Indian J Med Res 113, February 2001, pp 35-39

Outcome of hepatitis E virus infection in Indian pregnant women admitted to a tertiary care hospital

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Accepted January 22, 2001

Background & objectives : **Information on the incidence and prevalence of hepatitis E virus (HEV) infection in Indian pregnant women is scanty. Only a few studies have been done so far to document the vertical route of transmission of this virus. We therefore studied the prevalence of HEV infection in pregnant women with hepatitis and the outcome of their pregnancy.**

Methods : **Fifty pregnant women with clinical hepatitis were included in the study. After informed consent, their blood samples were tested for potential causes of hepatitis including hepatitis A, B, hepatitis C, and hepatitis E infections.**

Results : **Of the 50 cases, 20 (40%) patients were found to be positive for IgM anti-HEV (group A) and 30 (60%) were negative for IgM anti-HEV antibodies (group B). Overall 19 patients were in their second trimester while 30 were in third trimester. Of these 52.6 per cent (10/19) of those in second trimester and 50 per cent (15/30) in third trimester had fulminant hepatic failure (FHF). Only one patient presented in the first trimester who had acute viral hepatitis (AVH) and recovered completely. Of the HEV infected women, 70 per cent were in their third trimester and remaining 30 per cent in second trimester of pregnancy. A similar percentage of patients *i.e.*, 14 of 20 (70%) manifested with FHF while 6 (30%) had acute hepatitis leading to recovery. The percentage of women with FHF and acute hepatitis was 36.6 and 63 per cent, respectively, in group B. Upon follow up all the 13 of the 14 HEV infected patients with FHF expired and only one delivered a male baby during the illness. The fatality rate in HEV infected patients was not different between the second and third trimesters (66.6% vs. 71.43%, respectively).**

Interpretation & conclusions : **This study suggests that HEV causes high mortality in pregnant women as compared to non-HEV infected pregnant women. This pilot study indicates that steps should be taken to prevent HEV infection during pregnancy.**

Key words Dual infection - fetal infection - fulminant hepatitis - hepatitis B - India - pregnancy - transplacental infection - viral hepatitis

Acute viral hepatitis is a major public health problem in developing nations with poor sanitary conditions[1]. Enterically transmitted non-A, non-B hepatitis (NANB) virus now known as hepatitis E virus (HEV) has been identified as a major cause of water-borne epidemics in India[2] and also an important cause of enterically transmitted sporadic hepatitis[3]. The virus is transmitted by the faecal-oral route and has an incubation period of 25-40 days. The disease is usually self-limiting without the development of chronicity or long-term sequelae. However, HEV infection often leads to fulminant hepatitis especially

among pregnant women. As high as 40 per cent fatality has been reported in third trimester[4,5]. The mortality in HEV positive pregnant women is higher than in HEV positive non-pregnant women[2,6,7].

There is only one report of HEV infection in pregnant women from India and its effect on the outcome of pregnancy[8]. However, the number of pregnant mothers included was small. There is no other study from India on the prevalence of sporadic HEV infection in this particular group and its significance in terms of pregnancy outcome. Therefore, a prospective study was undertaken to assess the mortality rate in pregnant women hospitalised at a tertiary care hospital, to find out the difference in the outcome between HEV positive and HEV negative pregnant women.

Material & Methods

The study was conducted at the All India Institute of Medical Sciences (AIIMS), New Delhi a tertiary care center in north India. Serum samples were collected over a period of 14 months between January 1997 and February 1998 consecutively from pregnant women who presented with signs and symptoms suggestive of acute viral hepatitis or had a 2.5 fold elevation of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) and a serum bilirubin of > 2.0 mg/dl. All subjects with history of chronic liver disease or any other known cause of hepatitis were excluded from the study. Of the 53 pregnant women admitted with suspected viral hepatitis, only 50 fulfilled the inclusion criteria. Informed consent was obtained from these women. Other women either died before they were examined or were shifted to other hospitals. Whenever possible the spouses of the HEV positive women were also tested for HEV infection.

Acute viral hepatitis (AVH) was defined as an acute self limiting disease with serum AST and ALT levels at least 2.5 folds with or without clinical jaundice[9]. Diagnosis of fulminant hepatic failure (FHF) was made on the basis of criterion of Trey *et al*[10]. In brief, when the patient after having a typical acute hepatitis develops hepatic encephalopathy within four weeks after the onset, which is characterised by mental changes progressing from confusion, to stupor and coma as a result of severe impairment of hepatic function, without any history of pre-existing liver disease. The liver function tests including AST, ALT, alkaline phosphatase, bilirubin, total protein, and prothrombin time were done in all patients using standard methods as being practiced in our department for the past several years. For alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase ready-to-use Randox® kits (Randox Laboratories Ltd, UK) were used and tests were done on Hitachi 717 autoanalyser (Hitachi®, Japan) and expressed in international units (IU). The patients were followed till delivery or death.

Viral markers: Tests for hepatitis A (IgM and IgG anti-HAV), hepatitis B virus (HBsAg and IgM anti-HBc), hepatitis C virus (anti-HCV), and Cytomegalovirus (IgM antibodies) were carried out in all patients so as to rule out other potential causes of hepatitis. Highly specific enzyme immunoassay kits from Pasteur-Sanofi, France were used for IgM and IgG anti-HAV and HBs Ag and IgM anti-HBc Ag detection. For anti-HCV antibody detection a third generation (v-3) EIA kit (Core, NS-3, NS-4, & NS-5 antigens), (Ortho HCV 3.0, Ortho Diagnostic Systems GmbH, Germany) was used. Active infection of Cytomegalovirus was looked for by the IgG and IgM (μ-capture) ELISA kits from Organon-Teknika (Poland). Antibodies against HIV (1+2) were tested by the Innotest EIA kit (Innogenetic, N.V., Belgium) and the reactive cases if any, were retested three times and finally confirmed by Western blotting and excluded from the study.

Antibodies against hepatitis E virus (IgM anti-HEV) were detected using μ-capture enzyme immunoassay (Genelabs Inc., Singapore). The kit uses recombinant HEV antigen from the structural region of viral genome to detect the presence of IgM antibodies. All women found positive for IgM anti-HEV antibodies, were followed up till delivery of the baby.

Statistical analysis: Chi-square test (with Yate's correction) was used to find out the statistical significance between the two groups. However, to

compare the biochemical parameters between those dead and alive within each group, unpaired t-test/ Wilcoxen Rank Sum test was used[11]. The same method was applied to compare these parameters between the subgroups. Significant values were considered at 5 per cent level of significance (one tailed test).

Results

Fifty patients who fulfilled the inclusion criteria were registered during the study period. The mean age was 27±3.5 yr. Overall, 30 patients (60%) were in the third trimester at the time of hospitalisation with gestational period of 33±5.3wk. Nineteen patients (38%) were admitted in the second trimester of pregnancy with gestational period of 23±3.3 wk. Only one patient was in the first trimester (6 wk pregnancy). All our patients were sporadic cases and hailed from Delhi or surrounding areas. None of the patients had evidence of hepatitis A, hepatitis C, Cytomegalovirus infection. Twenty (40%) patients were positive for anti-HEV IgM (Group A), while 30 were negative for anti-HEV IgM antibodies (Group B). Of these 30 women, 5 had hepatitis B infection.

Of the 20 patients in group A, only six (30%) were in the second trimester, while 14 (70%) were in third trimester. This difference in preponderance of HEV infection in third trimester was statistically significant ($P < 0.005$). Of the 30 patients in group B, 16 (53.3%) were in third trimester, 13(43.3%) in second trimester and only one in the first trimester (Table I). This difference was not significant. Fourteen (70%) of the 20 HEV positive patients developed fulminant hepatic failure (FHF) while six (30%) had acute hepatitis and recovered. Thirteen (93%) of the 14 FHF patients died before delivery while one died just after delivering the baby, thus all had fatal outcome. The values of serum bilirubin, AST and ALT were significantly higher in those who had fulminant disease compared to those who had non-fulminant disease (Table II).

Mortality in HEV negative patients (group B) was significantly ($P < 0.005$) lower as compared to group A (Table I). Of the 30 patients of group B, only 11(36.6%) developed FHF. Nineteen (63.3%) patients had complete recovery in this group. The serum bilirubin, AST and ALT in both the groups were significantly higher in those who died than those who survived (Table II). However, if the women

Table I. Mortality rate and other clinical parameters in the HEV infected and uninfected pregnant women

	Trimester			Total
	I	II	III	
HEV infected (Group A):				
Number of women	0	6	14	20
Mean gestational period (wk)	NA	21.5±3.5	35.2±4.6	32±7.5
Fulminant hepatic failure	0	4	10	14
Acute viral hepatitis	0	2	4	6
Fatal outcome/Subtotal	NA	4/6(66.6)	10/14(71.4)	14/20(70.0)
Hepatitis E negative (Group B):				
Number of women	1	13	16	30
Mean gestational period (wk)	6	22.0±4.0	30.2±4.5	26.46±5.9
Fulminant hepatic failure	0	6	5	11
Acute viral hepatitis	1	7	11	19
Fatal outcome/Subtotal	0/1	6/13(46.0)	5/16(31.2)*	11/30(36.6)*

NA-Not applicable; *$P < 0.005$ compared to fatal outcome in group A. Figures in parentheses indicate percentages

Table II. Analysis of liver function parameters in HEV infected *vs.* uninfected pregnant women

Disease group	Bilirubin (mg/dl)	AST (IU/L)	ALT(IU)	Alk-Phos (IU)
HEV infected (n = 20)	14.35±4.59	669.5±406.8	589.3±256.5	426.8±184
Deceased (n = 14)	16.2±2.4**	847.8±398.9**	673.8±243.8*	481.4±203
Survivors (n = 6)	11.2±5.8	364±179	444.4±222.7	333.3±99.5
HEV uninfected (n = 30)	9.4±6.6	601±641	492.5±406	398.4±167.8
Deceased (n = 11)	15.8±6.2'	1159.4±1002.3'	862.7±729.4'	426.2±138.4
Survivors (n =19)	6.0±5.1	431.95±182.5	372.55±199.7	466±244.5

AST, aspartate aminotransferase; ALT, alanine aminotransferase, Alk-Phos, alkaline phosphatase; Data are mean ± SD; P *<0.05, ** < 0.01, ' < 0.001, compared to survivors

were grouped irrespective of etiology, the difference in liver function test values, in those who died and who survived, was not statistically significant.

Discussion

Hepatitis E is widely prevalent in India due to poor sanitation conditions[1-3,5-8]. It has also been reported that women in the third trimester of pregnancy who develop hepatitis E are at higher risk of developing FHF with high mortality[8]. In the present study, 10 of 14 HEV positive FHF patients (71.4%) were in third trimester while only 4 (28.5%) were in second trimester. Thus our findings are in accordance with previous findings. The mortality rate in HEV infected women was higher in this study as compared to a previous study from India[8] and this could probably be due to the inclusion of hospitalized patients who have a relatively serious course of illness and were referred to this tertiary care hospital from other hospitals/clinics.

Only very few studies have reported on sporadic fulminant hepatitis[5,12-14]. To the best of our knowledge this is probably the first study carried out prospectively to present the mortality rate and other clinical parameters in hospitalised pregnant women infected with hepatitis E virus. The only earlier study[8] reported that 9 out of 10 patients studied became ill during an epidemic and the mortality rate with FHF was only 50 per cent. Khuroo *et al*[8] also reported that 80 per cent (8/10) of their patients had normal delivery while all our patients with FHF died before or just after the child birth. The most plausible reason for these contradictions could be the nature of infection, all our patients were sporadically infected while Khuroo's cases were from a localised epidemic[8]. It is possible that several other factors beyond the scope of this study might have played role in such a high fatal outcome. Thus this study confirms the earlier reports that hepatitis E in a sporadic situation also carries a high mortality in pregnant women as in the case of epidemic hepatitis[2-5,7].

Acknowledgment

The authors thank Km Veena Kumari for technical assistance.

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