

Hepatitis E and Pregnancy

Subjects: Virology

Contributor: Mohammad Khuroo

The adverse relationship between viral hepatitis and pregnancy in developing countries had been interpreted as a reflection of retrospectively biased hospital-based data collection by the West. However, the discovery of hepatitis E virus (HEV) as the etiological agent of an epidemic of non-A, non-B hepatitis in Kashmir, and the documenting of the increased incidence and severity of hepatitis E in pregnancy via a house-to-house survey, unmasked this unholy alliance. The pathogenesis of the association is complex and several mechanisms are under intense studies. Management is multidisciplinary and needs a close watch for the development and management of acute liver failure. The development of vaccine is seen as a breakthrough in the control of hepatitis E.

Keywords: hepatitis E ; hepatitis E virus ; genotypes ; pregnancy ; epidemic hepatitis ; sporadic hepatitis ; acute liver failure ; fetus ; neonate ; delivery ; hepatitis E vaccine

1. Historical Background

Space-time clustering of events in which people fall acutely ill with jaundice, quickly slip into a coma and die, is an alarming situation, more so when the victims are mostly or exclusively pregnant women ^[1].

The association between epidemics of jaundice and pregnancy has long been reported in scientific literature. The earliest recorded epidemic of jaundice with high mortality in pregnant women was reported from the French Caribbean colony Martinique in the year 1858 ^[2]. A strange disease had struck the island which left 24 women dead, and 20 of these were pregnant. All the deceased pregnant women had delivered stillborn babies. None of the jaundiced soldiers, all males, in the nearby garrison had died. Another notable epidemic of jaundice occurred in Paris in 1871. Deaths occurred exclusively in gestating women and autopsies revealed acute yellow atrophy of the liver as the cause of death ^[3]. Over the ensuing decades until 1946, many countries in Europe recorded several epidemics of jaundice with high death rates in pregnant women ^[4]. These epidemics also reported high rates of fetal and neonatal deaths as a result of abortions, premature deliveries, miscarriages, and stillbirths in both dead and surviving pregnant women. All these outbreaks were likely to have been related to hepatitis E; however, no serological tests of sera from such outbreaks are available. With improvement in economic conditions and clean water supplies, epidemic disease with high mortality in pregnant women is no longer reported from industrialized countries ^[4].

2. Epidemic Hepatitis E and Pregnancy

Several large-scale water-borne epidemics of hepatitis have been reported from many regions of the developing world ^[1]. Initially, these epidemics were designated empirically as ET-NANBH based on serological testing for HAV and HBV infections. Later, once serological testing for HEV infection was available, most such epidemics were found to be caused by HEV. HEV strains, once characterized, were all of HEV-gt1 ^{[5][6]}. Epidemic HEV infections had several features in common including occurrence in young adults (15–45 years), significant cholestatic features, self-limiting disease, and high mortality in pregnancy.

From 1978 to 2013, 10 large-scale water-borne epidemics of hepatitis E were recorded in Kashmir ^{[7][8][9][10][11][12][13][14]}. A total of 55,563 persons had contracted the disease and 1775 died with a case fatality rate (CFR) of 3.19%. CFR of HEV in pregnant women during these epidemics was 22%. A retrospective analysis of sera from a large-scale water-borne epidemic that occurred in Delhi in 1955–56 revealed that the epidemic was caused by HEV ^{[5][15][16]}. This epidemic affected an estimated 29,300 patients with 266 deaths. Overall, CFR was 0.9% and CFR in pregnancy was 8.5%. A massive epidemic of hepatitis E involving an estimated 79,000 cases visited Kanpur, UP, India in 1992, with a CFR of 27% in pregnant women ^[17]. Several other outbreaks have been reported from other parts of India ^{[18][19][20][21][22]}, Pakistan ^{[23][24][25][26]}, Burma ^{[27][28]}, Nepal ^{[29][30][31]}, and Bangladesh ^{[32][33][34][35][36]}, and all of these showed high CFR in pregnant women ^[5]. Several regions in Central Asia namely Turkmenistan ^{[37][38]}, Uzbekistan ^{[39][40]}, Tajikistan ^[41], and Kirgizstan ^[42], have been hit by epidemics of viral hepatitis caused by HEV-gt1. These epidemics affected between 10,000 and

30,000 persons and saw high mortality in pregnant women with CFR ranging from 7% to 27%. Xinjiang region in the northwest of China recorded a massive outbreak of viral hepatitis affecting 120,000 people (mostly Uighurs) in the autumn of 1987–88. CFR in pregnant women was 13% [43]. The outbreak was later confirmed to be caused by HEV-gt1 [44]. Regions of South-East Asia, namely Indonesia [45] and Vietnam, [46] have reported several epidemics of hepatitis E with a high fatality rate of up to 26% in pregnant women. Several outbreaks caused by HEV-gt1 have been reported from many regions of Africa including Somalia [47][48], Algeria [49][50][51], Côte d'Ivoire [52], Botswana [53], Djibouti [47][54] and Central African Republic [47][55], with higher fatality in pregnant women. Of late, outbreaks of hepatitis E in refugee camps among displaced people in several African countries including Somalia [47][48][56], Kenya [57][58], Sudan [59][60] and Uganda [61][62] have occurred. All these epidemics have reported higher death rates in pregnant women.

HEV-gt2 was the incriminating agent for two outbreaks of hepatitis that occurred in two villages 70 km south of Mexico City in 1986 [63]. Of the 223 cases, three women died with an overall CFR of 1.35%. Higher fatality in pregnant women was not reported. The epidemic caused by HEV-gt2 from Namibia in 1995 also did not report higher deaths in pregnant women [58][64][65]. However, a previously reported epidemic from Namibia in 1983 was caused by HEV-gt1 [66][67] and of the 201 cases six of the seven deaths were seen in pregnant women. Epidemics of hepatitis in Nigeria [68][69], Central African Republic [70], and Chad [71][72] were caused by both HEV-gt1 and HEV-gt2 and all reported higher deaths in pregnant women. Few cases of HEV-gt3 and HEV-gt4 infections reported in pregnant women have not been associated with severe disease or deaths [73][74]. An HEV-gt3 outbreak on a cruise ship causing 33 infections did not cause higher mortality in pregnant women [75]. HEV-gt3 and HEV-gt4 are prevalent in industrialized countries and have not been associated with higher mortality in pregnant women [76]. Thus, higher mortality of epidemic hepatitis E in pregnancy is genotype-specific and associated with HEV-gt1 and not with other genotypes causing human infections, namely HEV-gt2, HEV-gt3, and HEV-gt4. However, adverse pregnancy outcomes including miscarriage and stillbirths have been reported in pregnant rabbits experimentally infected with HEV-gt3 and HEV-gt4 [77][78][79].

3. HEV-ALF and Pregnancy

Several large series of ALF and its relationship with pregnancy have been reported from India. HEV was the cause of ALF in 47 of the 49 pregnant women as against 14 of the 34 nonpregnant women of childbearing age. HEV was the etiological cause in 342 patients, while 651 patients had non-HEV etiology [80]. HEV was the cause of ALF in 145 of the 244 pregnant women, 100 of the 329 nonpregnant women, and 97 of the 420 men.

HEV-ALF in pregnant women starts with prodrome followed by other features of acute viral hepatitis [11]. However, a rapidly evolving devastating illness develops within a short pre-encephalopathy period (5.8 ± 5.3 days), characterized by encephalopathy, cerebral edema with features of cerebellar coning, coagulopathy, and upper GI bleed [81][82][83]. In addition, the occurrence of “Disseminated intravascular coagulation (DIC)” is a distinctive feature of HEV-ALF during pregnancy [84], resembling a Schwartzmann phenomenon.

The authors compared the mortality rates in 249 pregnant women, 341 non-pregnant women, and 425 men, 15 to 45 years of age. A prospective study on 180 pregnant women with ALF revealed 79 with HEV-ALF and 101 with non-HEV-ALF [81]. Factors predictive of poor prognosis included non-HEV etiology, prothrombin time > 30 s, grade of coma > 2, and age > 40 years and did not include pregnancy per se or duration of pregnancy. The fact that pregnant women acquired ALF more often did not mean that such patients will have higher mortality [85].

4. Management

HEV infection in pregnant women requires a team approach, determined by stage and severity of the disease in the mother, occurrence of obstetrical complications, and severity of vertically transmitted disease in the fetus/neonate.

HEV-AVH is usually a self-limiting disease and needs supportive medical treatment. At the onset, prodromal symptoms are limited to anorexia, fever, nausea, vomiting, and abdominal discomfort and generally subside within a week. A few patients may need a short hospital stay for intravenous fluids given for severe vomiting. Otherwise, patients are advised bed rest at home with bathroom privileges during prodrome and icteric disease. Later, physical activity is restricted and work can be resumed when disease recovery occurs. A portable high caloric diet with high carbohydrate and low fat is usually advised, but has no benefit in disease recovery. Cholestatic symptoms if intractable can be managed with antihistamines, cholestyramine, and/or ursodeoxycholic acid (UDCA). Corticosteroids should not be administered unless there is associated autoimmune hepatitis.

Patients are at high risk for ALF and the disease course can be unpredictable. So, a close watch on impending signs of liver failure (shrinking liver size, high or rising INR, rapid rise in serum bilirubin, and development of ascites or

coagulopathy) must be kept. Patients with impending signs of ALF need intensive care management. Management policies to treat complications of ALF, namely encephalopathy, cerebral edema, hypoglycemia, coagulopathy, and possible DIC, GI bleed, sepsis, and renal failure, have been well standardized and should be immediately enforced. Liver transplantation team if available must be involved and considered if prognostic criteria employed are met [81][82][86][87]. Unfortunately, as of today, only isolated case reports of liver transplantation in pregnant women with HEV-ALF are published in the literature [88][89][90].

A close obstetric watch is needed in both HEV-AVH and HEV-ALF patients to evaluate the stage of pregnancy, fetal wellbeing, and growth. Complications such as abortions, preterm labor, premature rupture of membranes, stillbirth, intrauterine deaths, and increased risk of bleeding associated with coagulopathy can occur and need to be aggressively managed by standard obstetric guidelines [91]. Therapeutic termination of pregnancy and its beneficial effects on liver disease in the mother needs serious consideration [92][93], as events in the maternal-fetal interface and the fetus are involved and are incriminated in the severity of the maternal disease [94][95]. Therapeutic termination has proved effective in two other clinical syndromes, namely HELLP syndrome and acute fatty liver in pregnancy, wherein fetal events drive the maternal disease [96][97]. Several investigators do not recommend termination of pregnancy in pregnant women with HEV-ALF [98][99]. This is based on the results of a retrospective study, in which 42 patients with HEV-ALF were studied [100]. Nine of the 22 women who delivered had died along with 14 of the women who continued their pregnancy. There was no significant difference in mortality in the two groups. However, in a subgroup analysis, the authors showed that patients with lesser degree (grade 1–3) of encephalopathy who delivered had lesser mortality (5/16) than those who continued their pregnancy (13/20, $p < 0.046$). Satia and Shilotri [101] from Mumbai, Maharashtra, India showed promising results of induction of labor in a pregnant woman with HEV-ALF with grade 2 hepatic encephalopathy and DIC. After induced vaginal delivery, the patient made an eventual recovery. The authors recommended therapeutic termination of pregnancy in HEV-ALF with lower grades of encephalopathy for a better maternal outcome. We showed that of the 16 pregnant women with HEV-ALF, 10 of whom also had DIC, all the six mothers (DIC in 3) who delivered babies within 4 days (mean \pm 1SD 2.3 ± 1.0 days) from onset of encephalopathy and with lower grades of encephalopathy (mean \pm 1SD 3.0 ± 0.89) survived. In contrast, all the 10 mothers, of whom six had DIC, who died had delivered babies after 4 days (mean \pm 1SD 9.6 ± 3.0 days) and with higher grades of encephalopathy (mean \pm 1SD 3.5 ± 0.53) ($p = 0.02$). The results of such an endeavor are striking in sick patients with severe metabolic problems and DIC (**Figure 1**). Thus, therapeutic or spontaneous termination of pregnancy with HEV-ALF early in the course of disease with lesser grades of encephalopathy was recommended [84]. Randomized trials on the therapeutic role of termination in HEV-ALF pregnant women need to be carried out. However, till the results of such trials are available, it is a safe practice to induce labor early in the course of disease with lower grades of encephalopathy for a better maternal outcome.

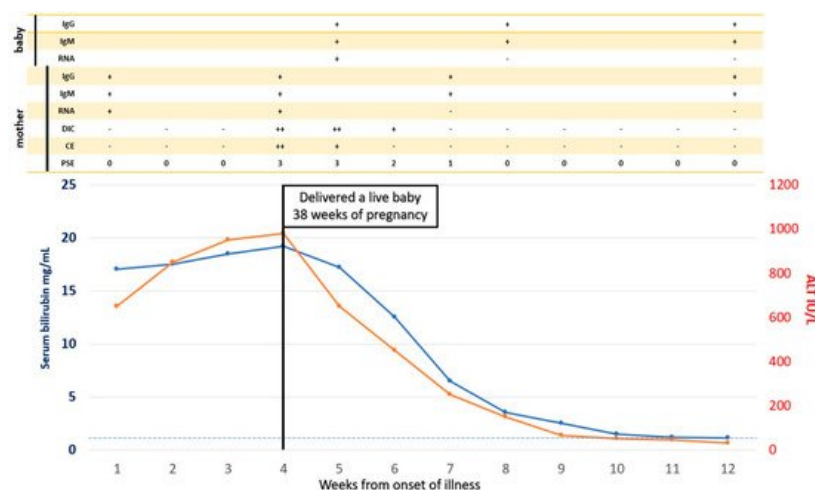


Figure 1. Spontaneous Vaginal Delivery in pregnancy with HEV-ALF and the outcome on maternal disease. A 30-year-old pregnant woman presented with features of icteric hepatitis E virus infection. On the 24th day of her illness, she had rapid deterioration with encephalopathy, cerebral edema, and laboratory features of DIC. She delivered a live baby vaginally with icteric hepatitis E four days after the onset of encephalopathy. Serial follow-up showed rapid clinical improvement in encephalopathy, cerebral edema, and DIC. PSE = portosystemic encephalopathy, CE = cerebral edema, DIC = disseminated intravascular coagulation, RNA = HEV RNA, IgM = IgM anti-HEV, IgG = IgG anti-HEV.

Neonatal care is essential as HEV is known to infect the fetus/neonate resulting in considerable fetal and perinatal morbidity and mortality [102].

Several drugs, namely ribavirin, pegylated IFN, and sofosbuvir, inhibit HEV replication, have an antiviral property, and are drugs of choice to manage chronic HEV-3 in solid organ transplant and patients with some hemopoietic malignancies ^[103]. Recently ribavirin has been successfully used to treat HEV acute-on-chronic-liver-failure and severe HEV infection in nonpregnant states ^[104]. Ribavirin is teratogenic and is contraindicated during pregnancy and there are no reports of ribavirin therapy in HEV-AVH and HEV-ALF.

5. Vaccination

The development of the HEV vaccine is seen as a breakthrough in the control of hepatitis E ^{[105][106]}. Vaccination against HEV in pregnant women and women of childbearing age in endemic regions may be the most important management strategy ^[107]. The Chinese vaccine, HEV 239 marketed as Hecolin ^[108], is protective against HEV-gt1. The vaccine has been shown to be safe in pregnant women ^[109] and protects against HEV infection and HEV-related adverse outcomes in pregnant rabbits ^[110]. Recently, a phase IV trial has been initiated to assess the effectiveness, safety, and immunogenicity of the HEV 239 vaccine in women of childbearing age in rural Bangladesh, where HEV infection is endemic ^[111]. Availability of the vaccine in developing countries is being watched with great interest ^[112].

References

1. Teo, C.G. Fatal outbreaks of jaundice in pregnancy and the epidemic history of hepatitis E. *Epidemiol. Infect.* 2012, 140, 767–787.
2. Saint-Vel, O. Note on a form of severe jaundice in pregnant women. *Gazette des Hôpitaux Civils et Militaires* 1862, 65, 538–539. (In French)
3. Decaisne, E. An epidemic of simple jaundice observed in Paris and in the vicinity. *Gazette Hebdomadaire de Médecine et de Chirurgie* 1872, 19, 44. (In French)
4. Khuroo, M.S.; Sofi, A.A. The Discovery of Hepatitis Viruses: Agents and Disease. *J. Clin. Exp. Hepatol.* 2020, 10, 391–401.
5. Arankalle, V.A.; Chadha, M.S.; Tsarev, S.A.; Emerson, S.U.; Risbud, A.R.; Banerjee, K.; Purcell, R.H. Seroepidemiology of water-borne hepatitis in India and evidence for a third enterically-transmitted hepatitis agent. *Proc. Natl. Acad. Sci. USA* 1994, 91, 3428–3432.
6. Gupta, N.; Sarangi, A.N.; Dadhich, S.; Dixit, V.K.; Chetri, K.; Goel, A.; Aggarwal, R. Acute hepatitis E in India appears to be caused exclusively by genotype 1 hepatitis E virus. *Indian J. Gastroenterol.* 2018, 37, 44–49.
7. Khuroo, M.S. Study of an epidemic of non-A, non-B hepatitis. Possibility of another human hepatitis virus distinct from post-transfusion non-A, non-B type. *Am. J. Med.* 1980, 68, 818–824.
8. Khuroo, M.S.; Teli, M.R.; Skidmore, S.; Sofi, M.A.; Khuroo, M.I. Incidence and severity of viral hepatitis in pregnancy. *Am. J. Med.* 1981, 70, 252–255.
9. Kamili, S.; Guides, S.; Khuroo, M.S.; Jameel, S.; Salahuddin, M. Hepatitis E: Studies on Transmission, Etiological Agent and Seroepidemiology. Ph.D. Thesis, University of Kashmir, Srinagar, India, 1994.
10. Khuroo, M.S.; Khuroo, M.S.; Khuroo, N.S. Transmission of Hepatitis E Virus in Developing Countries. *Viruses* 2016, 8, 253.
11. Khuroo, M.S. Hepatitis E: The enterically transmitted non-A, non-B hepatitis. *Indian J. Gastroenterol.* 1991, 10, 96–100.
12. Khuroo, M.S.; Khuroo, M.S. 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, 4, 494–499.
13. Jameel, S.; Durgapal, H.; Habibullah, C.M.; Khuroo, M.S.; Panda, S.K. Enteric non-A, non-B hepatitis: Epidemics, animal transmission, and hepatitis E virus detection by the polymerase chain reaction. *J. Med. Virol.* 1992, 37, 263–270.
14. Panda, S.K.; Nanda, S.K.; Zafrullah, M.; Ansari, I.H.; Ozdener, M.H.; Jameel, S. An Indian strain of hepatitis E virus (HEV): Cloning, sequence, and expression of structural region and antibody responses in sera from individuals from an area of high-level HEV endemicity. *J. Clin. Microbiol.* 1995, 33, 2653–2659.
15. Viswanathan, R. Infectious hepatitis in Delhi (1955–1956): A critical study—Epidemiology. *Indian J. Med. Res.* 1957, 45, 71–76.
16. Wong, D.C.; Purcell, R.H.; Sreenivasan, M.A.; Prasad, S.R.; Pavri, K.M. Epidemic and endemic hepatitis in India: Evidence for a non-A, non-B hepatitis virus aetiology. *Lancet* 1980, 2, 876–879.

17. Naik, S.R.; Aggarwal, R.; Salunke, P.N.; Mehrotra, N.N. A large waterborne viral hepatitis E epidemic in Kanpur, India. *Bull. World Health Organ.* 1992, 70, 597–604.
18. Tandon, B.N.; Joshi, Y.K.; Jawn, S.J. An epidemic of non-A non-B hepatitis in north India. *Indian J. Med. Res.* 1982, 75, 739–744.
19. Sreenivasan, M.A.; Sehgal, A.; Prasad, S.R.; Dhorje, S. A sero-epidemiologic study of a water-borne epidemic of viral hepatitis in Kolhapur City, India. *J. Hyg.* 1984, 93, 113–122.
20. Chakraborty, S.; Dutta, M.; Pasha, S.T.; Kumar, S. Observations on outbreaks of viral hepatitis in Vidisha and Rewa district of Madhya Pradesh, 1980. *J. Commun. Dis.* 1983, 15, 242–248.
21. Panda, S.K.; Datta, R.; Kaur, J.; Zuckerman, A.J.; Nayak, N.C. Enterically transmitted non-A, non-B hepatitis: Recovery of virus-like particles from an epidemic in south Delhi and transmission studies in rhesus monkeys. *Hepatology* 1989, 10, 466–472.
22. Sreenivasan, M.A.; Banerjee, K.; Pandya, P.G.; Kotak, R.R.; Pandya, P.M.; Desai, N.J.; Vaghela, L.H. Epidemiological investigations of an outbreak of infectious hepatitis in Ahmedabad city during 1975–76. *Indian J. Med. Res.* 1978, 67, 197–206.
23. Rab, M.A.; Bile, M.K.; Mubarik, M.M.; Asghar, H.; Sami, Z.; Siddiqi, S.; Dil, A.S.; Barzgar, M.A.; Chaudhry, M.A.; Burney, M.I. Water-borne hepatitis E virus epidemic in Islamabad, Pakistan: A common source outbreak traced to the malfunction of a modern water treatment plant. *Am. J. Trop. Med. Hyg.* 1997, 57, 151–157.
24. Tsarev, S.A.; Emerson, S.U.; Reyes, G.R.; Tsareva, T.S.; Legters, L.J.; Malik, I.A.; Iqbal, M.; Purcell, R.H. Characterization of a prototype strain of hepatitis E virus. *Proc. Natl. Acad. Sci. USA* 1992, 89, 559–563.
25. He, J. Molecular detection and sequence analysis of a new hepatitis E virus isolate from Pakistan. *J. Viral Hepat.* 2006, 13, 840–844.
26. van Cuyck-Gandre, H.; Zhang, H.Y.; Tsarev, S.A.; Warren, R.L.; Caudill, J.D.; Snellings, N.J.; Begot, L.; Innis, B.L.; Longer, C.F. Short report: Phylogenetically distinct hepatitis E viruses in Pakistan. *Am. J. Trop. Med. Hyg.* 2000, 62, 187–189.
27. Tam, A.W.; Smith, M.M.; Guerra, M.E.; Huang, C.C.; Bradley, D.W.; Fry, K.E.; Reyes, G.R. Hepatitis E virus (HEV): Molecular cloning and sequencing of the full-length viral genome. *Virology* 1991, 185, 120–131.
28. Hla, M.; Myint Myint, S.; Tun, K.; Thein-Maung, M.; Khin Maung, T. A clinical and epidemiological study of an epidemic of non-A non-B hepatitis in Rangoon. *Am. J. Trop. Med. Hyg.* 1985, 34, 1183–1189.
29. Kane, M.A.; Bradley, D.W.; Shrestha, S.M.; Maynard, J.E.; Cook, E.H.; Mishra, R.P.; Joshi, D.D. Epidemic non-A, non-B hepatitis in Nepal. Recovery of a possible etiologic agent and transmission studies in marmosets. *JAMA* 1984, 252, 3140–3145.
30. Gouvea, V.; Snellings, N.; Popek, M.J.; Longer, C.F.; Innis, B.L. Hepatitis E virus: Complete genome sequence and phylogenetic analysis of a Nepali isolate. *Virus Res.* 1998, 57, 21–26.
31. Shrestha, S.M. Hepatitis E in Nepal. *Kathmandu Univ. Med. J. KUMJ* 2006, 4, 530–544.
32. International Centre for Diarrhoeal Disease Research, Bangladesh. Outbreak of hepatitis E in a low income urban community in Bangladesh. *Health Sci. Bull.* 2009, 7, 14–20.
33. Sugitani, M.; Tamura, A.; Shimizu, Y.K.; Sheikh, A.; Kinukawa, N.; Shimizu, K.; Moriyama, M.; Komiyama, K.; Li, T.C.; Takeda, N.; et al. Detection of hepatitis E virus RNA and genotype in Bangladesh. *J. Gastroenterol. Hepatol.* 2009, 24, 599–604.
34. Haque, F.; Banu, S.S.; Ara, K.; Chowdhury, I.A.; Chowdhury, S.A.; Kamili, S.; Rahman, M.; Luby, S.P. An outbreak of hepatitis E in an urban area of Bangladesh. *J. Viral Hepat.* 2015, 22, 948–956.
35. Baki, A.A.; Haque, W.; Giti, S.; Khan, A.A.; Rahman, M.M.; Jubaida, N.; Rahman, M. Hepatitis E virus genotype 1f outbreak in Bangladesh, 2018. *J. Med. Virol.* 2020, 37, 35–37.
36. International Centre for Diarrhoeal Disease Research, Bangladesh. Hepatitis E outbreak in Rajshahi City Corporation. *Health Sci. Bull.* 2010, 8, 12–18.
37. Albetkova, A.; Drobeniuc, J.; Yashina, T.; Musabaev, E.; Robertson, B.; Nainan, O.; Favorov, M. Characterization of hepatitis E virus from outbreak and sporadic cases in Turkmenistan. *J. Med. Virol.* 2007, 79, 1696–1702.
38. Shakhgil'dian, I.V.; Khukhlovich, P.A.; Kuzin, S.N.; Favorov, M.O.; Nedachin, A.E. Epidemiological characteristics of non-A, non-B viral hepatitis with a fecal-oral transmission mechanism. *Vopr. Virusol.* 1986, 31, 175–179.
39. Sharapov, M.B.; Favorov, M.O.; Yashina, T.L.; Brown, M.S.; Onischenko, G.G.; Margolis, H.S.; Chorba, T.L. Acute viral hepatitis morbidity and mortality associated with hepatitis E virus infection: Uzbekistan surveillance data. *BMC Infect. Dis.* 2009, 9, 35.

40. Chatterjee, R.; Tsarev, S.; Pillot, J.; Coursaget, P.; Emerson, S.U.; Purcell, R.H. African strains of hepatitis E virus that are distinct from Asian strains. *J. Med. Virol.* 1997, 53, 139–144.
41. Rafiev Kh, K. Viral hepatitis E: Its epidemiological characteristics in the Republic of Tajikistan. *Zh Mikrobiol. Epidemiol. Immunobiol.* 1999, 4, 26–29.
42. Alatortseva, G.I.; Likhverchik, L.N.; Nesterenko, L.N.; Dotsenko, V.V.; Amiantova, I.I.; Mikhailov, M.I.; Kyuregian, K.K.; Malinnikova, E.Y.; Nurmatov, Z.S.; Nurmatov, A.Z.; et al. The estimation of the hepatitis E proportion in the etiological structure of acute viral hepatitis in certain regions of Kyrgyzstan. *Klin. Lab. Diagn.* 2019, 64, 740–746.
43. Cao, X.-Y.; Ma, X.-Z.; Liu, Y.-Z.; Jin, X.-M.; Gao, Q.; Dong, H.-J.; Zhuang, H.; Liu, C.-B.; Wang, G.-M. Epidemiological and etiological studies on enterically transmitted non-A non-B hepatitis in the south part of Xinjiang. *Chin. J. Exp. Clin. Virol.* 1989, 3, 1–10. (In Chinese)
44. Aye, T.T.; Uchida, T.; Ma, X.Z.; Iida, F.; Shikata, T.; Zhuang, H.; Win, K.M. Complete nucleotide sequence of a hepatitis E virus isolated from the Xinjiang epidemic (1986–1988) of China. *Nucleic Acids Res.* 1992, 20, 3512.
45. Corwin, A.; Jarot, K.; Lubis, I.; Nasution, K.; Suparmawo, S.; Sumardiati, A.; Widodo, S.; Nazir, S.; Orndorff, G.; Choi, Y.; et al. Two years' investigation of epidemic hepatitis E virus transmission in West Kalimantan (Borneo), Indonesia. *Trans. R. Soc. Trop. Med. Hyg.* 1995, 89, 262–265.
46. Corwin, A.L.; Khiem, H.B.; Clayson, E.T.; Pham, K.S.; Vo, T.T.; Vu, T.Y.; Cao, T.T.; Vaughn, D.; Merven, J.; Richie, T.L.; et al. A waterborne outbreak of hepatitis E virus transmission in southwestern Vietnam. *Am. J. Trop. Med. Hyg.* 1996, 54, 559–562.
47. Kim, J.H.; Nelson, K.E.; Panzner, U.; Kasture, Y.; Labrique, A.B.; Wierzbica, T.F. A systematic review of the epidemiology of hepatitis E virus in Africa. *BMC Infect. Dis.* 2014, 14, 308.
48. Bile, K.; Isse, A.; Mohamud, O.; Allebeck, P.; Nilsson, L.; Norder, H.; Mushahwar, I.K.; Magnus, L.O. Contrasting roles of rivers and wells as sources of drinking water on attack and fatality rates in a hepatitis E epidemic in Somalia. *Am. J. Trop. Med. Hyg.* 1994, 51, 466–474.
49. van Cuyck-Gandre, H.; Zhang, H.Y.; Tsarev, S.A.; Clements, N.J.; Cohen, S.J.; Caudill, J.D.; Buisson, Y.; Coursaget, P.; Warren, R.L.; Longer, C.F. Characterization of hepatitis E virus (HEV) from Algeria and Chad by partial genome sequence. *J. Med. Virol.* 1997, 53, 340–347.
50. Belabbes, E.H.; Bouguermouh, A.; Benatallah, A.; Illoul, G. Epidemic non-A, non-B viral hepatitis in Algeria: Strong evidence for its spreading by water. *J. Med. Virol.* 1985, 16, 257–263.
51. van Cuyck, H.; Juge, F.; Roques, P. Phylogenetic analysis of the first complete hepatitis E virus (HEV) genome from Africa. *FEMS Immunol. Med. Microbiol.* 2003, 39, 133–139.
52. Rioche, M.; Dubreuil, P.; Kouassi-Samgare, A.; Akran, V.; Nordmann, P.; Pillot, J. Incidence of sporadic hepatitis E in Ivory Coast based on still problematic serology. *Bull. World Health Organ.* 1997, 75, 349–354.
53. Byskov, J. An outbreak of suspected water-borne epidemic non-A non-B hepatitis in northern Botswana with a high prevalence of hepatitis B carriers and hepatitis delta markers among patients. *Trans. R. Soc. Med. Hyg.* 1989, 83, 110–116.
54. Coursaget, P.; Buisson, Y.; Enogat, N.; Bercion, R.; Baudet, J.M.; Delmaire, P.; Prigent, D.; Desramé, J. Outbreak of enterically-transmitted hepatitis due to hepatitis A and hepatitis E viruses. *J. Hepatol.* 1998, 28, 745–750.
55. Goumba, A.I.; Konamna, X.; Komasa, N.P. Clinical and epidemiological aspects of a hepatitis E outbreak in Bangui, Central African Republic. *BMC Infect. Dis.* 2011, 11, 93.
56. Mushahwar, I.K.; Dawson, G.J.; Bile, K.M.; Magnus, L.O. Serological studies of an enterically transmitted non-A, non-B hepatitis in Somalia. *J. Med. Virol.* 1993, 40, 218–221.
57. Ahmed, J.A.; Moturi, E.; Spiegel, P.; Schilperoord, M.; Burton, W.; Kassim, N.H.; Mohamed, A.; Ochieng, M.; Nderitu, L.; Navarro-Colorado, C.; et al. Hepatitis E outbreak, Dadaab refugee camp, Kenya, 2012. *Emerg. Infect. Dis.* 2013, 19, 1010–1012.
58. Mast, E. Hepatitis E among refugees in Kenya: Minimal apparent person-to-person transmission, evidence for age-dependant disease expression, and new serological assays. In *Viral Hepatitis and Liver Disease*; Kishioka, K., Suzuki, H., Mishior, S., Oda, T., Eds.; Springer: Tokyo, Japan, 1994; pp. 375–378.
59. Boccia, D.; Guthmann, J.P.; Klovstad, H.; Hamid, N.; Tatay, M.; Ciglenecki, I.; Nizou, J.Y.; Nicand, E.; Guerin, P.J. High mortality associated with an outbreak of hepatitis E among displaced persons in Darfur, Sudan. *Clin. Infect. Dis.* 2006, 42, 1679–1684.
60. Elduma, A.H.; Zein, M.M.; Karlsson, M.; Elkhidir, I.M.; Norder, H. A Single Lineage of Hepatitis E Virus Causes Both Outbreaks and Sporadic Hepatitis in Sudan. *Viruses* 2016, 8, 273.

61. Gerbi, G.B.; Williams, R.; Bakamutumaho, B.; Liu, S.; Downing, R.; Drobeniuc, J.; Kamili, S.; Xu, F.; Holmberg, S.D.; Teshale, E.H. Hepatitis E as a cause of acute jaundice syndrome in northern Uganda, 2010–2012. *Am. J. Trop. Med. Hyg.* 2015, 92, 411–414.
62. Howard, C.M.; Handzel, T.; Hill, V.R.; Grytdal, S.P.; Blanton, C.; Kamili, S.; Drobeniuc, J.; Hu, D.; Teshale, E. Novel risk factors associated with hepatitis E virus infection in a large outbreak in northern Uganda: Results from a case-control study and environmental analysis. *Am. J. Trop. Med. Hyg.* 2010, 83, 1170–1173.
63. Huang, C.C.; Nguyen, D.; Fernandez, J.; Yun, K.Y.; Fry, K.E.; Bradley, D.W.; Tam, A.W.; Reyes, G.R. Molecular cloning and sequencing of the Mexico isolate of hepatitis E virus (HEV). *Virology* 1992, 191, 550–558.
64. Maila, H.T.; Bowyer, S.M.; Swanepoel, R. Identification of a new strain of hepatitis E virus from an outbreak in Namibia in 1995. *J. Gen. Virol.* 2004, 85, 89–95.
65. Bustamante, N.D.; Matyenyika, S.R.; Miller, L.A.; N'Gawara, M.N. Notes from the Field: Nationwide Hepatitis E Outbreak Concentrated in Informal Settlements—Namibia, 2017–2020. *MMWR Morb. Mortal. Wkly. Rep.* 2020, 69, 355–357.
66. Isaacson, M.; Frean, J.; He, J.; Seriwatana, J.; Innis, B.L. An outbreak of hepatitis E in Northern Namibia, 1983. *Am. J. Trop. Med. Hyg.* 2000, 62, 619–625.
67. He, J.; Binn, L.N.; Tsarev, S.A.; Hayes, C.G.; Frean, J.A.; Isaacson, M.; Innis, B.L. Molecular characterization of a hepatitis E virus isolate from Namibia. *J. Biomed. Sci.* 2000, 7, 334–338.
68. Wang, B.; Akanbi, O.A.; Harms, D.; Adesina, O.; Osundare, F.A.; Naidoo, D.; Deveau, I.; Ogundiran, O.; Ugochukwu, U.; Mba, N.; et al. A new hepatitis E virus genotype 2 strain identified from an outbreak in Nigeria, 2017. *Virol. J.* 2018, 15, 163.
69. World-Health-Organization. Acute hepatitis E—Nigeria: Disease Outbreak News 2017. Available online: (accessed on 28 April 2021).
70. Escriba, J.M.; Nakoune, E.; Recio, C.; Massamba, P.M.; Matsika-Claquin, M.D.; Goumba, C.; Rose, A.M.; Nicand, E.; Garcia, E.; Leklegban, C.; et al. Hepatitis E, Central African Republic. *Emerg. Infect. Dis.* 2008, 14, 681–683.
71. Nicand, E.; Armstrong, G.L.; Enouf, V.; Guthmann, J.P.; Guerin, J.P.; Caron, M.; Nizou, J.Y.; Andraghetti, R. Genetic heterogeneity of hepatitis E virus in Darfur, Sudan, and neighboring Chad. *J. Med. Virol.* 2005, 77, 519–521.
72. Spina, A.; Lenglet, A.; Beversluis, D.; de Jong, M.; Vernier, L.; Spencer, C.; Andayi, F.; Kamau, C.; Vollmer, S.; Hogema, B.; et al. A large outbreak of Hepatitis E virus genotype 1 infection in an urban setting in Chad likely linked to household level transmission factors, 2016–2017. *PLoS ONE* 2017, 12, e0188240.
73. Anty, R.; Ollier, L.; Peron, J.M.; Nicand, E.; Cannavo, I.; Bongain, A.; Giordanengo, V.; Tran, A. First case report of an acute genotype 3 hepatitis E infected pregnant woman living in South-Eastern France. *J. Clin. Virol.* 2012, 54, 76–78.
74. Tabatabai, J.; Wenzel, J.J.; Soboletzki, M.; Flux, C.; Navid, M.H.; Schnitzler, P. First case report of an acute hepatitis E subgenotype 3c infection during pregnancy in Germany. *J. Clin. Virol.* 2014, 61, 170–172.
75. Said, B.; Ijaz, S.; Kafatos, G.; Booth, L.; Thomas, H.L.; Walsh, A.; Ramsay, M.; Morgan, D.; Hepatitis, E.I.I.T. Hepatitis E outbreak on cruise ship. *Emerg. Infect. Dis.* 2009, 15, 1738–1744.
76. Clemente-Casares, P.; Ramos-Romero, C.; Ramirez-Gonzalez, E.; Mas, A. Hepatitis E Virus in Industrialized Countries: The Silent Threat. *Biomed. Res. Int.* 2016, 2016, 9838041.
77. Ahn, H.S.; Han, S.H.; Kim, Y.H.; Park, B.J.; Kim, D.H.; Lee, J.B.; Park, S.Y.; Song, C.S.; Lee, S.W.; Choi, C.; et al. Adverse fetal outcomes in pregnant rabbits experimentally infected with rabbit hepatitis E virus. *Virology* 2017, 512, 187–193.
78. Lin, S.; Zhang, Y.-J. Advances in Hepatitis E Virus Biology and Pathogenesis. *Viruses* 2021, 13, 267.
79. Xia, J.; Liu, L.; Wang, L.; Zhang, Y.; Zeng, H.; Liu, P.; Zou, Q.; Wang, L.; Zhuang, H. Experimental infection of pregnant rabbits with hepatitis E virus demonstrating high mortality and vertical transmission. *J. Viral Hepat.* 2015, 22, 850–857.
80. Bhatia, V.; Singhal, A.; Panda, S.K.; Acharya, S.K. A 20-year single-center experience with acute liver failure during pregnancy: Is the prognosis really worse? *Hepatology* 2008, 48, 1577–1585.
81. Khuroo, M.S.; Kamili, S. Aetiology and prognostic factors in acute liver failure in India. *J. Viral Hepat.* 2003, 10, 224–231.
82. Acharya, S.K.; Dasarathy, S.; Kumer, T.L.; Sushma, S.; Prasanna, K.S.; Tandon, A.; Sreenivas, V.; Nijhawan, S.; Panda, S.K.; Nanda, S.K.; et al. Fulminant hepatitis in a tropical population: Clinical course, cause, and early predictors of outcome. *Hepatology* 1996, 23, 1448–1455.
83. Acharya, S.K.; Panda, S.K.; Saxena, A.; Gupta, S.D. Acute hepatic failure in India: A perspective from the East. *J. Gastroenterol. Hepatol.* 2000, 15, 473–479.

84. Khuroo, M.S.; Kamili, S. Association of severity of hepatitis E virus infection in the mother and vertically transmitted infection in the fetus. *JK Pract.* 2006, 13, 70–74.
85. Khuroo, M.S. Acute liver failure in India. *Hepatology* 1997, 26, 244–246.
86. Shalimar; Acharya, S.K. Management in acute liver failure. *J. Clin. Exp. Hepatol.* 2015, 5, S104–S115.
87. Dhiman, R.K.; Jain, S.; Maheshwari, U.; Bhalla, A.; Sharma, N.; Ahluwalia, J.; Duseja, A.; Chawla, Y. Early indicators of prognosis in fulminant hepatic failure: An assessment of the Model for End-Stage Liver Disease (MELD) and King's College Hospital criteria. *Liver Transpl.* 2007, 13, 814–821.
88. Bertuzzo, V.R.; Ravaioli, M.; Morelli, M.C.; Calderaro, A.; Viale, P.; Pinna, A.D. Pregnant woman saved with liver transplantation from acute liver failure due to hepatitis E virus. *Transpl. Int.* 2014, 27, e87–e89.
89. Babu, R.; Kanianchalil, K.; Sahadevan, S.; Nambiar, R.; Kumar, A. Liver transplantation for acute liver failure due to hepatitis E in a pregnant patient. *Indian J. Anaesth.* 2018, 62, 908–910.
90. Ockner, S.A.; Brunt, E.M.; Cohn, S.M.; Krul, E.S.; Hanto, D.W.; Peters, M.G. Fulminant hepatic failure caused by acute fatty liver of pregnancy treated by orthotopic liver transplantation. *Hepatology* 1990, 11, 59–64.
91. Patra, S.; Kumar, A.; Trivedi, S.S.; Puri, M.; Sarin, S.K. Maternal and fetal outcomes in pregnant women with acute hepatitis E virus infection. *Ann. Intern. Med.* 2007, 147, 28–33.
92. Khuroo, M.S. A Review of Acute Viral Hepatitides Including Hepatitis E. In *Viral Hepatitis: Acute Hepatitis*; Ozaras, R., Arends, J.E., Eds.; Springer: Berlin/Heidelberg, Germany, 2019; pp. 77–107.
93. Navaneethan, U.; Al Mohajer, M.; Shata, M.T. Hepatitis E and pregnancy: Understanding the pathogenesis. *Liver Int.* 2008, 28, 1190–1199.
94. Gouilly, J.; Chen, Q.; Siewiera, J.; Cartron, G.; Levy, C.; Dubois, M.; Al-Daccak, R.; Izopet, J.; Jabrane-Ferrat, N.; El Costa, H. Genotype specific pathogenicity of hepatitis E virus at the human maternal-fetal interface. *Nat. Commun.* 2018, 9, 4748.
95. Khuroo, M.S.; Kamili, S.; Dahab, S.; Yattoo, G.N. Severe fetal hepatitis E virus infection is the possible cause of increased severity of hepatitis E virus infection in the mother: Another example of mirror syndrome. *Am. J. Gastroenterol.* 2004, 99, S100.
96. Naoum, E.E.; Leffert, L.R.; Chitilian, H.V.; Gray, K.J.; Bateman, B.T. Acute Fatty Liver of Pregnancy: Pathophysiology, Anesthetic Implications, and Obstetrical Management. *Anesthesiology* 2019, 130, 446–461.
97. Celik, C.; Gezginc, K.; Altintepe, L.; Tonbul, H.Z.; Yaman, S.T.; Akyurek, C.; Turk, S. Results of the pregnancies with HELLP syndrome. *Ren. Fail.* 2003, 25, 613–618.
98. Shalimar; Acharya, S.K. Hepatitis e and acute liver failure in pregnancy. *J. Clin. Exp. Hepatol.* 2013, 3, 213–224.
99. Kar, P.; Karna, R. A Review of the Diagnosis and Management of Hepatitis E. *Curr. Treat. Options Infect. Dis.* 2020, 12, 1–11.
100. Banait, V.S.; Sandur, V.; Parikh, F.; Murugesh, M.; Ranka, P.; Ramesh, V.S.; Sasidharan, M.; Sattar, A.; Kamat, S.; Dalal, A.; et al. Outcome of acute liver failure due to acute hepatitis E in pregnant women. *Indian J. Gastroenterol.* 2007, 26, 6–10.
101. Satia, M.; Shilotri, M. Successful maternal and perinatal outcome of hepatitis E in pregnancy with fulminant hepatic failure. *Int. J. Reprod. Contracept. Obstet. Gynecol.* 2016, 5, 2475–2477.
102. Khuroo, M.S.; Kamili, S.; Khuroo, M.S. 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, 519–523.
103. Khuroo, M.S.; Khuroo, M.S.; Khuroo, N.S. Hepatitis E: Discovery, global impact, control and cure. *World J. Gastroenterol.* 2016, 22, 7030–7045.
104. Shrestha, A.; Gupta, B.P.; Lama, T.K. Current Treatment of Acute and Chronic Hepatitis E Virus Infection: Role of Antivirals. *Euroasian J. Hepatogastroenterol.* 2017, 7, 73–77.
105. Zhu, F.C. Efficacy and safety of a recombinant hepatitis E vaccine in healthy adults: A large-scale, randomised, double-blind placebo-controlled, phase 3 trial. *Lancet* 2010, 376, 895–902.
106. Zhang, J.; Zhang, X.F.; Huang, S.J.; Wu, T.; Hu, Y.M.; Wang, Z.Z.; Wang, H.; Jiang, H.M.; Wang, Y.J.; Yan, Q.; et al. Long-term efficacy of a hepatitis E vaccine. *N. Engl. J. Med.* 2015, 372, 914–922.
107. Wu, C.; Wu, X.; Xia, J. Hepatitis E virus infection during pregnancy. *Viol. J.* 2020, 17, 73.
108. Joshi, R.M. Hepatitis E Virus: A Renewed Hope with Hecolin. *Clin. Microbiol. Open Access* 2015, 04.

109. Wu, T.; Zhu, F.C.; Huang, S.J.; Zhang, X.F.; Wang, Z.Z.; Zhang, J.; Xia, N.S. Safety of the hepatitis E vaccine for pregnant women: A preliminary analysis. *Hepatology* 2012, 55, 2038.
110. Li, M.; Li, S.; He, Q.; Liang, Z.; Wang, L.; Wang, Q.; Wang, L. Hepatitis E-related adverse pregnancy outcomes and their prevention by hepatitis E vaccine in a rabbit model. *Emerg. Microbes Infect.* 2019, 8, 1066–1075.
111. Zaman, K.; Dudman, S.; Stene-Johansen, K.; Qadri, F.; Yunus, M.; Sandbu, S.; Gurley, E.S.; Overbo, J.; Julin, C.H.; Dembinski, J.L.; et al. HEV study protocol: Design of a cluster-randomised, blinded trial to assess the safety, immunogenicity and effectiveness of the hepatitis E vaccine HEV 239 (Hecolin) in women of childbearing age in rural Bangladesh. *BMJ Open* 2020, 10, e033702.
112. Hepatitis E vaccine: Why wait? *Lancet* 2010, 376, 845.

Retrieved from <https://encyclopedia.pub/entry/history/show/35438>