

Maternal-Fetal Hepatitis E Transmission: Is It Underestimated?

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Abstract

Hepatitis E virus (HEV) is an enterically transmitted virus; and several modes of transmission have been proposed, including blood transfusion, person to person transmission, and transplacental transmission. HEV during pregnancy is associated with an unfavorable prognosis for mothers and in severe cases can cause acute fulminant hepatitis and death. Transplacental transmission of HEV usually results in unfavorable outcomes of pregnancy, mainly fetal loss, preterm labor, and hepatic dysfunction in neonates. In this review, we will summarize the effects of HEV on maternal-fetal health in various clinical situations.

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Introduction

Hepatitis E virus (HEV) is a small RNA virus responsible for hepatitis E. HEV is a spherical, non-enveloped, single stranded, positive-sense 5'-capped RNA of 7.2 kb. It consists of short 5' and 3' untranslated regions (UTRs) and three partially overlapping open reading frames (ORF) called ORF1, ORF2, and ORF3.¹ There are five known major genotypes of HEV, and they differ according to geographical distribution. Genotype I includes Asian (India, Burma, Nepal, China-Xinjiang, Pakistan) strains²⁻⁸ and African (Chad, Algeria, Tunisia, Morocco, Egypt, Namibia) strains,⁹⁻¹² genotype II includes US and Japanese strains,¹³ genotype III includes Mexican and African (Nigeria) strains,^{14,15} genotype IV (4) includes Chinese (Shanga) and Japanese strains,¹³ and genotype V (5) includes European strains.^{14,15} The disease is endemic in large parts of developing countries in Asia, Africa, and Latin America.¹⁶

Contamination of drinking water is the most common mode for the spread of HEV. Studies indicate that hepatitis E may be a zoonotic disease with pigs and rats serving as reservoirs for human infection.¹⁷ Person-to-person transmission of HEV between family members has been documented

in only 1% to 2% of cases, whereas for person-to-person transmission in hepatitis A it is 15%.¹⁸ Transplacental transmission of HEV in the third trimester of pregnancy has been described; and in affected newborns it is associated with a high perinatal mortality.^{19,20}

HEV is considered an enterically transmitted self-limiting acute viral hepatitis. It also has been reported to cause acute viral hepatitis, especially among travelers to endemic areas, and to cause a small percentage of sporadic fulminant hepatic failure (FHF) in persons without history of travel to endemic areas. Overall, serological studies highlight a global distribution of this virus.¹⁶

Hepatitis E in pregnancy

The course of Hepatitis E in pregnancy is different than the mild self constraining infection described in other populations. Hepatitis E has both a high prevalence and rigorous course in pregnant women in some geographic regions of HEV endemic countries, such as Northern India.^{21,22} However, in Egypt, an HEV endemic country, it has been shown to have a benign course with little or no morbidity.²³ Similar findings were shown in pregnant women in western countries, where they suffer less morbidity and mortality. HEV infection during pregnancy could result in rigorous complications, which may lead to fetal and/or maternal mortality, abortion, premature distribution, or death of a live-born baby soon after birth. The severity of the complications depends on the rigor of the infection, stratified as acute viral hepatitis (AVH) or acute liver failure (ALF).^{24,25}

In a large-scale prospective study from Northern India on maternal and fetal outcomes of HEV, approximately 60% of viral hepatitis in pregnant women was due to HEV infection. Moreover, FHF was more likely among HEV-infected women (55%), who were at 2.7 times greater risk than non-HEV infected women (20%). Maternal mortality secondary to FHF was higher in the HEV infected group (41%) compared to the non-HEV group (7%).²²

In addition, sporadic HEV infection is associated with incremented incidence and astringency in pregnant women. HEV alone contributed to a subset of patients with acute viral hepatitis all over the world. Importantly, prevalence and the astringency of HEV infection in pregnant women did not differ significantly in various stages of gestation.²⁶ However, it was reported that high mortality was associated with infection in the third trimester.²⁶ In one case of second trimester ascites due to fetal HEV infection, the ascites resolved in utero, and a healthy infant was born at 38 weeks of gestation.^{27,28}

Incremented maternal and fetal mortality has been reported by many groups, mainly from developing countries.

Keywords: Hepatitis E virus; Vertical transmission; Prevention.

Abbreviations: ALF, acute liver failure; AVH, acute viral hepatitis; CDC, Center for Disease Control; FDA, Food and Drug Administration; FHF, fulminant hepatic failure; HBV, hepatitis B virus; HEV, hepatitis E virus; Ig, immunoglobulin; ORF, open reading frame; UTR, untranslated region.

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Poor prenatal care and maternal nutrition appear to have contributed significantly to the incremented astringency of infection in these countries.²⁹

In Egypt, where prevalence of anti-HEV in rural communities is very high, rigorous HEV-caused AVH in pregnant women has not been reported. In one study, the anti-HEV prevalence in a series of pregnant women was 84%, with no evidence for AVH.³⁰ The differences in the outcome of HEV in different geographical areas could be the result of early childhood immunity acquired from HEV exposures that may modify subsequent exposure to the virus. Alternatively, the predominant HEV genotypes in Egypt may be less virulent than those in Asia.^{30,31} The studies from developed countries differ over maternal-fetal outcomes of pregnancy associated with viral hepatitis. The pregnancy state associated with hepatitis E has not been linked to rigorous course with adequate nutrition. This is in contrast to the clinical course of hepatitis B virus (HBV) infection acquired perinatally by neonates. This is likely due to the different pathogenic effects of both viruses. Liver injury is caused by immune replication of the host against the pathogen in hepatitis B,³² whereas liver injury in HEV is related to direct cytopathogenic alterations in liver cells.³³

There is a relationship between HEV genotype and the unpropitious effects of HEV infection in pregnancy. Hepatitis E caused by HEV genotype 1 has consistently been observed to engender these negative effects in pregnancy. Although HEV genotype 2 was implicated in acute liver failure in a pregnant woman during an outbreak in Namibia,³⁴ the potential of genotypes 2–4 to cause adverse outcomes in pregnant women, given exposure, remains controversial.

Hepatitis E vertical transmission

There is emerging concerns from epidemiologic and clinical studies suggesting that vertical transmission of HEV may occur frequently from infected mothers and contribute to poor perinatal health outcomes in addition to the effects of maternal morbidity and mortality.³⁴

The risk of vertical transmission of HEV infection from mother to infant was 100% in an antecedent study of a series of pregnant women. There may, however, have been selection errors. The babies born to mothers with active disease either were either preterm or had anicteric hepatitis. This high transmission rate denotes the importance of vertical transmission of HEV infection.³⁵ In another study, vertical transmission of HEV was in 33% of newborns born to infected women in the third trimester of pregnancy. HEV infection was determined with detection of HEV-RNA or immunoglobulin (Ig)M anti-HEV antibodies.^{36,37}

Vertically transmitted HEV infection is known to cause acute hepatitis in neonates, but the clinical course and duration of viremia is unclear.³⁸ HEV in neonates is self-constraining and does not run a chronic or prolonged clinical course. This finding is consistent with another study by Khuroo *et al.*, 2009 that found HEV-infected neonates at birth survived when the infection cleared.³⁸ The clinical profile of HEV infected babies customarily varies from elevated liver enzymes alone, elevated bilirubin alone, and combination elevated bilirubin and elevated liver enzymes. Elevated bilirubin (unconjugated) could be due to physiological jaundice, which occurs in neonates. However, a pattern of serum bilirubin (commixed pattern) identified in three babies from this study was inconsistent with physiological jaundice and more consistent with an HEV infection. Nevertheless, fatal

outcomes were seen in other studies. Newborn babies of infected mothers developed a syndrome of fatal FHF, and this syndrome occurred in some babies with anicteric hepatitis.^{20,22} We could not find any reports of assiduous HEV infection in infants born to mothers with hepatitis E. This is consistent with the natural history of hepatitis E infection in adults, where, by convention, it occurs in a self-circumscribing pattern.³⁹ Although chronic HEV infections have been reported primarily in immunosuppressed and immunocompromised populations,^{39–57} there are no reports of chronic HEV infection in pregnant women or infants. Theoretically, among immunocompromised pregnant women or neonates, such infections could occur. Pregnant women may be coinfecting with other hepatotropic pathogens,^{58–65} but how such coinfections influence vertical HEV transmission and outcomes has not yet been studied. The astringency of HEV infection in the mother and baby may be linked. Findings from an anterior study suggested that fetal disease influenced the course of maternal HEV infection and provided a clear relationship between FHF of the fetus and mother.⁵⁴ Tables 1 and 2 summarize the different incidence of HEV infection in pregnancy and vertical transmission.

Pathogenesis of hepatitis E in pregnancy

Diminished cellular immunity, manifested by decreased CD4, increased CD8, and reduced CD4/CD8 ratio, may be the leading cause of astringency of HEV infection during pregnancy.⁶⁵ Moreover, increased levels of steroid that influence viral replication and expression may cause the rigor of HEV infection. Steroid hormones are immunosuppressive and mediate lymphocyte apoptosis through NF- κ B. NF- κ B is a dimeric transcription factor that has varied roles in liver development, liver regeneration, and immune replication.²⁸ When HEV infection occurs, a cytotoxic immune replication (Th1) may be elicited in Th2 partial pregnant women. FHF is always associated with high HEV viral load, leading to vigorous Th1 replication. If this elevated Th1 immune replication remains inadequate to control a high viral load, it is possible that Th1 replication will increase but that cytotoxic immune replication may result in reduced fetal defenses and eventually fetal death.²⁹

It has been theorized that fetal infection in the uterus may itself leads to adverse maternal outcomes.⁵⁴ Such upside-down vertical effects have been posited to occur with other viral infections as well in animal models.⁶⁶ For example, it was demonstrated in a murine model of herpes infection that fetal inflammatory replications to viral replication in the placenta may predispose the mother to morbidity and reduce the mother's capacity for sustaining the pregnancy.^{67,68} A prior study highlighted that hormone receptor mitigated inflammatory replications at the fetomaternal interface could affect pregnancy outcomes in human hepatitis E.⁶⁹ Fig. 1 summarizes the outcome of HEV infection during pregnancy associated with different immune responses and HEV genotypes.

Laboratory diagnosis of hepatitis E

During acute HEV infection, serological studies showed that anti-HEV IgM becomes detectable days before the onset of symptoms and vanishes over a 4–6 month period.⁷⁰ Anti-HEV IgG appears soon after the IgM replication and may persist for up to 12 years after infection.⁷¹ Fig. 2 summarizes

Table 1. Incidence of HEV infection in pregnancy and its consequences

	HEV pregnancy incidence	Severity	Mortality
Patra et al., ²³ 2007-India	Among 200 pregnant women screened for HEV, 60% of them had positive markers for HEV.	-Fulminant hepatic failure (FHF) -Obstetric complications were more common, such as antepartum hemorrhage, intrauterine fetal death, and preterm delivery	Maternal mortality was greater (relative risk, 6.0 [CI, 2.7 to 13.3]; $P < 0.001$)
Stoszek et al., ³¹ 2006-Egypt	Anti-HEV screening among 2,428 women was 84%	No clinical disease	No mortality
Khuroo&Kamili, ³⁹ 2009-India	HEV in 205 (49.6%)	FHF, cerebral edema, and disseminated intravascular coagulation	FHF died [25 (53.2%) pregnant women and 25 (69.5%) non-pregnant women ($P=0.06$)].
Tsega et al., ²⁷ 1993-Ethiopia	19(59%) of 34 pregnant women had HEV infection	FHF Premature deliveries as a direct result of acute viral hepatitis	Maternal death with FHF
Kumar et al., ³⁶ 2001-United Arab Emirates	Out of 469 mothers, 93 (20%) were anti-HEV positive and 28 (30%) were HEV-RNA positive and symptomatic with on-going infection.	FHF, non-fulminant acute viral hepatitis	Fetal outcomes with FHF
Rayis et al., ⁴¹ 2013-Sudan	38 pregnant women with outbreaks	FHF, post partum hemorrhage, intrauterine fetal death	Maternal deaths due FHF with hepatic encephalopathy was the most common cause of death among these patients.
Zaki et al., ³⁸ 2013-Egypt	HEV IgG (31%) in 29	Mild hepatic disorders	No death

Table 2. Vertical transmission of HEV from infected mother to neonates and its consequences

	Consequences of vertical hepatitis E transmission	Frequency of transmission from affected mother to neonate
Kumar et al., ³⁶ 2001	Acute viral hepatitis with complete recovery, limited early neonatal deaths	100%
Kumar et al., ³⁷ 2004	Preterm birth	33%
Zaki et al., ³⁸ 2013	Respiratory distress syndrome preterm birth sepsis Hepatosplenomegaly	33%
Khuroo et al., ³⁹ 2009	icteric hepatitis, anicteric hepatitis, and neonatal death All surviving babies had self-limiting disease and none had prolonged viremia.	79%
Khuroo et al., ²¹ 1995	Icteric neonatal hepatitis, non icteric neonatal hepatitis, hypothermia, and hypoglycaemia and died within 24 h; massive hepatic necrosis.	-
Patra et al., ²³ 2007	Intrauterine fetal death Still birth Preterm	-
Rayis et al., ⁴¹ 2013	Intrauterine fetal death Preterm	-

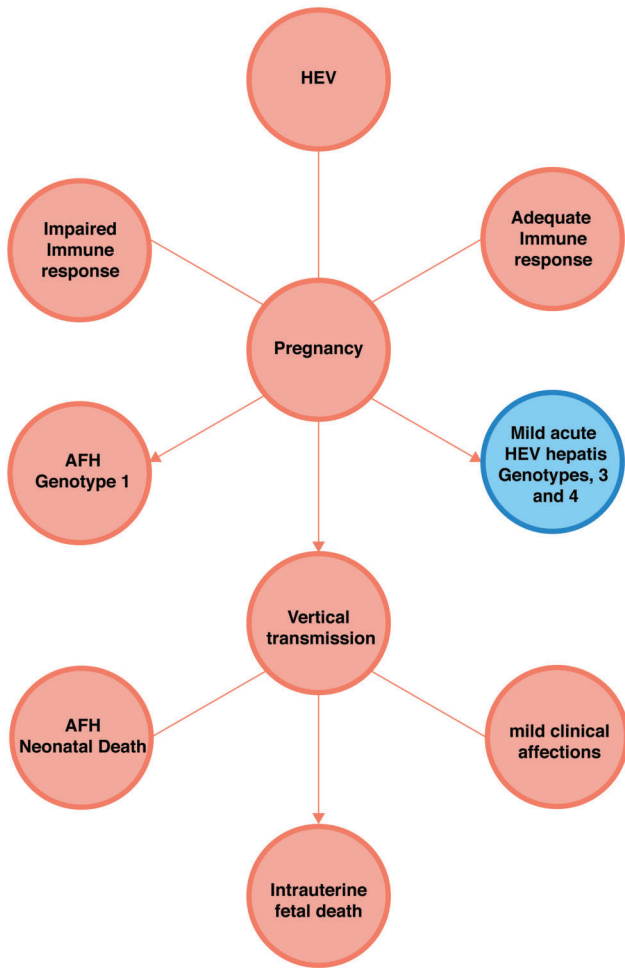


Fig. 1. Effects of HEV infection in pregnancy

the virological markers and clinical symptoms in the weeks after infection. This figure is a modification of one from the Center for Disease Control (CDC).

Several commercial assays are available internationally; however, no assay is currently approved by the US Food and Drug Administration (FDA). In addition to serological assays, nucleic acid amplification methods can be used to identify HEV RNA both in the blood and stool of infected individuals. In a human volunteer experiment, HEV RNA was detectable in blood at the apex of eccentric liver function tests starting from two weeks before and up to one week after onset of jaundice. HEV RNA appeared in stool later than in blood and vanished from stool within two weeks after it became undetectable in blood.⁷² Fig. 3 summarizes laboratory procedures used in the diagnosis of HEV.

HEV therapeutic modalities

To date, there are no efficient treatments for hepatitis E in pregnancy. Experimental use of ribavirin to treat acute hepatitis has promising results in non-pregnant patients,⁷³⁻⁷⁵ but unfortunately, this drug is contraindicated in pregnancy because of consequential embryocidal and/or teratogenic effects.⁷⁶ Several researchers have suggested that early induced distribution or even pregnancy termination may be considered to preserve the life of the mother.^{54,77} However, this line of treatment to avert death in women who present with astringent disease has not been studied systematically. Given the high rate of miscarriage, stillbirth, and premature distribution in pregnancies affected by astringent hepatitis E, the net impact of such a strategy on neonatal morbidity and mortality is questionable.

HEV aversion and control strategies

Aversion measures typically involve amelioration of unsanitary conditions and provision of safe to drink water. Efforts to reduce person-to-person transmission of HEV needs to focus on hand

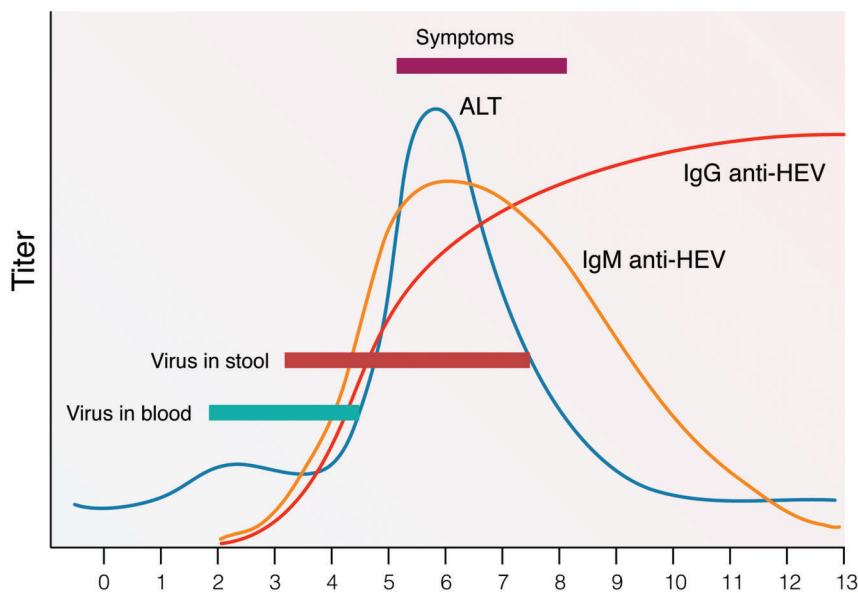


Fig. 2. Appearance of virological markers and symptoms of HEV infection according to weeks after infection.

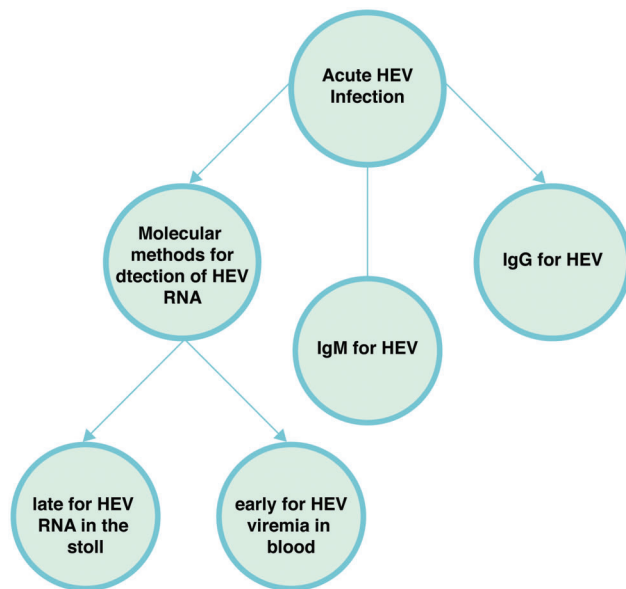


Fig. 3. Laboratory diagnosis of HEV

washing. According to CDC regulations, in order to prevent infections when visiting endemic areas, the safe drinking water will be sealed carbonated water or water disinfected by boiling, filtration, or treatment by other methods.

Because the prosperity of current therapeutic modalities is limited, there is an exigent need to develop and provide a reliable efficacious hepatitis E vaccine.⁷⁸ Albeit at least one HEV vaccine candidate has shown promise in clinical trials, none has been approved by the FDA or any international regulatory agency.

Recently developed HEV vaccines have shown good results in averting hepatitis E,^{79,80} and they may avail to decrease the necessity for treating rigorous illness. Nevertheless, future data will determine if HEV infections can still occur in efficiently vaccinated adults.⁸¹ There is very limited data available regarding safety and efficacy in pregnant women for the vaccine.⁸² Future studies are necessary to evaluate the efficacy of these vaccines in averting maternal disease and death and reducing fetal loss, premature distribution, and neonatal morbidity and mortality.³⁴ Such research should be a global maternal child health priority and will perhaps inspire the development of further vaccines and eventual implementation in susceptible populations.

Conclusions

From this article we can conclude that HEV represent a health problem during pregnancy for both mother and fetus. Different outcomes of pregnancy associated with HEV depend upon several factors. The spectrum of the disease and its outcome needs extended studies to know the missing parts of the puzzle.

Conflict of interest

None

Author contributions

Conception and designing of the article, acquisition of data, analysis and interpretation of data (MESZ); drafting the article or revising (MMAER, H,AER).

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