

Review Article

Epidemiology of Hepatitis E in Pregnant Women and Children in Iran: A General Overview

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Abstract

From an epidemiological point of view, hepatitis E is an old infection in Iran, but only recently has its importance as a public health concern been considered from research and public health standpoints. As such, there is still a long road ahead to clarify the real burden of hepatitis E virus (HEV) infection in Iran. According to the available epidemiological studies, the seroprevalence of HEV infection among pregnant women is between 3.6% and 7.4%, and among Iranian children is between 0.9% to 8.5%, varying by geographic regions within the country and directly dependent upon the sanitary status of each. In addition to evaluating the sanitation level of a society, community-based seroprevalence studies of HEV infection demonstrate the most prevalent risk factors, the major routes of transmission, and the epidemiological patterns of HEV among that country's population. In this review, the current knowledge about the pathogenesis and epidemiology of HEV infection in pregnant women and children in Iran, as well as the recent advances in diagnosis, prevention and treatment of HEV infection have been summarized.

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Introduction

Hepatitis E virus (HEV) infection is generally an enterically transmitted viral hepatitis with asymptomatic or acute self-limited manifestations.¹ However, progression to fulminant liver failure has also been reported in high-risk groups, such as pregnant women and patients with underlying liver problems.¹⁻⁷ Chronicity is rare and is mostly observed in immunocompromised and immunosuppressed patients, such as

patients who have received organ transplant, are infected with human immunodeficiency virus (HIV) or suffer from haematological malignancies.^{5,8-14} Therefore, despite the benign clinical presentation of hepatitis E in the general population, it is considered as an important health concern, especially in those high-risk populations.

According to the epidemiological data, 3.3 million acute cases and 20 million new cases of hepatitis E are diagnosed each year globally.^{3,15} Despite the mortality rate of 1-2% in the general population,¹⁶ 10-25% of pregnant women and >75% of patients with underlying liver disease lose their lives due to the HEV infection.^{17,18} According to a report from the World Health Organization (WHO), ~56600 deaths occur per year due to HEV-related hepatic failure.¹⁹ Overall, one-third of the world's population has been infected with HEV.^{20,21}

HEV is a small virus in the family *Hepeviridae*, with a positive single-stranded RNA genome and non-enveloped icosahedral capsid.^{5,9,22,23} The genome consists of three partially overlapping open reading frames (Fig. 1).^{5,24,25} HEV is usually transmitted via the faecal-oral route, particularly through contaminated food and water supplies. However, transmission through haemodialysis, organ transplantation, sexual intercourse, placenta, blood and blood product transfusion is also possible, but the importance of each is unknown.^{1,17,26} Only four genotypes capable of affecting human beings have been identified thus far.^{3,27} These four genotypes have been classified into the genus *Orthohepevirus* and the species *Orthohepevirus A*,^{1,28} and they differ in their mode of transmission, pathogenicity, severity, mortality rates, geographical and age distribution.^{1,17,26,29,30}

Genotypes 1 and 2 affect human beings and are responsible for large epidemics or acute outbreaks in developing countries. These outbreaks occur due to contamination of drinking water following heavy rainfall or flooding, and are more frequently observed among young adult males.^{1,3,5,13,26,29,31} Meanwhile, genotypes 3 and 4 use an animal reservoir and are mostly transmitted via consumption of contaminated meat; these two genotypes are the causative agents of locally-acquired sporadic HEV infections in developed countries and mostly affect middle-aged to elderly males.^{1,3,5,13,29,31-33} These variations in the epidemiological patterns of HEV reflect differences in the level of sanitation, lifestyle, risk factors and status of public health in the different groups and regions across the globe.^{14,34-36} Therefore, it is important to study the epidemiological patterns of hepatitis E in the different groups and regions to determine the burden of this viral infection.

Keywords: Hepatitis E virus; Pregnant women; Children; Epidemiology; Iran.

Abbreviations: HEV, hepatitis E virus; HIV, human immunodeficiency virus; WHO, World Health Organization; TGF- β , transforming growth factor-beta; NF- κ b, nuclear factor-kappa B; Th2, T helper 2; HCG, human chorionic gonadotropin; Th1, T helper 1; FLF, fulminant liver failure; HLA, human leukocyte antigen; MHC, major histocompatibility complex; NAT, nucleic acid amplification techniques; AST, aspartate aminotransferase; ALT, alanine aminotransferase; PEG-IFN, pegylated interferon.

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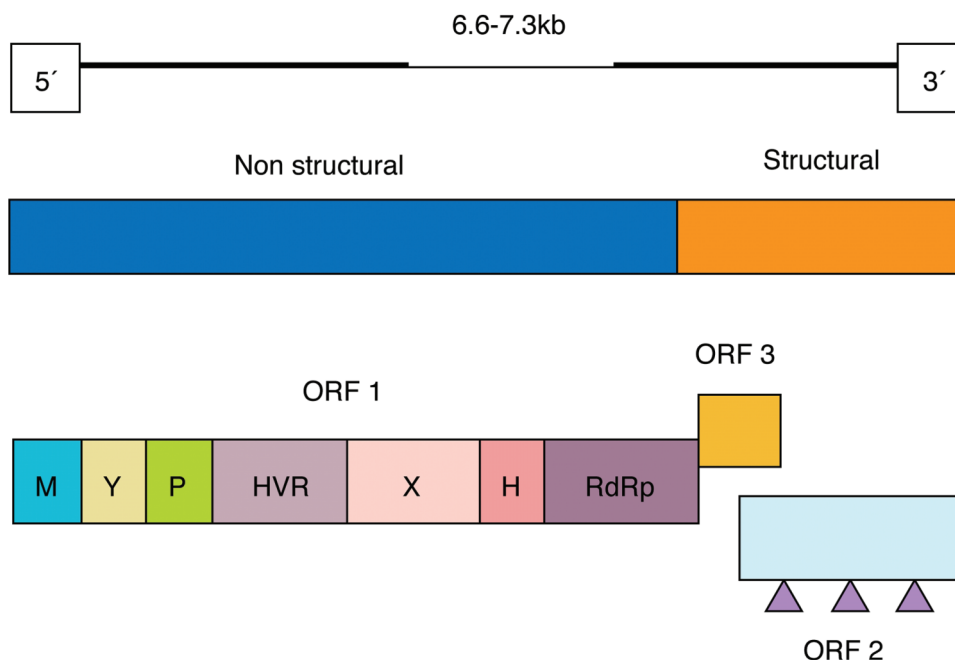


Fig. 1. Molecular structure of hepatitis E virus.¹ (Adapted from Fig. 1 of reference 1, with permission of the publisher).

Abbreviations: M, methyltransferase; Y, Y domain; P, papain-like cysteine protease; HVR, hypervariable region; X, macro-domain; H, helicase; RdRp, RNA-dependent RNA polymerase; Triangle, glycosylation site.

In Iran, HEV infection is endemic, but the epidemiology of this infection in two of the most vulnerable groups—pregnant women and children—remains unclear. Therefore, this study was conducted to provide a general overview of the pathogenesis and epidemiology of hepatitis E in these two groups in Iran.

HEV in pregnant women in Iran

HEV infection is not only generally a benign self-limited disease, but it can also adversely affect pregnant women and lead to fulminant hepatic failure, especially during the second and third trimesters, subsequently lowering survival of mothers and their fetuses.^{37–41} Overall, it is reported that 0% to 73% of mortalities in pregnant women are attributed to HEV infection in the endemic regions, representing 0% in Egypt, 3.4% in South India, 42% in Ethiopia and 39.1–73% in North India.³⁹ Besides maternal complications, HEV also causes serious consequences to the foetus following transplacental transmission, which varies in severity from low birth weight, prematurity, mild anicteric neonatal hepatitis or jaundice at birth with full recovery to miscarriage, stillbirth, preterm labour, perinatal death or neonatal death soon after birth.^{1,27,29,37,38,40,42} No extrahepatic manifestations or chronic carrier state has been reported in children born to mothers with HEV infection.^{27,38}

Such severe complications in pregnancy are not seen with the other known hepatitis viruses.^{5,22,40} Although the exact mechanism of this excess severity of hepatitis E in pregnancy has not yet been determined, it seems that a combination of host and viral factors contributes to the pathogenesis of hepatitis E during pregnancy.^{1,37,39}

Pregnancy is accompanied by significant changes in maternal hormonal and immunological responses to sustain

the foetus.^{39,40} These immunological changes include inhibition of cell-mediated immunity through secretion of transforming growth factor-beta (TGF- β) and IL-4 and IL-10 cytokines, down-regulation of nuclear factor-kappa B (NF- κ B), reduction in T cell activity and cytokine production, along with an alteration in cellular immune regulation towards an increase in CD8 cell counts and a decrease in CD4 cells with predominant T helper 2 (Th2) responses; all of these result in systematic suppression of the maternal immune system and subsequently increase susceptibility to infections.^{1,37,39,40} Moreover, the steroid hormones including beta-HCG (human chorionic gonadotropin), oestrogen and progesterone increase during pregnancy.^{5,39,40,42} These hormones have direct inhibitory effects on hepatocytes, cell-mediated immunity, T helper 1 (Th1) cell development and B cell production; moreover, through the decreased expression of NF- κ B, they promote lymphocyte apoptosis. In addition, these hormones induce viral replication and the development of Th2 cells.^{37,39,40,42}

Although the above-mentioned hormonal and immunological changes physiologically occur in normal pregnancy, when pregnancy is accompanied by HEV infection these changes increase.^{39,40,42} As such, HEV-infected pregnant women may suffer from decreased activity or absence of the p65 component of the NF- κ B complex, which likely induces acute liver damage.^{39,40} Moreover, HEV appears to have a direct cytopathogenic effect on hepatic cells or immune-mediated pathogenesis through induction of host inflammatory responses, which may result in destruction of hepatocytes.^{1,43} Although Th2 responses are predominant in normal pregnancy, a strong cytotoxic immune response may be induced through an alteration in T helper responses towards Th1 following HEV infection aimed at reducing the high viral load, but which in turn results in lower foetal survival rates.⁴²

Foetal infection with HEV will enhance the severity of infection and risk of liver failure in the mother.³⁸⁻⁴⁰ Moreover, the inhibitory effects of steroid hormones on hepatocytes can result in hepatic dysfunction when pregnancy is accompanied by HEV infection.^{40,42} Overall, it seems that HEV by itself does not induce these changes and requires pregnancy as a physiological factor to enhance the risk of hepatic damage. Therefore, pregnant women with hepatitis E are at an increased risk for developing liver failure.^{39,40}

It seems that viral load and genotype can influence severity of HEV infection during pregnancy. As such, high viral load, along with genotypes 1 and 2, known as the more virulent genotypes, contribute to the development of fulminant liver failure (FLF).^{1,5,37,38,42} In addition, poor maternal nutrition and the use of herbal medicines to relieve symptoms of HEV infection due to side effects are associated with increased severity of hepatitis E.^{39,40,42,43} Finally, the role of genetic factors, such as variation in human leukocyte antigen (HLA) alleles in different geographical regions, should also be considered in the pathogenesis of HEV infection during pregnancy.^{39,40}

An endotoxin-mediated effect has been proposed as another probable factor in the pathogenesis of FLF in pregnancy. In this process, the Kupffer cells, a type of liver sinusoidal cells, are destroyed by HEV, negating their ability to protect the liver cells against endotoxin derived from gram-negative bacteria of the intestinal tract.⁴⁰ In addition, release of prostaglandins due to HEV infection can indirectly damage hepatocytes through attraction of neutrophils, which result in inflammation, oedema and cholestasis in liver.⁴⁰

In endemic regions, the incidence and severity of HEV infection in pregnant women are much higher than that in non-pregnant women and men, with reported maternal mortality rates of 30–100% in the various studies.^{1,39,40,44} The rate of vertical transmission from mother to foetus varies from 30% to 79%, and sometimes up to 100%, in the different studies as well.²⁷ In addition, mother-to-child transmission via breastfeeding is also possible and mostly occurs during the acute phase of infection.³⁷ In developing countries, HEV infection accounts for approximately 3000 stillbirths annually.^{5,37} Interestingly, the above-mentioned epidemiological pattern is not observed in all endemic countries.^{5,44} In Egypt, for example, despite reporting high seroprevalence of HEV among pregnant women, the disease follows a mild or asymptomatic course, with very low mortality.^{38-40,44} However, the exact reason behind this benign pathogenicity remains unclear, but might be related to the presence of a highly contagious but less virulent strain of the HEV genotype predominantly found in Egypt^{5,22,38-40,44} or possibly the differences in major histocompatibility complex (MHC) phenotypes in this country as compared to the other endemic areas.⁵ It can also be explained by the high levels of previous exposure to HEV in early childhood, resulting in long-lasting immunity and probably attenuated infection upon re-exposure to HEV in adulthood.^{5,38-40} Similar findings have been reported in the United States (US) and Europe, where there is no difference in the severity of HEV infection in pregnant women compared to that in non-pregnant women,^{38,39,42} while HEV seroprevalence is considerably high but most HEV infections are asymptomatic or remain undiagnosed.⁴⁴

In Iran, however, the epidemiology is even more unclear. There are few reports on the seroprevalence of HEV infection among pregnant women in Iran. In the available studies,

however, the seroprevalence of HEV infection varies from 3.6% to 7.6%,⁴⁵⁻⁴⁹ which is more or less similar to HEV seroprevalence in the general population of Iran (Table 1 and Fig. 2). Moreover, age, level of education, parities, stage of gestation and the number of family members have been identified as risk factors for HEV seropositivity among these reported pregnant women.⁴⁶⁻⁴⁸ In particular, increasing gestational age, lower education, third trimester of pregnancy and more parities are associated with high seroprevalence of HEV infection among the pregnant women.⁴⁶⁻⁴⁸ Compared to the other endemic countries,⁵⁰⁻⁵² the seroprevalence of HEV infection among Iranian pregnant women is low.^{45,47,48} In addition, there is a considerable difference in rate of HEV seroprevalence between Iran and neighbouring countries such as the United Arab Emirates (20.0%)⁵³ and India (33.67%);⁵⁰ meanwhile, it is similar to that reported for Turkey (7.0%).⁵⁴

Considering the adverse effects of HEV infection on pregnancy outcomes, prevention strategies, appropriate precautions and training programs regarding the possible routes of exposure to HEV as well as routine screening for HEV infection before and during pregnancy are needed to reduce the occurrence and adverse consequences of HEV infection in the pregnant population.^{46,47} Overall, the importance of HEV infection during pregnancy is underestimated in Iran and there are no current data on the rate of maternal mortality in Iran.

HEV in children in Iran

There are few studies on the seroprevalence of HEV infection among children in Iran. In those studies, seroprevalence rates vary from 0.9% to 8.5% (Table 1 and Fig. 2).⁵⁵⁻⁵⁹ Although the seroprevalence of HEV among children in Iran is not as high as reported for Nepal (16%), Tibet (23.8%) and India (17.75%–24.7%),²⁷ it is still considerably higher than for Taiwan (0.3%), Mongolia (0.6%), Greenland (0.0%), Korea (0%–1%) and Argentina (0.15%).²⁷ Globally, the highest HEV prevalence, ranging from 36.2% to 75.5%, has been reported for children in Egypt.²⁷

The sero-epidemiological patterns of HEV infection among children in Iran are similar to those observed in other endemic countries, such as Bangladesh, Mexico, China, Turkey and Venezuela.²⁷ Those studies have shown that the HEV seroprevalence is low in early childhood but increases with age.^{27,55,57} Egypt is an exception, with the majority of children being exposed to HEV in early life, as evidenced by 65% of children under 10 years of age being seropositive.^{27,60} Globally, <10% of children aged under 10 years are HEV seropositive.²⁷

Most cases of HEV infection among children are subclinical.^{27,39,55} Despite this asymptomatic feature, the mortality rate is considerably high in children with jaundice; one study in Uganda reported a high mortality rate among icteric children, which was even higher than the mortality rates reported among the pregnant women in that country.¹⁶ However, there is no report on the mortality rate of HEV infection among children in Iran.

Some studies have evaluated the trends in seroprevalence of HEV infection among children over time and showed a slight but not significant increase in HEV seropositivity. One study from India indicated a significant increase in HEV seroprevalence over time.²⁷ However, due to inadequate

Table 1. Prevalence of hepatitis E virus among pregnant women and children in Iran

Study population	City or province	Location	Year(s) of study	No. of participants	Mean age \pm SD (age group) in years	No. of positive cases	HEV sero prevalence	HEV diagnosis	Manufacturer of serology kits used	Authors
Pregnant women	Urmia	Northwest	2011	136	25.12 \pm 4.91 (14 to 39)	5	3.6%	Anti-HEV IgG	DIA.PRO, Italy	Rostamzadeh Khameneh <i>et al.</i> ⁴⁵
Pregnant women	Ahvaz	Southwest	2010–2011	418	30 \pm 10	22 1	5.26% 0.23%	Anti-HEV IgG Anti-HEV IgM	DIA.PRO, Italy	Rasti <i>et al.</i> ⁴⁶
Pregnant women	Hamadan		2010–2011	1050	27.2 \pm 5.6 (14 to 49)	78	7.4%	Anti-HEV IgG	DIA.PRO, Italy	Mamani <i>et al.</i> ⁴⁷
Pregnant women	Gorgan	Northeast	2010	394	(15 to 47)	29	7.4%	Anti-HEV total antibodies	DIA.PRO, Italy	Tabarraei <i>et al.</i> ⁴⁸
Pregnant women	Gorgan		2009	1200	27.41 \pm 6.33 (17 to 45)	76	6.3%	Anti-HEV total antibodies	DIA.PRO, Italy	Moradi <i>et al.</i> ⁴⁹
Children	Sari, Mazandaran	North	2003	255	(< 10)	3	1.2%	Anti-HEV IgG	DIA.PRO, Italy	Saffar <i>et al.</i> ⁵⁵
Children	Isfahan	Centre	2005	110	(6 to 9)	1	0.9%	Anti-HEV total antibodies	DIA.PRO, Italy	Ataei <i>et al.</i> ⁵⁸
Children	Kashan	Centre	2012	558	(1 to 15)	21	3.7%	Anti-HEV IgG	DIA.PRO, Italy	Sharif <i>et al.</i> ⁵⁷
Children	Ahvaz	Southwest	2006–2007	566	10 \pm 2.7 (6 to 15)	48	8.5%	Anti-HEV IgG	Biokit, Spain	Shamsizadeh <i>et al.</i> ⁵⁶
Children	Shiraz	South	2011–2012	356	(6 to 15)	27 2	7.6% 0.6%	Anti-HEV total antibodies Anti-HEV IgM	DIA.PRO, Italy	Asaei <i>et al.</i> ⁵⁹

Abbreviations: No., number; SD, standard deviation; HEV, hepatitis E virus.



Fig. 2. Map of Iran.

studies in Iran, the changes in trends of HEV seroprevalence over time remain unclear.

Children are representative of a group at risk of HEV infection.²⁷ Recent studies have shown that the seroprevalence of HEV infection among children is related to sanitary status of different parts of the country.^{55,61} Considering the fact that contaminated drinking water supplies and inappropriate sewage disposal systems are associated with HEV seropositivity, the faecal-oral route is the main route of HEV transmission among Iranian children.⁵⁵ Therefore, age-specific community-based seroprevalence studies of HEV infection are used to describe the sanitation level and public health status of a society. Overall, these studies have indicated that children in Iran are exposed to HEV and, therefore, preventive strategies are needed to reduce this exposure.⁵⁵⁻⁵⁷

Diagnosis of HEV infection

HEV causes a vast range of clinical presentations, which vary in severity from FLF, liver fibrosis and cirrhosis following chronic hepatitis E, and acute icteric hepatitis to unapparent and asymptomatic infection.^{1,7,9,15,29,62} Most cases of hepatitis E among children are asymptomatic,^{27,39} and no cases of chronic hepatitis E have been reported in pregnant women

and infants.³⁸ Chronic HEV infection is, however, frequently observed among immunocompromised and immunosuppressed patients.^{7,9,14,29}

The clinical manifestations of HEV infection are indistinguishable from clinical symptoms of the other viral hepatitis forms.³⁵ In addition, these non-specific symptoms sometimes mask the diagnosis of HEV infection, making laboratory methods the most reliable criteria for diagnosis. The laboratory diagnosis methods are based on detection of HEV RNA in serum or stool samples by nucleic acid amplification techniques (NAT) or of anti-HEV antibodies in serum or plasma samples by serological tests (Fig. 3).^{1,5,17,63-65}

The presence of HEV RNA in blood and stool is short-lived, and becomes undetectable in serum at 3–4 weeks and in stool at 6 weeks after the onset of clinical symptoms (Fig. 4).^{17,29} In asymptomatic subjects, viremia can last for 4–6 weeks.¹⁷ However, a prolonged viremia is also possible, especially among children following acute HEV infection and immunosuppressed patients.^{4,17} Anti-HEV IgM increases during the acute phase of infection. IgM level remains high for about 8 weeks, but declines rapidly and becomes undetectable in most patients after 3–8 months.^{5,27} Meanwhile, long-lasting anti-HEV IgG antibodies appear shortly after the increase of IgM and persist for 1–14 years or more after the infection

short-lived and return to normal about 6 weeks after the onset of clinical symptoms.²⁷

Prevention and treatment of HEV infection

The current preventive strategies primarily aim at reducing exposure to HEV by improving water supply facilities and sewage disposal systems, since the disease is predominantly transmitted via the faecal-oral route.¹⁷ Therefore, provision of safe water supplies, sanitary preparation of food, sanitary disposal of human waste and hygienic infrastructure appear to be the most effective preventive measures.^{1,5,22,30,37,66}

Vaccination against HEV is another preventive strategy, although no commercial vaccine has yet become available worldwide.¹⁷ Several HEV vaccines have been designed and evaluated in the laboratory setting, including recombinant vaccines consisting of various truncated forms of the capsid protein (HEV 239,⁶⁷ trpE-C2,⁶⁸ 53 kDa,⁶⁹ pE2,⁷⁰ 56 kDa,⁶⁹ rHEV VLP,⁷¹ 62 kDa⁷² and T1-ORF2⁷³), DNA vaccines (pcHEVORF2 and Lipo-NE-DP⁷⁴⁻⁷⁶) and, more recently, epitope-based vaccines.^{18,77} Amongst them, only one recombinant vaccine, the HEV 239 vaccine based on a 26 kDa portion of the HEV capsid protein (aa 368-606), has been licensed by China's State Food and Drug Administration.^{3,18,78-81} Yet, this vaccine, despite showing promising results in human clinical trials, is not still approved for use in a susceptible population such as pregnant women, children and patients with pre-existing liver problems, and is not available worldwide.^{16,18,78}

Upon disease emergence, the treatment strategy is usually supportive, as the disease is generally asymptomatic or self-limited at this stage.^{9,17,82} Antiviral treatment is administered only for patients with hepatic complications due to fulminant or chronic HEV infection.^{9,17} These antiviral therapies include monotherapy with pegylated interferon (PEG-IFN) or ribavirin, or combination therapy with these antiviral agents.^{9,82,83} Although these antiviral treatments result in clearance of the

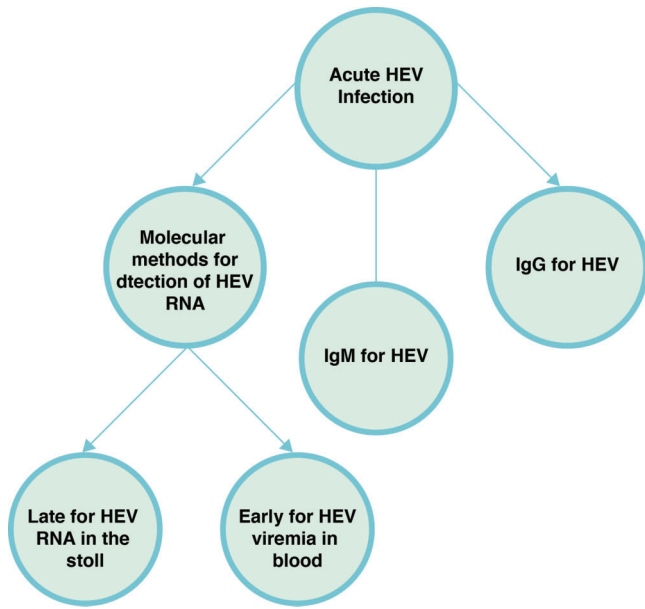


Fig. 3. Laboratory diagnosis of hepatitis E virus infection.³⁸ (Adapted from Fig. 3 of reference 38, with permission of the publisher).

(Fig. 4).^{5,29,63} Thus, detection of IgM is indicative of acute infection, and the presence of IgG is a sign of previous exposure to HEV.^{1,29}

Evaluation of liver parameters is another diagnostic criterion. At onset of clinical symptoms, liver function tests show abnormal findings, such as for the measurements of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, gamma-glutamyl transpeptidase and bilirubin.^{22,62} However, elevated levels of liver enzymes are

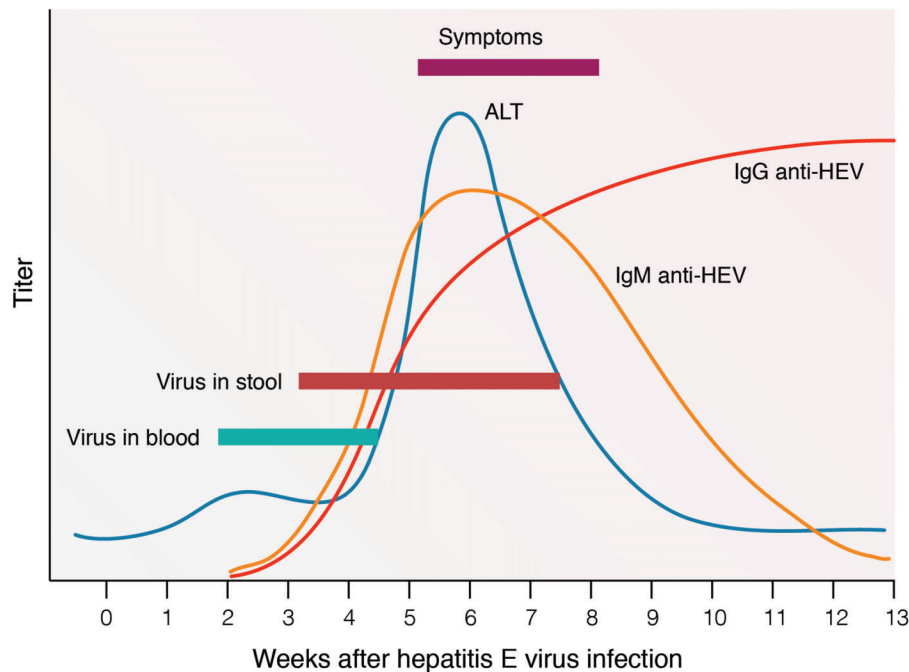


Fig. 4. Virological markers of hepatitis E virus infection.³⁸ (Adapted from Fig. 2 of reference 38, with permission of the publisher).

virus and reduction of the symptomatic period, they harbour their own limitations and side effects.^{26,83,84} PEG-IFN α has neuropsychiatric side effects and induces influenza-like symptoms, and ribavirin causes impaired renal function and anemia.^{83–85} Above all, these antiviral agents have teratogenic effects during pregnancy.^{9,38,84} Therefore, termination of pregnancy or early delivery of the foetus seems to be the most effective option to save mothers.^{38,39}

Conclusions

This review has provided a general overview of the pathogenesis and epidemiology of HEV infection in pregnant women and children in Iran. HEV infection is generally a benign self-limited disease, but it can lead to serious consequences in susceptible populations such as pregnant women. It seems that a combination of host and viral factors contributes to the pathogenesis of hepatitis E in pregnancy; although, the exact reason behind this excess severity during pregnancy is not yet fully understood.

HEV infection is an underestimated disease in Iran, most probably due to a lack of HEV consideration in the country's public health system. Despite being prevalent among children and pregnant women, our current knowledge regarding epidemiology of this viral infection in Iran is scarce. Therefore, further studies are required to more comprehensively determine the incidence and prevalence of HEV infection in these two groups in different regions of Iran. Once these data are obtained, the epidemiological pattern of this neglected infection in Iran will become clearer.

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Conflict of interest

None

Author contributions

Designing the study, collecting the data, drafting the manuscript and reading and approving the final draft of the manuscript (RT), designing the study, performing the literature review, drafting the manuscript, editing the manuscript and reading and approving the final draft of the manuscript (FF).

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