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Original Article

Feto-Maternal Outcomes of Hepatitis E Virus Infection in Pregnancy of Bangladeshi women

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Abstract
Hepatitis E virus (HEV) infection is responsible for more than half of acute viral hepatitis (AHV) with high feto-maternal complications. Bangladesh has high prevalence of HEV infection among pregnant women. This study was undertaken to observe fetal -maternal outcome of HEV infection in Bangladeshi pregnant women . For this purpose a total of 56 pregnant women with AVH were enrolled from two tertiary care hospitals of Dhaka, Bangladesh. Blood samples were collected and tested for HEV Ig-M, HBsAg and Anti HCV. Thirty one pregnant women were tested positive for HEV Ig-M, acted as case and rest 25 women had viral hepatitis other than HEV, acted as control group (non-HEV). Among the HEV infected pregnant women, 38.7% of the patients (12/31) were aged between 21-25 years with mean age of 23.7 + SD 4.5 years. Twelve (39%) AVH-E patient died due to fulminant hepatic failure (FHF), hepatic encephalopathy (HFE) and multiorgan dysfunction. Maternal mortality due to HEV was greater [(RR), 9.6; 95% CI, 1.3 to 69.5] in HEV-infected women than in non- HEV infected women and it was higher in 2nd trimester (55.5%) then the 1st and 3rd trimester of pregnancy. Babies born to pregnant women with acute Hepatitis due to HEV (AHV-E) were more likely to have intrauterine death (RR 18.68; p = 0.03) and preterm delivery (RR 7.25; p = 0.05) than the non-HEV infected pregnant women. Only 23% (7/31) babies reached up to term maturity. In conclusion, his study reveals that comparing with non-HEV infection, pregnant women with AHV-E infection causes worse feto-maternal outcomes especially in the second trimester of pregnancy which needs special attention of healthcare providers to reduce bad obstetric outcome in HEV endemic countries.

Keywords: Feto-metarnal; Hepatitis E virus; Mortality; Pregnancy

Introduction:

Hepatitis E virus (HEV) infection is one of the leading cause of human viral diseases with clinical and pathologica[l] features of acute hepatitis1. Globally an estimated 2.3 billion people are infected with HEV[2] and more than three million symptomatic cases of acute HEV that result in approximately 70,000 deaths in each year[3]. HEV infection is endemic in large parts of Asia, Africa and Latin America. Epidemic and sporadic cases has been reported from these areas[4]. Bangladesh is one of the endemic countries for HEV infection[5] where sero-prevalence of HEV infection among the general population is 22.5%[6]. Viral hepatitis in pregnancy has been a subject of continuing interest and controversy. In men and non-pregnant women, HEV infection is a self limited disease, rarely develops chronic state with a case fatality rate of less than <0.1%[7].

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Although the mortality rate is usually low, the illness may be severe among pregnant women particularly from certain geographical areas like Iran, Africa, Middle East, India, Pakistan, Nepal and other Asian countries, with mortality rates reaching as high as 25%[8]. In India, HEV infection causes 60% of cases of jaundice and acute viral hepatitis (AVH) among pregnant women[9]. In Bangladesh, a study showed 58.33% prevalence of HEV hepatitis among pregnant women[10]. Approximately 19%-25% of maternal and 7%-13% of neonatal deaths (NND) in Bangladesh are associated with acute onset of jaundice during pregnancy and 58% of this jaundice was due to HEV infection[11] . Presently there is no published study where the outcome of HEV infection among Bangladeshi pregnant women was measured. Therefore the present study was undertaken to asscess feto-maternal outcomes of pregnant women infected with HEV and to compare these outcomes with non-HEV viral hepatitis infections.

Methods:

This study was conducted between January to December 2012 on pregnant women presented with AVH to the Department of Medicine, Department of Obstetrics & Gynecology, and

Department of Hepatology of Dhaka Medical College Hospital (DMCH) and Bangabandhu Sheikh Mujib Medical University (BSMMU), Bangladesh were included in this study. AVH was defined as those who had prodromal features of nausea and/or vomiting, loss of appetite or yellow color of mucus membrane or urine and serum bilirubin level to ≥2 mg/dl. The serum was tested for HEV specific Ig-M (anti-HEV-IgM); hepatitis B surface antigen (HBsAg); antibody to hepatitis A virus-IgM (anti-HAV-IgM) and antibody to hepatitis C virus (anti-HCV) by Enzyme Linked ImmunoSorbent Assay (ELISA). Available data regarding serum bilirubin, alanine aminotransferase (ALT), and prothrombin time (PT) were collected from the patients treatment register. Pregnant women with positive anti-HEV-IgM result were considered as case and who had other viral hepatitis e.g., hepatitis B or C were considered as control (non HEV). Those who were admitted with negative results of viral serologic markers and clinical evidence of other causes of jaundice (e.g., biliary obstruction, drug-induced jaundice or evidence of chronic liver disease) or patients with dual viral hepatitis infections were excluded from this study. Gestational age of pregnant wonem was calculated from last menstrual period or available earliest ultrasonography scan. All these patients were interviewed with a structured questionnaire and kept on a follow-up until an outcome of the pregnancy was achieved either in hospital wards or followed up in the outpatient services or over phone calls. Maternal outcomes were noted in terms of death or alive during or within 15 days after delivery. Fetal outcome were measured in terms of intra uterine death (IUD), abortions, preterm labor (PL), NND and term live baby (TLB). Maternal deaths were defined as those that occurred during pregnancy, delivery or within 15 days after a live birth, IUD, or miscarriage. A death that occurs prior to 20 weeks' gestation regarded as abortion; those occurring after 20 weeks constitute a IUD. Delivery of live baby before 37 weeks of pregnancy was defined as PL. A NND was defined as a death occurring within 28 days of birth. TLB was defined as live baby delivered after 37 weeks of pregnancy. This study was approved by Institutional Review Board of BSMMU (No BSMMU/2013/3027 dated 18-03-2013) and DMCH (No DMC/Ethical/2012/65, dated 16.05.2012).

Statistical Analysis:

Statistical analysis was performed using SPSS, version 17 (Illinois, USA). Significance of difference was estimated by Pearson's Chi-square test and t-test to compare discrete values between groups. Relative risk (RR) was calculated for complications in HEV-infected pregnant women and non-HEV-infected pregnant women. Probability (p value) < 0.05 was considered significant.

Results:

During the study period, a total of 67 pregnant women with acute hepatitis were admitted in those two hospitals. Among them, 56 women were selected who fulfilled the inclusion criteria. Among them 55.35% (31/56) pregnant women tested positive with anti-HEV Ig-M, while rest 44.65 % (25/56) of the pregnant women had viral hepatitis other than HEV. Among the non-HEV infected viral hepatitis patients, 80% (20/25) were tested positive for HBV, 4% (1/25) for anti-HCV and 16% (4/25) for HAV. In HEV infected pregnant women group, 29% (9/31) were between 16-20 years, 38.7% (12/31) were between 21-25 years, 25.8% (8/31) were between 26-30 years and 6.45% (2/31) were between 31-35 years of age. The mean age was 23.7 with standard deviation (SD) of ± 4.5 years. While in non-HEV infected pregnant women 8% (2/25) were between 16-20 years, 32% (8/25) were between 21-25 years, 48% (12/25) were between 26-30 years and 12% (3/25) were between 31-35 years of age and the mean age was 26.4 ± SD 4.22 years. Though the difference between the groups is not statistically significant ($p > 0.05$), the serum bilirubin level was increased by two folds in HEV infected pregnant women (9.8 ± 1.1 milligram/ deciliter) than non-HEV infected pregnant women (4.8 ± 1.8 milligram/ deciliter). Similarly PT was increased three folds in HEV infected pregnant women (51.2 ± 30.3 seconds) than non-HEV infected pregnant women (16.2 ± 3.9 seconds), although that was not statistically significant ($p > 0.05$). The ALT level changes significantly ($p \leq 0.05$) in HEV infected pregnant women (751 ± 55.2 International Unit/ liter) and non-HEV infected pregnant women (611 ± 89.4 International Unit/ liter). Among the HEV positive pregnant women, 61.3 % (19/31) patients were in their 3rd trimester, 29 % (9/31) were in 2nd trimester and 9.7 % (3/31) were in 1st trimester of pregnancy (Table 1). In contrast, 60% (15/25) of the non-HEV infected pregnant women were in their 3rd trimester. A total of 38.7 % (12/31) HEV infected pregnant women died during the study period, whereas only 1 (4%) died in the non-HEV infected preganant women group. All these women died due to FHF leading to HE and multiorgan dysfunction. The percentage of maternal mortality was higher in second trimester of pregnancy (55.5%, 5/9) than in first trimester (0%, 0/3) and third trimester (36.8%, 7/19). Pregnant women infected with HEV were at more at risk to die in compared to the non-HEV infected women [RR) 12.09; 95% confidence interval (CI) 1.71 - 85.40].In addition, women with HEV infection were at risk to have IUD (RR 18.68; 95% CI 1.15-302.36) and PTm delivery (RR 7.25; 95% CI 0.98 - 53.50) than the non HEV infected pregnant women. Among the HEV infected mother, 48.38 % (15/31)) had IUD and 3.2% (1/31) had NND. Other 9.7% (3/31) death occurred due to

spontaneous abortion in first trimester of pregnancy. The highest fetal death (55.55 %) was observed in second trimester of pregnancy (table 1).

Table 1: Feto-maternal outcome of pregnant women with AHV due to HEV and non HEV infections.

HEV infected women (n=31)					Non-HEV infected women (n=25)				
Trimester of pregnancy	Maternal outcome		Fetal outcome		Trimester of pregnancy	Maternal outcome		Fetal outcome	
	Died	Alive	Died	Alive		Died	Alive	Died	Alive
1st Trimester n=3	0 (0%)	3 (100%)	0 (100) (Abortion 3)	0 (0)	1st Trimester n=3	0 (0%)	3 (100%)	0 (0%)	3 [Term 3 (100%)]
2nd Trimester n=9	5 (55.5%)	4 (44.4%)	5 (55.5%) [IUD 5]	4 (44.4) (Term 4)	2nd Trimester n=3	0 (0%)	7 (100%)	0 (0%)	7 [Term 7 (100%)]
3rd Trimester n=19	7 (36.8%)	12 (63.2%)	7 [IUD 6(31.5%); NND 1(5.2%)]	12 [Term 3(15.7%); PTm9(47.3%)]	3rd Trimester n=15	1 (6.7%)	14 (93.3%)	0 (0%)	15* [(Term 14 (93.3); PTm 1 (6.6%)]
Total	12 (38.7%)	19 (61.3%)	15 (48.4%)	16 (51.6%)		1(4%)	24 (96%)	0 (0%)	25 (100%)

IUD = Intra uterine death, NND = Neo-natal death; PTm = pre-term delivery

*Mother died after delivery of the baby

Discussion:

AVH is one of the major causes of jaundice in pregnancy caused by different hepatotropic viruses including HEV, HBV,HAV and HCV etc. Though HEV could infect all young adults, it shows fatality in pregnant women and has impact on fetal outcome[12]. This study shows that during one-year time more than half of the pregnant women who were admitted in two tertiary care hospitals were infected with HEV. The higher rate of HEV infection in pregnant women of Bangladesh was previously observed by other researchers also (10). Other HEV endemic countires like Pakistan and India also reported such high prevalence of infection[13,14]. In present study, highest prevalence of HEV infection was seen among the younger mothers who were aged between 21-25 years. As compared to non-HEV infected pregnant women, fatal feto-maternal outcome were seen in HEV infected women. The trend of early marriages[15] and lower education level (less than five years of education) might be the reasons of HEV infection among the young pregnant mother in Bangladesh. The overall maternal mortality of about 38.7% observed in this study compared well with studies from other asian countries[16,9]. Maternal mortality in HEV infection depends upon viral factors as well as maternal factors[17]. Researchers found. All the clones of HEV isolated from Bangladesh had high homology with South Asian, Southeast Asian and Chinese clones of genotype 1, which is virulent to cause the maternal mortality[18]. In addition, malnutrition, folate deficiency and unhygienic habits of pregnant women may predispose to have high mortality rate in developing country like Bangladesh [(19)]. The rate of maternal mortality due to HEV infection observed in this study was more in second trimester of pregnancy which contradicts with other studies where higher mortality observed in third trimester of pregnancy[20]. Reason behind such contradiction needs further evaluation.

In this study, the levels of serum bilirubin, ALT and PT were increased by approximately two to three fold in HEV positive women than non-HEV infected pregnant women. Greater proportion of HEV infected pregnant women might develop FHF because of these high serum level of liver enzymes. High level of liver enzyme indicates on going hepatocytes injury. Similar findings were also observed in other study in India, where significant relationship between higher level of total and direct bilirubin and mortality rate among HEV infected person was observed[(21)]. The higher proportion of IUDs and preterm babies observed in present study among HEV-infected women was reported before by others also9. Transplacental transmission of HEV from mother to baby might play important role in causing such outcomes of the baby[22].

In conclusion, results of this study identified that HEV infection in pregnancy is a high risk condition and had poor feto-maternal outcome comparing with other viral hepatitis in a developing country like Bangladesh. This fatal disease of pregnant women deserves more attention from clinicians and public health authorities.

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