Role of viral hepatitis in pregnancy and its triggering mechanism

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ABSTRACT

Hepatitis viral infection can cause severe complications, even mortality in pregnant women and their offspring. Multiple studies have shown that vertical transmission can cause viral hepatitis infections in newborns, especially in hepatitis B, C, and E. Screening for hepatitis viral infection in pregnant women is essential. Once infected, pregnant women should be given timely antiviral treatments, which could effectively alleviate the disease progression and reduce adverse outcomes. Besides, the mechanism of viral hepatitis mediating adverse pregnancy outcomes has been a hot topic. Hepatitis B virus has been found to mediate both mother-to-child and parent-child transmission. Liver injury in hepatitis C virus infection is associated with immune-mediated mechanisms, which can be regulated by hormonal factors as well. The mediating mechanism of adverse maternal and infant outcomes caused by hepatitis E virus infection is mainly related to viral replication in the placenta and changes in cytokine and estrogen. Nevertheless, the specific mechanisms related to hepatitis A virus and hepatitis D virus remain unclear, and more research is needed. This review shows that the existence of viral hepatitis during pregnancy can pose certain risks for pregnant women and infants, and different interventions have been used to treat pregnant women infected with viral hepatitis. It may provide deep insight into adverse pregnancy outcomes caused by viral hepatitis and give guidance on treatment.

Key words: viral hepatitis, pregnancy, adverse outcomes, triggering mechanism, vertical transmission

INTRODUCTION

Viral hepatitis is an infectious disease caused by hepatitis virus, mainly including hepatitis A, B, C, D, and E, which can replicate in human hepatocytes and result in liver injury.[1] Viral hepatitis is widespread all over the world and shows an increasing trend over the years. In 2015, over 10 million new infections were reported, and 1.34 million deaths are attributed to viral hepatitis per year.[3]

Hepatitis viral infection during pregnancy poses specific risks to both pregnant women and their offspring.[4-7] Therefore, it is necessary to explore the role of viral hepatitis and its mechanism-of-action in pregnancy. This review aims to discuss the role of viral hepatitis in pregnancy and its triggering mechanism, which will provide deep insight into adverse pregnancy outcomes and give guidance on treatment for pregnant women infected with hepatitis virus.

Hepatitis A

Hepatitis A, caused by hepatitis A virus (HAV) infection, is widespread worldwide.[8] According to the World Health Organization, approximately 7000 people died of hepatitis A in 2016.[9] HAV is a small, non-enveloped,

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single-stranded RNA virus with a diameter of about 27 nm.[10] Seven HAV genotypes have been described. HAV is mainly transmitted through close contact and fecal-oral route.[11] Hepatitis A is usually a self-limiting disease with manifestations of chills, fever, nausea, fatigue, appetite loss, hepatomegaly, abnormal liver function, black urine, and jaundice.[12] However, in some cases, it could lead to death. HAV infection during pregnancy have been frequently reported. For example, Sadeghi *et al.* prospectively enrolled 247 pregnant women to evaluate the seroprevalence of HAV, and anti-HAV antibody was detected in 111 pregnant women.[13]

Complications caused by HAV infection during pregnancy should not be ignored. In 12 pregnant women infected with HAV, Cho *et al*. found 2 preterm births and 2 cholestasis.[14] Ryu *et al.* also reported that preterm delivery and miscarriage may be complications of acute HAV infection in pregnant women.[15] Similarly, premature contractions, placental separation, premature rupture of membranes, and vaginal bleeding occurred in 9 pregnant women with acute HAV infection. HAV infection also caused preterm delivery in 8 pregnant women.[16] In a study from China, perinatal death occurred in 16 of 288 HAV-infected pregnant women during delivery.[17] In addition, acute liver failure (ALF), coagulopathy, and acalculous cholecystitis due to HAV infection during pregnancy have also been reported.[18-21] Overall, HAV infection could increase the incidence of complications in pregnant women, such as preterm birth, miscarriage, and damaged placenta, even resulting in death during the perinatal period. Furthermore, HAV infection would lead to complications in infants as well. For example, fetal ascites, fetal distress, and low birth weight have been reported.[14,15]

Vertical transmission of HAV during pregnancy is highly infrequent while there have been reported instances of intrauterine transmission of HAV.[22,23] Besides, there is no documented evidence that HAV can be transmitted to infants through breastfeeding. Although anti-HAV IgM, IgG and HAV RNA were detected in breastmilk samples, breastfeeding was not found to be associated with neonatal infection.[24] Hence, pregnant women with HAV infection should not be prevented from breastfeeding.

HAV infection could lead to severe adverse outcomes in pregnant women and infants, and the specific mechanisms of HAV infection triggering pregnancy complications remain unclear. Hence, more research needs to be carried out to explore HAV infection during pregnancy.

Hepatitis B

Hepatitis B virus (HBV) is a partially double-stranded DNA virus, with a diameter of 30–42 nm.[25,26] HBV is transmitted mainly through blood and sexual routes, which can cause both acute and chronic infection, with a global prevalence of approximately 3.5% in chronic infection, and more than 750,000 people die of HBV infection each year.[27,28] The diagnosis of HBV infection relies on the HBV surface antigen (HBsAg) in blood, while HBV e antigen (HBeAg) and HBV DNA can reflect the level of HBV replication and guide the antiviral treatment.[29] Many HBV-infected patients have no noticeable symptoms, while some patients may have general discomfort, appetite loss, nausea, vomiting, body pain, fever, dark urine and jaundice.[30] HBV infection poses a serious risk to pregnant mothers and infants, and it is of great significance to explore hepatitis B in pregnancy and its triggering mechanism.

Numerous studies have demonstrated that pregnant women with HBV infection have poor prognosis (Table 1). Xiao *et al.* concluded that HBV infection during pregnancy can result in the increased incidence of premature rupture of membranes and neonatal asphyxia.[31] HBsAg-positive women were reported to have a higher risk of gestational diabetes mellitus (GDM), intrahepatic cholestasis during pregnancy (ICP), preterm birth and neonatal asphyxia.[32] Through meta-analysis, Tan *et al.* speculated that HBsAg positivity during pregnancy has a moderate impact on the increased risk of GDM.[33] Similarly, Farsimadan *et al.* demonstrated that GDM and preterm birth are strongly associated with HBV infection during pregnancy.[34] Preterm delivery in the pregnant women infected with HBV cannot be ignored.[35] HBV infection can serve as an independent risk factor for preterm birth.[36] Besides, maternal HBV carrier status may also be an independent risk factor for miscarriage.[37] Ye *et al.* showed that HBV infection will increase the risk of miscarriage in early pregnancy, which may be related to HBV-infected embryos.[38] In a study from China, Wang *et al.* suggested that maternal HBsAg carrier is strongly associated with gestational hypertension, fetal distress, and macrosomia, and they showed that maternal HBV viral load in HBsAg carriers has a strong association with premature delivery.[39] A case of ALF during pregnancy caused by HBV infection has also been reported.[40] Notably, Govrin-Yehudain *et al.* showed that maternal HBV carrier status during pregnancy may increase offspring susceptibility to long-term respiratory disease.[41] Maternal HBV infection can increase the risk of ICP in pregnant women receiving assisted reproductive technology (ART).[42] Moreover, compared to pregnant women only with HBV infection, those with HBV infection and ICP suffered from more adverse pregnancy outcomes.[43,44]

Patients who tested positive for HBeAg and exhibited a high viral load faced an elevated risk of ICP and neonatal asphyxia, emphasizing the necessity of accurately quantifying

Table 1: Poor prognosis in pregnant women with hepatitis B virus infection

Authors	Studied population	Complications
Xiao *et al*.[31]	60 pregnant women infected with hepatitis B	Premature rupture of fetal membranes Neonatal asphyxia
Wu *et al*.[32]	1146 HBsAg-positive pregnant women	GDM ICP Preterm birth Neonatal asphyxia
Liu *et al*.[35]	20827 pregnant women infected with hepatitis B	Vertical transmission Preterm birth
Zheng *et al*.[36]	1302 HBV-infected pregnant women	Preterm birth
Cui *et al*.[37]	513 asymptomatic pregnant carriers	Miscarriage
Ye *et al*.[38]	25 couples with HBV infection	Miscarriage
Wan *et al*.[39]	1728 HBsAg-positive pregnant women	Gestational hypertension Fetal distress Macrosomia Premature delivery
Kimmich *et al*.[40]	A pregnant woman with acute HBV infection	ALF
Govrin-Yehudain *et al*. [41]	771 HBV/HCV pregnant carriers	Long-term respiratory morbidity in offspring
Xiong *et al*.[42]	795 HBsAg-positive pregnant women who received ART	ICP
Wei *et al*.[43]	198 pregnant women with HBV infection	ICP
Zhang *et al*.[44]	212 HBV-infected pregnant women	Vertical transmission ICP Neonatal asphyxia

Note: HBV, hepatitis B virus; HCV, hepatitis C virus; GDM, gestational diabetes mellitus; ICP, intrahepatic cholestasis during pregnancy; ALF, acute liver failure; ART, assisted reproductive technology.

HBV DNA levels in HBV-infected individuals.[32] As Cheung *et al.* recommended, quantification of HBV DNA should be performed 22 weeks before gestation to avoid delays in the treatment of pregnant women with HBV infection.[45]

Without clinical intervention, the risk of vertical transmission tends to be higher in HBV-infected pregnant women. Hence, the treatment for HBV vertical transmission is crucial (Table 2). HBV-infected infants contaminated through vertical transmission are usually chronic carriers.[5] Newborns should be vaccinated to effectively prevent HBV vertical transmission.[46] As a treatment for immunoprophylaxis, hepatitis B immunoglobulin (HBIG) injection can block vertical transmission of HBV during and after delivery. Despite adverse events, multiple injections of HBIG during pregnancy have been shown to be effective and safe in preventing intrauterine transmission of HBV.[47] Likewise, Xiao *et al.* demonstrated that maternal administration of HBIG can also prevent intrauterine HBV infection.[48]

Perinatal antiviral therapies are effective in preventing HBV vertical transmission.[49] No matter with high or low viremia, pregnant women need to receive antiviral therapies during the perinatal period due to the potential risk of HBV vertical transmission.[50] Compared with HBIG and vaccination alone, antiviral therapies can improve HBV suppression and reduce vertical transmission in patients with high viral load without adverse outcomes.[51] Nucleoside analog therapies also have an important role in the treatment of pregnant women with chronic hepatitis B (CHB) infection, mainly including lamivudine (LAM), telbivudine (LdT), and tenofovir disoproxil fumarate (TDF). LAM can act on the reverse transcription process of the virus and inhibit the synthesis of HBV DNA negative strands from mRNA, thus inhibiting HBV replication. The mechanism of LdT is similar to LAM. Besides, LdT can cause the termination of HBV DNA strand elongation by integration into HBV DNA, thus inhibiting the replication of HBV. TDF can inhibit HBV replication by inhibiting HBV reverse transcriptase activity.[52] In early pregnancy, LAM and LdT, with good tolerance, are effective in controlling maternal disease and interrupting vertical transmission in active CHB patients.[53,54] No major birth defects were observed using LAM and TDF.[55] Studies revealed that LAM can significantly prevent vertical transmission without serious adverse events.[56,57] Shang *et al.* demonstrated that LdT can effectively treat pregnant women with HBV infection and block vertical transmission. Meanwhile, long-term follow-up data suggested that LdT will not affect child growth.[58] The earlier LdT is applied, the better its preventive effect.[59] Besides, TDF was proved to be effective in reducing the risk of HBV vertical transmission.[60] In the meta-analysis, Sali *et al.* confirmed that LdT has a higher ability to prevent

Table 2: Treatment for hepatitis B virus vertical transmission

Greenup *et al*.[63]	TDF *vs.* LAM	TDF is considered to be safer and more effective than LAM.
Zeng *et al*.[65]	TAF	TAF has an effective therapeutic effect in preventing HBV vertical transmission.
Ding *et al*.[66]	TAF	HBV vertical transmission can be effectively prevented by TAF.
Chan *et al*.[67]	TAF *vs.* TDF	TAF has less renal and bone toxicity compared with TDF.
Farsimadan *et al*.[34]	IVF	IVF treatment has no negative effects on pregnancy outcomes.
Greenup *et al*.[63]	TDF *vs.* LAM	TDF is considered to be safer and more effective than LAM.
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Ding *et al*.[66]	TAF	HBV vertical transmission can be effectively prevented by TAF.

HBV: hepatitis B virus; HBIG: hepatitis B immunoglobulin; LAM: lamivudine; LdT: telbivudine disoproxil fumarate; TDF: tenofovir; TAF: tenofovir alafenamide fumarate; IVF: *in vitro* fertilization.

HBV vertical transmission than TDF.[61] However, TDF may not cause symptoms of kidney damage, and the long-term antiviral effect of TDF was thought to be superior to LdT.[62] In addition, TDF was considered to be safer and more effective than LAM.[63]

Furthermore, other treatments also achieved excellent results. Similar to TDF, tenofovir alafenamide fumarate (TAF) is a recently developed drug with an effective therapeutic effect in preventing HBV vertical transmission, and has been approved for the treatment of CHB.[27,64-66] Interestingly, TAF has less renal and bone toxicity compared to TDF.[67] *In vitro* fertilization (IVF) treatment has also been reported to have no negative effects on pregnancy outcomes, which is considered a safe and effective method.[34]

The mechanisms underlying HBV vertical transmission have garnered significant attention. HBV genes can self-express, and replicate in both female and male reproductive systems. It was confirmed that HBV can be present in human oocytes and embryos.[68,69] Ma *et al.* discovered HBV infection in different cells of the term placenta.[70] Yang *et al.* demonstrated that HBV infection during pregnancy can cause placental chorion angiopathy, which will reduce placental function and lead to fetal immune failure.[71] These studies provided new insights into the mechanism of mother-to-child transmission of HBV. Through transferring human sperm-mediated HBV genes into hamster oocytes using IVF methods, Ali *et al.* implied that sperm-mediated HBV genes can replicate in early embryonic cells, indicating that HBV DNA can be vertically transmitted through the male reproductive system, supported by the existence of HBV mRNA in the abandoned IVF embryos of HBV-infected fathers.[72,73]

Hepatitis C

Hepatitis C, caused by hepatitis C virus (HCV) infection, is mainly transmitted through blood, sexual and mother-to-child routes.[74] HCV is an enveloped, positive-sense, single-stranded RNA virus with seven genotypes.[75] In 2019, an estimated 58 million people worldwide were infected with HCV, of which 290,000 died from hepatitis C and its related diseases, while approximately 29,000 pregnant women infected with HCV in the United States each year.[76,77] HCV can cause both acute and chronic infection, which will result in liver fibrosis, cirrhosis and even cancer. HCV infection usually is asymptomatic, but a few patients with acute HCV infection may develop fatigue, muscle aches, itching and jaundice.[78] HCV infection has certain effects on pregnant women and newborns. Thus, it is necessary to study HCV infection in pregnant women.

HCV infection can cause many complications in pregnant women. It was reported that pregnant women infected with HCV have a higher rate of premature delivery, accompanied by edema, hypertension and itching.[79] Active HCV during pregnancy is associated with ICP and mother-to-child transmission.[80] The association between HCV infection and ICP had also been revealed in several studies.[81,82] Lawlor et al. showed that a pregnant woman with acute HCV infection had ICP and elevated bile acids, accompanied by itching and right upper abdominal pain.[83] Belay et al. also suggested that pregnant women infected with HCV had a high prevalence of ICP, and that HCV loads were higher in those with ICP.[84] Furthermore, similar to HBV, HCV carrier status can also increase offspring susceptibility to long-term respiratory disease.[41]

A large number of studies have assessed the risks of HCV vertical transmission. Gardenal et al. concluded that high serum maternal HCV viremia and maternal illicit drug use are associated with HCV vertical transmission.[85] By following 46 children of HCV seropositive mothers, Pinto et al. found that 6 children contracted HCV infection, which indicated the high risk of HCV vertical transmission. However, screening for HCV-exposed infants is not adequate, and it is imminent.[87]

HCV-infected pregnant women can be effectively treated with antiviral therapies. Direct antiviral therapies could reduce the risk of perinatal HCV transmission.[88] In addition, Lin et al., who found that serum HCV levels decreased at 1 and 3 months after delivery, speculated that puerperium should be the best time for HCV carrier mothers to receive antiviral therapies.[89] HCV RNA was not detected in breast milk samples obtained from HCV-infected mothers, suggesting that HCV infection is not a contraindication to breastfeeding.[90]

Pregnant women infected with HCV often develop a liver injury. HCV-infected women will experience a modest rebound in ALT levels but not in HCV RNA after delivery, implicating the immune mechanism of hepatocyte injury during HCV infection.[91,92] Significantly, Gervais et al. also revealed that hepatocyte injury is associated with immune-mediated mechanisms, which may be regulated by hormonal factors. Specifically, estrogen can activate the extra-thymus T-cell differentiation pathway in the liver and inactivate the intrathymus pathway. These changes in T cell differentiation can lead to a modulation of cytotoxic activity.[93]

Hepatitis D

Hepatitis D virus (HDV) is a negative-sense, single-stranded RNA virus with a diameter of 36 nm, belonging to the genus Deltavirus.[94] In 2020, it was estimated that approximately 48 million people were infected with HDV.[95] HDV is generally considered to be a defective RNA virus that requires the presence of HBV to replicate in hepatocytes.[96] HDV co-infection with HBV often can accelerate disease progression, resulting in liver cirrhosis, liver failure and even liver cancer.[97] Co-infection with HBV, hepatitis D has the highest mortality among all hepatitis.[98] Nevertheless, studies on HDV infection during pregnancy are limited.

So far, studies on HDV vertical transmission are rare. Figueroa et al. stated that HDV can only be transmitted vertically with HBV.[99] In a study of 22 pregnant women co-infected with HBV and HDV, Sellier et al. discovered that only 1 newborn was infected with HBV, and no newborn infected with HDV.[100] The impact of HDV infection on pregnant women is still controversial. HDV and HBV co-infections seem to be more likely to cause adverse outcomes in pregnant women than HBV infection alone.[5]

Hepatitis E

Hepatitis E virus (HEV) is a single-stranded, positive-sense RNA virus with a diameter of 27–34 nm, which can lead to hepatitis E.[101-103] HEV mainly has seven genotypes with a wide range of hosts, transmitted mainly by the fecal-oral route. It was estimated that more than 20 million people were infected with Hepatitis E in 2017.[104] Similar to HAV infection, HEV infection is usually self-limiting, with some patients developing symptoms of acute hepatitis, ALF and even death. Symptoms of acute hepatitis are more severe in pregnant women, the elderly and those with underlying liver disease.[105] In 2005, Rein *et al.* estimated the global burden of genotypes 1 and 2 of HEV and found a mortality rate of 19.8% among pregnant women infected with HEV.[106] Therefore, it may be important to investigate the relationship between HEV infection and pregnancy.

Kar *et al.* indicated that pregnancy appears to be a risk factor for HEV replication.[107] HEV loads were significantly higher in pregnant patients compared to the non-pregnant. High HEV load during pregnancy may be a factor leading to the severity of infection. Bergløv *et al.* demonstrated that HEV infection is associated with fulminant liver failure, premature delivery, postpartum hemorrhage, low birth weight and vertical transmission.[108] In the meta-analysis, Bigna *et al.* reported that the proportion of HEV vertical transmission was 36.9%, and they revealed that HEV infection is associated with multiple maternal and infant adverse outcomes, including maternal death, low birth weight, small gestational age, preterm delivery and stillbirth.[109] HEV infection has been reported to be closely associated with maternal mortality and intrauterine

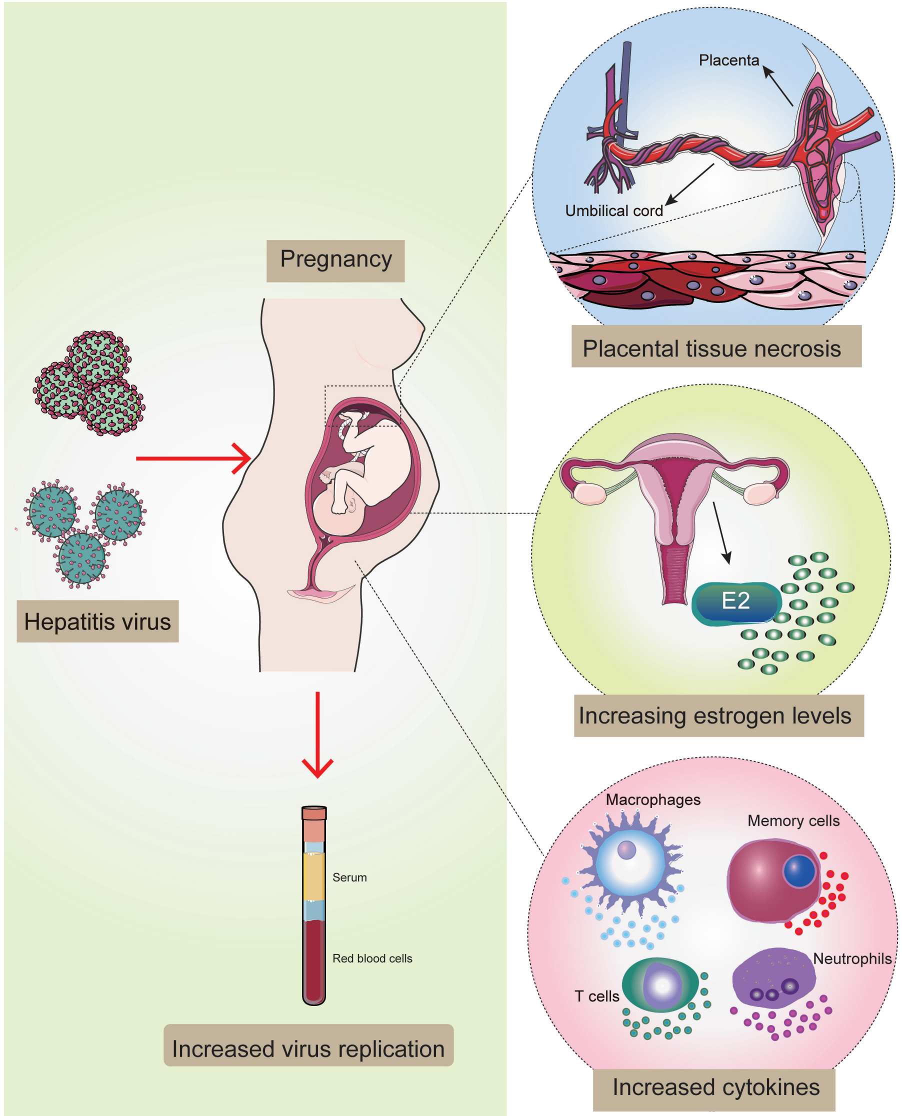

Figure 1: The triggering mechanism of hepatitis E virus infection during pregnancy.

mortality in preterm infants, and premature rupture of membranes was considered to be the most common fetal complication.[110]

Due to adverse pregnancy outcomes, the triggering mechanism of HEV infection during pregnancy has been emphasized (Figure 1). HEV infection can modulate a strong type 1 interferon response,[111] and pregnancy serum can promote HEV replication by inhibiting type 1 interferon during early infection.[112] The severity of HEV infection and associated adverse outcomes may be mediated by cytokines during pregnancy. Compared with non-pregnant women and healthy people, the levels of TNF-α, IL-6, IFN-γ and TGF-β1 in HEV-infected pregnant women were significantly increased, and adverse pregnancy outcomes were observed.[113] Salam *et al.* showed that HEV infection during pregnancy can increase TNF-α secretion, which will influence pregnancy outcomes.[114] IL-12/IL-10 ratio was also confirmed to be associated with fetal mortality in HEV-infected pregnant women.[115] In the rabbit models, high levels of AST, TNF-α, and IFN-γ were proved to significantly influence adverse fetal outcomes.[116] Furthermore, compared with pregnant women with acute hepatitis, functions of monocytes and macrophages in those with HEV-ALF were impaired, and the expression of TLR3, TLR7, and TLR downstream cytokines was down-regulated, indicating that inadequate trigger factors of innate immune response can contribute to the development and exacerbation of HEV-ALF.[117]

Studying the mediating mechanism of adverse pregnancy outcomes caused by HEV infection will contribute to a better understanding of HEV infection during pregnancy. Bose *et al*. demonstrated that HEV can replicate in human placenta.[118] Knegendorf *et al*. confirmed that HEV can replicate in the placental-derived cells.[119] HEV was also found to replicate in the non-decidualized primary human endometrial stromal cells, thus mediating vertical transmission.[120] Decidua basalis and fetal placenta were successfully used to simulate HEV infection ex vivo at the maternal-fetal interface.[121] Additionally, Ratho *et al*. proposed that the placenta is the inflammatory cytokine site for HEV replication and regulation of maternal HEV immune pathogenesis.[122] By infecting rhesus monkeys with genotype 4 HEV, Yu *et al*. found that impaired innate immune response, decreased progesterone levels, and altered immune status can exacerbate HEV infection and thus result in adverse outcomes.[123] Furthermore, endometrial thickness damage caused by HEV infection, severe inflammatory response, and increased intrauterine apoptosis were potential causes of adverse outcomes.[124,125]

Estrogen and its related signaling pathway have been emphasized in the adverse outcome of HEV-infected pregnant women. Pregnancy serum can accelerate HEV replication by inhibiting estrogen receptors during early HEV infection.[122] A high level of estrogen plays an prominent role in the adverse outcomes of HEV-infected pregnant women, and there is a significantly negative correlation between birth weight and estrogen level.[126] By evaluating the relationship between HEV infection and estrogen signaling pathways, Gong *et al*. mentioned that HEV infection can significantly inhibit the cAMP-PKA-CREB and PI3K-Akt-mTOR signaling pathways, independent of the Ras-Raf-MEK-ERK signaling pathway.[127] Moreover, Sooryanarain *et al*. demonstrated that progesterone during pregnancy can enhance HEV replication in human hepatocytes.[128]

Oxidative stress functions in HEV infection during pregnancy as well. Bhatnagar *et al*. demonstrated that low Glutathione (GSH) levels in HEV-infected pregnant women are associated with adverse outcomes, including preterm birth and low birth weight.[129] Tiwari *et al*. showed that placental stress caused by HEV infection can result in increased homocysteine as a mediating mechanism for premature delivery.[130] In addition, the upregulation of miR-450b was also considered to be significantly associated with the prognosis of pregnant women infected with HEV.[131]

Pregnancy does not appear to constitute a susceptibility to HEV.[132] However, the population of pregnant women susceptible to HEV still needs more attention. It's worth noting that both malnutrition and Arsenic exposure could result in increased susceptibility to HEV infection, and malnutrition may also exacerbate symptoms of HEV-ALF during pregnancy.[133,134] Previously, micronutrient deficiencies have also been found to cause dysregulated cytokine expression and impaired immune function, thereby increasing the risk of HEV infection.[135] Pregnant women with high estradiol or immunosuppression were confirmed to be more susceptible to HEV infection.[136]

Vaccines can effectively prevent the adverse outcomes caused by HEV infection. Among many HEV genotypes used for infecting rabbits, rabbit HEV genotype 3, porcine HEV genotype 4 and human HEV genotype 3 could cause adverse outcomes, which could be prevented by the HEV-239 vaccine in pregnant rabbits,[137] which suggested that women of childbearing age may receive HEV vaccination to avoid adverse outcomes associated with HEV infection. Similarly, Xia *et al*. also recommended that pregnant women at risk of HEV infection should be vaccinated.[138]

CONCLUSION

Viral hepatitis affects both women and newborns during pregnancy. Vertical transmission has been proved to be associated with HBV, HCV and HEV infections in newborns. There was limited evidence on whether HAV and HDV infections can be vertically transmitted, and more studies are needed.

Given the severe morbidity and mortality, screening for hepatitis infection in pregnant women is also essential. Clinically, timely antiviral treatment in pregnant women infected with viral hepatitis can effectively alleviate the disease progression and prevent adverse pregnancy outcomes, thereby reducing morbidity and mortality. In addition, liver injury caused by viral hepatitis infection also needs to be concerned, and liver transplantation is recommended in severe cases. Different hepatitis viral infections may pose different risks to pregnant women and newborns, so specific interventions should be adopted.

The mechanism of viral hepatitis mediating adverse pregnancy outcomes has been a hot topic. HBV has been found to mediate parents to child transmission. Liver injury in HCV infection is associated with immune-mediated mechanisms, which can also be regulated by hormonal factors. Adverse outcomes caused by HEV infection are mainly related to viral replication in the placenta and changes in cytokine and estrogen. Of note, the mediating mechanism of HAV and HDV remains unclear, and more research is needed.

Moreover, we can develop novel biomarkers to improve the diagnosis and prognosis of viral hepatitis (VH) in pregnant women. Through the latest omics technology for high throughput screening, including genomics, transcriptomics, proteomics and so on, we may identify some novel biomarkers of VH,[139,140] which are specific in pregnant women. Artificial intelligence and machine learning techniques can also aid in the identification of novel biomarkers.

Overall, the existence of viral hepatitis during pregnancy can pose certain risks for pregnant women and infants. Different interventions have been used for the treatment in pregnant women with viral hepatitis. Although several studies made efforts to the mechanism of viral hepatitis in pregnancy, the triggering mechanism remains to be investigated.

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Authors Contributions

Jian Wu had the idea for the article; Ze Xiang, Chun Jiang, Huiqing Wang, Guanghua Zhai and Yunyang Xu performed the literature search and drafted the work; Jian Wu and Zongxin Ling critically revised the work. Jian Wu, Huiqing Wang and Ze Xiang contributed equally to this work.

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Informed Consent

Not applicable.

Ethical Approval

Not applicable.

Conflict of Interest

The authors have declared no conflicts of interest.

Data Availability Statement

All data relevant to the study are included in the article.

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