcontinent in 1950s following contamination of drinking water during a flood. Then a large number of people developed jaundice. Although it was initially believed to be an outbreak of hepatitis A, a substantial number of cases in adults and the high risk of death from fulminant hepatitis in pregnant women made that speculation unlikely.[2]

HEV has been responsible for major outbreaks of acute hepatitis in the developing countries of Asia, Africa and Latin America over the last 50 years.[3] The virus is transmitted enterically from person to person through contaminated water and uncooked food resulting in hepatitis epidemics or sporadic cases. The highest incidence of sporadic cases in developing countries is observed in 15–35 years age group; in developed countries, individuals older than 45 years have the highest incidence.[4] In the industrialized countries, hepatitis E is considered as an emerging disease of global importance and has been reported in a number of developed countries. HEV has a peculiar trait of progression to chronic hepatitis E in immunocompromised patients and it has an alarming course in pregnant women in certain geographical regions of the world. Severe form of HEV is known to be more pronounced in pregnant women. Even though most of the described cases of acute hepatic failure associated with HEV during pregnancy had a favorable clinical course, some cases of fulminant liver failure and death are described. Studies from various developing countries have shown that the incidence of HEV infection in pregnancy is high and a significant proportion of pregnant women can progress to fulminant hepatitis with a mortality rate varying from 30–100%[5,6], whereas in men and non-pregnant women, the disease is usually self-limited and has a case fatality rate of less than 0.1%. The high mortality rate in pregnancy has been thought to be secondary to the associated hormonal (estrogen and progesterone) changes during pregnancy and consequent immunological changes.[1]

In many developing countries HEV infection is endemic for poor personal hygiene and inadequate sanitation. Outbreaks are associated with rainy season, flood when sewage water gain access to open water reservoirs or by sewage contamination of underground piped water through nearby sewerage lines. Moreover, use of contaminated river water for drinking, cooking, personal washing and improper disposal of human excreta appear to be closely associated with the prevalence of infection.[7]

The relationship between hepatitis E and pregnancy is quite interesting. In a large prospective study from Northern India on the maternal and fetal outcomes of hepatitis E infection, almost 60% of viral hepatitis in pregnant women was attributed to hepatitis E infection. HEV infected women were more prone to fulminant hepatic failure (55%) which was 2.7 fold higher than non-HEV infected women (20%); maternal mortality was also higher secondary to fulminant hepatic failure in the HEV infected group (41%) vs 7% in the non-HEV group.[8]

Vertical transmission of HEV infection from mother to fetus is also known to occur.[9] Hepatitis E poses a significant threat to the health of expectant mother, a well-noted epidemiologic feature of the disease, but little attention is given to the impact of HEV infection transmitted vertically that contributes fetal and neonatal morbidity and mortality. An evidence based study suggests that HEV transmission from mother to child may be frequent and deleterious to the fetus and newborn. Those women were more likely to have obstetric complications such as spontaneous abortion, antepartum hemorrhage and intrauterine fetal death. HEV infection also poses a significant threat to fetal health and development including preterm delivery and stillbirth.[8-10]

Now, questions arise why hepatitis E causes severe liver injury in pregnant women. Though it remains a mystery, few possible reasons that probably explain the direct interaction of HEV with the immune system in pregnancy come in front.

Hormonal factors during pregnancy may play a significant role in altering immune regulation or viral replication. The levels of progesterone, estrogen and human chorionic gonadotropin (HCG) are significantly increased in pregnancy.[11] In animal studies these hormones have been shown to have a clear suppressive effect on the cell-mediated immunity.[12] Pregnancy is also associated with high levels of steroid hormones and evidences show that steroid hormones may promote viral replication.[13]

Immunological changes may also contribute to the increased incidence of hepatitis E virus infection in pregnancy. A number of cytokines like IL-4, IL-10, TGF-β secreted by trophoblasts, inhibit cell mediated immunity. This cytokine production during pregnancy seems to favor antibody production over cytotoxic T cell response.[14] T cells are markedly decreased during early pregnancy up to 20$^{th}$ week of gestation leading to reduced level of cell-mediated immunity.[15] The decreased cell-mediated immunity has been suggested to increase susceptibility to viral infections like hepatitis, rubella, herpes and human papilloma virus and also parasitic infection like malaria during pregnancy.[16]

Severity of illness depends on genotype. Genotype 1 causes more severe disease whereas infection caused by genotypes 3 and 4 is clinically less severe, although genotype 4 is more likely to cause clinical illness than genotype 3. Genotype 1 infection in pregnant women during the second or third trimester carries the greatest risk for fulminant hepatitis with a mortality rate of up to 20%.[17,18] However, it is important to explore role of viral genotypes in the pathogenesis and severity of HEV infection.

The issues of interaction of hepatitis E and pregnancy creates a great enthusiasm among researchers. It can provide new insights into the pathophysiology, understanding the role of immune mechanisms in viral infections and host susceptibility factors and their interaction to produce the disease processes. The severe liver injury due to HEV infection in pregnancy may be related to differences in immune and hormonal factors, the genetic and environmental factors with its occurrence in certain developing countries. However, the immunological and hormonal factors interacting with the genetic susceptibility in Asian pregnant women needs further works to generate adequate data.

In conclusion, hepatitis E virus infection is an unrecognized problem of national significance in Bangladesh. The epidemiology and risk factors for HEV infections in Bangladeshi population are poorly described. Though socioeconomic status appeared to be the primary risk factor for this infection in pregnancy, health measures like improvement of education in personal and public hygiene and ensuring the supply of safe drinking water may be the effective measures for controlling the spread of infection. Early preventive measures may limit the maternal and perinatal mortality and morbidity of HEV infection. Immunological research in the future may provide us more information to improve the strategies of management and thus to protect hundreds of lives of expectant mothers. It is worth mentioning that on World Hepatitis Day, 28$^{th}$ July, 2014, WHO and partners urged policymakers, health workers and the public to think again about this silent killer.

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