REVIEW ARTICLE

CONTENTS

Hepatitis E virus in pregnancy – vaccine and HEV reinforced with polymer

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ABSTRACT

The hepatitis E virus (HEV) causes self-limiting viral hepatitis. It is now global, both in developing and low-industrialized countries. With infection, the predominance of infections is asymptomatic but can cause death. Pregnant women are particularly vulnerable to severe complications. This article summarizes the current knowledge about HEV infection during pregnancy, focusing on immunology, transmission, complications in both pregnant and newborn women, and polymer-boosted vaccines. The development of a polymer-reinforced vaccine may in the future solve the problem of the HEV virus, which is particularly dangerous for pregnant women.

KEY WORDS: HEV, chitosan chloride, pregnancy, biomaterials

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INTRODUCTION

HEV was the first to be officially named an epidemic of unexplained acute hepatitis in the early 80s [1]. It leads to about 20 million infections and up to 70,000 deaths per year [2]. Infection in the predominance of infections is asymptomatic but can reach mortality of up to 25% in pregnant women [3]. HEV has 8 genotypes [4]. Genotype 1 is found mainly in Asia and Africa and 2 is detected in Mexico and Africa [5], They are diagnosed only in humans. Genotypes 3 and 4 can infect both humans and animals worldwide, and in recent years there has been an increase in infections in Europe [6]. All genotypes belong to one serotype [7]. HEV is transmitted zoonotically through the consumption of infected undercooked meat or by the fecal-oral route through drinking contaminated water [8].

The pregnant woman's immune system suppresses immunity through T cells so that the environment for fetal development is optimal for growth, but this also leads to an increased susceptibility of the pregnant woman to viral infections, including HEV infections. The immunological destruction of hepatocytes is important in the pathogenesis of hepatitis E [9]. The level of the hormones progesterone, estrogen and chorionic gonadotropin, which increase with the course of pregnancy, significantly alters immune regulations and increases the replication of the virus [10, 11], which reaches a higher concentration in tissues and leads to the development of a more severe disease, replicating not only in hepatocytes but also in the placenta [12, 13]. High mortality in pregnancy may be associated with hormonal and immune changes, including "downregulation" of nuclear factor kappa-B and a change in the ratio of Th1 in favor of Th2, and with host susceptibility factors during gestation [14, 15]. Studies that used pregnant women's plasma to identify IFN-β pointed to delayed "upregulation" of HEV-infected cells enriched with pregnant plasma from the 3rd trimester. This means that delayed expression of IFN-β may accelerate the multiplication of HEV [16, 17].

AIM

This work aims to draw attention to the problem of HEV during pregnancy, show the complications of infection in the mother and child, and bring the topic of vaccinations in which polymers are used closer to the forefront. Research on the mechanisms of disease pathogenesis in pregnant women may help to understand the role of transplacental viral transmission, intrauterine death, and miscarriages. The development of a polymer-reinforced vaccine may in the future solve the problem of the HEV virus, which is particularly dangerous for pregnant women.

Table 1. Obstetric complications in women with HEV

	No Complication in women with HEV	Ref.
1.	Moderate jaundice	[9, 15]
2.	Elevated transaminase levels	[9]
3.	Fatal hepatic failure	[4, 18]
4.	Nausea and vomiting	[25]
5.	Acute liver failure	[25]
6.	Fulminant hepatic failure	[26]
7.	Encephalitis	[4]
8.	Guillain-Barré Syndrome	[4]

MATERIALS AND METHODS

A systematic literature search was performed utilizing PubMed, the Cochrane Library, Medline, Embase, and Web of Science databases. Studies in English or Chinese that reported data on the burden of HEV in Asia, Africa, Central America and were included.

REVIEW AND DISCUSSION

HEV is transmitted mainly by the fecal-oral route, studies indicate that mainly through contaminated drinking water and through the consumption of undercooked infected meat. Blood transmission and vertical transmission have also been reported [18, 19]. The stability of HEV remains viable even when heated to 56°C for 60 minutes with the remaining 1% infectious particles. Only reaching a temperature of 71°C for 20 minutes is it able to completely inactivate the virus [20]. The viability of the virus outside the host and environmental factors affecting the stability of the virus remain unknown [21]. Transmission to the fetus HEV is found up to 50% of cases and is associated with serious consequences such as: stillbirth, premature birth, low birth weight [22]. A PCR study conducted in 144 pregnant HEV-infected women showed vertical transmission in 46% of HEV-IgM-positive mothers [23]. HEV RNA was found in umbilical cord blood in most newborns of seropositive mothers before birth [13]. The mechanisms by which HEV is enabled are unclear, with FcRn and ORF3 protein assumed [24]. The ORF1 protein is involved in viral replication, and ORF3 is the ion channel necessary for HEV to pass through infected cells [9].

OBSTETRIC COMPLICATIONS IN WOMEN WITH HEV

HEV infection in most men and non-pregnant women is self-limiting, with an average incubation time of 40 days. Symptoms presented by patients are mild or moderate jaundice and elevated transaminase levels, which normalize within 1-6 weeks [9]. Clinical manifestations of HEV infection during pregnancy vary widely and include mild subclinical disease, self-limiting infections resolving within 1-4 weeks, are reaching vertical hepatic failure with mortality [4, 18]. Symptoms occurring in pregnant women are nausea, vomiting, jaundice being the main symptom. The time between jaundice and the development of encephalopathy is different in pregnant and non-pregnant women. The longer this period, the worse the clinical outcome in the form of acute hepatic insufficiency [25]. During pregnancy, patients develop jaundice of greater severity on average 6-15 mg/dl [15]. Fulminant liver failure is more common in pregnant women [26]. Infection during pregnancy is also associated with non-hepatic symptoms, which may include neurological disorders, encephalitis, or Guillain-Barré syndrome (Table 1) [4]. There is no evidence to suggest an association of HEV with glomerulonephritis [27]. In a study of 220 pregnant women by Borkakoti et al., it was shown that high HEV titers during pregnancy may be one of the factors of infection during pregnancy [28].

COMPLICATION IN THE NEWBORN

Most studies proving high maternal mortality come from India, where HEV is endemic. In 2 different prospective studies in New Delhi and Chennai, approximately 15% to >50% of live-born newborns of HEV-positive mothers died within 1 week after delivery. Such consequences were given only by a virus with a genotype [29, 30]. It has been confirmed that intrauterine infection and vertical HEV transmission lead to miscarriages and intrauterine death even in women without a fulminant course of the disease [31, 32]. 100% maternal and fetal mortality occurred with plasma viremia and tissue involvement with acute hepatic failure. In ALF patients with plasma viremia but without tissue involvement, maternal mortality was lower – 78.5% – 100% of fetuses experienced intrauterine death. The presence of genotype 1 leads to a more severe course of the disease [15]. Immune damage to the placenta due to HEV is a possible explanation. Pregnancy-related hormones and reduced cellular immunity are factors associated with the severity and complications of pregnancy. The placenta as a replication site for HEV is important because it is there that the endocrine and immune systems work together to protect the fetus. During pregnancy, placental cells regulate progesterone and its receptors upwards, which plays a key role in preserving the fetus's allograft in the mother's body and inhibiting cellular immunity. (Druckmann & Druckmann, 2005). Hence, when the placenta is destroyed by viral replication, the balance may be disturbed and intrauterine death of the fetus occurs [33, 34]. Hepatitis E is still a mystery

when it comes to the pathophysiological mechanisms of infection in pregnant women.

HEV VACCINE– CHITOSAN CHLORIDE

The global problem of HEV-causing epidemics, particularly affecting low-income per capita countries, requires the development of an effective HEV vaccine. Work on this problem has been going on for years. Clinical trials are conducted by many teams that test the effectiveness but also the safety of vaccines. The most promising vaccine is HEV 239 (Hecolin). It is a recombinant polypeptide with a molecular weight of 26 kDa corresponding to amino acid residues 368-606 of the capsid protein genotype 1 of the HEV strain. The vaccine is expressed in *Escherichia coli* (*E. coli*) and vaccine doses contain 30 μg purified antigen in 0.5 ml of buffered saline adsorbed into 0.8 mg of aluminum hydroxide[24, 35]. A phase IV clinical trial of HEV 239 with 600 participants showed 96.7% of subjects seroconverted just one month after the last dose [35] Another study with 126 participants showed that the use of the vaccine in the schedule (0, 7, 21 days) was safe and created protection [36] Phase IV trials of this vaccine are currently underway.

We are still looking for effective methods that would enhance the effectiveness of the HEV vaccine. The addition of chitosan derivatives, e.g. chitosan chloride, to vaccines to improve the humoral and/or cellular improvement of the immune response to vaccine antigens as an adjuvant, is promising. Chitosan is one of the promising adjuvants to improve the immune response. Chitosan is a derivative of chitin, from which > 55% of N-acetylated groups have been removed [37, 38]. Many studies confirm the mucoadhesive properties of chitosan, thanks to which it prolongs the stay of the preparation on the mucous membranes of the digestive, reproductive, urinary, or respiratory systems [39-43]. N-(2-hydroxy) propyl-3-trimethylammonium chitosan chloride (HTCC) may be used as an adjuvant for recombinant polypeptide vaccine against HEV. Animal experiments show that HTCC provides adjuvant activity when administered together with HEV vaccination by the intramuscular route [44] The search for more polymers to enhance the immune response is becoming more and more justified.

CONCLUSIONS

Research on the etiology of miscarriages and stillbirths is complicated due to many logistical, cultural, ethical, and financial aspects. Designing a prospective study with an appropriate study group, frequency of observations and follow-up visits requires large financial outlays and advanced scientific and research infrastructure. Therefore, studies showing the effects of HEV infection on the fetus, miscarriage, or intrauterine death in European countries are scarce. According to observations, the incidence of infection increases with the age of woman, gestational age, which suggests that pregnant women should undergo screening for clinical features of acute hepatitis during prenatal visits and should be examined especially in endemic regions. Due to the adverse outcomes of infection with the virus, its early detection may give a better chance of survival for both the mother and the fetus.

Challenges also include differences in viral genotypes, differences in exposure to infectious material and public health and dietary status across populations, genetic differences between populations, and other individual host factors influencing the course of infection. Research on the mechanisms of disease pathogenesis in pregnant women may help to understand the role of transplacental viral transmission and intrauterine death and miscarriages. The duration of HEV infection in pregnancy may be another important variable. Despite the increased predisposition to infection in the 3rd trimester of pregnancy, it is not known in what ratio the maternal response to infection remains to vertical transmission and fetal viability. HEV infection during pregnancy, especially genotype 1, is associated with a more severe course of infection and can lead to fulminant liver failure and maternal death.

RECOMMENDATIONS

Providing educational support to parents, especially mothers with lower education. A polymer-enhanced HEV vaccine may play an important role in controlling the epidemic, so it is worth exploring new polymers to find the ideal vaccine.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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