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Epidemiology of hepatitis E in pregnant women and children

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Literature review

Hepatitis E is a disease caused by infection with hepatitis E virus (HEV), an RNA virus that exists in both enveloped and non-enveloped forms and was first recognized in the early 1980s. The virus is member of the Hepeviridae family. It has at least 4 known mammalian genotypes (named 1 to 4), which belong to a single serotype. The viral genome contains three non-overlapping open reading frames (ORF 1-3). Of these, ORF2 codes for the viral capsid protein which is the target of neutralizing antibodies against HEV. To date, genotypes 1 and 2 have been found only in humans, whereas genotypes 3 and 4 have also been found in several mammalian species. The virus is relatively stable in the environment, and is sensitive to heat, chlorination and ultraviolet light (1).

Clinical features of hepatitis E are indistinguishable from acute hepatitis caused by other hepatotropic viruses. The incubation period ranges from 15–60 days, with a mean of 40 days. HEV-infected persons exhibit a wide clinical spectrum, ranging from asymptomatic infection through acute icteric hepatitis to fulminant hepatitis. The ratio of symptomatic to asymptomatic infection has not been reliably determined, and may vary with viral genotype and epidemiologic setting. Acute hepatitis E usually manifests with icterus, malaise, anorexia, fever, hepatomegaly, and occasionally pruritus (2). Studies in non-human primates have shown a relationship between the host's immunological response and degree of liver injury with the dose of viral inoculum. Immunosuppressed persons, in particular solid organ transplant recipients on immunosuppressive drugs, fail to clear the virus leading to chronic HEV infection (lasting >6 months); such cases have mostly had HEV genotype 3 infection, except for one child who had infection with genotype 4 HEV. The laboratory abnormalities in acute hepatitis E are similar to those in acute viral hepatitis caused by other viruses (3).

Laboratory diagnosis of recent HEV infection is based on detection of HEV-specific IgM (IgA in some countries) antibodies or detection of HEV RNA in clinical samples. Past HEV infection is characterized by specific IgG antibodies against ORF2, which may confer protection against reinfection; however, the protective titer and the duration of their persistence are uncertain (4).

Certain population sub-groups are at a higher risk for severe disease following HEV infection. These include pregnant women, persons with pre-existing liver disease and persons with immunosuppression. During HEV epidemics, fulminant hepatitis occurs with a disproportionately high rate among pregnant women. During a recent outbreak in northern Uganda, a high mortality rate was recorded among children younger than 2 years; however, the cause of death in these children was not verified. Overall case-fatality rates from hepatitis E have ranged from 0.1% to 4%; however, case-fatality rates among pregnant women are much higher, being 10%-25% (5).

Treatment for acute hepatitis E is generally supportive. Chronic hepatitis E in solid organ transplant (SOT) recipients on immunosuppressive treatment has been successfully treated by withdrawal or reduction of immunosuppressive drugs, administration of ribavirin, administration of interferon or a combination of these measures (6).

Epidemiologic and clinical characteristics of hepatitis E in different parts of the world depend in a large measure on the human HEV genotype circulating in a particular region and the water, sanitation and hygiene conditions, which in turn depend on socioeconomic circumstances. The population vulnerable to severe disease also depends on the geographic location where infection is acquired, which in turn depends on HEV genotype. For this reason, this paper presents the epidemiology and burden of disease caused by human genotypes

associated with waterborne transmission (genotypes 1 and 2) and zoonotic transmission (genotypes 3 and 4) separately (7).

Surveillance for hepatitis E disease is very limited and information on disease occurrence and distribution are available only from a few European countries, and most of the data from other parts of the world are limited to reports of outbreaks and case series. By contrast, much more information is available on the seroprevalence of antibodies to HEV, a marker of previous exposure to HEV (8). However, the interpretation of seroprevalence data is immensely challenging for several reasons. These challenges include the lack of comparability of results from the different assays, high seroprevalence in populations where disease is rare or never reported, the presence of multiple genotypes with different disease patterns and inability of serological tests to distinguish between genotypes (9), and lack of data for reliable mathematical modelling to determine disease burden from seroprevalence. Furthermore, the majority of seroprevalence studies do not involve a representative sample of any population making it difficult to infer prevalence and trends to the population (10).There are several studies that have examined the prevalence of antibodies against HEV in different population groups. However, the sero-epidemiology of hepatitis E in developing countries is not uniform and often does not follow the pattern of clinical disease.

HEV infection in pregnant women is typically severe during the third trimester of pregnancy. Mortality rates among pregnant women in the third trimester range from 10%-25%. To date, the exact mechanism for the disproportionately high mortality among pregnant women is unknown (11). The causes of death include fulminant liver failure and obstetric complications including excessive bleeding. This HEV-associated high mortality occurs in countries where disease is commonly caused by HEV genotype 1. Similar high mortality in pregnant women has not been reported from western countries. A

case of genotype 3 hepatitis E was reported in a 26 weeks pregnant woman from Germany who did not develop fulminant hepatitis and had a normal fetal outcome. HEV genotype 1 infection during pregnancy is associated with poor fetal outcomes including abortion, premature delivery, and stillbirths (12).

HEV infection can lead to more severe, acute liver disease in pregnant women and sometimes progress to fulminant hepatic failure (FHF). It also leads to severe complications which may result in fetal and/or maternal mortality, abortion, premature delivery, or death of a live-born baby soon after birth (13).

HEV is transmitted primarily by the fecal–oral route. Vertical transmission of HEV from a pregnant woman to unborn fetus is very well documented. The risk factors for HEV infection are related to resistance of HEV to environmental conditions, poor sanitation in large areas of the world, and HEV shedding in feces. Following an incubation period of 2 to 6 weeks, an initial short lived IgM response is followed by longer-lasting IgG antibodies. The presence of anti-HEV IgM is a marker of acute infection and increased titers of anti-HEV IgG can indicate recent HEV infection (14). HEV is a small virus in the family Hepeviridae, with a positive single-stranded RNA genome and non-enveloped icosahedral capsid. The genome consists of three partially overlapping open reading frames (Fig. 1) (15).

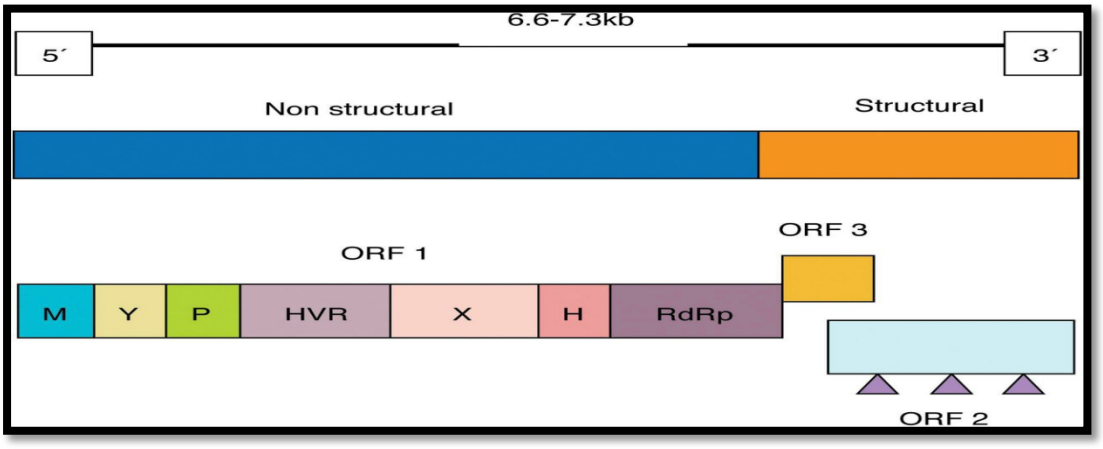

Figure (1): Molecular structure of hepatitis E virus

Seroprevalence of HEV infection among study population in selected health facilities, Addis Ababa Ethiopia was (31.6%) which is comparable with a study done in Darfur, Western-Sudan where the seroprevalence of hepatitis E virus in pregnant women was 31.1%. Our finding was higher than the result of similar studies done in BurkinaFaso (11.6%), Gabon (14.1%) and Ghana (28.6%), but lower than the seroprevalence of HEV infection among pregnant women in Egypt (84.3%), Sudan (41%) and India (33.6%) (17).

And use of different test systems with varying sensitivity. For example in Egypt a study found higher HEV seroprvalence among pregnant women (84.3%). They suggested that reasons for high HEV seroprevalence could be the result of early childhood HEV exposures, producing long-lasting immunity and/or modify subsequent responses to exposure.

Mansuy et al. recently reported 53% prevalence of HEV antibodies in blood donors in southwestern France, a figure considerably higher than the 17% prevalence reported earlier for the same geographic region, when a different test system was used (13).We found a significant association between age and higher anti-HEV positive values ($p<0.05$) which was consistent with a study done by Stoszek et al.. Our findings showed that the odds of pregnant women whose age was between 26–34 being infected with HEV is 1.68 times higher than the odds of pregnant women whose age was < 25 years. The strong association between age and HEV seroprevalence in our study most likely reflects cumulative lifetime exposure to the virus (18).

A study conducted in Northern India has shown that the low socio-economic status of pregnant women appeared to be the only risk factor associated with HEV seropositivity, but in our study it was difficult to assess the hypothesis that correlates income with seropositive status, because most of the pregnant women were not volunteers to fill their income on the questionnaires.

But the high prevalence of HEV infection in pregnant women in our study might be due to the fact that in the study the samples were collected from governmental health institutions in which medical care is free or very cheap and therefore women of low socio-economic status frequently attend and our study population may lack a portion of pregnant women with higher socioeconomic and educational level (13).

Breastfeeding is considered safe in asymptomatic women infected with HEV despite the presence of anti-HEV antibodies and HEV RNA in the colostrum. However, it is considered unsafe if the mother has acute hepatic disease or an increased viral load. In these cases, feeding formula is advised, as there is a possibility of transmission from infected breast milk or lesions on the nipple through suckling (19).

High case-fatality rate among pregnant women infected with hepatitis E virus as well as a tendency towards maternal and neonatal adverse outcomes in relation to the infection. Especially among those who have severe complications like fulminant hepatic failure. However, the case-fatality rate might be overestimated due to the inclusion of mainly symptomatic women (20). The results from this review apply exclusively to symptomatic women in endemic countries(21). Further research should be conducted to elucidate maternal and neonatal outcomes associated with hepatitis E virus infections during pregnancy(22), especially in other settings, preferably including asymptomatic HEV-infected pregnant women and with a control group of healthy pregnant women (23,24). **Aim of study** The aim of study is to determine the prevalence of hepatitis E virus infection among pregnant women and children in Baqubah city during 2019 and 2020.

Result & Discussion

The data were collected from Al Batool hospital during 2019 and 2020. In 2019, the number of suspected cases of HEV was 939 cases, all of them were children aged from (1 day-16 year). From all of these samples, there was only one sample gave a positive result which was for a child aged 10 years old. In 2020, there was247 suspected cases and all for children aged (1 day-15 year), all of these samples were negative. For the pregnant women, they did not do a screening test during 2019 and 2020. We also try to collect data from Baqubah teaching hospital, but they don't have a department for screening HEV cases.

Studies conducted in different countries among pregnant women, such as in Tunisia of 5.1%, Mexico of 5.7%, France of 7.7%, Pakistan of 8.86%, Sudan of 10.3%, and in Serbian blood donors of 15.0%. On the other hand, a high prevalence of HEV was reported among pregnant women in Egypt of 83.4%, and India of 60.0%. In addition, some other studies reported a high prevalence of HEV IgG antibody in Iran, with 46.1% in the adult population. In a study conducted in German blood donors, only 3 of 13 HEV RNA positive results had detectable IgM antibody titers. Spread of HEV through contaminated blood products remains unknown (24).

Iraq is a country with few suspected outbreaks of HEV. Starting in May 2004, an outbreak of acute hepatitis was identified in several cities of Baghdad including Al-Sader, AL-Ubidy and AL-Kamalya, in Al- Rusafa district, Al-Mahmodya and Abu Graib Cities, in Al -Karkh district. Hepatitis is now also reported from Basrah governorate, south of Iraq. The disease was recognized among young adults, pregnant women with few deaths among them and was therefore clinically diagnosed as HEV. Hepatitis E is prevalent in most developing countries, and common in any country with a hot climate. In this paper, assess the importance of HAV and HEV as a possible diagnosis for

clinically diagnosed patients with acute viral hepatitis. Calculate a national estimate for point prevalence of IgG antibodies of HAV and HEV. In addition, study the association of age, gender and governorate with serum positivity of HAV and HEV (25).

HEV infection is endemic in Iraq, acquired early in life and its seroprevalence rate increased steadily with age, reaching 26.6 % in age group 41+. HEV is an important cause of Non-A Non-B viral hepatitis. Epidemics and point source out-breaks are common in rainy season when flooding leads to sewage contamination of drinking water. Occurrence of HEV specific IgM was noted in 19.4% of serum samples from patients with a clinical suspicion of hepatitis. Our data fits with the existing epidemiological features of HEV in endemic areas. HEV specific IgM was noted in 18.8% of tested serum samples of a hospital based study of Hepatitis E by serology in India. In the national general population sample hepatitis E infection represented 20.3% of the total Iraqi sample (26). This means that the disease is endemic in Iraq. A steady increase in prevalence is observed with advancing age. Studies from Yemen and India revealed the etiological role of HEV in 28% and 38% of cases with acute sporadic NANBH. The patterns of increase are similar to those reported in many other studies from different endemic countries. In north India, a region with high endemicity for HEV infection, exposure to HEV was shown to occur in early life and seropositivity for anti-HEV IgG increased progressively from 7.2%–14.2% in infancy to 33.3%–38.0% by 10 years of age in rural and urban children respectively. A similar epidemiological picture was also seen in other studies from Turkey, Saudi Arabia and Egypt (27).

Among patients with a clinical diagnosis of acute viral hepatitis, only two fifths had serologic evidence of type A and another one fifth type E viral hepatitis. Hepatitis A is hyper-endemic in Iraq, with no gender differences. Serologic evidence of previous exposure to the infective agent is present in the

majority of general population (96.4%). It is a disease of childhood. After the second decade of life no obvious increase in its prevalence is noticed. Hepatitis E is endemic in Iraq with a prevalence of its serologic marker (IgG antibody) of 20.3%. Males have a slightly higher prevalence rate. A steady increase in prevalence is observed with advancing age (26).

	Total examined	Positive		
Overall	**N**	**N**	**%**	**95% CI for prevalence rate (%)**
Anti – HAV IgM	**2975**	**1219**	**41.0**	**(39.2 – 42.8)**
Anti – HEV IgM	**2975**	**577**	**19.4**	**(18 – 20.8)**

Table (1): The relative frequency of positive anti-HAV and anti-HEV IgM antibodies among subjects with a clinical diagnosis of acute hepatitis (26).

	Total examined	Positive serum Ab		
Overall	**N**	**N**	**%**	**95% CI for prevalence rate (%)**
Positive Anti – HAV IgG	**9610**	**9268**	**96.4**	**(96 – 96.8)**
Positive Anti – HEV IgG	**6972**	**1415**	**20.3**	**(19.4 – 21.2)**

Table (2): The prevalence rate of anti-HAV and HEV IgG antibodies in a nationally representative Iraqi general population sample (26).

	Total examined	Positive Anti-HAV IgG		95% CI for	Prevalence		
	N	**N**	**%**	**Prevalence rate (%)**	**ratio (PR)**	**95%CI for PR**	**P**
Age group							
(1-10)	**1641**	**1498**	**91.3**	**(89.9 - 92.7)**	**Ref**		

(11-20)	**2235**	**2164**	**96.8**	**(96.1 - 97.5)**	**1.06**	**(1.04 -1.08)**	**<0.001**
(21-30)	**2374**	**2323**	**97.9**	**(97.3 - 98.5)**	**1.07**	**(1.05 -1.09)**	**<0.001**
(31-40)	**1603**	**1562**	**97.4**	**(96.6 - 98.2)**	**1.07**	**(1.05 -1.09)**	**<0.001**
41+	**1757**	**1721**	**98**	**(97.3 - 98.7)**	**1.07**	**(1.06 -1.09)**	**<0.001**
Gender							
Female	**4856**	**4676**	**96.3**	**(96.1 - 97.1)**	**Ref**		
Male	**4754**	**4592**	**96.6**	**(95.8 - 96.8)**	**1.00**	**(1 -1.01)**	**0.43[NS]**

Table (3): The prevalence rate of positive serum anti-HAV IgG antibodies by age and gender in a nationally representative sample (26).

	Total examined	**Positive Anti-HEV IgG**					
	N	**N**	**%**	**95% CI for prevalence rate (%)**	**Prevalence ratio (PR)**	**95% CI for PR**	**P**
Age group							
(1-10)	**1051**	**143**	**13.6**	**(11.5 - 15.7)**	**Ref**		
(11-20)	**1648**	**305**	**18.5**	**(16.6 - 20.4)**	**1.36**	**(1.13 -1.63)**	**<0.001**
(21-30)	**1737**	**358**	**20.6**	**(18.7 - 22.5)**	**1.51**	**(1.27 -1.81)**	**<0.001**
(31-40)	**1244**	**265**	**21.3**	**(19 - 23.6)**	**1.57**	**(1.3 -1.89)**	**<0.001**
41+	**1292**	**344**	**26.6**	**(24.2 - 29)**	**1.96**	**(1.64 -2.34)**	**<0.001**
Gender							
Female	**3573**	**677**	**18.9**	**(20.3 - 23.1)**	**Ref**		
Male	**3399**	**738**	**21.7**	**(17.6 - 20.2)**	**1.15**	**(1.04 -1.26)**	**0.004**

Table (4): The point prevalence rate of positive serum anti-HEV IgG antibodies by age and gender in a nationally representative sample (26).

The clinical manifestations of HEV infection are indistinguishable from clinical symptoms of the other viral hepatitis forms. In addition, these non-specific symptoms sometimes mask the diagnosis of HEV infection, making laboratory methods the most reliable criteria for diagnosis. The laboratory diagnosis methods are based on detection of HEV RNA in serum or stool

samples by nucleic acid amplification techniques (NAT) or of anti-HEV antibodies in serum or plasma samples by serological tests (28).

Conclusion

Ribavirin was classified in Pregnancy Category X by the United States Food and Drug Administration (FDA) because of its embryocidal and teratogenic effects in animals Thus, ribavirin is not recommended for use in pregnant women. IFN-α was classified in Pregnancy Category C by the FDA, taking into account its abortifacient effect in animals and adverse effects. Therefore, IFN-α was not recommended to be administered to pregnant women. Recently, sofosbuvir showed antiviral activity against HEV both in vitro and in vivo and thus may be a promising antiviral drug against HEV in pregnancy as a pregnancy category B drug. As far as other antiviral candidates are concerned, interferon λ1–3 was shown to inhibit HEV replication. The antisense peptide-conjugated morpholino oligomers (PPMO) HP1, targeting a highly conserved sequence in the start site region of ORF1, can lead to a significant reduction in the levels of HEV RNA and capsid protein, suggesting its potential as a promising antiviral candidate. A recent study showed that nucleoside analogs NITD008, 2′-C-methylguanosine (2CMG), and the non-nucleoside inhibitor GPC-N114 can inhibit HEV in cell culture. However, more controlled studies are needed before sofosbuvir can be recommended for HEV infection in pregnancy. For the other antiviral candidates mentioned above, there is a long way to go. Therefore, the management of HEV infection in pregnancy is currently supported by diligent monitoring and intensive care.

Vaccination against HEV is another preventive strategy, although no commercial vaccine has yet become available worldwide. Several HEV vaccines have been designed and evaluated in the laboratory setting, including

recombinant vaccines consisting of various truncated forms of the capsid protein.

References

1. Albinana-Gimenez N, Clemente-Casares P, Bofill-Mas S, et al. Distribution of human polyomaviruses, adenoviruses, and hepatitis E virus in the environment and in a drinking water treatment plant. Environ Sci Technol. 2006 1;40(23):7416-22.

2. Radha Krishna Y, Saraswat VA, Das K, et al. Clinical features and predictors of outcome in acute hepatitis A and hepatitis E virus hepatitis on cirrhosis. Liver Int. 2009 ar;29(3):392-8.

3. Fujiwara S, Yokokawa Y, Morino K, et al. Chronic hepatitis E: a review of the literature. J Viral Hepat. 2014 ;21 (2):78-89.

4. Khudyakov Y, Kamili S. Serological diagnostics of hepatitis E virus infection. Virus Res. 2011 ;161(1):84-92.

5. Teshale EH, Hu DJ. Hepatitis E: Epidemiology and Prevention. World J. Hepatol. 2011; 3(12):285-91.

6. Pischke S, Hardtke S, Bode U, et al. Ribavirin treatment of acute and chronic hepatitis E: a single-centre experience. Liver Int. 2013 ;33(5):722-6.

7. Rein DB, Stevens GA, Theaker J, et al. The global burden of hepatitis E genotypes 1 and 2 in 2005. Hepatology 2012; 55(4):988-97.

8. Khuroo MS, Khuroo MS. Seroepidemiology of a second epidemic of hepatitis E in a population that had recorded first epidemic 30 years before and has been under surveillance since then. Hepatol Int. 2010 3;4(2):494-9.

9. Drobeniuc J, Meng J, Reuter G, Greene-Montfort T, et al. Serologic assays specific to immunoglobulin M antibodies against hepatitis E virus: pangenotypic evaluation of performances. Clin Infect Dis. 2010 1;51(3):e24-7.

10. Abravanel F, Chapuy-Regaud S, Lhomme S, et al. Performance of anti-HEV assays for diagnosing acute hepatitis E in immunocompromised patients. J Clin Virol. 2013 ;58(4):624-8.

11. Navaneethan U, Al Mohajer M, Shata MT. Hepatitis E and pregnancy: understanding the pathogenesis. Liver Int. 2008 ;28(9):1190-9.

12. Tabatabai J, Wenzel JJ, Soboletzki M, et al. First case report of an acute hepatitis E subgenotype 3c infection during pregnancy in Germany. J Clin Virol. 2014 ;61(1):170-2.

13. Abebe, Meseret, et al. "Seroprevalence and risk factors of Hepatitis E Virus infection among pregnant women in Addis Ababa, Ethiopia." PloS one 12.6 2017.

14. Kamar N, Dalton HR, Abravanel F, Izopet J. Hepatitis E virus infection. Clinical microbiology reviews. 2014; 27(1):116–38.

15. Lapa D, Capobianchi MR, Garbuglia AR. Epidemiology of hepatitis E virus in European countries. Int J Mol Sci 2015;16:25711–25743.

16. Pérez-Gracia MT, García M, Suay B, Mateos-Lindemann ML. Current Knowledge on Hepatitis E. J Clin Transl Hepatol 2015;3:117–126.

17. Traore KA, Rouamba H, Nebie Y, Sanou M, Traore AS, Barro N, et al. Seroprevalence of fecal-oral transmitted hepatitis A and E virus antibodies in Burkina Faso. PLoS One. 2012; 7(10):e48125.

18. Mansuy JM, Bendall R, Legrand-Abravanel F, Saune K, Miedouge M, Ellis V, et al. Hepatitis E virus antibodies in blood donors, France. Emerg Infect Dis. 2011; 17(12):2309–12.

19. Chaudhry, Shahnaz A., Natasha Verma, and Gideon Koren. "Hepatitis E infection during pregnancy." Canadian Family Physician 61.7 2015: 607-608.

20. Bergløv, Anne, Sofie Hallager, and Nina Weis. "Hepatitis E during pregnancy: Maternal and foetal case-fatality rates and adverse outcomes—A systematic review." Journal of viral hepatitis 26.11 2019: 1240-1248.

21. Sridhar S, Teng J, Chiu T-H, Lau S, Woo P. Hepatitis E virus genotypes and evolution: emergence of camel hepatitis E variants. Int J Mol Sci. 2017;18(4):869.

22. Kumar, A., et al. "Hepatitis E in pregnancy." International Journal of Gynecology & Obstetrics 85.3 2004: 240-244.

23. La Fauci V, Facciolà A, Riso R, Calimeri S, Giudice DL, Squeri R. Seroprevalence of HEV antibodies in a sample of pregnant women in the city of Messina. Ann Ig. 2017; 29: 232-8.

24. Ahmad, Tauseef, et al. "Seroprevalence of hepatitis E virus infection in pregnant women: a systematic review and meta-analysis." Annals of Saudi medicine 40.2 2020: 136-146.

25. Minstry of health / Iraq/ CDC Baghdad, Viral Hepatitis Section 2004, 2005, 2006.

26. Turky, Ataallah M., et al. "Analysis of acute viral hepatitis (A and E) in Iraq." Global Journal of Health Science 3.1 2011: 70.

27. A hospital based study of Hepatitis E by serology. Indian J Med Microbiol, 2003. 21:115-7.

28. Taherkhani R, Farshadpour F. Epidemiology of hepatitis E virus in Iran. World J Gastroenterol 2016;22:5143–5153.