Viral hepatitis, a common disease in all parts of the world, is caused by infection with one of the several hepatotropic viruses, some of which have possibly still not been identified. Two of these viruses, namely, the hepatitis A virus and the hepatitis E virus (HEV), are transmitted by the enteric route. Both these viral infections are self-limited, causing only acute hepatitis. In India, though infection with hepatitis A virus is more widespread, it is often asymptomatic. In contrast, illness due to HEV infection is the most frequent cause of clinical acute hepatitis in India.

Hepatitis E has several interesting epidemiological features. The disease occurs either in the form of large epidemics, which are related to contamination of drinking-water supplies, or in the form of sporadic cases in the absence of a discernible outbreak. The disease attack rates are particularly high among young adults. Though children do acquire HEV infection, they develop clinical disease only occasionally. Person-to-person transmission of infection from patients with epidemic and sporadic hepatitis E is uncommon; the reason for this remains unknown. Transmission of HEV from mother to fetus and through transfusion of HEV-infected blood has been shown to occur; however, the contribution of these routes of transmission to the total burden of hepatitis E in disease-endemic areas remains unclear.

Animal viruses genetically related to the human HEV have been identified in the last 10 years, raising the possibility that HEV may be a zoonotic disease. These animal isolates of HEV have been shown to be associated with human disease in non-endemic regions. However, the human and animal isolates of HEV from India have been shown to be genetically distinct, indicating that animal HEV may not be a cause of human disease here.

An interesting and intriguing observation with HEV infection has been its relationship with pregnancy. Hepatitis E is usually a self-limiting disease with a low rate of fulminating hepatic failure (FHF). However, when this infection occurs in pregnant women, the consequences are particularly disastrous. Pregnant women, particularly those in the second and third trimesters, are more frequently affected during hepatitis E outbreaks. In addition, among pregnant women, especially those infected in the third trimester, the disease is more severe with high mortality rates. In an epidemic in Kashmir, attack rates among those in the first, second, and third trimesters were 8.8%, 19.4%, and 18.6%, respectively, as compared with 2.1% among non-pregnant women and 2.8% among men. Further, FHF developed in 22.2% of the affected pregnant women, in comparison with 2.8% and none of affected men and non-pregnant women, respectively. Similarly, during a large epidemic of hepatitis E in Kanpur affecting an estimated 79,000 persons, 13 of 48 deaths were among pregnant women; this suggests increased mortality rate among pregnant women since such women constitute only around 2% of the total population in India at any time.

As indicated earlier, vertical transmission of HEV infection from mother to infant is known. In one study, five of eight babies born to mothers with acute hepatitis E had HEV RNA in their blood specimens obtained at birth. Further, HEV infection also appears to adversely affect the fetal outcome, with increased frequencies of abortions, still-births and neonatal deaths. In addition, the infected babies frequently had hypoglycemia and biochemical evidence of liver injury.

The mechanism of severe liver injury in pregnant women with acute hepatitis E remains unknown. In an animal study, the course of liver injury among pregnant primates experimentally infected with HEV was similar to that among non-pregnant animals. However, this may not be surprising since HEV infection in primates leads to mild liver injury, with only liver enzyme elevation, but no bilirubin elevation or symptoms. The severe liver injury due to HEV infection during pregnancy may be related to one of several possible host factors, such as differences in immune response or hormonal factors. In a recent study, we looked at immune parameters in pregnant women with HEV infection and compared these with those in non-pregnant women with this infection as also pregnant and non-pregnant healthy women. This study showed that HEV infection during pregnancy was associated with a shift in the Th1/Th2 balance towards a Th2 response. However, since the mechanisms of liver cell injury in hepatitis E remain unknown, it is difficult to ascribe the severity of liver injury in these patients to this immune phenomenon.
No studies have been undertaken on the effect of estrogens and progesterone on the HEV or on host response to this infection.

In a recent study published in abstract form, it was suggested that infection of the fetus with HEV may be responsible for the increased severity of the disease in the mother; however, this hypothesis will need further proof before it can be accepted. Thus, based on current evidence, the mechanism of liver injury in pregnant women remains inconclusive.

Failure to understand the mechanism of liver injury in hepatitis E should however not preclude attempts at therapeutic or prophylactic interventions in pregnant women in regions where hepatitis E is endemic, since such a measure may save precious young lives. Unfortunately, very few such studies have been undertaken. In one study, Arankalle et al assessed the efficacy of an Indian preparation of immune serum globulin in preventing hepatitis E among pregnant women during an epidemic. Although the frequency of HEV infection was significantly lower in women receiving immune serum globulin than in control women (10/55 versus 18/53), the study did not have sufficient power to detect a reduction in the number of clinical cases. Unfortunately, the role of therapeutic termination of pregnancy, a measure that has been shown to be useful in liver failure due to acute fatty liver of pregnancy, in the treatment of liver failure due to hepatitis E has not been studied.

In this issue of the Journal, Banait et al report their experience with the outcome of acute liver failure associated with hepatitis E in pregnant women. For this, they retrospectively analyzed the records of 42 pregnant women with this condition who had been admitted to an intensive care unit during a one and a half year period.

As would be expected, hepatitis E was the commonest cause of acute liver failure, being responsible for 42 of 48 patients. Most of the women with acute liver failure due to hepatitis E were in the third (26/42) or second (14/42) trimester of pregnancy, and most had grade II or III hepatic encephalopathy at admission. Nearly half of these women (23/42) died, with the mortality rate being higher in those with higher grades of hepatic encephalopathy.

Of the 42 pregnant women, 22 delivered; of these, 13 were spontaneous deliveries and 9 underwent induced labor because of intrauterine fetal death. All these deliveries were by the vaginal route and only 8 resulted in live birth. Of these 22 mothers, 9 (41%) died. Among the remaining 20 women in whom pregnancy continued, 14 (70%) died, 5 had normal delivery at term, and one had pre-term delivery with the infant dying in early neonatal period. The overall maternal mortality rates were similar in those women who delivered during the phase of liver failure and those who did not. However, on excluding the six women who presented with grade IV hepatic encephalopathy, maternal mortality was lower among those who had delivered versus those who had not (7/20 vs. 11/16; p=0.046).

Do these results suggest that we should offer termination of pregnancy to women who present with this condition? The answer is no. First, retrospective studies such as the one under consideration have their limitations. Thus, the patients with continuation of pregnancy or otherwise may have been different in several other respects. As the authors themselves point out, in a multivariate analysis, the grade of initial hepatic encephalopathy was the only factor significantly associated with maternal survival; in contrast, discontinuation of pregnancy showed no such association. Also, the discontinuation of pregnancy in most cases was spontaneous and not induced; thus, it is difficult to say whether elective termination with therapeutic intent would lead to improvement in mortality or not. The only significant difference observed was found on subgroup analysis (pregnant women excluding those with grade IV encephalopathy), which had not been defined a priori. Thus, the observations of this study can at best be hypothesis generating.

So, what should be the current recommendations for the treatment of pregnant patients with hepatitis E? In the absence of any evidence that termination of pregnancy can prevent the development of or ameliorate the course of FHF in such patients, it is not possible to recommend induction of delivery. Such an intervention carries a higher risk than usual in patients with liver failure because of their critical general condition, hemostatic defects, hemodynamic instability, and possible risk of increase of intracranial pressure during uterine contractions. Thus, till definitive evidence of benefit of delivery is available, the decision to induce labor should be based on considerations other than potential improvement of
liver function. If induction of labor is decided upon or if the patient enters labor spontaneously, vaginal delivery may be preferable to cesarean section in view of the high risk of intraoperative and postoperative bleeding. Episiotomy too may be avoided, if possible. It may be advisable to routinely use ergometrine in such patients in the immediate postpartum period to reduce the chances of postpartum bleeding. If postpartum bleeding occurs, infusion of fresh frozen plasma may be indicated. Systemic infections are common in these patients and broad-spectrum antibiotic cover may be useful.

While continuing to follow these general guidelines, we need to embark on prospective studies on the role of termination of pregnancy on the outcome of pregnant women with FHF due to hepatitis E. Such a study will be difficult to conduct because it will have to be multicentric if it has to have sufficient power. Further, it will need cooperation of obstetricians and hepatologists, an uphill task when several centers are involved. Though such a study may appear to be ethically implausible, the current state of knowledge on the subject provides a perfect equipoise, i.e., absence of evidence to either support or undermine the proposed intervention, an essential condition for beginning a randomized trial.

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References


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