Original Article

Seroprevalence of Subclinical HEV Infection in Healthy Pregnant Urban Dwellers of Bangladesh: Identification of Possible Risk Factors

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Abstract

***Background**: Hepatitis caused by hepatitis E Virus (HEV) is not uncommon in developing countries. It is usually a self-limiting conferring immunity against subsequent infection. However, HEV infection during pregnancy results in varying degree of morbidity, often fatal. The present study was designed to find out the seroprevalence of subclinical HEV infection during pregnancy at different trimesters without history of hepatitis. **Materials and Methods**: A total 255 asymptomatic healthy pregnant women of three trimesters (85×3=255) with no history of jaundice were included in this cross-sectional study. The subjects were sub-grouped according to socioeconomic status and education level. HEV IgG antibody in serum was determined by enzyme linked immunosorbent assay (ELISA). Results were expressed as number (percent). Chi-square, Odds Ratio and 95% CI were calculated as applicable. Data analyses were carried out using statistical package for social science for Windows Version 15.0. A $p<0.05$ was taken as level of significance. **Results**: Seropositivity for HEV IgG was 38% (96/255) in pregnant women; the higher percentages were recorded in the 2nd and 3rd trimesters − 41% and 46% respectively. The seropositivity of HEV IgG was significantly high in pregnant women with low education level ((p=0.001; OR=2.70, 95% CI=1.602−4.575) and low socioeconomic status (OR=7.54, 95% CI=4.118−13.029) having monthly income below 27,000 taka (p=0.001). **Conclusion**: Data concluded that seroprevalence of anti-HEV IgG is higher at third trimester in pregnant women in Bangladesh where low socio-economic status and less education level were identified as possible risk factors. Appropriate measures may diminish the possible exposure to infection and reduce maternal mortality.*

***Key words**: ELISA; Hepatitis E virus; HEV IgG; Pregnancy; Seroprevalence; Trimester*

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Introduction

Hepatitis E virus is a major public health concern in developing countries causing sporadic and epidemic forms of acute viral hepatitis.[1] The virus is found to cause acute hepatitis in a significant number of populations, affecting more than 20 million individuals annually with three million symptomatic cases and 56,000 recognized HEV-related deaths globally.[2] It is reported that the majority of the global population with HEV infection hail from South Asian countries.[3] Outbreak of acute hepatitis E is common, particularly in developing countries where contaminated drinking water is considered to be the main source of infection.[4] In India nearly 30−70% of sporadic hepatitis cases are due to hepatitis E virus.[5] A Southeast Asian country like Bangladesh having a number of population of 160 million lacks safe water supply and hygienic disposal of sewage.[6] An estimated 22.5% rural Bangladeshi people reported to have previous exposure to HEV infection as indicated by HEV IgG.[7] For most cases

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HEV infection is asymptomatic, but in 20−30% of cases primarily in adolescent and young adults, signs and symptoms of acute viral hepatitis become more evident.[8] Previously thought to run with self-limiting behavior in men and non-pregnant women, HEV infection can persist in immunocompromised patients as chronic hepatitis.[9] However, severity of disease is more common during pregnancy with high mortality (20−25%), though aggressive nature is often observed in third trimester.[1,10] A study from New Delhi reported that prevalence of HEV infection during pregnancy was 49.23%.[11] Even though most of the described cases of acute hepatic failure associated to HEV during pregnancy had a favorable clinical course, some cases of fulminant liver failure and death were reported.[12] The verbal autopsy data from four population-based studies in Bangladesh demonstrated that 19−25% of all maternal and 7−13% of all neonatal deaths were associated with pregnancies complicated by hepatitis.[13]

Hepatitis E has an intimate relationship with pregnancy though the exact reason is still obscured. A large prospective study from North India reported that approximately 60% of the causative agent of viral hepatitis in pregnant women was HEV. Moreover, HEV infected pregnant women had 2.7 fold higher rate of fulminant hepatic failure (55%) than non-HEV infected women (20%) and higher maternal mortality (41%) than non-HEV group (7%).[14] The highest mortality rate in pregnancy has been thought to be due to liver injury resulting from possible interplay of hormonal and immunological changes during pregnancy along with a high viral load of HEV.[15] Few studies reported that the prevalence of HEV infection in second trimester (19.4%) and third trimester (18.4%) of pregnancy was found to be higher than in the first trimester (8.8%) or in non-pregnant women (2.1%) or in men (2.8%). In Spain and Turkey, prevalence of HEV IgG in pregnancy was found to be 0.6−2% and 12.6% respectively.[16,17] Pregnancy appears to be a potential risk factor for viral replication and leads extreme low immune status of Asian pregnant women, especially those infected in the 3rd trimester.[18] Socio-economic status also seems to be a risk factor for higher prevalence of HEV in pregnant women. A study on pregnant women in North India observed that exposure to HEV during pregnancy was higher in urban slum areas that rural population where prevalence of HEV IgG was found to be 33.67% among the pregnant women. It is to be noted that IgM antibody to HEV is used as a marker of acute phase of HEV infections whereas HEV IgG is used to determine the exposure to HEV in a given population.[19]

A few studies on seroprevalence of HEV IgG among general population are available in Bangladesh,[7,20] there is a lack of data with respect to Bangladeshi pregnant women. The present study was carried out to determine the seroprevalence of subclinical HEV infection in healthy pregnant women attending urban centers of the Health Care Development Project under Diabetic Association of Bangladesh.

Materials and Methods

This cross-sectional study was performed in the Department of Immunology, Bangladesh Institute of Health Sciences (BIHS) General Hospital, an enterprise of Diabetic Association of Bangladesh from July to December, 2014. Subjects were recruited from different urban centers located in and around Dhaka city under Health Care Development Project (HCDP) including BIHS General Hospital, Mirpur, Dhaka. This study was designed to carry out on pilot basis and a total of 255 asymptomatic healthy pregnant women (gestational age 1−40 weeks) with no history of jaundice were recruited. Subjects were divided into 3 groups: 1st trimester (1−12 weeks), 2nd trimester (13−26 weeks) and 3rd trimester (27−38 weeks). About 85 unrelated pregnant women were recruited for each trimester (85×3=255). The study subjects were classified into lower middle class (n=136, per capita income <27,000 BDT) and upper middle class (n=119, per capita income >27,000 BDT) (Bangladesh Bureau of Statistics, May 13, 2013). The breakdown of study subjects according to level of education were as: below higher secondary level (n=126) and higher secondary level and above (n=129). Results were expressed as mean±SD and percentage unless otherwise stated. Both parametric and non-parametric tests were performed where applicable. P value <0.05 was taken as level of significance and statistical analyses were done using Statistical Package for Social Science (SPSS).

Results

A total of 255 pregnant women were screened for the presence of anti-HEV IgG antibodies in the present

study. Mean age (±SD) of the study subjects was 28.1±5.2 years [range: 19−40 and median: 28 years]. Out of the 255 asymptomatic pregnant women, 96 (37.6%) tested positive for anti-HEV IgG antibodies. Among the pregnant women higher seroprevalence for anti-HEV IgG was observed in the women of third trimester (45.9%) than in the women of second (41.2%) and first (25.9%) trimesters of pregnancy.

Table 1: HEV IgG seroprevalence on the basis of the stages of pregnancy

Trimesters	Anti-HEV IgG +ve	Anti-HEV IgG -ve
	N (%)	N (%)
1st trimester (n=85)	22 (25.9)	63 (74.1)
2nd trimester (n=85)	35 (41.2)	50 (58.8)
3rd trimester (n=85)	39 (45.9)	46 (54.1)
Total, N=255	96 (37.6)	159 (62.4)

Higher seroprevalence of anti-HEV IgG (57.4%, 78 out of 136) was observed among pregnant women of lower middle class compared to the upper middle class (15.1%, 18 out of 119). An inverse relationship of socio-economic class with HEV seroprevalence was more pronounced among pregnant women.

HEV IgG seropositivity was more common in women who did not complete their higher secondary level of education (49.2%, 62 out of 126) compared to the women who had higher secondary and above level of education (26.4%; 34 out of 129).

Discussion

Hepatitis E infection is a major public health problem causing acute hepatitis. It causes epidemics, especially in developing countries where sanitation and hygienic practices are poor and drinking water supplies are often contaminated by sewage.[20] Pregnant women are at increased risk of contracting acute HEV infection that often leads to acute liver failure.[21] A study done at Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka on 31 pregnant women indicated HEV as a principal etiological agent (45.16%) for acute hepatitis, the fatality for which approaches >75% when the infection occurs in the second/ third trimester of pregnancy with fulminant hepatic failure.[22] Presence of HEV IgG antibody in healthy subjects indicates the previous exposure to the virus.[19] A small proportion of subjects of many industrialized countries found to have circulatory antibodies to HEV, while in Bangladesh which is endemic for HEV and where seroprevalence rate of anti-HEV IgG antibodies are higher though considerable variations have been observed in other studies in Bangladesh.[20,7] In our study, seroprevalence of anti-HEV IgG on pregnant women demonstrates the high prevalence (37.6%), a considerable potential for the transmission of HEV infection in pregnant women. In one study from rural area Matlab, Chandpur reported lower anti-HEV positivity rates (22.5%, 255 out of 1134) in asymptomatic healthy subjects and another study from BSMMU, Dhaka also reported nearly same prevalence (20.6%) of anti-HEV IgG in people of

Table II: Odd ratio for HEV IgG seropositivity on the basis of socio-economic classes

Groups	Anti-HEV IgG +ve N (%)	Anti-HEV IgG −ve N (%)	OR	95% CI	p value
Lower middle class (n=136)	78 (57.4)	58 (42.6)	0.546	4.12−13.83	<0.001
Upper middle class (n=119)	18 (15.1)	101 (84.9)	0.133	0.072−0.243	
N=255	96 (37.6)	159 (62.4)			

Table III: Odd ratio for HEV seropositivity on the basis of level of education attained by pregnant women

Education level	Anti-HEV IgG +ve	Anti-HEV IgG −ve	Odd ratio	95% CI	p value
Below higher secondary level	62 (49.2%)	64 (50.8%)	2.707	1.602−4.575	0.001
Above higher secondary level	34 (26.4%)	95 (73.6%)	0.369	0.219−0.624	
Total	96 (37.6%)	159 (62.4%)			

0−69 years of age where seropositivity was found higher in urban (26%) than rural population (15%).[7,20] The overall seroprevalence of HEV infection among pregnant women in Bangladesh is higher than the results of other studies done in Ghana (28.66%)[23], India (33.67%)[19], United Arab Emirates (20%)[24], Gabon (14.1%)[25], but lower than that in Egypt (84.3%)[26], Ethiopia (59%)[27], and Sudan (41.1%)[28].

Present study showed a gradual increasing trend of HEV seroprevalence in successive trimester of pregnancy. The prevalence of anti-HEV IgG in second and third trimester of pregnancy was found higher than in the first trimester. However, the differences of prevalence of HEV IgG among the groups were not statistically significant. Socioeconomic status and educational background had shown to influence HEV seroprevalence in pregnant women.[29] The significantly higher prevalence of anti-HEV IgG in lower socioeconomic class in our study again proves this comment. Prevalence of anti-HEV IgG was higher (49.2%) in lower education group and lower (26.4%) in higher education group which also correlates with the North Indian study done by Begum and her colleagues.[19] Similarly, few studies[30] also showed higher prevalence of HEV infection in urban subjects than that of their rural counterparts,which also supports our study as all of our study subjects came from the urban part of the country. The findings of higher HEV antibody prevalence among pregnant women in our study is widely attributable to poor sanitation and contamination of the water supply. Both low socio-economic status and educational background appeared to be the risk factors for the anti-HEV IgG in pregnant women.

In Bangladesh, huge social differences and sanitary conditions are quite precarious in many areas of urban Bangladesh. Necessary effective measures like upgrading the level of education in order to improve the socio-economic status may be the known priority for controlling the spread of HEV infection. Higher HEV seroprevalence in Bangladeshi pregnant women reasonably speculates that HEV may circulate in the general population and this call for population-based study to confirm this speculation. Early preventive measures, if taken, may decrease the maternal mortality and morbidity in HEV infection.

References

1. Devhare PB, Desai S, Lole KS. Innate immune responses in human hepatocyte-derived cell lines alter genotype 1 hepatitis E virus replication efficiencies. Scientific Reports 2016; 6: 26827.
2. Tong HV, Hoan NX, Wang B, Wedemeyer H, Bock C-T, Velavan TP. Hepatitis E virus mutations: functional and clinical relevance. E Bio Med 2016; 11: 31−42.
3. Hamid SS, Shehzad F, Yasmeen A, Nissa T, Salam A, Siddiqui A et al. Hepatitis E virus super infection in patients with chronic liver diseases. Hepatology 2002; 36(2); 474−478.
4. Sugitani M, Tamura A, Shimizu YK, Sheikh A, Kinukawa N, Shimizu K et al. Detection of hepatitis E virus RNA and genotype in Bangladesh. J Gastroenterol Hepatol 2009; 24: 599−604.
5. Majumdar M, Ratho RK, Chawla Y, Singh MP. Role of TLR gene expression and cytokine profiling in the immunopathogenesis of viral hepatitis E. J Clin Virol 2015; 73: 8−13.
6. Rashid MH, Akbar SMF, Takahashi K, Mahtab MA, Khan MSI, Alim MA et al. Epidemiological and molecular analyses of a non-seasonal outbreak of acute icteric hepatitis E in Bangladesh. J Med Virol 2013; 85: 1369−1376.
7. Labrique AB, Zaman K, Hossain Z, Saha P, YunusM, Hossain A et al. Population seroprevalence of Hepatitis E virus antibodies in rural Bangladesh. Am J Trop Med Hyg 2009; 81(5): 875−881.
8. Epidemiology of hepatitis E virus (HEV) infections in Matlab ─ some preliminary findings. icddr,b Health Science Bull (English) 2005.
9. Ankcorn MJ. Hepatitis E: the current state of play. Transfus Med 2017; 27: 84−95.
10. Iqbal T, Idrees, M, Ali L, Hussain A, Ali M, Butt S et al. Isolation and characterization of two new hepatitis E virus genotype 1 strains from two mini-outbreaks in Lahore, Pakistan. Virol J 2011; 8: 94−98.
11. Kar P, Singh S. Prevalence of Hepatitis E virus infection during pregnancy. J Clin Exp Hepatol 2014; 4(2): S13.
12. Navaneethan U, Mohajer MA, Shata MT. Hepatitis E and pregnancy ─ understanding the pathogenesis. Liver Int 2008; 28(9): 1190−1199.
13. Gurley ES, Halder AL, Streatfield PK, Sazzad HMS, Huda TMN, Hossain MJ et al. Estimating the burden of

maternal and neonatal deaths associated with jaundice in Bangladesh: possible role of hepatitis E infection. Am J pub Health 2012; 102(12): 2248−2254.

14. Zaki MES, Razek MMAE, Razek HMAE. Maternal-fetal hepatitis E transmission: is it underestimated? J Clin Translat Hepatol 2014; 2: 117−123.
15. Chaudhry SA, Verma N, Koren G. Hepatitis E infection during pregnancy. JUILLET 2015; 61: 607−608.
16. Suarez GA, Solis SG, Otero GL, Viejo DL, Guerra G, Alvarez NC et al. Prevalence of immunity to hepatitits viruses in pregnant women from the health area of Gijon (Spain). Immunology 2003; 10: 579−586.
17. Cevrioglu AS, Altindis M, Tanir HM, Aksoy F. Investigation of the incidence of hepatitis E virus among pregnant women in Turkey. J Obstet Gynaecol Res 2004; 30: 48−52.
18. Khuroo MS, Teli MR, Skidmore S, Sofi MA. Incidence and severity of viral hepatitis in pregnancy. Am J Med 1981; 70: 252−255.
19. Begum N, Devi SG, Hussain SA, Kumar A, Kar P. Seroprevalence of subclinical HEV infection in pregnant women from North India: a hospital based study. India J Med Res 2009; 130: 709−713.
20. Begum A, Tabassum S, Islam MN, Nessa A. Seroprevalence of hepatitis E virus (HEV) infection among patients attending BSMMU, Dhaka. Bang J Med Microbiol 2007; 01 (02): 52−55.
21. Shalimar, Acharya SK. Hepatitis E and acute liver failure in pregnancy. J Clin Exp Hepatol 2013; 3(3): 213−224.
22. Mahtab MA, Rahman S, Khan M, Karim F. HEV infection as an aetiologic factor for acute hepatitis: experience from a tertiary hospital in Bangladesh. J Health, Popul Nutri 2009; 27: 14−19.
23. Adiei AA, Tettey Y, Aviyase JT, Gyamfi CA, Obed S, Mingle JAA et al. Hepatitis E virus infection is highly prevalent among pregnant women in Accra, Ghana. Virol J 2009; 6: 108.
24. Kumar RM, Uduman S, Rana S, Kochiyil JK, Usman A, Thomas L. Seroprevalence and mother to infant transmission of hepatitis E virus among pregnant women in the United Arab Emirates. Eur J Obstetr Gynaecol Rep Biol 2001; 100: 9−15.
25. Caron M, Kanzanji M. Hepatitis E virus is highly prevalent among pregnant women in Gabon, Central Africa, with different patterns between rural and urban areas. Virol J 2008; 5: 158−168.
26. Stoszek SK, Abdel HM, Kafrawy SE, Narooz S, Hawash Y, Said A et al. High prevalence of hepatitis E antibodies in pregnant Egyptian women. Trans Roy Soc Trop Med Hyg 2006; 100: 95−101.
27. Tsega E, Krawczynski K. Hepatitis E virus infection in pregnancy in Ethiopia. Ethiopia Med J 1993; 31: 173−181.
28. Boccia D, Guthman JP, Klocstad H, Hamid N, Tatay M, Nizou JY et al. High mortality associated with an outbreak of hepatitis E among displaced persons in Darfur, Sudan. Clin Infect Dis 2006; 42: 1679−1684.
29. Zuhal A, Mohammed N, Mustafa EM. Frequency of hepatitis E virus among pregnant women attending Khartoum Hospital. Am J Res Commun 2014; 2(4): 241−247.
30. Gurley ES, Hossain MJ, Paul RC, Sazzad HMS, Islam MS, Parveen S et al. Outbreak of Hepatitis E in urban Bangladesh resulting in maternal and perinatal mortality. Clin Infect Dis 2014; 59(5): 658−665.