Hepatitis E Virus IgG in Serum of Pregnant Women

Salem Youssef Mohamed, Emad AbdeLatif Emam, Amr Ahmed Omar, Osama Abd El-Aziz Gaber

BACKGROUND: The prevalence of anti-HEV in Egypt is among the highest of any country in the world. The outcomes of pregnancy in infected women need to be delineated.

AIM: To screen pregnant females for hepatitis E IgG and to assess the effect of HEV IgG on the pregnancy outcome.

METHODS: 142 consecutive pregnant women were subjected to full history-taking, thorough clinical examination, abdominal ultrasonography and IgG antibody to HEV using ELISA kits. HEV avidity index was estimated for anti-HEV positive cases.

RESULTS: There was a significant elevation of HEV IgG antibody in the serum of pregnant women, especially in the countryside, in age group more than 30 years and in the third trimester of pregnancy. There was a possible association between HEV IgG antibody and liver fatty infiltration and neonatal jaundice. There was a significant inverse correlation between HEV IgG avidity index and age. No clinical correlation noticed between HEV IgG avidity index and history of previous abortion, the number of pregnancy, complete blood picture (CBC), liver enzymes, INR or serum creatinine. There was no statistically significant association between HEV IgG avidity indices and outcome of gestation.

CONCLUSION: HEV IgG is prevalent in serum of pregnant women but with benign course of both the pregnant lady and her outcome.

Key words: HEV IgG; Pregnant women; Avidity index; Neonatal outcome

© 2017 The Author(s). Published by ACT Publishing Group Ltd. All rights reserved.

Mohamed SY, Emam EA, Omar AA, El-Aziz Gaber OA. Hepatitis E Virus IgG in Serum of Pregnant Women. Journal of Gastroenterology and Hepatology Research 2017; 6(5): 2435-2440 Available from: URL: http://www.ghrnet.org/index.php/jghr/article/view/2090

BACKGROUND
Hepatitis E virus(HEV) is endemic in Egypt, but has a relatively benign course with no morbidity, the prevalence of HEV is very high in rural communities, but researchers did not find any cases of acute viral hepatitis or fulminant hepatic failure due to HEV[1].

The relationship between HEV and pregnancy is attractive due to its high prevalence and severe manifestations in pregnant women in some regions such as North India[2]. The IgG avidity index was high (> 60%) in patients with previous infection or polyclonal activation but was low (< 40%) in patients with acute infection[3].

In Egypt, the prevalence of anti-HEV is among the highest of any country in the world approaching 80%; yet, outbreaks have not been reported. A prospective study estimated the HEV incidence at 41.6/1000 person-years[4].

Stoszek detected no mortality among more than 2000 pregnant women with serological markers for infection[5].

The aim of this study was to screen pregnant females admitted to Zagazig University Hospitals for anti-HEV IgG and to assess the effect of HEV IgG on the pregnant women and their outcome.
SUBJECTS AND METHODS

Study area and subjects

We conducted this study in the Obstetrics, Gynecology, Medical Biochemistry and internal medicine Departments in Zagazig University Hospitals between June, 2015 and October, 2015. Most of the patients are referral cases from various parts of El-Sharqia Governorate.

Inclusion criteria: The cases included were the first 142 consecutive pregnant women admitted to Obstetrics and Gynecology Department during the period of the study.

Exclusion criteria: Subjects with manifestations of chronic liver disease or had positive viral markers for HBV or HCV. Also, patients who refused to give a written consent were excluded from the study.

Patient assessment: All patients were subjected to the following evaluations. (A) A full history-taking, (B) Full clinical examination, (C) Abdominal ultrasonography. (D) The samples used for the study were the sera from blood samples drawn from these 142 pregnant women for their routine investigations. Hepatitis B virus surface antigen-core antibody, Hepatitis C virus antibody, CBC, Albumin, Bilirubin, ALT, AST, Creatinine, and Urea. (E) All sera were screened for IgG antibody to HEV using ELISA kits. We score results as positive or negative according to the standard procedures recommended by the manufacturer. Positive and negative controls were included in all the ELISA Microplates assayed. (F) We estimated the neonatal liver functions and birth weight at the time of delivery. (G) HEV avidity index was estimated for anti-HEV positive cases: IgG avidity index was expressed in percentage, as follows: IgG avidity index (%) = (optical density of well with urea/optical density of well without urea) ×100. We considered values below 40% were as low, and those above 60% were considered as high. IgG avidity index values between 40-60% were found to be equivocal.

Ethical considerations

The study protocol was approved by the Institutional Review Board of the Faculty of Medicine, Zagazig University, Egypt (ZU-IRB # 1922). All patients gave written informed consent to participate in the study and for performing all appropriate interventions.

Statistical Analysis

All data were collected, tabulated and statistically analyzed using SPSS 22.0 for Windows (SPSS Inc., Chicago, IL, USA) & MedCalc 13 for Windows (MedCalc Software bvba, Ostend, Belgium).

RESULTS

Most of the cases included in the study were housewives 90.8%, the age of most cases were between 21 and 30 years (mean age of 25.35 ± 5.66). The least size of the sample was in the age group more than 30 years old. We noticed relatively increased the number of rural than urban women (65.5% against 34.5%) (Table 1).

HEV IgG was present in rural individuals (69.9%) compared to (63.3%) in urban. There was no statistically significant relationship between infection and demographic features of the subjects of our study as occupation, age, history of blood transfusion, hypertension or diabetes mellitus. No statistically significant relationship between HEV IgG and history of previous abortion.

HEV IgG was present in 67.6% of the studied group.

Forty-three patients had a high avidity index denoting chronic infection, 26 had a low avidity index indicating recent infection while 27 had intermediate avidity.

Table 1 HEV IgG and its correlation with demographic data.

| The studied group | N  | Number Positive anti-HEV IgG Prevalence (%) (95% CI) | p   |
|------------------|----|-----------------------|-----|
| Total            | 142| 96                    | 67.6| 0.648 |
| Rural women      | 93 | 65                    | 69.9| 0.738 |
| Urban women      | 49 | 31                    | 63.3| 0.526 |
| Housewife        | 129| 89                    | 69  | 0.867 |
| Student          | 13 | 7                     | 53.8| ---   |
| ≤ 20 years       | 42 | 22                    | 52.4| 0.235 |
| 21 – 30 years    | 72 | 51                    | 70.8| 0.128 |
| > 30 years       | 28 | 23                    | 82.1| 0.119 |
| Blood transfusion| 24 | 15                    | 62.5| 0.738 |
| Blood transfusion| 118| 81                    | 68.6| 0.498 |
| Diabetes mellitus| 11 | 7                     | 63.6| ---   |
| No diabetes mellitus| 131| 89                | 67.9| 0.002 |
| 1st trimester    | 47 | 25                    | 53.2| ---   |
| 2nd trimester    | 32 | 22                    | 52.4| 0.008 |
| 3rd trimester    | 63 | 49                    | 77.8| < 0.001 |
| Previous abortion| 12 | 7                     | 58.3| 0.003 |
| No previous abortion| 130| 89                | 68.5| 0.001 |
| 3-5 pregnancies  | 66 | 48                    | 72.7| 0.002 |
| ≥ 2 pregnancies  | 76 | 48                    | 63.2| ---   |

Table 2 Risk factors for HEV infection.

| Risk factors | No Frequency of HEV infection No% | p   |
|--------------|----------------------------------|-----|
| Residence    | Rural                            | 93  | 65  | 69.9 | < 0.001 |
|              | Urban                            | 49  | 31  | 63.3 |       |
| Occupation   | Housewife                        | 129 | 89  | 69   | < 0.001 |
|              | Student                          | 13  | 7   | 53.8 |       |
| Age          | ≤ 20 years                       | 42  | 22  | 52.4 |       |
|              | 21 – 30 years                    | 72  | 51  | 70.8 | 0.001 |
|              | > 30 years                       | 28  | 23  | 82.1 | < 0.001 |
| Blood transfusion| No                              | 118 | 81  | 68.6 | < 0.001 |
|              | Yes                              | 24  | 15  | 62.5 |       |
| Diabetes mellitus| No                             | 131 | 89  | 67.9 | < 0.001 |
|              | Yes                              | 11  | 7   | 63.6 |       |
| Trimester    | 1st                              | 47  | 25  | 53.2 |       |
|              | 2nd                              | 32  | 22  | 68.8 | 0.039 |
|              | 3rd                              | 63  | 49  | 77.8 | < 0.001 |
| Abortion     | No                               | 130 | 89  | 68.5 | < 0.001 |
|              | Yes                              | 12  | 7   | 58.3 |       |
| Pregnancy    | 1-2 pregnancies                  | 76  | 48  | 63.2 | < 0.001 |
|              | 3-5 pregnancies                  | 66  | 48  | 72.7 |       |
| Delivery     | Vaginal delivery                 | 59  | 40  | 67.80%| 0.967 |
|              | Cesarean section                 | 83  | 56  | 67.50%|       |

There was a statistically significant high prevalence of HEV IgG in rural subjects, homemakers, and age group > 30 years. Also, there was a substantial increase in infection in the 3rd trimester of pregnancy. We noticed the significant inverse relationship between HEV IgG antibody and history of blood transfusion, diabetes mellitus, and previous abortions.

No statistically significant relationship noticed between HEV IgG and history of chronic diseases like hypertension, diabetes mellitus, congenital heart disease or blood transfusion. There was a statistically significant association between HEV IgG and trimester of pregnancy as it was increased in the 3rd trimester of gestation (p = 0.024).
However, there was no statistically significant relationship between prevalence of HEV infection and history of previous abortion, pregnancy number or method of delivery.

There was no statistically significant association between HEV IgG antibody and the cause of hospital admission as vaginal bleeding, placenta previa, pre-eclampsia, hyperemesis gravidarum, premature rupture of membranes, anemia, abdominal colic or cesarean section.

There was no statistically significant relationship with HEV IgG antibody infection and fatty liver or splenomegaly. There was no statistically significant association between HEV IgG antibody and hemoglobin, white blood cells, platelet count, albumin, ALT, AST, total and direct serum bilirubin, INR or serum creatinine level.

There was a statistically significant relationship between HEV IgG avidity index and age as the subjects ≤ 20 years had a high avidity index denoting that increased rate of chronic infection in young subjects (p = 0.011). Subjects more than 30 years had the lowest avidity index denoting increased risk of recent infection in this age group.

There was no statistically significant relationship between HEV IgG avidity index and history of medical disease as diabetes mellitus, hypertension or history of blood transfusion.

There was no significant association between HEV IgG avidity index and trimester of pregnancy, history of previous abortions, the number of current pregnancy, a method of delivery or the cause of hospital admission.

We found a significant relationship between direct serum bilirubin level and avidity index as cases with intermediate avidity index showed increased levels of direct serum bilirubin compared to cases with low or high avidity index. There was no statistically significant relationship between HEV IgG avidity index and CBC, liver enzymes, serum albumin, total bilirubin, INR or serum creatinine level (Table 4).

There was a statistically significant relationship between low avidity index and fatty liver in cases included in the study denoting possibility of increased risk of liver fatty infiltration with recent HEV infection. However, there was no significant relation between avidity index and splenomegaly.

### Table 3
Comparison between pregnant women with negative anti-HEV IgG and those with positive anti-HEV IgG as regarding medical history.

| Medical History                  | All (N = 142) | Anti-HEV IgG |              | P     |
|----------------------------------|---------------|-------------|--------------|-------|
|                                  |               | Negative (N = 46) | Positive (N = 96) |       |
|                                  | No. | %   | No. | %   | No. | %   |       |
| Diabetes Mellitus                |     |     |     |     |     |     |       |
| Absent                           | 131 | 92.3 | 42  | 32.1 | 89  | 67.9 | 0.747 |
| Present                          | 11  | 7.7  | 4   | 36.4 | 7   | 32.6 |       |
| Hypertension                     |     |     |     |     |     |     |       |
| Absent                           | 134 | 93.7 | 45  | 33.8 | 88  | 66.2 | 0.271 |
| Present                          | 9   | 6.3  | 1   | 11.1 | 8   | 33.8 |       |
| Congenital heart disease         |     |     |     |     |     |     |       |
| Absent                           | 134 | 99.3 | 45  | 31.9 | 96  | 61.3 | 0.324 |
| Present                          | 1   | 0.7  | 1   | 100  | 0   | 0    |       |
| Blood transfusion                |     |     |     |     |     |     |       |
| No                               | 118 | 83.1 | 37  | 31.4 | 81  | 66.6 | 0.558 |
| Yes                              | 24  | 16.9 | 9   | 37.5 | 15  | 33.4 |       |
| Trimester                        |     |     |     |     |     |     |       |
| 1st                              | 47  | 33.1 | 22  | 46.8 | 25  | 53.2 | 0.024 |
| 2nd                              | 32  | 22.6 | 10  | 31.3 | 22  | 68.8 |       |
| 3rd                              | 63  | 44.4 | 14  | 22.2 | 49  | 77.8 |       |
| Previous abortion                |     |     |     |     |     |     |       |
| No                               | 130 | 91.5 | 41  | 31.5 | 89  | 68.5 | 0.331 |
| Once                             | 11  | 7.7  | 4   | 36.4 | 7   | 63.6 |       |
| Twice                            | 1   | 0.7  | 1   | 100  | 0   | 0    |       |
| Pregnancy number                 |     |     |     |     |     |     |       |
| 1st                              | 42  | 29.6 | 15  | 35.7 | 27  | 64.3 | 0.726 |
| 2nd                              | 34  | 23.9 | 13  | 38.2 | 21  | 61.8 |       |
| 3rd                              | 52  | 36.6 | 15  | 28.8 | 37  | 71.2 |       |
| < 3                              | 14  | 9.8  | 3   | 51.5 | 11  | 48.5 |       |
| Delivery                         |     |     |     |     |     |     |       |
| Vaginal delivery                 | 59  | 41.5 | 19  | 32.2 | 40  | 67.8 | 0.967 |
| Cesarean section                 | 83  | 58.5 | 27  | 2.5  | 56  | 72.2 |       |

§ Chi-square test.

### Table 4
The relationship between anti-HEV IgG avidity and laboratory findings.

| Laboratory Findings                          | Anti-HEV IgG avidity | P     |
|----------------------------------------------|----------------------|-------|
|                                              | Low (N = 26)         |       |
|                                              | Intermediate (N = 27) |       |
|                                              | High (N = 43)        |       |
| Hemoglobin (gm/dL)                           | 0.50 ± 1.20          |       |
|                                             | 9.69 ± 1.90          | 10.42 ± 1.39 | 0.258 |
| WBC (×10³/mm³)                               | 9.53 ± 1.02          |       |
|                                             | 9.71 ± 1.53          | 9.14 ± 1.34 | 0.129 |
| Platelet count (×10³/mm³)                    | 220.23 ± 42.96       |       |
|                                             | 222.29 ± 61.17       | 224.04 ± 41.40 | 0.776 |
| Albumin (gm/dL)                              | 3.61 ± 0.41          |       |
|                                             | 3.58 ± 0.32          | 3.57 ± 0.27 | 0.815 |
| Total serum bilirubin (mg/dL)                | 0.79 ± 0.19          |       |
|                                             | 0.93 ± 0.27          | 0.84 ± 0.22 | 0.131 |
| Direct serum bilirubin (mg/dL)               | 0.15 ± 0.13          |       |
|                                             | 0.23 ± 0.16          | 0.18 ± 0.14 | 0.027 |
| AST (U/L)                                    | 29.34 ± 13.98        |       |
|                                             | 32.81 ± 16.46        | 30.76 ± 11.26 | 0.575 |
| ALT (U/L)                                    | 24.03 ± 10.93        |       |
|                                             | 27.77 ± 15.92        | 24.74 ± 8.64 | 0.648 |
| INR                                          | 0.97 ± 0.19          |       |
|                                             | 1.05 ± 0.29          | 0.98 ± 0.26 | 0.569 |
| Creatinine (mg/dL)                           | 0.89 ± 0.26          |       |
|                                             | 1.00 ± 0.42          | 0.88 ± 0.29 | 0.699 |

Kruskal-Wallis H test
Mohamed SY et al. HEV IgG in pregnant women

There was a significant inverse correlation between HEV IgG avidity index and age ($p = 0.004$) as a low avidity index was increased in age group more than 30 years. No clinical correlation noticed between HEV IgG avidity and history of previous abortion, the number of pregnancy, CBC, liver enzymes, INR or serum creatinine.

15.5% of the outcome of cases included in the study suffered from low birth Weight, 17.6% was preterm labor while 15.5% suffered from neonatal jaundice but no cases of stillbirth had been reported.

There was a statistical significance between anti-HEV IgG and newborn jaundice. However, there was no relationship between anti-HEV IgG and preterm labor or low birth weight.

There was no statistically significant association between HEV IgG avidity indices and outcome of pregnancy as regards neonatal jaundice, low birth weight or preterm labor.

DISCUSSION

HEV is an enterically transmitted pathogen and is responsible for a large-scale epidemic of hepatitis around the world, according to the epidemiological data, 3.3 million acute cases and 20 million new cases of hepatitis E are diagnosed each year[8].

Diagnosis of HEV infection depends on the clinical features and the exclusion of other causes of acute hepatitis; assays of sera make the serological diagnosis for the presence of anti-HEV IgM or IgG by ELISA screening[9].

HEV infection among pregnant women in Egypt was not associated with a history of jaundice or liver disease[10]. The reasons for the infrequent clinical hepatitis could be the result of early childhood exposure.

The prevalence of HEV is higher in rural communities, but no cases of acute viral hepatitis due to HEV have been reported[11]. That study examined a cohort of 2428 pregnant women in the Nile Delta to assess the prevalence of, and risk factors for, anti-HEV and correlated these with a history of liver disease. Anti-HEV prevalence was 84.3%. The subjects included in that study were outpatient pregnant women in rural villages at Nile Delta[11].

In our study, anti-HEV IgG was present in 67.6% of pregnant women admitted to Zagazig University Hospitals. The cause of this relative difference may be due to small the sample size compared to previous large-scale one and the type of our sample (all cases were inpatients).

Our findings when compared with the international studies, pregnant women showed a higher prevalence of anti-HEV IgG than those in other countries like Spain (2-13%)[12] and this can be explained by the association between HEV infection and inadequate food and water sanitation.

HEV IgG is increased in rural areas. It is in agreement with Medhat et al[13] and Darwish et al[14] in a study at Nile delta. The high prevalence in both studies may be attributed to similar environmental factors as water[15] and food sanitation also, anti-HEV antibodies have been detected in swine, rodents, dogs, cattle, sheep, and poultry[16].

We noticed a high rate of HEV IgG in the third trimester of pregnancy (77.8%) compared to women in their second (68.8%) and first trimester (53.2%). That was in agreement with Matthiesen et al[17] and Singh et al[17].

Anti-HEV IgG positive individuals in our study had normal ALT, AST, bilirubin levels and this is in agreement with Debing and Neyts[18] and Amer et al[19] but in contrary to a study that was published by Verghese and Robinson[20] that showed the elevation of liver enzymes and jaundice with HEV infection.

We found no significant laboratory abnormalities in HEV IgG-positive subjects included in the survey as CBC, serum creatinine, prothrombin time, and INR. It is in line with Amer et al[22]. However, in contrary to other studies, there were extrahepatic manifestations due to HEV infection in the form of hemolysis, purpura, glomerulonephritis, and neurological manifestations[21].

We found that most of the positive cases of HEV antibodies (IgG) showed fatty liver as a significant finding during abdominal examination with ultrasound, which could be a normal variant or due to fat deposition in the liver. There is no clinical significance of liver enlargement or fatty infiltration in relation to HEV IgG positivity. There was a relationship between low avidity index and fatty liver in our cases denoting possibility of increased risk of liver fatty infiltration with recent HEV infection, but, there was no significant relation between avidity index and cases with splenomegaly.

Concerning acute HEV infection, the presence of HEV RNA in blood and stool is short-lived, and becomes undetectable in serum at 3–4 weeks and in the stool at six weeks after the onset of clinical symptoms in asymptomatic subjects, viremia can last for 4-6 weeks[5].

Given the limited performance of serological markers, IgG avidity index is a useful tool that is simple to use for the diagnosis of HEV infection. Given the problems encountered for the detection of viral RNA or anti-HEV IgM, combinations of markers are required for

| Variables                  | Avidity Index (%) | p   |
|---------------------------|-------------------|-----|
| Age (years)               | -0.239            | 0.004|
| Previous abortions        | -0.054            | 0.604|
| Number of pregnancy       | 0.032             | 0.755|
| Hemoglobin (gm/dL)        | -0.048            | 0.639|
| WBC ($x10^3/mm^3$)        | -0.149            | 0.148|
| Platelet count ($x10^9/mm^3$) | 0.041             | 0.694|
|Albumin (gm/dL)            | -0.094            | 0.36 |
| Total serum bilirubin (mg/dL) | 0.126             | 0.221|
| Direct serum bilirubin (mg/dL) | 0.1              | 0.333|
| AST (U/L)                 | 0.044             | 0.667|
| ALT (U/L)                 | 0.014             | 0.892|
| INR                       | -0.047            | 0.648|
| Creatinine (mg/dL)        | -0.072            | 0.488|

Table 5 The correlation between Avidity Index and the study parameters.

$r$ Spearman's correlation coefficient

| HEV IgG       | Low birth weight | Preterm labor | Neonatal jaundice |
|---------------|------------------|---------------|-------------------|
|               | Absent (120)     | Present (22)  | Absent (117)      | Present (25)  | Absent (120) | Present (22) |
| negative      | 42               | 4             | 56                | 10            | 43           | 3             |
| positive      | 78               | 18            | 81                | 15            | 77           | 19            |
| p             | 0.121            | 0.371         | 0.041             |               |              |

Table 6 Neonatal outcome in relation to infection.

| HEV avidity   | Low (26)          | Intermediate (27) | High (43)       |
|---------------|------------------|-------------------|----------------|
|               | Absent (120)     | Present (22)      | Absent (120)   | Present (22) |
| Low           | 23               | 3                 | 21              | 5             |
| Intermediate  | 20               | 7                 | 25              | 2             |
| High          | 35               | 8                 | 35              | 8             |
| p             | 0.406            | 0.381             | 0.737           |

§ Chi-square test.
reliable diagnosis. IgG avidity index may, therefore, help to improve the diagnosis of acute hepatitis E infection. So, we use HEV avidity index to check for recent infection.

We noticed increased prevalence of HEV IgG in age group more than thirty years, and this was in agreement with Amer et al\cite{14}. In our study, no cases of fulminant hepatitis had been reported, and mortality rate of our subjects was zero, and this was in line with other studies in Egypt\cite{17-18}. It was in contrary to a study in North India\cite{22} and a study in Darfur in Sudan\cite{39}.

Concerning delivery method, we found no statistically significant relationship between HEV IgG and delivery method. Also, we found that the neonatal jaundice is increased in cases with positive HEV IgG as 19.8% of total cases with neonatal jaundice were delivered by HEV IgG positive mothers while HEV IgG negative mothers delivered only 6.5%. It was in agreement with Khuroo et al\cite{39} denoting a possible relation between HEV infection in the mother and the possibility of occurrence of neonatal jaundice.

Also, there is no significant relationship between HEV IgG and both low birth weight and preterm labor, and that was in agreement with Navaneethan et al\cite{21}. In contrast, another study upon HEV in pregnant women in Iran denoted that infected babies suffered from prematurity, mild anicteric neonatal hepatitis or jaundice, stillbirth, preterm labor, perinatal death or neonatal death soon after birth\cite{22} and\cite{39}. It is explained by the difference in virus virulence in both studies.

In our study, follow up six months, there was no mortality, and this was in agreement with El Sayed Zaki et al\cite{21}. In a study published upon HEV infection in pregnant women in South Asia, HEV infection is typically severe during the third trimester of pregnancy, mortality rates among pregnant women in the third-trimester range from 10%-25%. It may be due to the differences in major histocompatibility complex (MHC) phenotypes in this country as compared to the other endemic areas\cite{34}.

However, the findings and conclusions of this study are limited by the small sample size. So, a larger scale prospective survey of HEV infection among pregnant women should be conducted to validate our findings, to analyze in more detail the clinical and the epidemiological features of this disease and to evaluate the cost-effectiveness of antenatal HEV screening in Egypt. Also, we had no available data about HEV state of our subjects before the study.

**CONCLUSIONS**

HEV IgG is prevalent in the serum of pregnant women but with a benign course of both the pregnant lady and her outcome.

**REFERENCES**

1. Medhat A, El-Sharkawy MM, Shaaban MM, Makhlof MM, Ghanima SE. “Acute viral hepatitis in pregnancy.” Int J Gynaecol Obstet 1993; 40(1): 25-31. [DOI: 10.1016/0020-7292(93)90768-R]

2. Beniwal M, Kumar A, Kar F, Jilani N, Sharma JB. Prevalence and severity of acute viral hepatitis and fulminating hepatitis during pregnancy: a prospective study from north India. Indian J Med Microbiol 2003; 21(3): 184-185. [http://www.ijnmm.org/text.asp?2003/21/3/184/8012]

3. Renou C, Latefeullade A, Cadranel JF, Pavio N, Pariente A, Allegre T, Poggi C, Penaara G, Cordier F, Nicand E. ANGH: Hepatitis E virus in HIV-infected patients. AIDS 2010, 24: 1493-9. [DOI: 10.1097/QAD.0b013e28253ca29b]

4. Stoszek SK, Engle RE, Abdel-Hamid M, Mikhail N, Abdel-Aziz F, Medhat A, Fix AD, Emerson SU, Purcell RH, Strickland GT. Hepatitis E antibody seroconversion without disease in highly endemic rural Egyptian communities. Trans R Soc Trop Med Hyg 2006; 100: 89-94. [DOI: 10.1016/trstmh.2005.05.019]

5. WHO. “Hepatitis E vaccine: WHO position paper, May 2015—Recommendations. Vaccine 2015; 34(3): 304-305. [DOI: 10.1016/vaccine.2015.07.056]

6. Ahmed A, Ali IA, Ghazal H, Fazili J, NusratS. Mystery of hepatitis e virus: recent advances in its diagnosis and management. Int J Hepatol 2015: 782431. [DOI: 10.1155/2015/782431]. Epub 2015 Jan 19.

7. Darwish MA, Faris R, Clemens JD, Rao MR, Edelman R. High seroprevalence of hepatitis A, B, C, and E viruses in residents in an Egyptian village in The Nile Delta: a pilot study. Am J Trop Med Hyg 1996; 54(6): 554-558. [PMID: 8686770]

8. Suarez Gonzalez A, Solis Sanchez G, Otero-Guerra L, De La Guerra GV, Navascues CA, Lopez RG. Prevalence of immunity to hepatitis viruses in pregnant women from the health area of Gijon (Spain). Gastroenterol Hepatol 2004; 27(6): 347-352. [PMID: 15207132]

9. El-Esnawy NA. Examination for hepatitis E virus in wastewater treatment plants and workers by nested RT-PCR and ELISA. J Egypt Public Health Assoc 2000; 75(1-2): 219-231. [PMID: 17219857]

10. Huang FF, Haqshenas G, Shivaaprasad HL, Guenette DK, Woolcock PR, Larsen CT, Pierson FW, Elvinger F, Toth TE, Meng XJ. Heterogeneity and seroprevalence of a newly identified avian hepatitis E virus from chickens in the United States. J. Clin. Microbiol 2002; 40: 4197-4202. [DOI: 10.1128/JCM.40.11.4197-4202.2002]

11. Matthiesen L, Berg G, Erinrudh J, Hakansson L. Lymphocyte subsets and mitogen stimulation of blood lymphocytes in normal pregnancy. Am J Reprod Immunol 1996; 35(2): 70-79. [DOI: 10.1111/j.1600-0897.1996.b00010.0.x]

12. Singh S, Mohanty A, Joshi YK, Deka D, Mohanty S Panda SK. Mother-to-child transmission of hepatitis E virus infection. Indian J Pediatr 2003; 70(1): 37-39. [DOI: 10.1007/BF02727243a]

13. Debing Y, Neyts J. Antiviral strategies for hepatitis E virus. Antiviral Res 2014; 102: 106-118. [DOI: 10.1016/j.antiviral.2013.12.005]

14. Amer AF, Zaki SA, Nagati AM, Darwish MA. Hepatitis E antibodies in Egyptian adolescent females: their prevalence and possible relevance. J Egypt Public Health Assoc 1996; 71(3-4): 273-284 [PMID: 17217013]

15. Verghese VP, Robinson JL. A systematic review of hepatitis E virus infection in children. Clin Infect Dis 2014; 59(5): 689-697. [DOI: 10.1093/cid/ciu371]

16. Kar P, Jilani N, Husain SA, Pasha ST, Anand R, Rai A, Das BC. Does hepatitis E viral load and genotypes influence the final outcome of acute liver failure during pregnancy? Am J Gastroenterol 2008: 103: 2945-51. [PMID: 18785952]. [DOI: 10.1111/j.1572-0241.2008.02032.x]

17. Fix AD, Abdel-Hamid M, Purcell RH, Shehata MH, Abdel-Aziz F, Mikhail N, el Sebai H, Nafeh M, Habib M, Arthur RR, Emerson SU, Strickland GT. Prevalence of antibodies to hepatitis E in two rural Egyptian communities. Am. J. Trop. Med. Hyg. 2000 Apr; 62(4): 519-23. 519-523. [PMID: 11220771]

18. Stoszek SK, Engle RE, Abdel-Hamid M, Mikhail N, Abdel-Aziz F, Medhat A, Fix AD, Emerson SU, Purcell RH, Strickland GT. Hepatitis E antibody seroconversion without disease in highly endemic rural Egyptian communities. Trans R Soc Trop Med Hyg 2006; 100: 89-94. [DOI: 10.1016/trstmh.2005.05.019]

19. Boccia D, Guthmann J-P, Klovstad H, Hamid N, Tatay M, Ciglenecki I, Nizou JY, Nicand E, Guerin PJ. High mortality associated with an outbreak of hepatitis E among displaced persons in Darfur, Sudan. Clin Infect Dis. 2006; 42: 1679-1684. [DOI: 10.1086/504322]

20. Khuroo MS, Kamili S, Khuroo MS. Clinical course and duration
of viremia in vertically transmitted hepatitis E virus (HEV) infection in babies born to HEV-infected mothers. J Viral Hepat 2009; 16(7): 519-523. [DOI: 10.1111/j.1365-2893.2009.01101.x]

21. Navaneethan U, Al Mohajer M, Shata MT. Hepatitis E and pregnancy: understanding the pathogenesis. Liver Int 2008; 28(9): 1190-1199. [DOI: 10.1111/j.1478-3231.2008.01840.x]

22. Lapa D, Capobianchi MR, Garbuglia AR. Epidemiology of Hepatitis E Virus in European Countries. Int J Mol Sci 2015; 16(10): 25711-25743. [DOI: 10.3390/ijms161025711]

23. El Sayed Zaki M, El Razek MM, El Razek HM. Maternal-Fetal Hepatitis E Transmission: Is It Underestimated? J Clin Transl Hepatol 2014; 2(2): 117-123. [DOI: 10.14218/JCTH.2014.00006]

24. Kamar N, Bendall RP, Peron JM, Cintas P, Prudhomme L, Mansuy JM, Rostaing L, Keane F, Ijaz S, Izopet J, Dalton HR. Hepatitis E virus and neurologic disorders. Emerg Infect Dis 2011; 17: 173-179. [DOI: 10.3201/eid1702.100856]; [PMCID: PMC3298379]

Peer reviewers: Hee Bok Chae; Mohamed Emara