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REVIEW ARTICLE

Viral hepatitis in pregnancy

Mohamed Tarek M. Shata[1] | Helal F. Hetta[1,2] | Yeshika Sharma[1] | Kenneth E. Sherman[1]

[1]Division of Digestive Disease, Department of Internal Medicine, University of Cincinnati, Cincinnati, Ohio, USA

[2]Department of Medical Microbiology and Immunology, Faculty of Medicine, Assiut University, Assiut, Egypt

Correspondence
Mohamed Tarek M. Shata, Division of Digestive Disease, Department of Internal Medicine, University of Cincinnati, Cincinnati, OH, USA.
Email: mohamed.shata@uc.edu

Abstract

Viral hepatitis is caused by a heterogenous group of viral agents representing a wide range of phylogenetic groups. Many viruses can involve the liver and cause liver injury but only a subset are delineated as 'hepatitis viruses' based upon their primary site of replication and tropism for hepatocytes which make up the bulk of the liver cell population. Since their discovery, beginning with the agent that caused serum hepatitis in the 1960s, the alphabetic designations have been utilized. To date, we have five hepatitis viruses, A through E, though it is postulated that others may exist. This chapter will focus on those viruses. Note that hepatitis D is included as a subset of hepatitis B, as it cannot exist without concurrent hepatitis B infection. Pregnancy has the potential to affect all aspects of these viral agents due to the unique immunologic and physiologic changes that occur during and after the gestational period. In this review, we will discuss the most common viral hepatitis and their effects during pregnancy.

KEYWORDS
epidemiology of viral hepatitis, foetal outcome, hepatitis A, hepatitis B, hepatitis C, hepatitis D, hepatitis E, immunopathogenesis of viral hepatitis, maternal transmission, pathogenicity of viral hepatitis, pregnancy, viral hepatitis

1 | HEPATITIS A VIRUS

1.1 | Introduction

Globally, hepatitis A virus (HAV) is a common cause of acute viral hepatitis. It is highly endemic in Middle East, North Africa, Sub-Saharan Africa, South and Central Asia and Latin America. HAV is a single-stranded RNA virus that belongs to the *Picornaviridae* family.[1] Infection with HAV is mainly self-limited and rarely causes life-threatening complications, with an estimated mortality rate of 0.3% to 0.6% which may increase to 1.8% in adults older than 50 years.[2] It is estimated that 1.5 million new cases are reported annually; however, the true incidence may be much higher, as milder cases are under-reported.[3] HAV infection is prevented by a safe and effective vaccine.[4]

1.1.1 | Virology and pathogenesis of HAV

HAV is a single-strand positive sense RNA virus belonging to *Hepatovirus* genus, *Picornaviridae* family.[1] HAV consists of 6 genotypes. Genotypes I to III infect humans.[5,6] There are two infectious forms of HAV existing in the host: naked virions that are shed in the faeces and quasi-enveloped virions that circulate in the blood. The synthetic genome length RNA is also infectious.[5,6]

Abbreviations: AASLD, American Association for the study of liver disease; AVH, Acute Viral Hepatitis; CMI, Cell-mediated Immune; DAAs, Direct-Acting Anti-viral; EASL, European association for the study of liver; FHF, Fulminant Hepatic Failure; HAV, hepatitis A virus; HBV, hepatitis B virus; HCC, hepatocellular cancer; HCV, hepatitis C virus; HDV, hepatitis D virus; HEV, hepatitis E virus; HIV, human immunodeficiency virus; ICP, Intrahepatic cholestasis of pregnancy; IFN-g, Interferon-Gamma; IG, immunoglobulin; IL28B, Interleukin 28B; IVDU, intravenous drug use; NK, Natural Killer; ORFs, Open Reading Frames; PEP, post-exposure prophylaxis; PHA, Phytohemagglutinin; Th, T helper; WHO, World Health Organization.

HAV is not directly cytopathic to hepatocytes, and the liver injury is mainly due to the host immune response. Viral clearance after the primary infection is achieved by cellular immunity, whereas humoral immune response is responsible for protection and prevention of infection. Individuals with defects in cellular immune response, as in human immunodeficiency virus (HIV) infection, can produce longer viral shedding with high infectivity, but without an apparent increase in the severity of symptoms.[5]

1.2 | HAV Epidemiology

1.2.1 | Mode of transmission

HAV infection is common in developing countries with poor hygiene and sanitation systems. Faecal contamination of food and water supplies is the main cause of infection in early childhood with a mild form of the disease.[7] HAV is transmitted via the faecal-oral route either by direct contact with an infected person or indirectly by ingestion of contaminated water and food, especially raw and undercooked shellfish.[8,9] The incubation period for HAV is 15–50 days, with a mean of 28 days.[10] In a dried state, HAV can survive for more than 1 week in ambient conditions, and it can survive in fresh or salty water for up to 1 year.[11,12]

1.2.2 | Paradox of HAV epidemiology

It is estimated that HAV infects between 1 and 2 million people annually[5,13] with low mortality rate of 0.3% to 0.6%.[5] Based on the prevalence of anti-HAV IgG in human serum, the endemicity of HAV is classified into low, intermediate and high levels.[5]

In high-endemic areas with poor sanitation, HAV is transmitted mainly through water; therefore, more than 90% of the populations have anti-HAV IgG by the age of 10 years. In these settings, large epidemics are paradoxically infrequent, as the majority of people are immune due to mild HAV infection or acute hepatitis A during childhood as asymptomatic infection.[5,13,14]

In intermediate-endemic areas, HAV infection transmission occurs mostly through contaminated food and water and the prevalence of anti-HAV IgG is equal to or more than 50% by age 30 but less than 50% at the age of 15 years. The wide distribution of HAV causes large-scale cyclic outbreaks.[15–17]

In low-endemic areas, HAV infection transmission occurs mainly through food handlers, travel to high-endemic areas and with oral-anal sex. Infection rates are very low, and less than 50% of people older than 30 have immunity against HAV.[15]

1.2.3 | Effects of HAV on pregnancy

Although HAV infection is one of the most common causes of acute viral hepatitis, it is rarely reported in pregnant women. Hence, there are limited data on the incidence and outcome of HAV infection during pregnancy.[4,18,19] The transmission of HAV from the mother to the foetus is uncommon, although there are numerous case reports of vertical transmission, with 2 cases associated with meconium peritonitis and perforation of the distal ileum requiring surgery.[7,20,21] Nosocomial spread is also possible from pregnant women and neonates to other infants, adults or healthcare workers.

In general, no serious outcomes have been reported to be associated with HAV infection during pregnancy.[4,22] However, there are some data that supports the relationship between HAV infection and preterm labour, especially if HAV infection occurs in the second or third trimester.[7]

There is some evidence that acute HAV infection during the third trimester of pregnancy may be associated with some gestational complications and premature labour. The gestational complications associated with HAV infection include increased premature uterine contractions, placental abruption and premature rupture of membranes.[7] Fever and hypoalbuminemia are suggested as markers for a more aggressive course of disease, leading to complications during pregnancy.[7] The direct correlation between the gestational age at diagnosis of HAV infection and the week of delivery suggests that HAV is responsible for the early labour.[7]

Most infants born to mothers with HAV infection were not affected and had normal antibody and transaminase levels. However, in the rare cases in which mother-to-child HAV infection occurs, it can be associated with foetal ascites, meconium peritonitis, neonatal icteric HAV infection and distal ileum perforation.[23] Overall, no mortality was documented among mothers and infants exposed to HAV infection, with full resolution of the infection.[24]

1.2.4 | Breastfeeding and maternal transfer of anti-HAV

Although mothers infected with HAV have anti-HAV antibodies and HAV RNA in their breast milk, there is no evidence that breastfeeding transmits HAV to suckling infants. Therefore, breastfeeding should not be discouraged.[25] The child could be further protected from HAV infection through administration of immunoglobulin or the inactivated vaccine.[25] When given to children <2 years of age, HAV vaccine induces seropositivity that could persist for at least 10 years regardless of presence of maternal anti-HAV.[26]

Maternal anti-HAV IgG antibodies may persist well till the second year of life, depending on the level of HAV endemicity and the average anti-HAV antibody levels in a given maternal population.[27–29] Timing is critical for efficient HAV vaccination in high-endemic areas because high levels of maternal anti-HAV IgG antibodies present in the first year of life may impede the vaccine response. Therefore, it is recommended that young children in endemic areas should preferably not be vaccinated against HAV before first year of age.[25,30,31]

1.2.5 | Treatment and prevention

Although there is no specific therapy for hepatitis A,[6] pre-exposure and post-exposure prophylaxis are recommended. Pre-exposure

prophylaxis against HAV infection by administration of HAV vaccine or immunoglobulins (IG) provides protection for unvaccinated individuals who are working or travelling to countries with high or intermediate HAV endemicity.[32] Post-exposure prophylaxis (PEP) with HAV vaccine or IG prevents infection with HAV when administered within 2 weeks of exposure.[33,34] The dose of IG and the selection of HAV vaccine or IG depend on the age and the immune status of the patient. HAV vaccine for PEP has several advantages over IG including ease of administration, greater acceptability and availability, induction of active immunity and longer duration of protection.[35] Liver transplantation may be an option in the rare cases of fulminant hepatic failure[7]. Additionally, to reduce the risk of HAV infection during travel to endemic areas, it is recommended to maintain hygienic practices such as frequent hand washing with safe water, particularly before handling food, avoiding drinking water or using ice cubes of unknown purity, and avoiding eating unpeeled fruits and vegetables. Pregnant women and women of reproductive age need protection against HAV before visiting HAV-endemic countries or underdeveloped countries with poor sanitation and hygienic standards.[5]

1.2.6 | HAV vaccine

Hepatitis A virus vaccine is prepared from the inactivated virus and is considered safe during pregnancy provided that there is a clear indication for giving HAV vaccine during pregnancy.[32] Hepatitis A virus vaccine is available both in a monovalent form and in combination with hepatitis B virus. After 2 weeks of the first dose of HAV vaccine, about 70% of individuals develop protective levels of antibodies.[33] Therefore, giving HAV vaccine immediately before travel will ensure adequate protection in most individuals, because the incubation period for HAV is 15 to 50 days. After receiving the second dose of HAV vaccine, individuals will have adequate levels of antibodies that will likely persist for at least 10 to 29 years or perhaps for life.[34]

2 | HEPATITIS B

2.1 | Transmission, epidemiology and natural history

Hepatitis B is a member of the *Hepadnaviridae* family, which also includes viruses that cause infections in the livers of woodchucks, ground squirrels and ducks. Cross-species infection does not occur, though primates are susceptible to human hepatitis B virus (HBV) infection.[36] Transmission is primarily through parenteral blood exposure, sexual contact or spread vertically from mother to child during/after delivery. Overall, the WHO estimates there are 257 million people living with chronic HBV worldwide which contribute to the development of cirrhosis and hepatocellular carcinoma, ultimately leading to nearly 900,000 deaths/year. The highest prevalence of disease is in Sub-Saharan Africa, Southeast Asia and the Eastern Mediterranean regions. In these highly endemic regions, the disease is maintained in the population by either maternal-foetal transmission or child-to-child spread. The risk of chronicity is highly related to the age of acquisition, which is thought to be directly linked to the maturation of the thymus and recognition of self vs. non-self antigens. Regardless of the mechanism, rates of chronicity approach 100% following HBV infection in the neonatal period and exceed 70% in early childhood.[37] Post-puberty rates of chronicity after acute infection are less than 1% except in immunosuppressed persons.[38]

The natural history of hepatitis B is complex. Acute infection may lead to development of acute viral hepatitis, characterized by development of jaundice, right upper quadrant pain, nausea, vomiting, anorexia, low-grade fever and fatigue. Serum transaminases may peak in the thousands. Acute liver failure occurs in 1–2% of infected individuals, typically in adults. Acutely infected children tend to have less severe symptoms and may be asymptomatic. The incubation period ranges from 4 weeks to 5 months before symptoms appear and liver enzymes rise. The clinical course of acute infection generally resolves within 2 months, but development of chronicity may lead to smouldering liver injury. Neonates and younger children who acquire HBV have high rates of chronicity and may enter an immunotolerant phase with high levels of replication (high HBV DNA in serum) which can persist for decades. At some point over the next 10–30 years, a high percentage will pass into a more immunoactive phase with immune-mediated liver injury. Some patients in this phase will remain here for years while others will transition to a less replicative stage with decreased liver injury or complete clearance of active replication. Active disease is characterized by presence of hepatitis B surface antigen (HBsAg) which is detected in the blood of infected persons. The clearance of HBsAg represents functional cure. However, with loss of immune function (e.g. steroid exposure or chemotherapy) relapse may occur, as infected individuals harbour cccDNA from the HBV virus in their hepatocytes. Some individuals will develop functional cure but continue to produce HBsAg due to incorporation of the coding portion of that gene into their host chromosomes. Over time, active replicative infection leads to progressive liver scarring (fibrosis) which will progress to cirrhosis and/or development of liver cancer (HCC). The level of replication is closely related to the HCC risk.[39]

The prevalence of maternal HBV infection in the United States was reported in the Nationwide Inpatient Sample study with data collected between 1998 and 2011. Overall prevalence of HBV infection was 85.8 cases per 100,000 deliveries, with rates increasing in all population subgroups over time.[40]

2.2 | Acute and chronic HBV infection during and after pregnancy

Development of an acute hepatitis during pregnancy is occasionally observed, and HBV infection is part of the differential diagnosis. In non-immune patients with risk exposures (sex, blood exposure), the presentation is quite similar to that in non-pregnant persons. However, the diagnosis could be delayed because symptoms like

nausea/vomiting, fatigue and abdominal discomfort may be attributed to the pregnancy or to conditions like hyperemesis gravidarum during the first trimester. Pregnancy alters immune function and associated liver injury. Therefore, chronic inactive and non-replicative HBV infection in a woman who becomes pregnant is associated with an increased risk of HBV flare, typically characterized by increased levels of ALT and HBV DNA. Flares have been reported to occur in over 10% of women with chronic hepatitis B. This risk is significantly increased during the postpartum period. While levels of ALT can be significant, most flares are relatively mild, with few leading to hepatic decompensation. Jaundice can occur but the process is generally self-limited. When flares occur, other aetiologies should be considered including development of coinfection with hepatitis A, C, D or E. Drug toxicity can sometimes be mistaken for a flare of HBV.

The linkage between HBV infection and other maternal complications of pregnancy including eclampsia, preterm labour and development of gestational diabetes is uncertain, though some studies support these associations.[41,42] If chronic hepatitis B has progressed to cirrhosis, both maternal and foetal morbidity and mortality may be increased. Cirrhotic patients should be evaluated by both hepatologists and maternal-foetal specialists before embarking on planned pregnancy.

Postpartum breastfeeding is not associated with transmission, though theoretical concerns about blood exposure to the baby from cracked nipples or biting in older children remain. However, prevention strategies discussed below probably limit risk to the newborn.

2.3 | Treatment and prevention of HBV during and after pregnancy

Prevention of hepatitis B can be achieved through use of vaccines containing recombinant hepatitis B surface antigen. In immunocompetent persons, a three dose vaccine series achieves 90–95% protective efficacy, defined as a serum titre of anti-HBs antibody of 10 mIU/ml or greater. In the United States, childhood vaccination has been recommended for more than 15 years, but catchup vaccination of adults has not been deployed, except for recommendations based upon high-risk behaviour. It is estimated that coverage of children with HBV vaccine in the United States exceeds 90%.[43] However, the duration of this broad vaccination coverage in the U.S. population suggests that many young pregnant women are not immune to hepatitis B. Furthermore, high-risk immigrant groups have not received childhood vaccination and may indeed have high rates of HBV chronic infection.[44] Therefore, universal HBV screening of pregnant women is now recommended. Vaccination of non-immune women during pregnancy is recommended for women at higher risk of HBV exposure during pregnancy.

Treatment of HBV during pregnancy may be recommended for two reasons. In those with active liver disease, characterized by high HBV DNA levels and elevated liver enzymes, treatment is indicated for reduction of liver injury. In most patients, this will be long-term therapy. The second reason is related to risk of transmission to the foetus or newborn. The risk of infection in the infant is linked to the HBV DNA level in the blood of the mother. Higher HBV DNA levels lead to increased risk of transmission. Thus, up to 25% of newborns will acquire HBV infection if the mothers' HBV viral titre exceeds 200,000 IU/mL.[45] Clinical trials of intervention with nucleoside/nucleotide-based medications given in the third trimester show a significant effect on reduction of transmission.[46] However, different clinical trials have started drug at varying levels of HBV titre ranging from 50,000 IU/ml to 200,000 IU/ml. Current guidelines from the American Association for the Study of Liver Disease (AASLD) and the European Association for the Study of Liver (EASL) recommend use of anti-viral therapy in woman with HBV DNA levels of >200,000 IU/ml.[47,48] Because the risk of vertical transmission is also mitigated by the use of hepatitis B immune globulin (HBIG) with HBV vaccination at birth, it is difficult to assess the absolute effect any one intervention. Both lamivudine and tenofovir have been extensively used in HIV-infected pregnant women with a high degree of safety. Therefore, both agents are generally regarded as safe, though registries continue to gather data to evaluate ongoing safety. However, lamivudine should only be used for short-term therapy in the mother due to it possessing a relatively low barrier to development of resistance leading to HBV viral breakthrough. In contrast, tenofovir responses appear to be quite durable. Recently, a newer formulation called tenofovir alafenamide has been introduced. There are only limited data regarding pharmacokinetics and safety in pregnancy for this agent.[49]

The use of preventive practices during delivery such as C-section to reduce risk of transmission has been evaluated but study designs were highly variable. A large study in China failed to benefit caesarian section in reducing infant transmission compared to normal vaginal delivery or use of vacuum/forceps delivery.[50]

2.4 | Hepatitis D coinfection

Hepatitis D virus (HDV) is a unique RNA virus which is considered a subviral satellite virus of HBV. It consists of a very small single-stranded RNA genome of less than 1700 bases which requires the presence of HBV infection to complete its replication cycle. The virus does not have sufficient genetic size to code for a protein coat, so it utilizes excess HBsAg protein to coat itself and then uses the hepatocyte receptor for hepatitis B (the sodium taurocholate cotransporter receptor) to enter the hepatocyte. Coinfection with hepatitis B and D yields a more severe inflammatory response, faster rates of fibrotic progression and increased risk of developing hepatocellular carcinoma in infected patients. There are very limited data regarding HDV in pregnancy. However, early reports did describe vertical transmission of HBV with HDV at time of birth.[51] Sellier et al. described outcomes in 22 women with HDV/HBV coinfection who gave birth to 54 children. In all, 36 children were tested for HDV at 24 months of age or older and were negative in all.[52] Thus, prevention of HBV transmission also prevents HDV infection from mother to child.

3 | HEPATITIS C

3.1 | Epidemiology, transmission and natural history

Hepatitis C virus (HCV) infects an estimated 3.5 million persons in the United States with young persons who inject drugs contributing a substantial proportion of women of reproductive age.[53,54] Worldwide, the World Health Organization estimates 71 million people who have chronic HCV.[55] The primary mode of transmission of HCV is through percutaneous exposure to infected blood. In addition, vertical transmission can also occur from mother to infant. Although less common, sexual transmission can also occur, most likely in HIV-infected men who have unprotected sex with men.[56] The greatest risk factor for acquiring HCV is intravenous drug use (IVDU), which accounts for 60% of the acute HCV infections in the United States. Other risk factors include intranasal illicit drug use, blood transfusion prior to 1992, clotting factor concentrates prior to 1987, recipient of a HCV organ transplant, long-term haemodialysis, incarceration, men who have sex with men and tattoos at unlicensed parlours.[57]

In the last decade, there has been a change in the populations infected with HCV due to the opioid crisis and increase rates of IVDU in the 20–40 year age group.[54] From 1998 to 2011, there has been a fivefold increase in the prevalence of HCV during pregnancy.[40] Based on data from 2006 to 2014, 40.4% of confirmed cases of HCV were in women of reproductive age.[54] Hence, nationally the proportion of infants born to HCV-infected mother has increased by 68%, between 2011 and 2014.[58] There has been an increase in the detection of HCV among children aged 2–3, suggesting perinatal transmission of HCV.[54]

Chronic HCV can lead to progressive fibrosis and cirrhosis with its associated complications of portal hypertension (varices, ascites) and hepatocellular carcinoma. Approximately, 20–30% of patients with chronic HCV will progress to cirrhosis. Patients who have HCV are diagnosed in the acute phase or chronic phase. Majority of the patients, especially in the chronic state, are asymptomatic and diagnosed when routine laboratories suggest liver enzyme elevation. In acute hepatitis C, the most common symptoms include jaundice, nausea, abdominal pain and flu-like symptoms. Serum amino transferases during this period are 10–20 times upper limit of normal. If the HCV RNA persists in the blood for more than 6 months after the onset of the acute infection, it defined as chronic hepatitis C. Once the infection becomes chronic, the rate of spontaneous clearance is low.[59] HCV infection resolves spontaneously after the acute phase in 20–50% of patients and proceeds to the chronic state in the remaining patients.[60] There is a higher rate of spontaneous clearance of HCV among women as compared to men.[61] In the postpartum period, women chronically infected with HCV can spontaneously clear the infection, as there is a significant decrease in the viral load in the first 3 months post-delivery.[62] This is thought to be due to the release of tolerance in HCV-specific T lymphocyte responses that develop during pregnancy and the presence of the favourable IL28B allele.[62,63] However, larger studies are needed to determine additional risk factors for spontaneous clearance of HCV postpartum.

The goal of HCV therapy is sustained virologic response (virologic cure), defined as the continued absence of detectable HCV RNA for at least 12 weeks after completion of therapy.[64] The eradication of HCV infection has multiple health benefits, including decrease in liver inflammation, reduction in the rate of liver fibrosis progression, improvement in liver fibrosis, reduction in the risk of liver cancer, reduction in the risk of liver-related mortality and liver transplantation.[65–68]

3.2 | Influence of HCV on Maternal and Foetal Outcomes

There is no substantial effect of pregnancy on the progression of active HCV infection. There is a decrease in the maternal serum aminotransferase during pregnancy, reflecting the less immune-reactive state of pregnancy.[69] During the second and third trimesters of pregnancy, although the serum aminotransferase decrease, there is an increase in the HCV RNA levels, though to be due to the downregulation of the maternal immune system during pregnancy. HCV RNA levels decrease during the postpartum period.[70] Prior studies have demonstrated a 10% chance of spontaneous clearance of HCV in the postpartum period.[63] Women should have their HCV RNA re-evaluated after delivery due to the possibility of spontaneous viral clearance and if viraemia is detected, then treatment should be started postpartum.

The major factor that plays a role in poor pregnancy outcomes with maternal HCV infection is the presence of concurrent risk factors, such as poor perinatal care and the use of drugs or alcohol. These risk factors were found to have pregnancy-related complications such as gestational diabetes, pre-eclampsia and miscarriage.[71] Maternal HCV infection is a risk factor for the development of intrahepatic cholestasis of pregnancy (ICP), especially at an earlier gestation age. In a meta-analysis, compared to pregnant patients without HCV, HCV-infected pregnancy women had a higher incidence of ICP (pooled OR 20.40 [95% CI, 9.39–44.33, $I^2 = 55\%$]).[72] It is postulated that persistent HCV viraemia can induce modifications in the hepatocytes causing direct cytopathic effect creating an environment that facilitates the occurrence of ICP at an earlier gestational age. The course of ICP in pregnant patients with HCV viraemia including maternal and foetal outcomes is comparable to non-viraemic pregnant patients.[72]

Maternal infection with HCV has shown to have poor outcomes in infants, including low birth weight and preterm birth.[73–75] A prospective study of 145 pregnant women who were HCV positive observed a 3.4% rate of intrauterine foetal death, 17.9% rate of preterm delivery, 11.3% rate of small for gestational age and 12.5% rate of low birth weight infants. These rates were significantly higher than rates in the general population.[76] Pregnant women with cirrhosis are at increased risk for poor maternal outcomes (i.e. pre-eclampsia,

caesarean section, haemorrhagic complication and death) and neonatal outcomes (i.e. preterm delivery, low birth weight and neonatal death).[77,78]

3.3 | Perinatal transmission of HCV

Hepatitis C virus mother-to-child transmission occurs at an overall rate of 5% to 15%, with 3% to 5% progressing to chronic infection.[79] There is a higher rate of transmission of up to 10.8% among coinfection with HIV as compared to a rate of 5.8% with only HCV infection. The risk of transmission is among those mothers who are viraemic with higher viral loads; however, no cut-off has been proposed. Mothers who are only anti-HCV positive who have spontaneously cleared their infection or have been treated are not at risk for transmission.[80] The majority of HCV transmission from mother to child occurs during late intrauterine or intrapartum period.[81]

Perinatal transmission accounts for 60% to 90% of cases of HCV in children with an estimated 23,000 to 46,000 children living with chronic HCV.[82] Interventions to reduce perinatal transmission of HCV to the infant are limited. Although the majority of transmission occurs during delivery, studies have not shown any difference between the rates of vertical transmission in patients who undergo vaginal delivery vs caesarean section.[83] Therefore, elective caesarean section for HCV is not recommended. There is an increased risk of vertical transmission with prolonged rupture of membranes, internal foetal monitoring and episiotomy. Given the potential associated risk of vertical transmission, it is advisable to avoid invasive procedures (e.g. foetal scalp monitors and forceps delivery); however, the data are limited.[84] In terms of invasive perinatal testing, data on the risk of vertical transmission are reassuring but limited and if testing is required then amniocentesis is recommended over chorionic villus sampling given the lack of data on the latter.[85] Breastfeeding does not increase the risk of vertical transmission of HCV and is safe to do in women with HCV infection. However, breastfeeding should be avoided when the nipples are cracked, damaged or bleeding, and in the context of HIV coinfection.[81,83]

3.4 | Treatment of HCV

The treatment of HCV in pregnancy is usually deferred postpartum as there have been no trials approving these agents for during use in pregnancy. There is a lack of data evaluating the safety of direct-acting anti-viral (DAAs) during pregnancy. DAAs have been labelled as pregnancy category B. However, early trials in the United States and in the other parts of the world seem promising. A phase 1 study evaluating the use of sofosbuvir in pregnancy demonstrated 100% virologic cure at 12 weeks post-treatment and no safety concerns.[86] Similarly, a case series of 15 pregnant women in India treated with ledipasvir/sofosbuvir reported 100% clearance of virus 12 weeks post-treatment and no adverse outcomes reported in the women or the infants.[87] The optimal timing of HCV treatment in relation to pregnancy is to be determined. Given the lack of safety data, the treatment of HCV is either delayed until after pregnancy or treated prior to pregnancy.[88]

4 | HEPATITIS E

4.1 | Introduction

Hepatitis E virus is the most common cause of acute viral hepatitis (AVH in many lesser developed countries, particularly among young adults).[89–92] Acute cases of HEV are not *clinically* distinguishable from other types of AVH.[93] Asymptomatic infection is common. There are an estimated 20 million HEV infections worldwide, leading to an estimated 3.3 million symptomatic cases of hepatitis E.[94] In Asia and Africa, there have been many large water-borne outbreaks of HEV-caused AVH.[95–104] In the United States and developed countries, most of the infection are zoonotic.[105–107]

Although most patients with HEV infections recover fully, mortality rates of 1–4% in the general population have been reported.[18,108–114] HEV morbidity in pregnant women is variable according to the geographic regions. In the Indian subcontinent, the mortality rate may reach 20–40% among pregnant women with a high incidence of still birth and spontaneous abortion.[18,108–114] In Egypt, despite high seroprevalence, morbidity is very low in HEV-infected pregnant women and their offspring.[115] The reasons for these variations are still unknown.

4.2 | Molecular virology of HEV

4.2.1 | HEV genome

Hepatitis E virus is a single-stranded RNA virus of approximately 7.2 kb in length. Analysis of its RNA helicase and RNA-dependent RNA polymerase regions show that HEV forms a phylogenetically separate genus, *Hepevirus*.[116] HEV has a short (27–35 nucleotides) 5′ non-translated region, followed by 3 partially overlapping open reading frames (ORFs) regions, a 3′ non-translated region of about 65–74 nucleotides, and a poly A tract (Figure 1).[117–121]

4.2.2 | HEV genotypes

Characterization of HEV genomes from geographically distinct locations has identified at least 8 major genotypes that may differ up to 20–50% at the nucleotide level.[122] While these are diverse in all three ORF regions, they are serologically indistinguishable and cross-reactive.[123–127]

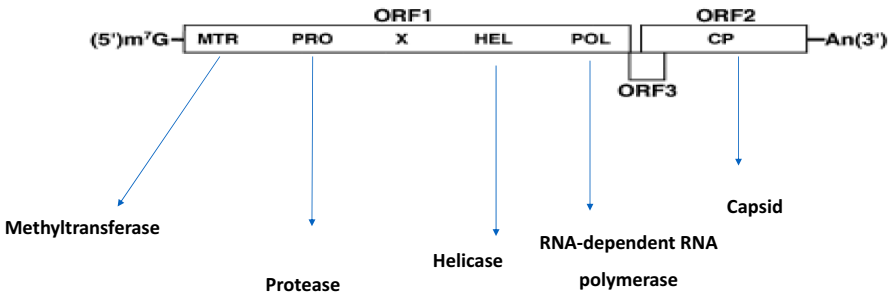

FIGURE 1 HEV genome

4.2.3 | HEV variability and quasispecies

A hallmark of RNA viruses is their extreme genetic diversity. The HEV RNA polymerase lacks a proof-reading mechanism, resulting in a population of distinct but closely related viral variants, termed the viral *quasispecies*, within a single individual.[128] These viral variants may display divergent phenotypic properties, allowing for rapid, adaptive changes in response to immunologic selection pressure and the cellular microenvironment. Further HEV complexity is found in the form of dual infections with multiple distinct HEV genotypes,[129,130] as well as the presence of recombinant viruses.[131,132] Moreover, accumulating data suggested that mutations in the glycosylation motifs in the ORF2 capsid protein[133] or in the helicase domain of ORF1[134] can significantly impact infectivity and virulence.

4.3 | Hepatitis E epidemiology

4.3.1 | HEV transmission

Hepatitis E virus is heat inactivated at 60°C, a 10°C lower temperature than hepatitis A virus (HAV).[135] Viraemia in infected humans and animals is believed to persist for ~20 days and faecal shedding for ~35 days.[123,135]

Hepatitis E virus genotypes 1 and 2 are transmitted through feco-orally (contamination of food and water sources) while genotypes 3 and 4 are endemic in Europe and the Americas (including highly developed, industrialized countries) and transmitted by eating undercooked wild boar, deer and pork,[136–141] with primary zoonotic reservoir in those animals. Newly discovered genotypes 5 and 6 are mainly present in Japan and infect boars and potential humans. Genotypes 7 and 8 are mainly present in the Middle East and infect camels and humans. Limited reports suggest that HEV may also be transmitted parenterally through blood transfusions.[142–144]

HEV outbreaks frequently occur through contaminated water or food in about 90–95% of cases.[110] Outbreaks occur when water supplies are contaminated with faecal material, particularly after natural disasters, heavy rain or drought periods, or when refugees are forced to use unclean water sources during conflicts. Examples of the latter are the recent large outbreaks of HEV in Darfur, Sudan and Chad.[104,145]

Perinatal transmission of HEV has been reported and varies from 30 to 100%.[146–148] Anti-HEV antibody and HEV-RNA are present in the colostrum of HEV-infected mothers; however, breastfeeding is not associated with transmission.[149] Postpartum transmission of HEV infection may occur through close contact of mothers and their infants, especially when the mother has HEV-caused AVH.[149]

4.3.2 | Hepatitis E as a zoonotic infection

Hepatitis E virus or agents serologically related to HEV have been isolated from swine, sheep, rats, mice, chickens, donkeys, camels and horses. However, experimental transmission of HEV genotypes across different animal species is controversial.[150–153] Humans are the primary host for *genotypes 1 and 2*, although certain species of primates may be co-primary hosts in some regions.[154] *Genotype 3* is highly endemic in swineherds in North America and throughout Europe and parts of Asia with anti-HEV prevalence ranging from 60 to 100%.[155,156] Genotype 3 has also been isolated from a few human cases of AVH in industrialized countries and the United States.[157,158]

In developing countries, both genotypes 1 and 3 co-exist. *Genotype 1* has been isolated from human cases of hepatitis E,[159,160] while *genotype 3* was recovered from swine. Additionally, isolation of HEV-RNA from two donkey serum samples during the HEV outbreaks in the Darfur area in Sudan is interesting[104] and implies that HEV infection of donkeys may also occur. Recently identified *genotypes* 5 and 6 were found in wild boars and endemic mainly in Japan.[124,125] Additionally, *genotypes* 7 and 8 were identified in Middle East and China and infect camels and humans.[126,127]

4.3.3 | Virulence of HEV genotypes

Hepatitis E virus genotypes correlate with the severity of infection.[161–163] Genotype 3 does not cause disease in swine and appears to be attenuated in experimentally infected primates.[154,164] Furthermore, accumulating evidence suggests that genotypes 3 and 4 are less pathogenic in humans than genotype 1. During the HEV Darfur outbreak, the numbers of cases with mild symptoms were sixfold greater than severe symptomatic AVH cases and many more individuals had subclinical infections.[104] Additionally, in outbreaks in Pakistan[165] and Nepal,[98] the ratio of patients with mild anicteric

symptoms to severe jaundiced cases was 4:1 and 3:1, respectively. In contrast, human infections with genotypes 3 and 4 are much less virulent with 100:1 or more asymptomatic infections to cases of AVH.[166] Thus, genotypes 3 or 4 have not been reported to cause outbreaks of AVH. However, a small number of genotypes 3 and 4 isolates have been sequenced from sporadic cases of AVH in the United States, Europe and other regions where HEV-caused human illness is rare.[157,158,167–171] However, in immunosuppressed persons, HEV may lead to chronic HEV infection in *genotype* 3.[172–174]

4.4 | Immune response to HEV

4.4.1 | Humoral immune responses to HEV

Humoral immune responses against HEV have been studied in detail.[175–181] The data show prominent antibody responses against immunodominant epitopes in the ORF2 and ORF3 proteins.[175–180] In addition, several B-cell epitopes have also been identified in the ORF1 protein.[181] The anti-HEV IgM response appears during the early phase of clinical illness and diminishes over 4–5 months.[101,175,179,182] IgG antibodies appear a few days later and persist for several years.[183]

There is considerable evidence that antibodies against ORF2 can neutralize HEV.[182] For example, antibodies against a recombinant protein spanning amino acids 452–617 of ORF2 inhibit the adsorption of HEV into cultured cells.[184] Additionally, animal studies suggested anti-HEV ORF2 is protective.[185–191]

4.4.2 | Cell-mediated immune (CMI) responses to HEV

Hepatitis E virus ORF2 protein and peptides stimulate T cells, especially $CD4^+$ T cells from patients with acute HEV infection, to proliferate and secrete cytokines.[192–197] The role of CMI responses in HEV infection is still poorly understood. It is expected that T cells may supply help for antibody production or downregulate viral replication. Additionally, CMI could play a role in cell-mediated injury and disease morbidity. Host cell injury during HEV infection may be mediated by either a direct effect of the virus or indirectly through the anti-viral host immune response, or through a combination of both.

4.4.3 | Innate immune responses and HEV

Innate immune responses are important for viral clearance, especially in acute infection. Antigen non-specific natural killer (NK) cells lyse virus-infected targets in several viral infections, but their role in HEV infection has been poorly investigated. NK cells can also be potent sources of interferon-gamma (IFN-γ) in the liver.[198,199] Accumulating data suggest that NK cells are the main source of pro-inflammatory cytokines in HEV infection,[194] and may play a role in resolving acute HEV cases.[200]

4.5 | Clinical and laboratory diagnosis

4.5.1 | Clinical diagnosis of HEV

Acute cases of HEV are not *clinically* distinguishable from other types of AVH.[93] Asymptomatic infection is common. The incubation period is 2–6 weeks. When symptoms developed, the patients suffer from low-grade fever, nausea, vomiting and anorexia. In about 40% of patients, they develop hepatitis-like symptoms (Jaundice, pruritis, dark urine and pale stools).

Immunosuppressed persons, in particular solid organ transplant recipients receiving immunosuppressive medication, may fail to clear the virus after primary infection, leading to chronic HEV infection (lasting >6 months).[201]

4.5.2 | Laboratory diagnosis

The laboratory diagnosis of HEV infection depends on the detection of HEV antigen, HEV RNA and antibodies against HEV.[202] Anti-HEV IgM antibodies can be detected during the acute phase of the illness and last 4–5 months, representing recent exposure, whereas anti-HEV IgG antibodies can last more than 10 years, representing remote exposure.

4.5.3 | Serological diagnosis

ELISA assays are used to measure anti-HEV-specific IgG and IgM. Sera/plasma samples are tested for anti-HEV IgG, and IgM as described.[203–206] Positive anti-HEV IgM and/or rising anti-HEV IgG within 1 month could be considered diagnostic for active infection.[207,208]

4.5.4 | HEV antigens

Detection of HEV antigen has been developed as an interesting low cost, and rapid diagnostic technique to ascertain HEV viraemia where facilities for reverse transcriptase polymerase chain reaction (RT PCR) are unavailable.[209,210]

4.5.5 | Molecular diagnosis of HEV

RT-PCR is used for detection HEV RNA in suspected cases of acute HEV infection.[211,212] Due to the limited duration of viraemia and the low viral load, viral RNA amplification could be successfully achieved

TABLE 1 Studies on HEV and mortality in pregnancy

Study site	Patients (*n*)	Seroprevalence of HEV infection (%)	Prevalence of fulminant liver failure (%)	Mortality rate (%)	References
North India	127	58	58	45	(Jaiswal, Jain, Naik, Soni, & Chitnis, 2001)
North India	60	37	64	64	(Singh et al., 2003)
North India	76	86	69	55	(Khuroo & Kamili, 2003)
North India	97	47.4	75	39.1	(Beniwal, Kumar, Kar, Jilani, & Sharma, 2003)
Ethiopia	32	59	–	42	(Tsega, Krawczynski, Hansson, & Nordenfelt, 1993)
North India	65	45	32	73	(Kumar, Beniwal, Kar, Sharma, & Murthy, 2004)
North India	220	60	55	41	(Patra, Kumar, Trivedi, Puri, Sarin, 2007)
North India	61	58	50	57	(Saravanabalaji et al., 2009)
Egypt	2428	84.3	0	0	(Stoszek et al., 2006)
South India	115	75	3.4	3.4	(Rasheeda, Navaneethan, Jayanthi, 2008)

in only 10–50% of anti-HEV IgM-positive cases.[213] Therefore, serological assays are the main tools to diagnose acute HEV.

4.6 | HEV and pregnancy

4.6.1 | Epidemiology of HEV in pregnant women

An interesting and intriguing observation with HEV is the high incidence of infection and morbidity in pregnant women. In endemic areas such as the Indian subcontinent and Africa, the most common viral cause of acute fulminant hepatic failure (FHF) during pregnancy is HEV.[214]

In an outbreak in Kashmir, the incidence of HEV-caused AVH among pregnant women in the 2nd and 3rd trimester ranged from 15 to 20% compared to 2–3% among non-pregnant women or men. Furthermore, FHF developed in 22% of the affected pregnant women compare to 3% and 0% among men and non-pregnant women, respectively.[215] In Saudi Arabia, the incidence of HEV-caused sporadic AVH was significantly higher ($p < 0.001$) in pregnant women compared to non-pregnant women of childbearing age.[216] Approximately 60% of the pregnant women developed FHF and 70% of these had HEV infections ($p < 0.001$).[216] A controversial retrospective study from India questioned the role of pregnancy in increasing HEV-caused mortality rate among pregnant women, although the study confirmed the high frequency (59%) of HEV-associated FHF in pregnant women.[217]

Hepatitis E virus infection during pregnancy is also associated with an increased risk of foetal infection. A study from the United Arab Emirates reported 100% vertical transmission from HEV RNA-positive mothers to their infants resulting in significant perinatal morbidity and mortality. All 12 infants born to HEV RNA-positive mothers developed acute clinical infection and were HEV RNA positive. Two babies were born with hypothermia and hypoglycaemia and died within 48 h. Two babies were preterm, and three had anicteric hepatitis. The remaining infants had full recoveries.[112]

In Egypt, the prevalence of anti-HEV in rural communities is very high; yet, severe HEV-caused AVH in pregnant women has not been reported. In a published study, 2428 pregnant women were enrolled to assess the prevalence of anti-HEV and its association with liver disease. The anti-HEV prevalence was 84.3%; however, history of jaundice and liver disease was rare and did not increase during pregnancy. Moreover, none of the 34 women seroconverting for anti-HEV IgG during pregnancy experienced AVH.[218] In contrast, another study in Egypt identified HEV-caused AVH in at least 20% of the pregnant women admitted to fever hospitals in Egypt with a broad spectrum of morbidity but with very little morbidity to the infants.[160] The main difference between the two studies is the former was community-based, while the later included in-patients with AVH.

The controversial data from India, as well as the low morbidity of HEV infection in pregnant women in Egypt and South India (Table 1), highlight a critical gap in our understanding of the various factors that affect HEV morbidity in pregnant women.[219]

4.6.2 | Immunological changes during pregnancy

During pregnancy, the maternal immune system is altered to tolerate a genetically distinct foetus.[220] For example, trophoblasts do not express major histocompatibility complex (MHC) class proteins; hence, they are resistant to T-cell-mediated injury to protect the foetus.[221–223] The placenta also expresses indoleamine 2, 3-dioxygenase enzyme which inactivates and depletes tryptophan, an amino acid essential to T-cell function and hence suppresses cell-mediated immune responses at the foetal-placental interface.[224,225]

Cytokines also contribute to the immunological tolerance as both the placenta and trophoblasts secrete cytokines, including TGF-β, IL-4 and IL-10 which inhibit CMI. The levels of most cytokines are depressed particularly during the initial 20 weeks of pregnancy which is an important phase to sustain the foetus. During pregnancy, there is a clear shift in the Th1:Th2 cell paradigm towards Th2 cells which favours antibody production over cytotoxic T-cell responses.[226]

T cells are markedly reduced during early pregnancy up to the 20th week of gestation leading to reduced level of immunity.[227] This modulation of CMI occurs to allow foetal allograft retention, but it also alters the immune response mounted against infections.[228] The decrease in T-cell activity may increase susceptibility to viral,[229] and parasitic infections during pregnancy,[230,231] but also explains why autoimmune diseases like rheumatoid arthritis improve during gestation. While some studies have argued that there is no alteration in the number of total T-lymphocytes or in $CD4^+$ lymphocytes in pregnancy[232]; others have suggested an initial decrease until 20 weeks to sustain the foetus during the implantation phase and then increase or normalize later during pregnancy or in the postpartum period.[233] Although less studied, the apparent response of CD8 lymphocytes during pregnancy is either slightly decreased or stabilized throughout gestation.[233,234]

In summary, the immunological changes during pregnancy promote the maintenance of the foetus in the maternal environment by suppression of T-cell-mediated immunity, stimulation of Th2 cytokines and antibody production. Whether this modified immune system results in increased risk of HEV-associated morbidity/mortality during pregnancy is still not clear.

4.6.3 | Hormonal factors in pregnancy

Hormonal factors during pregnancy may also play a significant role in altering immune regulation and/or viral replication.[235,236] Progesterone, oestrogen and human chorionic gonadotropin (HCG) increase with pregnancy. In animal studies, these hormones have a clear suppressive effect on CMI. HCG has been shown to inhibit CMI,[237,238] while oestrogen induces shrinkage of thymus and depletes the CD4 and CD8 populations in mice.[239,240] On the contrary, progesterone produces involution of the thymus and blocks T-cell development while inhibiting Th1 cell and promoting Th2 cell development.[241] Despite these changes, the numbers of peripheral T and B cells are unchanged as the half-life of peripheral lymphocytes is higher.[242,243] There is also a decrease in bone marrow B-cell production, mainly pre-B and immature bone marrow B cells of pregnant mice due to increased oestrogen and progesterone levels during pregnancy.[244]

In addition, steroid hormones may influence viral replication.[245,246] For example, hormonal enhancement of cytomegalovirus (CMV) replication may be a mechanism for the increased incidence of CMV infection observed during pregnancy.[245] There are also reports of increased predisposition to viral infection in certain high-oestrogen states.[246,247] The role of hormonal imbalance during pregnancy in HEV viral replication has not been fully investigated.

4.6.4 | Mechanisms for high morbidity of hepatitis E in pregnancy

Little is known about the mechanisms of liver injury in patients with acute hepatitis E. It remains unknown whether the hepatocyte damage in HEV is mediated primarily by the virus or by the host immune response. The importance of an intact immune response to protect against HEV infection was confirmed in post-transplant patients from France who developed chronic HEV infection.[248] These immunocompromised patients receiving immunosuppressive drugs had low levels of CD4 and CD8 T cells. These findings highlight the importance of T-cell-mediated immunity for clearance of the HEV infection. In contrast, during pregnancy, CMI differs significantly in that patients progress to fulminant liver failure rather than AVH.[214] This important difference in disease presentation in pregnant women could be due to enhanced immunological injury, decreased immunologic control of viral replication and/or hormonal stimulation of viral replication.[242,249]

Jilani et al. investigated the role of hormonal changes during pregnancy in immune alterations and HEV infection. They found that HEV-infected pregnant women with FHF had lower CD4 counts, higher CD8 counts and decreased ratio of CD4 and CD8. Their levels of oestrogen, progesterone and beta-HCG were significantly higher than in HEV negative patients or healthy control pregnant females.[250]

A published report confirmed the role of viral load and CMI in the morbidity of HEV infection in pregnant women in India with AVH or FHF.[251] In this study, 14 pregnant women with FHF and 47 with AVH were examined. Significant increases in Th1/Th2 responses and anti-HEV titre were noted in women with FHF compared to AVH patients. Additionally, pregnant women with HEV-caused AVH had detectable viraemia in contrast to the FHF pregnant women who had undetectable HEV RNA. This study suggests HEV-caused FHF in pregnant women is immune-mediated while HEV-caused AVH is viral-mediated. However, no HEV-infected pregnant women with asymptomatic or mild AVH were examined in this study.

Pal et al. studied CMI in both pregnant and non-pregnant women with acute HEV and normal healthy pregnant and non-pregnant control population.[193] They reported pregnant women with HEV had generalized immune suppression with decreased lymphocyte response to Phytohemagglutinin (PHA), and a predominant Th2 bias when compared to non-pregnant women with HEV and normal healthy pregnant controls. This study was important from a number of perspectives. The theory that normal pregnancy is an immunosuppressed status is challenged because normal healthy pregnant women did not demonstrate a decreased response to PHA. Also, non-pregnant patients with HEV did not show a defective PHA response. These findings highlight that HEV alone does not produce the observed immunological changes; pregnancy is required as a physiological state to produce the severe hepatic pathological changes. This study confirmed the existence and importance of CMI responses to HEV in patients with this disease. Additionally, there were no significant differences in Th2 responses between healthy pregnant and non-pregnant women, although pregnancy itself was believed to skew the cytokine responses towards Th2 type.

Pregnancy is associated with high levels of steroid hormones which may promote viral replication. They also have a direct inhibition on hepatic cells, which potentially predisposing to

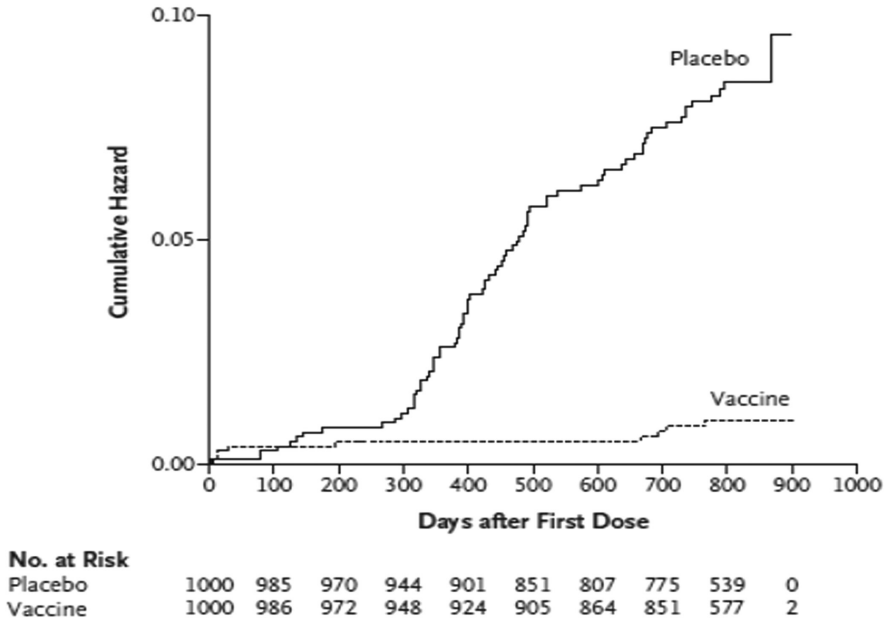

FIGURE 2 HEV vaccine

hepatic dysfunction/failure when exposed to infectious pathogens. Additionally, steroid hormones are immunosuppressive[252] and mediate lymphocyte apoptosis through NF-κB. NF-κB is a eukaryotic dimeric transcription factor which has a multiple cellular effects on liver development and regeneration and on the immune response.[253] Prusty et al. studied the changes in NF-κB activity using electrophoretic assays of the p50 and p65 components of NF-κB in pregnant and non-pregnant patients with FHF due to any viral aetiology including hepatitis B, C and E.[254] They found that the activity of the p65 component of NF-κB was diminished in both the PBMC and postmortem 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. They concluded that the absence of p65 was probably responsible for severe liver damage in pregnant FHF patients. The expression of NF-κB physiologically downregulated during pregnancy also plays an important role in sustaining the foetus during pregnancy.[255] Collectively, these studies suggest a high mortality of HEV infection during pregnancy in all endemic regions.[250,256]

However, this is clearly not the case. In one study from southern India and another from Egypt, the mortality rate during HEV infection was low (3.4%)[257] and absent,[218] respectively. In those two studies, there were normal term deliveries compared to 30–70% reported mortality among pregnant women with high infant morbidity in various studies in other HEV endemic regions (Table 1).[18,112,146,258–262] It has been speculated that the difference in the genotype or its subtypes of HEV infection and or the rate of viral replication could be an important factor in HEV morbidity.[256] Genotype 1 is the commonest genotype causing HEV infection in India and Egypt. Genotype 1 has been further classified into 4 subtypes, and most of them have been grouped to genotype 1A. Sub-genotype shift[263] may have been responsible for the different geographic morbidity in pregnant women in Southern India and Egypt. If this hypothesis holds true, it opens the intriguing possibility of the exploration of the genotype and its subsequent role in HEV infection during pregnancy.

Finally, nutritional status and availability of high-level supportive medical care may influence mortality outcomes. Evaluation of the outbreak in Chad and Niger by the WHO suggested that poor maternal healthcare and malnutrition were major factors in mortality among pregnant women.

4.6.5 | HEV vaccine

An efficacious hepatitis E vaccine was licensed (by China) in 2011 with a trade name of Hecolin®. The antigen contained in this vaccine is a truncated version of the capsid protein encoded by ORF2.[264] Safety and efficacy of this vaccine were demonstrated in a large-scale phase III clinical trial[265] (Figure 2). The administration of the HEV vaccine Hecolin to pregnant women still needs further investigation. Preliminary data suggest that the Hecolin is safe for both mother and foetus.[266] No FDA-approved vaccine for HEV is currently available in the United States; however, in 2012, a Hecolin® was approved for use in China.

5 | DISCUSSION

Viral hepatitis during pregnancy requires special management depending on the types of the viruses (hepatitis A, B, C, D and E), and the epidemiology of the virus, its chronicity, the presence of liver complications as well as the availability of successful antiviral therapies. During viral hepatitis in pregnancy, there might be considerable immunopathogenic effects on the liver of both the mothers and the infants. Hepatitis A and hepatitis E represent the greatest risk for the mothers and infants among the viral hepatitis infection. They may also change the outcome of pregnancy and

TABLE 2 Characterization of Viral hepatitis in Pregnancy

Character	Hepatitis A (HAV)	Hepatitis B (HBV)	Hepatitis C (HCV)	Hepatitis E (HEV)	Hepatitis D (HDV)
Classification	*Picornaviridae*	*Hepadnaviridae*	*Flaviviridae*	*Hepeviridae*	*Deltaviridae*
Genome	RNA (+)	DNA	RNA (+)	RNA (+)	RNA (-)
Envelop	No	Lipid envelop	Lipid envelop	No	Lipid envelop from HBV
Spread	Feco-oral/sexual	Parenteral/sexual	Parenteral/sexual	Feco-oral/zoonotic	Parenteral/sexual
Course in pregnancy	Benign/self- limiting	acute/chronic	acute/chronic	Acute/fulminant 20% mortality	coinfection with HBV
Maternal to child transmission (MTCT)	(++)	(+++)	(+)	(+++)	(-)
Caesarian section recommendation	No	No	No	May be	No
Breastfeeding	Yes	Yes	Yes	No	Yes
Vertical transmission	Rare	30%	5%	50%	Rare
Complications	Rare preterm/foetal liver injury	Preterm delivery/chronic HBV	Rare	Preterm delivery/stillbirth/infant mortality	Require HBV coinfection
Treatment	Post-exposure prophylaxis IgG	Monitor/assesses for anti-viral treatment	Anti-viral therapy after delivery	Supportive care	Monitor/assesses for anti-viral treatment
Prevention	HAV vaccine	HBV vaccine	No vaccine available	Vaccine is available but not FDA approved yet	HBV vaccine

the newly born infants. However, for HBV and HCV, the main effects are related to the underlying maternal liver diseases and the potential transmission of the virus to the infants. This review discussed the pathogenesis of acute and chronic viral hepatitis infection during pregnancy, their effect of the outcome of pregnancy as well as the influence of the viral infection on maternal and infant outcomes (Table 2).

CONFLICT OF INTEREST

There are no conflict of interest for the authors.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in [PubMed]

ORCID

Mohamed Tarek M. Shata https://orcid.org/0000-0003-1907-0570

Kenneth E. Sherman https://orcid.org/0000-0002-0560-0019

REFERENCES

1. Koff RS. Hepatitis A. *Lancet*. 1998;351:1643-1649.
2. Fiore AE, Wasley A, Bell BP. Prevention of hepatitis a through active or passive immunization: recommendations of the advisory committee on immunization practices (ACIP). *MMWR Recomm Rep*. 2006;55:1-23.
3. WHO. Hepatitis A vaccines. *Wkly Epidemiol Rec*. 2000;75:38-44.
4. Chaudhry SA, Koren G. Hepatitis a infection during pregnancy. *Can Fam Physician*. 2015;61:963-964.
5. Lemon SM, Ott JJ, Van Damme P, Shouval D. Type a viral hepatitis: a summary and update on the molecular virology, epidemiology, pathogenesis and prevention. *J Hepatol*. 2018;68:167-184.
6. Lanini S, Ustianowski A, Pisapia R, Zumla A, Ippolito G. Viral Hepatitis: etiology, epidemiology, transmission, diagnostics, treatment, and Prevention. *Infect Dis Clin North Am*. 2019;33:1045-1062.
7. Elinav E, Ben-Dov IZ, Shapira Y, et al. Acute hepatitis a infection in pregnancy is associated with high rates of gestational complications and preterm labor. *Gastroenterology*. 2006;130:1129-1134.
8. Ornoy A, Tenenbaum A. Pregnancy outcome following infections by coxsackie, echo, measles, mumps, hepatitis, polio and encephalitis viruses. *Reprod Toxicol*. 2006;21:446-457.
9. Lemon SM, Thomas DL. Vaccines to prevent viral hepatitis. *N Engl J Med*. 1997;336:196-204.
10. Spira AM. A review of combined hepatitis a and hepatitis B vaccination for travelers. *Clin Ther*. 2003;25:2337-2351.
11. McCaustland KA, Bond WW, Bradley DW, Ebert JW, Maynard JE. Survival of hepatitis A virus in feces after drying and storage for 1 month. *J Clin Microbiol*. 1982;16:957-958.
12. Tallon LA, Love DC, Moore ZS, Sobsey MD. Recovery and sequence analysis of hepatitis a virus from Springwater implicated in an outbreak of acute viral hepatitis. *Appl Environ Microbiol*. 2008;74:6158-6160.
13. WHO. Position paper on hepatitis a vaccines. *Wkly Epidemiol Rec*. 2012;28:261-275.
14. Mohd Hanafiah K, Jacobsen KH, Wiersma ST. Challenges to mapping the health risk of hepatitis a virus infection. *Int J Health Geogr*. 2011;10:57.
15. Alventosa Mateu C, Urquijo Ponce JJ, Diago Madrid M. An outbreak of acute hepatitis due to the hepatitis a virus in 2017: are we

witnessing a change in contagion risk factors? *Rev Esp Enferm Dig*. 2018;110:675-676.
16. Wang H, Gao P, Chen W, et al. Changing epidemiological characteristics of Hepatitis a and warning of anti-HAV immunity in Beijing, China: a comparison of prevalence from 1990 to 2017. *Hum Vaccin Immunother*. 2019;15:420-425.
17. Croker C, Hathaway S, Marutani A, et al. Outbreak of Hepatitis a virus infection among adult patients of a mental hospital - Los Angeles County, 2017. *Infect Control Hosp Epidemiol*. 2018;39:881.
18. Khuroo MS, Kamili S. Aetiology, clinical course and outcome of sporadic acute viral hepatitis in pregnancy. *J Viral Hepat*. 2003;10:61-69.
19. Dahiya M, Kumar A, Kar P, Gupta RK, Kumar A. Acute viral hepatitis in third trimester of pregnancy. *Indian J Gastroenterol*. 2005;24:128-129.
20. McDuffie RS Jr, Bader T. Fetal meconium peritonitis after maternal hepatitis A. *Am J Obstet Gynecol*. 1999;180:1031-1032.
21. Leikin E, Lysikiewicz A, Garry D, Tejani N. Intrauterine transmission of hepatitis A virus. *Obstet Gynecol*. 1996;88:690-691.
22. Cuthbert JA. Hepatitis A: old and new. *Clin Microbiol Rev*. 2001;14:38-58.
23. Motte A, Blanc J, Minodier P, Colson P. Acute hepatitis a in a pregnant woman at delivery. *Int J Infect Dis*. 2009;13:e49-e51.
24. Fiore S, Savasi V. Treatment of viral hepatitis in pregnancy. *Expert Opin Pharmacother*. 2009;10:2801-2809.
25. Daudi N, Shouval D, Stein-Zamir C, Ackerman Z. Breastmilk hepatitis A virus RNA in nursing mothers with acute hepatitis a virus infection. *Breastfeed Med*. 2012;7:313-315.
26. Sharapov UM, Bulkow LR, Negus SE, et al. Persistence of hepatitis A vaccine induced seropositivity in infants and young children by maternal antibody status: 10-year follow-up. *Hepatology (Baltimore, md)*. 2012;56:516-522.
27. Franzen C, Frösner G. Placental transfer of hepatitis a antibody. *N Engl J Med*. 1981;304:427.
28. Lieberman JM, Chang S-j, Partridge S, et al. Kinetics of maternal hepatitis A antibody decay in infants: implications for vaccine use. *Pediatr Infect Dis J*. 2002;21:347-348.
29. Derya A, Necmi A, Emre A, Akgün Y. Decline of maternal hepatitis A antibodies during the first 2 years of life in infants born in Turkey. *Am J Trop Med Hyg*. 2005;73:457-459.
30. Bell BP, Negus S, Fiore AE, et al. Immunogenicity of an inactivated hepatitis a vaccine in infants and young children. *Pediatr Infect Dis J*. 2007;26:116-122.
31. Prevention C. Prevention of hepatitis A through active or passive immunization; recommendations of the advisory committee on immunization practices (ACIP). *MMWR*. 1999;48:1-37.
32. Duff B, Duff P. Hepatitis A vaccine: ready for prime time. *Obstet Gynecol*. 1998;91:468-471.
33. Werzberger A, Mensch B, Kuter B, et al. A controlled trial of a formalin-inactivated hepatitis A vaccine in healthy children. *N Engl J Med*. 1992;327:453-457.
34. Wiedermann G, Kundi M, Ambrosch F, Safary A, D'Hondt E, Delem A. Inactivated hepatitis A vaccine: long-term antibody persistence. *Vaccine*. 1997;15:612-615.
35. Nelson NP, Link-Gelles R, Hofmeister MG, et al. Update: recommendations of the advisory committee on immunization practices for use of Hepatitis A vaccine for postexposure prophylaxis and for preexposure prophylaxis for international travel. *MMWR Morb Mortal Wkly Rep*. 2018;67:1216-1220.
36. Schaefer S. Hepatitis B virus taxonomy and hepatitis B virus genotypes. *World J Gastroenterol*. 2007;13:14-21.
37. Mulligan MJ, Stiehm ER. Neonatal hepatitis B infection: clinical and immunologic considerations. *J Perinatol*. 1994;14:2-9.
38. Norman JE, Beebe GW, Hoofnagle JH, Seeff LB. Mortality follow-up of the 1942 epidemic of hepatitis B in the U.S. Army. *Hepatology*. 1993;18:790-797.
39. Kwon H, Lok AS. Hepatitis B therapy. *Nat Rev Gastroenterol Hepatol*. 2011;8:275-284.
40. Salemi JL, Spooner KK, Mejia de Grubb MC, Aggarwal A, Matas JL, Salihu HM. National trends of hepatitis B and C during pregnancy across sociodemographic, behavioral, and clinical factors, United States, 1998-2011. *J Med Virol*. 2017;89:1025-1032.
41. Peng S, Wan Z, Lin X, Li X, Du Y. Maternal hepatitis B surface antigen carrier status increased the incidence of gestational diabetes mellitus. *BMC Infect Dis*. 2019;19:147.
42. Liu J, Zhang S, Liu M, Wang Q, Shen H, Zhang Y. Maternal pre-pregnancy infection with hepatitis B virus and the risk of preterm birth: a population-based cohort study. *Lancet Glob Health*. 2017;5:e624-e632.
43. Hill HA, Elam-Evans LD, Yankey D, Singleton JA, Kolasa M. National, state, and selected local area vaccination coverage among children aged 19-35 months - United States, 2014. *MMWR Morb Mortal Wkly Rep*. 2015;64:889-896.
44. Tang X, Allain JP, Wang H, et al. Incidence of hepatitis B virus infection in young Chinese blood donors born after mandatory implementation of neonatal hepatitis B vaccination nationwide. *J Viral Hepat*. 2018;25:1008-1016.
45. Zou H, Chen Y, Duan Z, Zhang H, Pan C. Virologic factors associated with failure to passive-active immunoprophylaxis in infants born to HBsAg-positive mothers. *J Viral Hepat*. 2012;19:e18-e25.
46. Pan CQ, Han G, Wang Y. Prevention of peripartum hepatitis B transmission. *N Engl J Med*. 2016;375:1497-1498.
47. European Association for the Study of the Liver. Electronic address eee, European Association for the Study of the Liver. EASL 2017 Clinical practice guidelines on the management of hepatitis B virus infection. *J Hepatol*. 2017;67(2):370-398.
48. Terrault NA, Bzowej NH, Chang KM, et al. AASLD guidelines for treatment of chronic hepatitis B. *Hepatology*. 2016;63:261-283.
49. Momper JDBB, Wang J, Stek A, et al. Tenofovir alafenamide pharmacokinetics with and without cobicistat in pregnancy. *J Int AIDS Soc*. 2018;21:67-68.
50. Wang J, Zhu Q, Zhang X. Effect of delivery mode on maternal-infant transmission of hepatitis B virus by immunoprophylaxis. *Chin Med J (Engl)*. 2002;115:1510-1512.
51. Zanetti AR, Ferroni P, Magliano EM, et al. Perinatal transmission of the hepatitis B virus and of the HBV-associated delta agent from mothers to offspring in northern Italy. *J Med Virol*. 1982;9:139-148.
52. Sellier PO, Maylin S, Brichler S, et al. Hepatitis B virus-hepatitis D virus mother-to-child co-transmission: a retrospective study in a developed country. *Liver Int*. 2018;38:611-618.
53. Denniston MM, Jiles RB, Drobeniuc J, et al. Chronic hepatitis C virus infection in the United States, National Health and nutrition examination survey 2003 to 2010. *Ann Intern Med*. 2014;160:293-300.
54. Ly KN, Jiles RB, Teshale EH, Foster MA, Pesano RL, Holmberg SD. Hepatitis C virus infection among reproductive-aged women and children in the United States, 2006 to 2014. *Ann Intern Med*. 2017;166:775-782.
55. (WHO) WHO. Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection. *WHO Report*. 2018:1-84.
56. Schmidt AJ, Falcato L, Zahno B, et al. Prevalence of hepatitis C in a swiss sample of men who have sex with men: whom to screen for HCV infection? *BMC Public Health*. 2014;14:3.
57. Hellard ME, Hocking JS, Crofts N. The prevalence and the risk behaviours associated with the transmission of

hepatitis C virus in Australian correctional facilities. *Epidemiol Infect*. 2004;132:409-415.
58. Koneru A, Nelson N, Hariri S, et al. Increased hepatitis C virus (HCV) detection in women of childbearing age and potential risk for vertical transmission - United States and Kentucky, 2011-2014. *MMWR Morb Mortal Wkly Rep*. 2016;65:705-710.
59. Lingala S, Ghany MG. Natural history of hepatitis C. *Gastroenterol Clin North Am*. 2015;44:717-734.
60. Kamal SM. Acute hepatitis C: a systematic review. *Am J Gastroenterol*. 2008;103:1283-1297. quiz 1298.
61. Page K, Hahn JA, Evans J, et al. Acute hepatitis C virus infection in young adult injection drug users: a prospective study of incident infection, resolution, and reinfection. *J Infect Dis*. 2009;200:1216-1226.
62. Hashem M, Jhaveri R, Saleh DA, et al. Spontaneous viral load decline and subsequent clearance of chronic hepatitis C virus in postpartum women correlates with favorable interleukin-28B gene allele. *Clin Infect Dis*. 2017;65:999-1005.
63. Honegger JR, Kim S, Price AA, et al. Loss of immune escape mutations during persistent HCV infection in pregnancy enhances replication of vertically transmitted viruses. *Nat Med*. 2013;19:1529-1533.
64. Swain MG, Lai MY, Shiffman ML, et al. A sustained virologic response is durable in patients with chronic hepatitis C treated with peginterferon alfa-2a and ribavirin. *Gastroenterology*. 2010;139:1593-1601.
65. Poynard T, McHutchison J, Manns M, et al. Impact of pegylated interferon alfa-2b and ribavirin on liver fibrosis in patients with chronic hepatitis C. *Gastroenterology*. 2002;122:1303-1313.
66. Morgan RL, Baack B, Smith BD, Yartel A, Pitasi M, Falck-Ytter Y. Eradication of hepatitis C virus infection and the development of hepatocellular carcinoma: a meta-analysis of observational studies. *Ann Intern Med*. 2013;158:329-337.
67. Veldt BJ, Heathcote EJ, Wedemeyer H, et al. Sustained virologic response and clinical outcomes in patients with chronic hepatitis C and advanced fibrosis. *Ann Intern Med*. 2007;147:677-684.
68. van der Meer AJ, Veldt BJ, Feld JJ, et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. *Jama*. 2012;308:2584-2593.
69. Dibba P, Cholankeril R, Li AA, et al. Hepatitis C in pregnancy. *Diseases*. 2018;6:31-40.
70. Gervais A, Bacq Y, Bernuau J, et al. Decrease in serum ALT and increase in serum HCV RNA during pregnancy in women with chronic hepatitis C. *J Hepatol*. 2000;32:293-299.
71. Karampatou A, Han X, Kondili LA, et al. Corrigendum to "Premature ovarian senescence and a high miscarriage rate impair fertility in women with HCV" [J Hepatol 68 (2018) 33–41]. *J Hepatol*. 2018;68:867.
72. Wijarnpreecha K, Thongprayoon C, Sanguankeo A, Upala S, Ungprasert P, Cheungpasitporn W. Hepatitis C infection and intrahepatic cholestasis of pregnancy: a systematic review and meta-analysis. *Clin Res Hepatol Gastroenterol*. 2017;41:39-45.
73. Huang QT, Hang LL, Zhong M, Gao YF, Luo ML, Yu YH. Maternal HCV infection is associated with intrauterine fetal growth disturbance: a meta-analysis of observational studies. *Medicine (Baltimore)*. 2016;95:e4777.
74. Pergam SA, Wang CC, Gardella CM, Sandison TG, Phipps WT, Hawes SE. Pregnancy complications associated with hepatitis C: data from a 2003-2005 Washington state birth cohort. *Am J Obstet Gynecol*. 2008;199:38 e31-39.
75. Connell LE, Salihu HM, Salemi JL, August EM, Weldeselasse H, Mbah AK. Maternal hepatitis B and hepatitis C carrier status and perinatal outcomes. *Liver Int*. 2011;31:1163-1170.
76. Money D, Boucoiran I, Wagner E, et al. Obstetrical and neonatal outcomes among women infected with hepatitis C and their infants. *J Obstet Gynaecol Can*. 2014;36:785-794.
77. Puljic A, Salati J, Doss A, Caughey AB. Outcomes of pregnancies complicated by liver cirrhosis, portal hypertension, or esophageal varices. *J Matern Fetal Neonatal Med*. 2016;29:506-509.
78. Tan J, Surti B, Saab S. Pregnancy and cirrhosis. *Liver Transpl*. 2008;14:1081-1091.
79. Jhaveri R, Hashem M, El-Kamary SS, et al. Hepatitis C virus (HCV) vertical transmission in 12-month-old infants born to HCV-infected women and assessment of maternal risk factors. Open forum. *Infect Dis*. 2015;2:ofv089.
80. Yeung CY, Lee HC, Chan WT, Jiang CB, Chang SW, Chuang CK. Vertical transmission of hepatitis C virus: current knowledge and perspectives. *World J Hepatol*. 2014;6:643-651.
81. Resti M, Azzari C, Mannelli F, et al. Mother to child transmission of hepatitis C virus: prospective study of risk factors and timing of infection in children born to women seronegative for HIV-1. Tuscany study group on Hepatitis C virus infection. *BMJ*. 1998;317:437-441.
82. Pawlowska M, Sobolewska-Pilarczyk M, Domagalski K. Hepatitis C virus infection in children in the era of direct-acting antiviral. *World J Gastroenterol*. 2018;24:2555-2566.
83. Cottrell EB, Chou R, Wasson N, Rahman B, Guise JM. Reducing risk for mother-to-infant transmission of hepatitis C virus: a systematic review for the U.S. preventive services task force. *Ann Intern Med*. 2013;158:109-113.
84. Mast EE, Hwang LY, Seto DS, et al. Risk factors for perinatal transmission of hepatitis C virus (HCV) and the natural history of HCV infection acquired in infancy. *J Infect Dis*. 2005;192:1880-1889.
85. Gagnon A, Davies G, Wilson RD, Genetics C. Prenatal invasive procedures in women with hepatitis B, hepatitis C, and/or human immunodeficiency virus infections. *J Obstet Gynaecol Can*. 2014;36:648-653.
86. Kushner T, Chappell CA, Kim AY. Testing for hepatitis C in pregnancy: the time has come for routine rather than risk-based. *Curr Hepatol Rep*. 2019;18:206-215.
87. Yattoo GN. Treatment of chronic hepatitis C with ledipasvir/sofosbuvir combination during pregnancy. *Hepatology Int*. 2018;12:12-14.
88. Kushner T, Terrault NA. Hepatitis C in pregnancy: a unique opportunity to improve the hepatitis C cascade of care. *Hepatol Commun*. 2019;3:20-28.
89. Arankalle VA, Chobe LP, Jha J, et al. Aetiology of acute sporadic non-a, non-B viral hepatitis in India. *J Med Virol*. 1993;40:121-125.
90. Ghabrah TM, Stickland GT, Tsarev S, et al. Acute viral hepatitis in Saudi Arabia: seroepidemiological analysis, risk factors, clinical manifestations, and evidence for a sixth hepatitis agent. *Clin Infect Dis*. 1995;21:621-627.
91. Krawczynski K, Aggarwal R, Kamili S. Hepatitis E. *Infect Dis Clin North Am*. 2000;14:669-687.
92. Clayson ET, Myint KS, Snitbhan R, et al. Viremia, fecal shedding, and IgM and IgG responses in patients with hepatitis E. *J Infect Dis*. 1995;172:927-933.
93. Debing Y, Moradpour D, Neyts J, Gouttenoire J. Update on hepatitis E virology: implications for clinical practice. *J Hepatol*. 2016;65:200-212.
94. Rein DB, Stevens GA, Theaker J, Wittenborn JS, Wiersma ST. The global burden of hepatitis E virus genotypes 1 and 2 in 2005. *Hepatology*. 2012;55:988-997.
95. Corwin A, Putri MP, Winarno J, et al. Epidemic and sporadic hepatitis E virus transmission in West Kalimantan (Borneo), Indonesia. *Am J Trop Med Hyg*. 1997;57:62-65.

96. Corwin A, Jarot K, Lubis I, et al. Two years' investigation of epidemic hepatitis E virus transmission in West Kalimantan (Borneo), Indonesia. *Trans R Soc Trop Med Hyg*. 1995;89:262-265.
97. Corwin AL, Khiem HB, Clayson ET, et al. A waterborne outbreak of hepatitis E virus transmission in southwestern Vietnam. *Am J Trop Med Hyg*. 1996;54:559-562.
98. Clayson ET, Vaughn DW, Innis BL, Shrestha MP, Pandey R, Malla DB. Association of hepatitis E virus with an outbreak of hepatitis at a military training camp in Nepal. *J Med Virol*. 1998;54:178-182.
99. Iqbal M, Ahmed A, Qamar A, et al. An outbreak of enterically transmitted non-a, non-B hepatitis in Pakistan. *Am J Trop Med Hyg*. 1989;40:438-443.
100. Naik SR, Aggarwal R, Salunke PN, Mehrotra NN. A large waterborne viral hepatitis E epidemic in Kanpur. *India Bull World Health Organ*. 1992;70:597-604.
101. Arankalle VA, Chadha MS, Tsarev SA, et al. Seroepidemiology of water-borne hepatitis in India and evidence for a third enterically-transmitted hepatitis agent. *Proc Natl Acad Sci USA*. 1994;91:3428-3432.
102. Buisson Y, Joussemet M, Schill H, Martet G. Epidemiology and prevention of hepatitis A. *Med Trop (Mars)* 1994;54:9–13. (fre).
103. Coursaget P, Buisson Y, Enogat N, et al. Outbreak of enterically-transmitted hepatitis due to hepatitis a and hepatitis E viruses. *J Hepatol*. 1998;28:745-750.
104. Guthmann JP, Klovstad H, Boccia D, et al. A large outbreak of hepatitis E among a displaced population in Darfur, Sudan, 2004: the role of water treatment methods. *Clin Infect Dis*. 2006;42:1685-1691.
105. Nan Y, Wu C, Zhao Q, Zhou EM. Zoonotic Hepatitis E virus: an ignored risk for public health. *Front Microbiol*. 2017;8:2396.
106. Wen GP, Tang ZM, Wang SL, et al. Classification of human and zoonotic group hepatitis E virus (HEV) using antigen detection. *Appl Microbiol Biotechnol*. 2017;101:8585-8594.
107. Rodriguez-Lazaro D, Hernandez M, Cook N. Hepatitis E virus: a new foodborne zoonotic concern. *Adv Food Nutr Res*. 2018;86:55-70.
108. Khuroo MS. Viral hepatitis in international travellers: risks and prevention. *Int J Antimicrob Agents*. 2003;21:143-152.
109. Poddar U, Thapa BR, Prasad A, Sharma AK, Singh K. Natural history and risk factors in fulminant hepatic failure. *Arch Dis Child*. 2002;87:54-56.
110. Aggarwal R, Naik SR. Hepatitis E: intrafamilial transmission versus waterborne spread. *J Hepatol*. 1994;21:718-723.
111. Aggarwal R, Shahi H, Naik S, et al. Fulminant hepatic failure due to hepatitis E virus. *J Hepatol*. 1994;21:1156-1157.
112. Kumar A, Beniwal M, Kar P, Sharma JB, Murthy NS. Hepatitis E in pregnancy. *Int J Gynaecol Obstet*. 2004;85:240-244.
113. Clayson ET, Shrestha MP, Vaughn DW, et al. Rates of hepatitis E virus infection and disease among adolescents and adults in Kathmandu. *Nepal J Infect Dis*. 1997;176:763-766.
114. Boccia D, Guthmann JP, Klovstad H, et al. High mortality associated with an outbreak of hepatitis E among displaced persons in Darfur. *Sudan Clin Infect Dis*. 2006;42:1679-1684.
115. Stoszek SK, Abdel-Hamid M, Saleh DA, et al. High prevalence of hepatitis E antibodies in pregnant Egyptian women. *Trans R Soc Trop Med Hyg*. 2006;100:95-101.
116. Emerson SU, Nguyen H, Graff J, Stephany DA, Brockington A, Purcell RH. In vitro replication of hepatitis E virus (HEV) genomes and of an HEV replicon expressing green fluorescent protein. *J Virol*. 2004;78:4838-4846.
117. Ropp SL, Tam AW, Beames B, Purdy M, Frey TK. Expression of the hepatitis E virus ORF1. *Arch Virol*. 2000;145:1321-1337.
118. Ansari IH, Nanda SK, Durgapal H, et al. Cloning, sequencing, and expression of the hepatitis E virus (HEV) nonstructural open reading frame 1 (ORF1). *J Med Virol*. 2000;60:275-283.
119. Reyes GR, Yarbough PO, Tam AW, et al. Hepatitis E virus (HEV): the novel agent responsible for enterically transmitted non-a, non-B hepatitis. *Gastroenterol Jpn*. 1991;26(Suppl 3):142-147.
120. Tyagi S, Jameel S, Lal SK. The full-length and N-terminal deletion of ORF2 protein of hepatitis E virus can dimerize. *Biochem Biophys Res Commun*. 2001;286:214-221.
121. Velazquez O, Stetler HC, Avila C, et al. Epidemic transmission of enterically transmitted non-a, non-B hepatitis in Mexico, 1986-1987. *Jama*. 1990;263:3281-3285.
122. Schlauder GG, Mushahwar IK. Genetic heterogeneity of hepatitis E virus. *J Med Virol*. 2001;65:282-292.
123. Fields BN, Knipe DM. *Fields Virology*. Vol 2. Raven Press; 1990.
124. Takahashi H, Tanaka T, Jirintai S, et al. A549 and PLC/PRF/5 cells can support the efficient propagation of swine and wild boar hepatitis E virus (HEV) strains: demonstration of HEV infectivity of porcine liver sold as food. *Arch Virol*. 2012;157:235-246.
125. Sato Y, Sato H, Naka K, et al. A nationwide survey of hepatitis E virus (HEV) infection in wild boars in Japan: identification of boar HEV strains of genotypes 3 and 4 and unrecognized genotypes. *Arch Virol*. 2011;156:1345-1358.
126. Khuroo MS, Khuroo MS, Khuroo NS. Transmission of hepatitis E virus in developing countries. *Viruses*. 2016;8:253.
127. Woo PC, Lau SK, Teng JL, et al. New hepatitis E virus genotype in camels, the Middle East. *Emerg Infect Dis*. 2014;20:1044-1048.
128. Grandadam M, Tebbal S, Caron M, et al. Evidence for hepatitis E virus quasispecies. *J Gen Virol*. 2004;85:3189-3194.
129. Shrestha SM, Shrestha S, Tsuda F, et al. Molecular investigation of hepatitis E virus infection in patients with acute hepatitis in Kathmandu. *Nepal J Med Virol*. 2003;69:207-214.
130. Shrestha SM, Shrestha S, Tsuda F, et al. Genetic changes in hepatitis E virus of subtype 1a in patients with sporadic acute hepatitis E in Kathmandu, Nepal, from 1997 to 2002. *J Gen Virol*. 2004;85:97-104.
131. van Cuyck H, Fan J, Robertson DL, Roques P. Evidence of recombination between divergent hepatitis E viruses. *J Virol*. 2005;79:9306-9314.
132. van Cuyck H, Juge F, Roques P. Phylogenetic analysis of the first complete hepatitis E virus (HEV) genome from Africa. *FEMS Immunol Med Microbiol*. 2003;39:133-139.
133. Graff J, Zhou YH, Torian U, et al. Mutations within potential glycosylation sites in the capsid protein of Hepatitis E virus prevent the formation of infectious virus particles. *J Virol*. 2007;82:1185-1194.
134. Takahashi K, Okamoto H, Abe N, et al. Virulent strain of hepatitis E virus genotype 3. *Japan Emerg Infect Dis*. 2009;15:704-709.
135. Emerson SU, Arankalle VA, Purcell RH. Thermal stability of hepatitis E virus. *J Infect Dis*. 2005;192:930-933.
136. Balayan MS. Epidemiology of hepatitis E virus infection. *J Viral Hepat*. 1997;4:155-165.
137. Hyams KC. New perspectives on hepatitis E. *Curr Gastroenterol Rep*. 2002;4:302-307.
138. Okamoto H, Takahashi M, Nishizawa T. Features of hepatitis E virus infection in Japan. *Intern Med*. 2003;42:1065-1071.
139. Smith JL. A review of hepatitis E virus. *J Food Prot*. 2001;64:572-586.
140. Goens SD, Perdue ML. Hepatitis E viruses in humans and animals. *Anim Health Res Rev*. 2004;5:145-156.
141. Tei S, Kitajima N, Takahashi K, Mishiro S. Zoonotic transmission of hepatitis E virus from deer to human beings. *Lancet*. 2003;362:371-373.
142. Mitsui T, Tsukamoto Y, Yamazaki C, et al. Prevalence of hepatitis E virus infection among hemodialysis patients in Japan: evidence for infection with a genotype 3 HEV by blood transfusion. *J Med Virol*. 2004;74:563-572.
143. Khuroo MS, Kamili S, Yattoo GN. Hepatitis E virus infection may be transmitted through blood transfusions in an endemic area. *J Gastroenterol Hepatol*. 2004;19:778-784.
144. Matsubayashi K, Nagaoka Y, Sakata H, et al. Transfusion-transmitted hepatitis E caused by apparently indigenous hepatitis E virus strain in Hokkaido, Japan. *Transfusion*. 2004;44:934-940.

145. Nicand E, Armstrong GL, Enouf V, et al. Genetic heterogeneity of hepatitis E virus in Darfur, Sudan, and neighboring Chad. *J Med Virol*. 2005;77:519-521.
146. Singh S, Mohanty A, Joshi YK, Deka D, Mohanty S, Panda SK. Mother-to-child transmission of hepatitis E virus infection. *Indian J Pediatr*. 2003;70:37-39.
147. Khuroo MS, Kamili S, Jameel S. Vertical transmission of hepatitis E virus. *Lancet*. 1995;345:1025-1026.
148. Kumar RM, Uduman S, Rana S, Kochiyil JK, Usmani A, Thomas L. Sero-prevalence and mother-to-infant transmission of hepatitis E virus among pregnant women in The United Arab Emirates. *Eur J Obstet Gynecol Reprod Biol*. 2001;100:9-15.
149. Chibber RM, Usmani MA, Al-Sibai MH. Should HEV infected mothers breast feed? *Arch Gynecol Obstet*. 2004;270:15-20.
150. Balayan MS, Usmanov RK, Zamyatina NA, Djumalieva DI, Karas FR. Brief report: experimental hepatitis E infection in domestic pigs. *J Med Virol*. 1990;32:58-59.
151. Usmanov RK, Balaian MS, Dzhumalieva DI, et al. Experimental hepatitis E infection in piglets. *Vopr Virusol* 1991;36:212–216. (rus).
152. Lu L, Drobeniuc J, Kobylnikov N, et al. Complete sequence of a Kyrgyzstan swine hepatitis E virus (HEV) isolated from a piglet thought to be experimentally infected with human HEV. *J Med Virol*. 2004;74:556-562.
153. Clayson ET, Innis BL, Myint KS, et al. Detection of hepatitis E virus infections among domestic swine in the Kathmandu Valley of Nepal. *Am J Trop Med Hyg*. 1995;53:228-232.
154. Meng XJ, Halbur PG, Haynes JS, et al. Experimental infection of pigs with the newly identified swine hepatitis E virus (swine HEV), but not with human strains of HEV. *Arch Virol*. 1998;143:1405-1415.
155. Erker JC, Desai SM, Schlauder GG, Dawson GJ, Mushahwar IK. A hepatitis E virus variant from the United States: molecular characterization and transmission in cynomolgus macaques. *J Gen Virol*. 1999;80(Pt 3):681-690.
156. Meng XJ. Novel strains of hepatitis E virus identified from humans and other animal species: is hepatitis E a zoonosis? *J Hepatol*. 2000;33:842-845.
157. van der Poel WH, Verschoor F, van der Heide R, et al. Hepatitis E virus sequences in swine related to sequences in humans, The Netherlands. *Emerg Infect Dis*. 2001;7:970-976.
158. Herremans M, Vennema H, Bakker J, et al. Swine-like hepatitis E viruses are a cause of unexplained hepatitis in The Netherlands. *J Viral Hepat*. 2007;14:140-146.
159. Tsarev SA, Binn LN, Gomatos PJ, et al. Phylogenetic analysis of hepatitis E virus isolates from Egypt. *J Med Virol*. 1999;57:68-74.
160. Blackard JT, Rouster S, Nady S, et al. Genotypic characterization of symptomatic hepatitis E virus (HEV) infections in Egypt. *J Clin Virol*. 2009;46:140-144.
161. Mizuo H, Yazaki Y, Sugawara K, et al. Possible risk factors for the transmission of hepatitis E virus and for the severe form of hepatitis E acquired locally in Hokkaido. *Japan J Med Virol*. 2005;76:341-349.
162. Emerson SU, Purcell RH. Hepatitis E virus. *Rev Med Virol*. 2003;13:145-154.
163. Halbur PG, Kasorndorkbua C, Gilbert C, et al. Comparative pathogenesis of infection of pigs with hepatitis E viruses recovered from a pig and a human. *J Clin Microbiol*. 2001;39:918-923.
164. Meng XJ, Purcell RH, Halbur PG, et al. A novel virus in swine is closely related to the human hepatitis E virus. *Proc Natl Acad Sci USA*. 1997;94:9860-9865.
165. Bryan JP, Iqbal M, Tsarev S, et al. Epidemic of hepatitis E in a military unit in Abbotrabad, Pakistan. *Am J Trop Med Hyg*. 2002;67:662-668.
166. Krawczynski K, Kamili S, Aggarwal R. Global epidemiology and medical aspects of hepatitis E. *Forum (Genova)*. 2001;11:166-179.
167. Kwo PY, Schlauder GG, Carpenter HA, et al. Acute hepatitis E by a new isolate acquired in the United States. *Mayo Clin Proc*. 1997;72:1133-1136.
168. Schlauder GG, Dawson GJ, Erker JC, et al. The sequence and phylogenetic analysis of a novel hepatitis E virus isolated from a patient with acute hepatitis reported in the United States. *J Gen Virol*. 1998;79(Pt 3):447-456.
169. Schlauder GG, Desai SM, Zanetti AR, Tassopoulos NC, Mushahwar IK. Novel hepatitis E virus (HEV) isolates from Europe: evidence for additional genotypes of HEV. *J Med Virol*. 1999;57:243-251.
170. Takahashi K, Iwata K, Watanabe N, et al. Full-genome nucleotide sequence of a hepatitis E virus strain that may be indigenous to Japan. *Virology*. 2001;287:9-12.
171. Dong C, Dai X, Shao JS, Hu K, Meng JH. Identification of genetic diversity of hepatitis E virus (HEV) and determination of the seroprevalence of HEV in eastern China. *Arch Virol*. 2007;152:739-746.
172. Pischke S, Wedemeyer H. Chronic hepatitis E in liver transplant recipients: a significant clinical problem? *Minerva Gastroenterol Dietol*. 2010;56:121-128.
173. Koning L, Pas SD, de Man RA, et al. Clinical implications of chronic hepatitis E virus infection in heart transplant recipients. *J Heart Lung Transplant*. 2013;32:78-85.
174. Riezebos-Brilman A, Verschuuren EA, van Son WJ, et al. The clinical course of hepatitis E virus infection in patients of a tertiary Dutch hospital over a 5-year period. *J Clin Virol*. 2013;58:509-514.
175. Favorov MO, Fields HA, Purdy MA, et al. Serologic identification of hepatitis E virus infections in epidemic and endemic settings. *J Med Virol*. 1992;36:246-250.
176. Khudyakov YE, Khudyakova NS, Fields HA, et al. Epitope mapping in proteins of hepatitis E virus. *Virology*. 1993;194:89-96.
177. Riddell MA, Li F, Anderson DA. Identification of immunodominant and conformational epitopes in the capsid protein of hepatitis E virus by using monoclonal antibodies. *J Virol*. 2000;74:8011-8017.
178. Khudyakov YE, Lopareva EN, Jue DL, Crews TK, Thyagarajan SP, Fields HA. Antigenic domains of the open reading frame 2-encoded protein of hepatitis E virus. *J Clin Microbiol*. 1999;37:2863-2871.
179. Dawson GJ, Chau KH, Cabal CM, Yarbough PO, Reyes GR, Mushahwar IK. Solid-phase enzyme-linked immunosorbent assay for hepatitis E virus IgG and IgM antibodies utilizing recombinant antigens and synthetic peptides. *J Virol Methods*. 1992;38:175-186.
180. Coursaget P, Buisson Y, Depril N, et al. Mapping of linear B cell epitopes on open reading frames 2- and 3-encoded proteins of hepatitis E virus using synthetic peptides. *FEMS Microbiol Lett*. 1993;109:251-255.
181. Kaur M, Hyams KC, Purdy MA, et al. Human linear B-cell epitopes encoded by the hepatitis E virus include determinants in the RNA-dependent RNA polymerase. *Proc Natl Acad Sci USA*. 1992;89:3855-3858.
182. Bryan JP, Tsarev SA, Iqbal M, et al. Epidemic hepatitis E in Pakistan: patterns of serologic response and evidence that antibody to hepatitis E virus protects against disease. *J Infect Dis*. 1994;170:517-521.
183. Khuroo MS, Kamili S, Dar MY, Moecklii R, Jameel S. Hepatitis E and long-term antibody status. *Lancet*. 1993;341:1355.
184. Meng J, Dai X, Chang JC, et al. Identification and characterization of the neutralization epitope(s) of the hepatitis E virus. *Virology*. 2001;288:203-211.
185. Tsarev SA, Tsareva TS, Emerson SU, et al. Successful passive and active immunization of cynomolgus monkeys against hepatitis E. *Proc Natl Acad Sci USA*. 1994;91:10198-10202.
186. Arankalle VA, Chadha MS, Chobe LP. Long-term serological follow up and cross-challenge studies in rhesus monkeys experimentally infected with hepatitis E virus. *J Hepatol*. 1999;30:199-204.

187. Tsarev SA, Tsareva TS, Emerson SU, et al. Recombinant vaccine against hepatitis E: dose response and protection against heterologous challenge. *Vaccine*. 1997;15:1834-1838.
188. Im SW, Zhang JZ, Zhuang H, et al. A bacterially expressed peptide prevents experimental infection of primates by the hepatitis E virus. *Vaccine*. 2001;19:3726-3732.
189. Zhang M, Emerson SU, Nguyen H, et al. Recombinant vaccine against hepatitis E: duration of protective immunity in rhesus macaques. *Vaccine*. 2002;20:3285-3291.
190. Purcell RH, Nguyen H, Shapiro M, et al. Pre-clinical immunogenicity and efficacy trial of a recombinant hepatitis E vaccine. *Vaccine*. 2003;21:2607-2615.
191. Schofield DJ, Purcell RH, Nguyen HT, Emerson SU. Monoclonal antibodies that neutralize HEV recognize an antigenic site at the carboxyterminus of an ORF2 protein vaccine. *Vaccine*. 2003;22:257-267.
192. Naik S, Aggarwal R, Naik SR, et al. Evidence for activation of cellular immune responses in patients with acute hepatitis E. *Indian J Gastroenterol*. 2002;21:149-152.
193. Pal R, Aggarwal R, Naik SR, Das V, Das S, Naik S. Immunological alterations in pregnant women with acute hepatitis E. *J Gastroenterol Hepatol*. 2005;20:1094-1101.
194. Srivastava R, Aggarwal R, Jameel S, et al. Cellular immune responses in acute hepatitis E virus infection to the viral open reading frame 2 protein. *Viral Immunol*. 2007;20:56-65.
195. Aggarwal R. Hepatitis E and pregnancy. *Indian J Gastroenterol*. 2007;26:3-5.
196. Aggarwal R, Shukla R, Jameel S, et al. T-cell epitope mapping of ORF2 and ORF3 proteins of human hepatitis E virus. *J Viral Hepat*. 2007;14:283-292.
197. Shata MT, Barrett A, Shire NJ, et al. Characterization of hepatitis E-specific cell-mediated immune response using IFN-gamma ELISPOT assay. *J Immunol Methods*. 2007;328:152-161.
198. Sardinha LR, Elias RM, Mosca T, et al. Contribution of NK, NK T, gamma delta T, and alpha beta T cells to the gamma interferon response required for liver protection against Trypanosoma cruzi. *Infect Immun*. 2006;74:2031-2042.
199. Shin EC, Protzer U, Untergasser A, et al. Liver-directed gamma interferon gene delivery in chronic hepatitis C. *J Virol*. 2005;79:13412-13420.
200. Srivastava R, Aggarwal R, Bhagat MR, Chowdhury A, Naik S. Alterations in natural killer cells and natural killer T cells during acute viral hepatitis E. *J Viral Hepat*. 2008;15:910-916.
201. Fujiwara S, Yokokawa Y, Morino K, Hayasaka K, Kawabata M, Shimizu T. Chronic hepatitis E: a review of the literature. *J Viral Hepat*. 2014;21:78-89.
202. Zhao C, Wang Y. Laboratory diagnosis of HEV infection. *Adv Exp Med Biol*. 2016;948:191-209.
203. Fix AD, Abdel-Hamid M, Purcell RH, et al. Prevalence of antibodies to hepatitis E in two rural Egyptian communities. *Am J Trop Med Hyg*. 2000;62:519-523.
204. Zhao C, Geng Y, Harrison TJ, Huang W, Song A, Wang Y. Evaluation of an antigen-capture EIA for the diagnosis of hepatitis E virus infection. *J Viral Hepat*. 2015;22:957-963.
205. Souza AJS, Malheiros AP, Sarmento VP, et al. Serological and molecular retrospective analysis of hepatitis E suspected cases from the eastern Brazilian Amazon 1993-2014. *Rev Soc Bras Med Trop*. 2019;52:e20180465.
206. Sampedro A, Casanovas I, Ceballos J, Rodriguez-Granger J, Cobo F, Navarro JM. Comparative evaluation of two immunoassays for serological diagnosis of hepatitis E. *J Med Virol*. 2019;92:260-262.
207. Herremans M, Duizer E, Jusic E, Koopmans MP. Detection of hepatitis E virus-specific immunoglobulin a in patients infected with hepatitis E virus genotype 1 or 3. *Clin Vaccine Immunol*. 2007;14:276-280.
208. Mitsui T, Tsukamoto Y, Suzuki S, et al. Serological and molecular studies on subclinical hepatitis E virus infection using periodic serum samples obtained from healthy individuals. *J Med Virol*. 2005;76:526-533.
209. Mishra S, Borkakoti J, Kumar S, Kar P. Role of HEV antigen detection in HEV-related acute viral hepatitis and acute liver failure. *J Med Virol*. 2016;88:2179-2185.
210. Zhang F, Li X, Li Z, et al. Detection of HEV antigen as a novel marker for the diagnosis of hepatitis E. *J Med Virol*. 2006;78:1441-1448.
211. Abravanel F, Lhomme S, Chapuy-Regaud S, et al. A fully automated system using transcription-mediated amplification for the molecular diagnosis of hepatitis E virus in human blood and faeces. *J Clin Virol*. 2018;105:109-111.
212. Sridhar S, Lo SK, Xing F, et al. Clinical characteristics and molecular epidemiology of hepatitis E in Shenzhen, China: a shift toward foodborne transmission of hepatitis E virus infection. *Emerg Microbes Infect*. 2017;6:e115.
213. Marrone G, Biolato M, Mercurio G, et al. Acute HEV hepatitis: clinical and laboratory diagnosis. *Eur Rev Med Pharmacol Sci*. 2019;23:764-770.
214. Mushahwar IK. Hepatitis E virus: molecular virology, clinical features, diagnosis, transmission, epidemiology, and prevention. *J Med Virol*. 2008;80:646-658.
215. Khuroo MS, Teli MR, Skidmore S, Sofi MA, Khuroo MI. Incidence and severity of viral hepatitis in pregnancy. *Am J Med*. 1981;70:252-255.
216. Khuroo MS, Kamili S. Aetiology and prognostic factors in acute liver failure in India. *J Viral Hepat*. 2003;10:224-231.
217. Bhatia V, Singhal A, Panda SK, Acharya SK. A 20-year single-center experience with acute liver failure during pregnancy: is the prognosis really worse? *Hepatology*. 2008;48:1577-1585.
218. Stoszek SK, Engle RE, Abdel-Hamid M, et al. Hepatitis E antibody seroconversion without disease in highly endemic rural Egyptian communities. *Trans R Soc Trop Med Hyg*. 2006;100:89-94.
219. Navaneethan U, Al Mohajer M, Shata MT. Hepatitis E and pregnancy: understanding the pathogenesis. *Liver Int*. 2008;28:1190-1199.
220. Marzi M, Vigano A, Trabattoni D, et al. Characterization of type 1 and type 2 cytokine production profile in physiologic and pathologic human pregnancy. *Clin Exp Immunol*. 1996;106:127-133.
221. Tilburgs T, van der Mast BJ, Nagtzaam NM, Roelen DL, Scherjon SA, Claas FH. Expression of NK cell receptors on decidual T cells in human pregnancy. *J Reprod Immunol*. 2009;80:22-32.
222. Trowsdale J, Moffett A. NK receptor interactions with MHC class I molecules in pregnancy. *Semin Immunol*. 2008;20:317-320.
223. Saito S, Nakashima A, Myojo-Higuma S, Shiozaki A. The balance between cytotoxic NK cells and regulatory NK cells in human pregnancy. *J Reprod Immunol*. 2008;77:14-22.
224. Mellor AL, Munn DH. Extinguishing maternal immune responses during pregnancy: implications for immunosuppression. *Semin Immunol*. 2001;13:213-218.
225. Mellor AL, Sivakumar J, Chandler P, et al. Prevention of T cell-driven complement activation and inflammation by tryptophan catabolism during pregnancy. *Nat Immunol*. 2001;2:64-68.
226. Chaouat G. The Th1/Th2 paradigm: still important in pregnancy? *Semin Immunopathol*. 2007;29:95-113.
227. Chaouat G, Ledee-Bataille N, Dubanchet S. Immune cells in uteroplacental tissues throughout pregnancy: a brief review. *Reprod Biomed Online*. 2007;14:256-266.
228. Meeusen EN, Bischof RJ, Lee CS. Comparative T-cell responses during pregnancy in large animals and humans. *Am J Reprod Immunol*. 2001;46:169-179.
229. Jamieson DJ, Theiler RN, Rasmussen SA. Emerging infections and pregnancy. *Emerg Infect Dis*. 2006;12:1638-1643.
230. Riley EM, Schneider G, Sambou I, Greenwood BM. Suppression of cell-mediated immune responses to malaria antigens in pregnant Gambian women. *Am J Trop Med Hyg*. 1989;40:141-144.

231. Okoko BJ, Enwere G, Ota MO. The epidemiology and consequences of maternal malaria: a review of immunological basis. *Acta Trop*. 2003;87:193-205.
232. Priddy KD. Immunologic adaptations during pregnancy. *J Obstet Gynecol Neonatal Nurs*. 1997;26:388-394.
233. Barnett MA, Learmonth RP, Pihl E, Wood EC. T helper lymphocyte depression in early human pregnancy. *J Reprod Immunol*. 1983;5:55-57.
234. Tallon DF, Corcoran DJ, O'Dwyer EM, Greally JF. Circulating lymphocyte subpopulations in pregnancy: a longitudinal study. *J Immunol*. 1984;132:1784-1787.
235. Ponta H, Ball R, Steinmetz M, Groner B. Hormonal regulation of cell surface expression of the major histocompatibility antigen H-2Ld in transfected cells. *EMBO J*. 1985;4:3447-3453.
236. Ponta H, Kennedy N, Skroch P, Hynes NE, Groner B. Hormonal response region in the mouse mammary tumor virus long terminal repeat can be dissociated from the proviral promoter and has enhancer properties. *Proc Natl Acad Sci USA*. 1985;82:1020-1024.
237. Han T. Human chorionic gonadotropin. Its inhibitory effect on cell-mediated immunity in vivo and in vitro. *Immunology*. 1975;29:509-515.
238. Wan H, Versnel MA, Leijten LM, et al. Chorionic gonadotropin induces dendritic cells to express a tolerogenic phenotype. *J Leukoc Biol*. 2008;83:894-901.
239. Boll G, Reimann J. Oestrogen treatment depletes extrathymic T cells from intestinal lymphoid tissues. *Scand J Immunol*. 1996;43:345-350.
240. Rijhsinghani AG, Thompson K, Bhatia SK, Waldschmidt TJ. Estrogen blocks early T cell development in the thymus. *Am J Reprod Immunol*. 1996;36:269-277.
241. Tibbetts TA, DeMayo F, Rich S, Conneely OM, O'Malley BW. Progesterone receptors in the thymus are required for thymic involution during pregnancy and for normal fertility. *Proc Natl Acad Sci USA*. 1999;96:12021-12026.
242. Aggarwal R, Goel A. Natural history, clinical manifestations, and pathogenesis of Hepatitis E virus genotype 1 and 2 infections. *Cold Spring Harb Perspect Med*. 2019;9:a032136.
243. Mannheimer EE, Harritshoj LH, Katzenstein TL. Hepatitis E and pregnancy. *Ugeskr Laeger*. 2016;178:178-183.
244. Medina KL, Smithson G, Kincade PW. Suppression of B lymphopoiesis during normal pregnancy. *J Exp Med*. 1993;178:1507-1515.
245. Styrt B, Sugarman B. Estrogens and infection. *Rev Infect Dis*. 1991;13:1139-1150.
246. Hussaini SH, Skidmore SJ, Richardson P, Sherratt LM, Cooper BT, O'Grady JG. Severe hepatitis E infection during pregnancy. *J Viral Hepat*. 1997;4:51-54.
247. Anzivino E, Fioriti D, Mischitelli M, et al. Herpes simplex virus infection in pregnancy and in neonate: status of art of epidemiology, diagnosis, therapy and prevention. *Virol J*. 2009;6:40.
248. Kamar N, Selves J, Mansuy JM, et al. Hepatitis E virus and chronic hepatitis in organ-transplant recipients. *N Engl J Med*. 2008;358:811-817.
249. Tosone G, Simeone D, Spera AM, Viceconte G, Bianco V, Orlando R. Epidemiology and pathogenesis of fulminant viral hepatitis in pregnant women. *Minerva Ginecol*. 2018;70:480-486.
250. Jilani N, Das BC, Husain SA, et al. Hepatitis E virus infection and fulminant hepatic failure during pregnancy. *J Gastroenterol Hepatol*. 2007;22:676-682.
251. Saravanabalaji S, Tripathy AS, Dhoot RR, Chadha MS, Kakrani AL, Arankalle VA. Viral load, antibody titers and recombinant open Reading frame 2 protein-induced Th1/Th2 cytokines and cellular immune responses in self-limiting and fulminant Hepatitis E. *Intervirology*. 2009;52:78-85.
252. Heideman M, Bengtsson A. Immunological interference of high dose corticosteroids. *Acta Chir Scand Suppl*. 1985;526:48-55.
253. Siebenlist U, Franzoso G, Brown K. Structure, regulation and function of NF-kappa B. *Annu Rev Cell Biol*. 1994;10:405-455.
254. Prusty BK, Hedau S, Singh A, Kar P, Das BC. Selective suppression of NF-kBp65 in hepatitis virus-infected pregnant women manifesting severe liver damage and high mortality. *Mol Med*. 2007;13:518-526.
255. McCracken SA, Drury CL, Lee HS, Morris JM. Pregnancy is associated with suppression of the nuclear factor kappaB/IkappaB activation pathway in peripheral blood mononuclear cells. *J Reprod Immunol*. 2003;58:27-47.
256. Kar P, Jilani N, Husain SA, et al. Does hepatitis E viral load and genotypes influence the final outcome of acute liver failure during pregnancy? *Am J Gastroenterol*. 2008;103:2495-2501.
257. Rasheeda CA, Navaneethan U, Jayanthi V. Liver disease in pregnancy and its influence on maternal and fetal mortality: a prospective study from Chennai, Southern India. *Eur J Gastroenterol Hepatol*. 2008;20:362-364.
258. Beniwal M, Kumar A, Kar P, Jilani N, Sharma JB. Prevalence and severity of acute viral hepatitis and fulminant hepatitis during pregnancy: a prospective study from North India. *Indian J Med Microbiol*. 2003;21:184-185.
259. Tsega E, Krawczynski K, Hansson BG, Nordenfelt E. Hepatitis E virus infection in pregnancy in Ethiopia. *Ethiop Med J*. 1993;31:173-181.
260. Strand RT, Franque-Ranque M, Bergstrom S, Weiland O. Infectious aetiology of jaundice among pregnant women in Angola. *Scand J Infect Dis*. 2003;35:401-403.
261. Patra S, Kumar A, Trivedi SS, Puri M, Sarin SK. Maternal and fetal outcomes in pregnant women with acute hepatitis E virus infection. *Ann Intern Med*. 2007;147:28-33.
262. Jaiswal SP, Jain AK, Naik G, Soni N, Chitnis DS. Viral hepatitis during pregnancy. *Int J Gynaecol Obstet*. 2001;72:103-108.
263. Arankalle VA, Paranjape S, Emerson SU, Purcell RH, Walimbe AM. Phylogenetic analysis of hepatitis E virus isolates from India (1976-1993). *J Gen Virol*. 1999;80(Pt 7):1691-1700.
264. Li SW, Zhao Q, Wu T, Chen S, Zhang J, Xia NS. The development of a recombinant hepatitis E vaccine HEV 239. *Hum Vaccin Immunother*. 2015;11:908-914.
265. Zhu FC, Zhang J, Zhang XF, et al. Efficacy and safety of a recombinant hepatitis E vaccine in healthy adults: a large-scale, randomised, double-blind placebo-controlled, phase 3 trial. *Lancet*. 2010;376:895-902.
266. Wu T, Zhu FC, Huang SJ, et al. Safety of the hepatitis E vaccine for pregnant women: a preliminary analysis. *Hepatology*. 2012;55:2038.

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