

# Hepatitis E in Pregnancy: An Insight into Etiopathogenesis.

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**Abstract** :Hepatitis E virus (HEV), which occurs in epidemic and sporadic form, cause acute self-limiting hepatitis. It is one of the major public health problems in encountered developing countries; usually manifests as water-borne epidemic. Outbreaks have most often been associated with poor personal hygiene, inadequate sanitation and unsafe water supplies. Viral hepatitis in pregnancy has been a subject of continuing interest and controversy. It accounts for more than 50% of acute viral hepatitis in young adults in developing countries and carries a mortality rate of 20-30% among infected pregnant women, primarily those in their third trimester. The mortality rate in case of pregnant women with fulminant liver failure (FHF) has been reported to be significantly higher, with maximum severity in the third trimester. The progression to FHF in pregnant women could be because of immunological injury, while chronic hepatitis could be mediated by failure to inhibit viral replication, given that these patients were immunosuppressed and immunological injury was absent. Further research is required to understand the implications of immunology and hepatitis E infection. This review is an effort to appraise about the effect of Hepatitis E in pregnancy and its etiopathogenesis.

## INTRODUCTION

Hepatitis E virus (HEV), which occurs in epidemic and sporadic form, is an acute self-limiting hepatitis. It is one of the major public health diseases in many developing countries with water-borne epidemics<sup>1</sup>. Outbreaks have most often been associated with poor personal hygiene, inadequate sanitation and unsafe water supplies. In one of the recent studies it has been found that 4.25 % HEV RNA in sewage samples and 1.42% in drinking water samples indicating faecal contamination of drinking water<sup>2</sup>. This study indicates that poor supply of drinking water is an important factor for HEV outbreaks. Due to higher risk of public health, it is major area of concern. The disease mainly affects young adults and has relatively low mortality rate of about 1% in the general population. Although largely a self-limited infection, it results in morbidity and mortality, especially among pregnant women<sup>3,4</sup>. Hepatitis E virus (HEV) infection is not associated with chronicity, but a fraction of the patient's progress to fulminant hepatitis<sup>5</sup> the most severe form of acute hepatitis.

## EPIDEMIOLOGY & CLINICAL PRESENTATION

Viral hepatitis in pregnancy has been a subject of continuing interest and controversy. It accounts for more than 50% of acute viral hepatitis in young adults in developing countries and carries a mortality rate of 20-30% among infected pregnant women, primarily those in their third trimester<sup>6</sup>. The mortality rate in case of pregnant women with FHF has been reported to be significantly higher, with maximum severity in the third trimester<sup>7,8</sup>. In contrast, none of the other recognized hepatitis viruses cause such severe hepatitis in pregnancy.

The relationship between hepatitis E and pregnancy is quite interesting. Hepatitis E has both a high incidence and a severe course in pregnant women in some geographical regions of HEV-endemic countries, such as Northern India<sup>7,9</sup> while in other HEV-endemic countries, such as Egypt, it has been shown to have a benign course with little or no morbidity<sup>10</sup>. In a recent large prospective study from Northern India on the maternal and fetal outcomes of hepatitis E infection, close to 60% of viral hepatitis in pregnant women was attributed to hepatitis E infection. Fulminant hepatic failure (FHF) was more common among HEV-infected women (55%), who were at a 2.7 times higher risk than non-HEV-infected women (20%); maternal mortality was also higher secondary to FHF in the HEV-infected group (41%) vs. 7% in the non-HEV group<sup>9</sup>.

Sporadic hepatitis E infection is also associated with increased incidence and severity in pregnant women as reported by a study from India. Hepatitis E alone contributed to approximately 50% of cases of AVH. Fulminant liver failure was significantly higher in pregnant women with HEV infection as opposed to other causes of AVH (69.2 vs. 10%,  $P < 0.001$ ). Also, the prevalence and severity of HEV infection in pregnant women did not differ significantly in various stages of gestation<sup>11</sup>.

In contrast, in Egypt, where the prevalence of anti-HEV in rural communities is very high, severe HEV-caused AVH in pregnant women has not been reported. In one study of 2428 pregnant women, the anti-HEV prevalence was 84.3%. No patients with AVH were reported<sup>10</sup>. The reasons for the differences in the outcome of HEV in different geographical areas remain unclear but could be the result of early childhood HEV exposures, producing long-lasting immunity and/or modifying subsequent responses to exposure to the virus. Alternatively, the predominant HEV genotype(s) in Egypt could be less virulent than those in Asia<sup>10,12</sup>. The high risk of vertical transmission of HEV infection from mother to infant was investigated in a study of 469 pregnant women and a mother-to-infant transmission of 100% was reported, although there may have been a selection bias. Nonetheless, the high transmission rate indicates the importance of vertical transmission of HEV infection. A small percentage of the babies born to mothers with active disease were either preterm or had antenatal hepatitis. Two of the babies died within 48 h, while the remaining 24 alive infants showed full recovery<sup>13</sup>. It is not known whether HEV causes other sequelae or extrahepatic manifestations. Common complications during pregnancy may include death of the mother and fetus, abortion, premature delivery, or death of a live-born baby soon after birth<sup>14</sup>.

Though the *mechanism(s)* is not known, a hypothesis has been put forward to explain the pathogenesis of fulminant hepatitis E in pregnancy<sup>1</sup>. This suggests that the liver sinusoidal cells, particularly the Kupffer cells, are damaged by HEV, which diminishes the ability of these cells to protect hepatocytes against endotoxins that originate from Gram-negative bacteria found in the intestinal tract. Hepatocytes can be injured directly by endotoxins or indirectly by eicosanoids, which are 20-carbon chain ( $C_{20}$ ) polyunsaturated fatty acids that cause platelet aggregation, inflammation, and other effects. Release of prostaglandins (a type of eicosanoid) can lead to chemotactic attraction of inflammatory neutrophils. This can result in swelling of the tissue by water accumulation (oedema) and arrest of bile flow (cholestasis). The enhanced sensitivity of pregnant women to such an endotoxin-mediated effect is well recognized and might explain

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the striking high mortality of hepatitis E in pregnancy<sup>1</sup>. However, the validity of this hypothesis and the precise cellular/molecular mechanisms underlying it has not been confirmed.

Liver histology of patients with hepatitis E reveals portal triaditis, cholestasis, lobular inflammation and degeneration of the liver to varying degrees, which are all suggestive of acute viral hepatitis. However, nearly half of the patients have distinctive morphological changes designated as cholestatic viral hepatitis. The discrepancy between the time of appearance of viral replication in the liver with histopathological and biochemical changes suggests that HEV might not be directly cytopathic and its pathogenesis might be immunologically mediated<sup>15</sup>. The severe liver injury because of HEV infection during pregnancy may be related to one of several possible host factors, such as differences in immune and hormonal factors occurring during pregnancy and genetic and environmental factors, with its occurrence in certain developing countries. It has been reported that poor prenatal care and maternal nutrition appear to have contributed significantly to the increased severity of infection<sup>16,17</sup>.

## IMMUNOLOGICAL & HORMONAL FACTORS

During pregnancy, the maternal immune system is clearly altered to tolerate a genetically different fetus<sup>18,19</sup>. The outer layer of the placenta is made of trophoblasts, which forms the interface between the maternal and the fetal circulations. Trophoblasts do not express major histocompatibility complex (MHC) class proteins and are hence resistant to T-cell-mediated injury, which is a protective phenomenon to sustain the fetus. However, the natural killer (NK) cells do not require MHC proteins and the trophoblasts are protected against the NK cells as they express a unique human leucocyte antigen (HLA) molecule called HLA-G, which binds to NK receptors CD 16 and CD 56 and inactivates them<sup>20</sup>. The placenta also expresses an enzyme called indoleamine 2, 3-dioxygenase, which inactivates and depletes tryptophan, an amino acid essential to T-cell function, and hence suppresses cell-mediated immunity at the fetus-placental interface.

Prusty *et al.*, (2007) studied the changes in NF- $\kappa$ B activity using electrophoretic assays of the p50 and p65 components in pregnant and non-pregnant patients with FHF because of hepatitis B, C and E<sup>21</sup>. They found that the activity of the p65 component of NF- $\kappa$ B was diminished in both the peripheral blood mononuclear cells and the post-mortem liver biopsy specimens in pregnant patients with fulminant liver failure. There was a higher than normal level of p50 expression, but there was a near-complete absence or a minimal expression of p65. The absence of p65 from the NF- $\kappa$ B complex produced fulminant liver damage<sup>21</sup>. Their results established that the absence of p65 was probably responsible for severe liver damage in pregnant FHF patients. The expression of NF- $\kappa$ B, physiologically downregulated during pregnancy, also plays an important role in sustaining the fetus during pregnancy<sup>22</sup>.

Jilani *et al.*, (2007) found that HEV-infected pregnant women with FHF had lower CD4 counts and higher CD8 counts<sup>23</sup>. Pal *et al.*, (2005) studied the cellular immune response in both pregnant and non-pregnant women with acute hepatitis E and the control population and found that pregnant women with HEV had generalized immune suppression characterized by a decrease in lymphocyte response to phytohaemagglutinin (PHA) with a predominant Th2 bias as compared with non-pregnant women with hepatitis E and normal healthy controls<sup>24</sup>. This study was important from a number of perspectives. The thought that normal pregnancy is an immunosuppressed state is challenged because normal healthy pregnant women did not demonstrate a decreased response to PHA. Also, non-pregnant patients with HEV did not show any defective PHA response, probably indicating that HEV by itself does not produce the immunological changes and needs pregnancy as a physiological state to produce the

above-mentioned changes. The Th2 bias observed in the above study was specific to HEV infection during pregnancy. It may be just that the Th2 bias is very much prominent in HEV infection as compared with normal pregnancy. The mechanism by which Th2 bias may lead to a more severe disease course in pregnant women with hepatitis E needs further investigation. With this Th2 bias, it was suggested that decreased cellular-mediated immunity is considered a major cause of death in Asian pregnant women with fulminant hepatitis caused by HEV infection. A shift in the Th1/Th2 balance towards Th2 has been observed in pregnant women infected with HEV compared to non-pregnant women<sup>25</sup>. It is yet not known how such a shift in T helper cell balance would influence the severity of hepatitis E infection in expectant mothers.

Pregnancy is associated with high levels of steroid hormones. These steroid hormones may promote viral replication. It also directly inhibits hepatic cells, which may predispose to hepatic dysfunction/failure when exposed to infectious pathogens<sup>26</sup>. There are evidences indicating that steroid hormones may influence viral replication<sup>27,28</sup>. Steroid hormones are immunosuppressive and mediate lymphocyte apoptosis through NF- $\kappa$ B. It was observed that the levels of oestrogen, progesterone and  $\beta$ -HCG were significantly higher in the HEV pregnant when compared with HEV-negative patients or control healthy pregnant females. 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.

## GENETIC FACTOR

If all the hypotheses of immunological and hormonal factors interacting with the genetic susceptibility in Asian women hold true, a high mortality in pregnancy from all HEV-endemic regions should be expected. But this is not always true. Two studies, from Chennai, Southern India, and Egypt, despite indicating the high prevalence of hepatitis E infection in pregnancy, also had very interesting observations. The mortality rate of hepatitis E infection was absent and very low (3.4%) respectively<sup>10,29</sup>, as against 30-100% reported in various studies in HEV-endemic regions<sup>7-9, 11, 30, 31</sup>. Also, most of the HEV-infected pregnant women had normal-term deliveries. These studies may underline the importance of viral genotypes in the pathogenesis and severity of HEV infection. Rasheeda *et al.*, (2008) hypothesized that the difference in the genotype or subtypes of the HEV infection could be the answer<sup>29</sup>. Genotype 1 is the most common subtype causing HEV infection in India, while genotype 3 predominates in the US. Genotype 1 has been further classified into four subtypes and most of them have been grouped into genotype 1A. A subgenotype shift may have been responsible for the different geographical morbidity in pregnant women in Southern India and Egypt<sup>32</sup>. If this hypothesis holds true, it opens up the intriguing possibility of the exploration of the genotype in pregnancy.

In addition to the above-mentioned factors, Khuroo *et al.*, (2004) suggested that infection of the fetus with HEV may be responsible for the increased severity of the disease in the mother<sup>33</sup>. Variations in the MHC, which mediate antigen presentation, may also explain some of the differences in the mortality in different geographical areas in women infected with HEV<sup>34, 35</sup>. An editorial commented that HEV-infected pregnant women as a group may be more commonly taking herbal medications, which could explain the high mortality in certain geographical regions<sup>36</sup>. However, in India, where herbal medication use is very common, it had been observed that the mortality rate is low<sup>29,37</sup>. At the same time, the use of herbal medications was an independent predictor for poor prognosis in patients with acute liver failure because of other aetiologies<sup>37</sup>.

Also, a recent study of post-transplant patients from France, reporting the increased risk of acute hepatitis E progressing to chronicity, has reiterated the importance of an immune response to protect against infection<sup>38</sup>.

However, as observed, all these patients were post-transplant and patients who progressed to chronic hepatitis had significantly lower levels of CD3 and CD4 cells, highlighting the importance particularly of T-cell-mediated immunity for pathogen clearance. This difference in presentation is really interesting. The progression to fulminant liver failure in pregnant women could be because of immunological injury, while chronic hepatitis could be mediated by failure to inhibit viral replication, given that these patients were immunosuppressed and immunological injury was absent. Further research is required to understand the implications of immunology and hepatitis E infection.

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