Commentary

Seroprevalence of hepatitis E infection in pregnancy - more questions than answers

Hepatitis E (HEV), a single-stranded RNA virus of the Hepeviridae family is an emerging infectious disease of global importance. While HEV is the most frequent cause of acute viral hepatitis in developing countries, HEV infection can also progress to chronic hepatitis and cirrhosis in organ transplant recipients. Also, antibodies to HEV have been found to be highly prevalent in HEV non-endemic areas in Western Europe and the US despite acute clinical hepatitis seldom-reported. This difference in the natural history and epidemiology of so thought benign self limited HEV has fueled recent interest in the study of HEV infection.

In men and non pregnant women, acute HEV infection is usually self-limited and has a case-fatality rate of less than 0.1 per cent. However, in pregnant women in their second and third trimesters, particularly from certain geographical areas in India, HEV infection is more severe, often leading to fulminant hepatic failure and death in 30-100 per cent of patients. IgG antibodies to HEV represent the exposure to HEV and are markers of seroprevalence in a population. Seroprevalence data from endemic regions of India have been reported in children, general population and in patients with cirrhosis. However, the data on pregnant women have not been reported.

In this issue, Begum et al. report the seroprevalence of anti-HEV IgG antibodies in pregnant primigravidae. In their study of 300 asymptomatic pregnant women with no previous history of jaundice, the prevalence of anti-HEV IgG was found to be 33.67 per cent. Also the prevalence of anti-HEV IgG was significantly higher in urban population and people using drinking water source other than tap water such as wells, and ponds. Interestingly, increasing age was not associated with increased prevalence of anti-HEV IgG antibodies.

This study from northern India is significant in the sense that HEV infection in pregnancy is associated with increased mortality. Also, the prevalence of antibodies in pregnant women has not been investigated from north India. The increased mortality of HEV infection during pregnancy is not seen in all endemic regions. Studies from southern India, and Egypt, despite indicating the high prevalence of hepatitis E infection in pregnancy were associated with a low mortality. The reasons for the difference in mortality remain unclear, although genotype or subtype differences in genotype are proposed. This study highlighted the low prevalence of anti-HEV IgG antibodies and the authors suggested the increased susceptibility of this population to HEV infection and the probable need for vaccination.

A number of things need to be clarified before making this recommendation. The role of anti-HEV IgG antibodies in HEV infection remains unclear. Subclinical infection defined by the presence of anti-HEV IgG antibodies without previous history of jaundice is speculated to serve as a possible reservoir for infection in endemic regions. Asymptomatic subclinical HEV infection may be important because subjects without clinical symptoms may continue to shed virus and thus maintain an environmental reservoir of HEV. Although earlier studies highlighted that subclinical infection with seroconversion was not associated with symptoms or with liver enzyme elevation, a recent study from Japan reported that subclinical infection was associated with elevations in liver function, and 3 per cent of participants with elevated alanine aminotransferase levels had evidence of subclinical infection. Thus the mechanisms for subclinical infection remain unclear. Whether subclinical infection is attributable to low level exposure to infectious virus from zoonotic sources or represents protective immunity in the host requires further exploration.
Given the lack of data on the role of anti-HEV IgG in HEV infection, the seroprevalence data need to be carefully interpreted. The half-life of anti-HEV IgG is 28 days during early convalescence and from 0.5-4.0 yr when measured later\textsuperscript{17,18}. Thus the duration of anti-HEV IgG positivity following infection remains unclear. The low prevalence could be explained because of disappearance of antibodies which have a short half life. However a study from Egypt in 2428 pregnant women of which 44 per cent were primigravida, highlighted that 85 per cent of women had anti-HEV IgG antibodies without prior history of clinical hepatitis or jaundice\textsuperscript{11}. Thus, the disappearance of antibodies may not entirely explain the low prevalence in pregnant women in north India. There is a clear discrepancy in the prevalence and mortality based on the geographic location as the mortality rate due to HEV infection in pregnancy is very low in Egypt. This difference in the seroprevalence could also be due to the presence of a less virulent circulating strain of HEV in Egypt which produces asymptomatic disease or the presence of cross-reacting antibodies to an HEV-like virus which is not associated with clinical disease and may explain the high seroprevalence\textsuperscript{11}. Also, if the other hypothesis that pregnant woman may not be able to mount an immune response holds true, the high seroprevalence in Egypt cannot be explained.

Thus, the low seroprevalence data from northern India may be a true representation highlighting the increased susceptibility of this population. However, a number of weaknesses exist in the study which need to be discussed before extrapolating the results. The study did not have an age matched control group to see if there was a difference in the seroprevalence of anti-HEV IgG in pregnancy when compared to age matched non pregnant women. The authors selected antenatal women between 16-24 wk and did not enroll women in the third trimester. It would have been interesting as HEV infection in the third trimester is associated with increased mortality and foetal complications in pregnant women. Also epidemiological data on contact with animals were not highlighted in the study. A number of studies from India have highlighted the zoonotic source of HEV infection as demonstrated by the presence of anti-HEV antibodies in various animal species\textsuperscript{19}. Also, the study is not a community based prevalence study, but focused on a specific population of pregnant women visiting the antenatal clinic and results may not be applicable in the community.

Nevertheless this study has shed light on the low prevalence of anti-HEV IgG in pregnant women in north India. This study suggests that significant proportions of pregnant women are at risk of developing HEV infection during pregnancy. Further well designed studies incorporating control population of age-matched women in a larger population and also in other endemic regions of India are required to confirm these findings. Also studies incorporating serial liver function tests to detect whether subclinical infection is associated with changes in liver functions are required to further understand the pathophysiology of subclinical infections.

The role of HEV vaccination is still not explored in pregnant women. A phase II trial of a recombinant HEV vaccine administered to a group of volunteers, mostly male (\textgtrsim\textasciitilde99\%), in the Nepalese Army was reported recently with the primary end point being prevention of clinically overt HEV infection\textsuperscript{20}. The efficacy of the vaccine against clinically overt HEV infection was 95.5 per cent in subjects who received all three vaccine doses and no obvious adverse events were identified. However, the study included exclusively male subjects. Also the duration of the induced immunity is unknown, as well as the efficacy of the vaccine in preventing asymptomatic HEV infection. Also the safety and efficacy of the vaccine in pregnant women have not been investigated. We still have a way to go before routine vaccination can be recommended in pregnant women at risk of HEV infection.

To conclude, HEV infection is one of the newly emerging zoonotic infectious diseases in developed countries and a considerable source of morbidity and mortality in the developing world that has not yet been fully explored. Further research is required to understand the pathogenesis of subclinical HEV infection in pregnant women, the high mortality in pregnancy in certain endemic regions in India and clarify the role of routine vaccination of pregnant women.

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References


