

## Acute Hepatitis E Virus Infection in Pregnancy: A Mini Review

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### Abstract

Hepatitis E Virus infection is an important cause of mortality and morbidity. Acute Hepatitis E Virus infection is responsible for many maternal and fetal deaths in different countries in Asia, Africa and Latin America. Recent epidemics in Central African Republic, India, Bangladesh, Pakistan, and Sudan revealed harmful effects of Hepatitis E Virus infection on pregnancy. Acute Hepatitis E Virus infection in pregnancy is associated with an increased incidence of acute liver failure resulting in high morbidity and mortality in mothers. In addition, Hepatitis E Virus infection is also associated with increased fetal and neonatal morbidity and mortality. Although the aetiology of Hepatitis E induced severe liver disease and acute liver failure in pregnancy is still unknown, the current management of these patients is not different than the management of Acute Hepatitis E Virus infection in males and non-pregnant females. Patients with acute liver failure require admission in an intensive care unit and many of these patients with severe acute liver failure require liver transplantation. Ribavirin, an anti-viral medication often used in the management of Hepatitis C infection, may play an important role in the management of severe cases of acute Hepatitis E Virus infection in Pregnancy. However, the use of Ribavirin is restricted in pregnancy due to its teratogenic effects. Although some published reports did not show any teratogenic effects in pregnant patients when this drug was used in the third trimester of pregnancy, further clinical trials are needed before this drug can be approved for use in pregnant women with Hepatitis E Virus infection. Currently, there is no effective vaccine for the prevention of Hepatitis E Virus infection in pregnancy. Prevention of Hepatitis E Virus infection with an effective vaccine and proper management of patients after they develop acute Hepatitis E Virus infection can save many pregnancies and lives.

**Keywords:** Acute Hepatitis E; Pregnancy; Acute Liver Failure; Intensive Care Unit; Ribavirin; Hepatitis E Vaccine

### Introduction

Every year, more than 20 million Hepatitis E Virus infection results in approximately 70,000 deaths worldwide [1]. The majority of Hepatitis E related deaths occurs in countries in Asia, Africa, and Latin America. Hepatitis E Virus is faeco orally transmitted and contaminated water. Contaminated water is the most common source of infection in these countries where flooding of low lying areas results in epidemics of Hepatitis E infection almost every year [1,2]. Numerous studies [3] revealed high rates of maternal, fetal, and neonatal mortality and morbidity resulting from Hepatitis E infection in pregnancy. Hepatitis E infection is responsible for 2,400-3,000 stillbirths in developing countries every year [1,4]. In addition, death of pregnant mothers also result in many fetal deaths (5). Furthermore, Hepatitis E Virus infection was found to be associated with preterm delivery and reduced neonatal survival in different studies [4,6].

**The global scenario of Hepatitis E Virus infection in pregnancy**

During an epidemic in Central African Republic in 2002, all pregnant women with serologically confirmed Hepatitis E Virus infection (total number of patients nine) had a premature delivery. According to the report, three of these babies were stillborn and one died immediately after delivery [7]. Newborns with mothers having Acute Hepatitis E infection at the time of delivery comprised fifty per cent of the deaths in the 1993 - 1994 outbreak in Islamabad, Pakistan [8]. During the 2008 - 2009 Hepatitis E outbreak of Tongi, Bangladesh, pregnant women with jaundice were two times more likely than non-jaundiced pregnant women to miscarry or deliver a stillborn baby [9]. In two separate hospital-based prospective studies in India, 15% to 60% of the live-born infants of mothers with acute Hepatitis E infection died during the first week after delivery [4,10]. During the 2010-2011 outbreak of Sudan, 14 intrauterine deaths and 9 premature deliveries were reported among 39 pregnant Hepatitis E cases [11]. Besides, acute Hepatitis E infection is also associated with eclampsia, hemorrhagic complications, and liver failure [12-14].

**What happens when a pregnant patient develops acute Hepatitis E Virus infection?**

Pregnant patients with acute Hepatitis E Virus infections usually present with nausea, vomiting and mild to moderate rise of amino-transferase levels. Clinical features in pregnant patients are not different than those observed in Hepatitis E infections in male and non-pregnant females. However, pregnant women often develop acute liver failure with coagulopathy and encephalopathy. Maternal death, fetal death, abortion, and premature delivery are all complications of Hepatitis E infection during pregnancy [15]. Why these complications occur during pregnancy is unknown. However, hormonal, immunological, and genetic factors may play a role in the pathogenesis of Hepatitis E induced acute liver failure in pregnancy. Steroid hormones, known for their immunosuppressive properties, remain elevated during pregnancy and may enhance viral replication [13,16,17]. Reports suggest an association between the reduced expression of the progesterone receptor and complications of Hepatitis E infection during pregnancy [18]. Estrogen receptors ESR1\_ and ESR2\_ were reported as potential biomarkers predicting worse fetal and maternal outcome in pregnancy with Hepatitis E infection [19]. Moreover, Hepatitis E virus can grow in the human placenta resulting in fetal and maternal complications in pregnancy [20]. So, multiple factors - Hepatitis E genotypes, hormonal and immunological factors and host and environmental factors - may influence the clinical outcome of Hepatitis E infection and Hepatitis E induced liver failure in pregnancy [17].

**Management of acute Hepatitis E Virus infection in pregnancy**

Currently, there is no specific treatment for Hepatitis E infection and acute liver failure during pregnancy. Different centres used different modalities of treatments and some centres also used steroids as a supportive treatment. Liver transplantation remains the only option in most of these patients who develops severe acute liver failure [21].

Genotypes 1 and 2 Hepatitis E virus are commonly associated with liver failure in pregnant women in tropical countries. A similar association is not found with Hepatitis E genotypes 3 and 4. Some case reports indicate that under special circumstances Hepatitis E genotype 3 infections in Europe may also take a clinical overt course [22,23]. However, these patients cleared their infection without any signs of severe complication of liver failure. According to some recent findings, genotype 4 infection may also be associated with preterm birth and abortion [24] which need further evaluation.

Acute Hepatitis E infection is a self-limited disease and in the majority of cases, patients do not need any specific treatment for this infection. However, genotype 1 or 2 infections in pregnant patients with acute liver failure may warrant specific treatment. Ribavirin was used in five non-pregnant patients with acute liver failure or acute on chronic liver failure due to genotype 1 hepatitis E infection [25,26]. All these patients survived and no severe adverse effects were observed in them. The prognosis of acute liver failure due to Hepatitis E infection in pregnant women can be worse than in non-pregnant female and male patients. Currently, Ribavirin is not approved in pregnant women due to its teratogenic effects. No published data are available on the use of Ribavirin in pregnant women with Hepatitis E induced acute liver failure. Two hundred and seventy-two cases of pregnant women treated with Ribavirin immediately before or during

pregnancy or with partners taking Ribavirin currently or in the past six months have been enrolled in a large pregnancy registry [27]. Data from this registry did not reveal any teratogenic effects of Ribavirin in pregnant women. Acute liver failure due to hepatitis E infection usually occurs in the third trimester of pregnancy when organogenesis has already been completed. Furthermore, acute liver failure due to acute hepatitis E infection has a mortality of 20% in pregnant women. Ribavirin can be used in pregnancy with acute Hepatitis E infection after rigorously designed and controlled clinical trials prove both its efficacy and safety.

### Management of Hepatitis E induced liver failure in pregnancy

Acute liver failure in pregnancy is managed as acute liver failure in other patient populations. The management of complications of acute liver failure is done on an individual basis. Abortions, preterm labour, premature rupture of membranes and stillbirth are treated as in other cases of pregnancy. Acute liver failure patients should ideally be managed in an intensive care unit with continuous, non-invasive cardiac, oxygen saturation and blood pressure monitoring. Elective ventilation should be done for patients with grade IV encephalopathy and those with grade III encephalopathy and evidence of cerebral oedema. All patients should be started on prophylactic antibiotics for the prevention of infection. The preferable mode of delivery is vaginal delivery. Fresh frozen plasma is used in cases of active bleeding. Successful liver transplantation can be done in pregnant females with acute liver failure [28,29]. Termination of pregnancy in endemic regions does not change the outcome of acute liver failure due to acute hepatitis E infection in pregnancy. Unless the mother is critically ill, there is no evidence to support stopping breastfeeding to prevent transmission [30].

### Prevention of Hepatitis E in pregnancy

New vaccines against Hepatitis E seem to be effective in preventing hepatitis E infection [31,32] and may prevent Hepatitis E infection and complications including acute liver failure. However, according to some studies, infections can still occur among vaccinated adults [33]. Data on safety and efficacy in pregnant women are not adequate [34]. Further studies need to be undertaken to evaluate the effectiveness of these vaccines in the prevention of maternal and neonatal morbidity and mortality. A large vaccine trial is currently studying the Chinese HEV vaccine (Hecolin) in more than 20,000 women in Bangladesh ([clinicaltrials.gov](https://clinicaltrials.gov), NCT02759991) which, when complete, can give us future direction on effective prevention of Hepatitis E infection in pregnancy and resulting maternal and fetal mortality and morbidity [35].

### Conclusion

Hepatitis E infection in pregnancy is an important cause of maternal and fetal morbidity and mortality in many developing countries. Currently, there is no proper guideline for the management of acute Hepatitis E infection and its complications in pregnancy. Moreover, no effective vaccine against Hepatitis E infection is available to the vulnerable populations which include pregnant women. An effective vaccine, a proper management guideline for Hepatitis E infection in pregnancy, and effective medications for severe Hepatitis E infection can save many lives and pregnancies. Hepatitis E infection in pregnancy is a maternal and child health issue which needs to be considered as a priority.

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