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Seroprevalence and Risk Factors of Hepatitis E Among Women of Reproductive Age Residing in Birjand in 2016

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Abstract

Background: Hepatitis E is one of the major health concerns in most developing countries. Hepatitis E is associated with high mortality rate among pregnant women. Yet, there is limited information about its prevalence among the women of reproductive age in Birjand, Iran.

Objectives: The aim of this study is sought to assess the seroprevalence and the risk factors of hepatitis E among the women of reproductive age in Birjand.

Methods: This descriptive-analytical study was conducted on 360 women aged 17 - 45 years who were conveniently recruited from the Women's Clinic of ValiasrHospital, Birjand, Iran. Data collection tool was a researcher-made questionnaire with items on participants' demographic characteristics, medical history, pregnancy profile, and source of drinking water. A five-milliliter blood sample was obtained from each participant and the titer of anti-HEV IgG was measured through the enzyme-linked immunosorbent assay (ELISA). Data were analyzed using the SPSS software (v. 16.0) through conducting the independent-sample *t* test at a significance level of less than 0.05.

Results: This study was conducted on 360 women with an age mean of 31.1 ± 7.0. Most participants were non-pregnant (70.8%). The titer of anti-hepatitis E immunoglobulin G was positive in 42 cases (11.7%). The prevalence of anti-HEV IgG seropositivity had no significant relationships with pregnancy and marital status, while it had significant relationships with the place of residence (OR= 4.73)and the source of drinking water($P < 0.001$). Moreover, anti-hepatitis E immunoglobulin G seropositivity was significantly lower among participants with university degree ($P = 0.004$) and significantly higher among older participants ($P = 0.018$).

Conclusions: By the research finding the seroprevalence of hepatitis E is higher among women with lower educational level, women who drink untreated water, and women who live in rural areas. Health education and promotion may help reduce the prevalence of hepatitis E, particularly in rural areas.

Keywords: Hepatitis E, Seroepidemiology, Women, Reproduction

1. Background

Hepatitis E virus is a small virus without any coatings, which has a positive-sense single-stranded RNA genome. This virus belongs to the Hepevirus genus. It was discovered for the first time in 1955 in New Delhi, India (1). It is mainly spread through the fecal-oral route. Other transmission ways of the virus include consuming half-baked meat products, blood transfer, and vertical transfer from mother to offspring.

It is estimated that one-third of the world population is infected by hepatitis E virus and more than 20 million new cases occur each year leading to 44,000 deaths. These deaths mostly occur in low-income countries such as Asian, African, and Latin American countries (2).

This disease is a self-limiting disease and in most cases does not have any clinical symptoms and does not lead to chronic hepatitis or chronic carrier (3). In contrast to other hepatitis viruses, this virus can cause acute liver disease in pregnant women, especially those who are in their third trimester. In addition, in 20% - 25% of the cases, it can lead to the sudden death of the mother due to renal failure. Other complications of this infection include fetal death, miscarriage, premature infant, and neonatal death (1, 4).

According to several studies conducted in Iran, this country is endemic for HEV (4). HEV prevalence in develop-

ing countries is 10% - 35% and in Iran its 9.6%. In the general population, the prevalence of hepatitis E is different across various parts of Iran. Specifically, it was 9.3% in Nahavand, 8.1% in Isfahan, 7.3% in Sari, 7.9% - 15% in Tehran, and 46.1% in Ahvaz (5). In a study conducted by Jahanbakhsh et al., the prevalence of HEV was 24.37% (6).

The prevalence of HEV in the Iranian pregnant women is reported to be 3.6% - 7.4% (5, 7-10). Therefore, HEV is an important general health concern all over the world, especially in developing countries due to their low hygienic conditions and the lack of standard sewage systems (5, 11).

The reason for the intense symptoms of the disease during pregnancy is not apparent and is still under investigation. Hormonal changes (estrogen and progesterone) during pregnancy, decreased expression of progesterone receptors, progesterone inhibiting factors, the high ratio of interleukin 12 to interleukin 10 (IL-12/IL-10), high prevalence of folate deficiency in pregnant women in endemic areas, the high load of the virus during pregnancy due to the sex hormones, reduced cellular immunity, and the production of inflammation interleukins such as T cell CD4, TNFα, interleukins 12, 10, 6, and 2, especially during the third trimester of pregnancy, are probably some reasons for the intensity of the disease. In this regard, the escalation of estrogen and progesterone and HCG hormones leads to reduced T-cells and their diminished development. Specifically, Th1 declines while Th2 grows, leading to the enhanced proliferation of the virus (12). Despite the importance of hepatitis E in pregnancy, a few studies have been conducted on this disease among women who are in their reproductive age. Accordingly, due to the lack of data about the prevalence of hepatitis E in the population of women of reproductive age in the city of Birjand, Eastern Iran, and because of the vicinity of South Khorasan to Afghanistan.

2. Objectives

This study was conducted to investigate the prevalence of hepatitis E in women of reproductive age.

3. Methods

This descriptive-analytical study was conducted cross-sectionally on women of reproductive age who had visited the Women's Clinic of Valiasr Hospital located in Birjand during 2016 to receive routine cares. The sample size was calculated as 360 subjects based on a study conducted by Jahanbakhsh et al. (6) and using the following formula:

$$n = \frac{z^2_{1-\frac{\alpha}{2}} pq}{d^2}$$

Where, d = 0.042, p = 0.21, and α = 0.05. Using the convenience sampling method, the study subjects were selected from among women of reproductive age who had visited the Women's Clinic of Valiasr Hospital. The inclusion criteria of the study included informed consent to participate in the study, lack of infectious diseases in the subjects, and visiting the clinic due to problems associated with women's health except for infectious diseases. Demographic data such as age, place of residence, education level, occupation, and risk factors associated with hepatitis E (education level, place of residence, and type of drinking water) were collected by trained medical students. Afterward, 5-cc blood samples were taken from the radial vein and then stored at -30°C after preparation. Then, the titer of the anti-HEV IgE was measured using a third-generation ELISA Kit manufactured by the Delaware Company. The collected data were analyzed using SPSS-16 software by independent *t*-test. Further, odds ratios were estimated by the logistic regression model at a significance level of α = 0.05. The ethical protocol of the research was approved by the local ethics committee of the university with ethics code Ir. BUMS.REC.1394.62 BUMS.

4. Results

In this study, 360 women of reproductive age with the mean age of 31.1 $\pm$ 7 were recruited in the study. The minimum age of the participants was 17 and the maximum age was 45. A total number of 105 subjects (29.2%) were pregnant and the rest was not. Moreover, 26 subjects (7.2%) were single and 278 (77.2%) resided in the city. The prevalence of positive anti-HEV was determined as 11.7% (n = 42). The mean age of HEV positive and HEV negative women was 33.5 $\pm$ 7.2 and 30.8 $\pm$ 6.9, respectively. No significant difference was observed in the age of HEV positive and negative women (P = 0.18)

The chance of contracting hepatitis E was 4.73 times more in rural women compared to their urban counterparts and this difference was statistically significant. However, no significant relationship was observed between the chance of contracting hepatitis E and the pregnancy and the marital status (Table 1).

In addition, higher education levels decreased the chance of contracting hepatitis E significantly; in illiterate subjects, the chance of contracting hepatitis E was 163.5 times more than in subjects with a college education. Notably, this chance was 3.01 times more in subjects who had a primary level of education compared to subjects who had a college education. The subjects who used untreated water were 312 times more likely to contract this disease as compared to subjects who consumed tap water.

Table 1. The Chance of Contracting HEV Based on the Place of Residence, Pregnancy Status, Marital Status, Education Level, and the Type of Drinking Water in Women Under Study

Variable Name/HEV Condition	Positive Frequency (Percentage)	Negative Frequency (Percentage)	OR (95% CI)	P Value
Pregnancy status				0.79
Non-pregnant	29 (11.4)	226 (88.6)	1	
Pregnant	13 (12.4)	92 (87.6)	1.1 (0.55 - 2.21)	
Marital status				0.1
Married	36 (10.8)	298 (89.2)	1	
Single	6 (23.1)	20 (76.9)	2.48 (0.93 - 6.59)	
Place of residence				0.001
Urban	20 (7.2)	258 (92.8)	1	
Rural	22 (26.8)	60 (73.2)	4.73 (2.43 - 9.22)	
Education level				
College education	7 (6.5)	101 (93.5)	1	
Illiterate	34 (50)	3 (50)	163.5 (40 - 667.9)	< 0.001
Primary school	19 (17.3)	91 (82.7)	3.01 (1.21 - 7.5)	0.01
High school	13 (9.6)	122 (90.4)	1.54 (0.59 - 3.99)	NS
Drinking water				< 0.001
Tap water	6 (1.9)	312 (98.1)	1	
Untreated water	36 (85.7)	6 (14.3)	312 (95.6 - 1018.4)	

5. Discussion

In this study, the prevalence of HEV in women residing in Birjand who were in their reproductive age was 11.7%. Having compared the results of the study with previous studies conducted in this region, it was observed that the prevalence of hepatitis E was lower in women of reproductive age than in the general population (25%) (5).

Iran as a Middle Eastern country is endemic for hepatitis E. A population-based study conducted in Iran reported the prevalence of positive anti-HEV as 9.6 % among the healthy population. Most studies conducted in women in Iran and other parts of the world have focused on pregnant women. In a study performed in Urmia, the seroprevalence of anti-HEV was reported as 3.6% (12). Also, the prevalence of positive anti-HEV in pregnant women in Ahvaz and Hamadan was reported as 5.2% and 7.4%, respectively (4, 7). In studies conducted in Gorgan and Isfahan, the prevalence of anti-HEV in women of fertility age was reported as 6.3% and 4.2%, respectively (13, 14). In all of these studies, the prevalence of hepatitis E in women was lower than the prevalence observed in our study.

Also, the prevalence of anti-HEV in pregnant women in other parts of the world such as Africa was reported as follows: Tunisia 12% (15), Gabon 14% (16), Ghana 28% (17), and Egypt 84% (18). In a study conducted on Indian women, the seroprevalence of HEV was 33% (19) which is more than the rate in our study. However, in a study conducted in Turkey, 7% of the pregnant women were positive for anti-HEV (20), which is lower than our study finding.

The discrepancies between the studies are due to the differences in ecology, living environment, and cultural differences, as well as differences in the hygiene conditions, accessibility of safe water resources, and sanitary sewage disposal in the regions under study. In the present study, HEV positive subjects were older than their HEV negative counterparts were, but this difference was not statistically significant. This may have been due to the small sample size. In the study conducted by Hannachi et al. (15) in Tunisia, the age of over 30 was an independent factor for the positive serology of HEV. Also, Stoszek et al. (18) and Cevrioglu et al. (21) found that age has a connection with the positive serology of HEV. The relationship between age and the positive serology of HEV can be a sign of a relationship between contact and infection.

Another factor investigated in this study was the literacy level of the subjects. The results of the study revealed that the serology of HEV declines with an increase in education level. These results are similar to the results of studies conducted in Iran and other parts of the world. Similarly, in studies conducted in Hamadan and Urmia and research conducted in Turkey, the positive serology of HEV was significantly higher in women with lower education levels (4,

12). This shows the effect of education on hygiene and hygienic activities among women.

In addition, the results of this study suggested that there was a significant relationship between the place of residence and the positive serology of HEV. Positive serology was significantly more in women residing in rural areas than in those living in urban regions.

Positive serology was also higher in subjects who consumed untreated water. In a study conducted in India and research performed by Cevrioglu et al., similar to our study, there was a significant relationship between the type of drinking water and positive serology (19, 21). However, in a study conducted in Iran (4), there was no significant relationship between positive HEV serology in pregnant women and type of drinking water. These results were also different from the findings of a study conducted by Caron and Kazanji (16). Another study conducted in Tunisia by Hannachi et al. (15) revealed that a history of agricultural work, the condition of water and sewage treatment, and animal contact, which were related to rural works, had no significant relationship with positive anti-HEV. However, in a study conducted by Cevrioglu et al. (21) in Turkey, a significant relationship was observed between residence in cities and higher prevalence of anti-HEV.

This may be due to the use of unsafe water, especially in rural areas, as well as low hygiene and the inefficient health system. In addition, the geographical conditions of the region due to its vicinity to Afghanistan and the season of sampling can be some other reasons for the vast heterogeneity between the current study and various other studies performed in Iran.

Hepatitis E is an important cause of morbidity and mortality during pregnancy. The incidence of HEV in pregnant women all around the world was reported as 45% - 50% (22). The mechanism of hepatitis in pregnancy is not completely clear. The liver injury during pregnancy due to HEV depends on multiple factors. Pregnancy is associated with high levels of steroid hormones. Steroid hormones increase the proliferation of the virus. In addition, they have a direct inhibiting effect on hepatocytes, causing liver dysfunction and its failure to fight infectious pathogens. Meanwhile, steroid hormones are immunosuppressants. In addition, the enhancement of estrogen, progesterone, and HCG hormones leads to the reduction of T-cells and their evolution. In this regard, Th1 falls and Th2 rises, causing increased virus proliferation (12). The dominance of Th2 in T-cell responses is due to HLA (23). On the other hand, HEV is prevalent in women who have low economic-social status or live in regions with low hygiene. In this regard, the addition of malnutrition to pregnancy and the reversal of B and T lymphocytes early in the pregnancy can be some of the influential factors (22). In a study conducted on pregnant and non-pregnant women, there was no significant difference in contracting hepatitis E. Different outcomes of HEV in different regions may be due to exposure to the virus during childhood, long-term immunity, and changes in the response to the virus. In addition, dominant genotypes in some geographical regions can cause different viral virulence in different regions. Regarding the mortality of hepatitis E during pregnancy, it seems that high mortality in the second pregnancy is due to the hormonal changes during pregnancy and subsequent immunological changes (24).

5.1. Conclusions

Paying attention to general health and health education plus disinfecting drinking water is of utmost importance. Based on the results of the present study and concerning the high prevalence of hepatitis E in the neighboring country, Afghanistan, this issue becomes further significant. In this study, although there was no difference in pregnant and non-pregnant women concerning the prevalence of HEV, it is suggested that further studies be conducted with larger sample sizes. The strength of this study was investigating the serology of hepatitis E in both pregnant and non-pregnant women. The limitation of this study was not adjusting women for different economic and education states.

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Footnotes

Authors' Contribution: Gholam Reza Sharifzadeh and Nahid Ghanbarzadeh carried out the data analysis, made substantial intellectual contributions to the interpretation and conceptualization of the results, and drafted and revised the manuscript. Zohreh Azarkar contributed to the design of the study and laboratory work, made substantial intellectual contributions to the conceptualization and design of this study, and reviewed and revised the manuscript. All the authors have read and approved the final version of the manuscript.

Conflict of Interests: The authors declare that they have no competing interest.

Ethical Considerations: BUMS.REC.1394.62 BUMS.

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