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Title: Hepatitis E and Pregnancy: An Unholy Alliance

Short title: Hepatitis E and Pregnancy

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Abstract

The adverse relationship between viral hepatitis and pregnancy in developing countries was seen as a reflection of retrospective biased hospital-based data collection by the West. However, the discovery of HEV from an epidemic of non-A, non-B hepatitis in Kashmir and documenting increased incidence and severity of hepatitis E in pregnancy from a house-to-house survey unmasked the unholy alliance. Among the family of HEV's, genotype (gt)-1, with a unique ORF4-encoded protein enhancing viral polymerase activity and viral replication, is the sole HEV that shows this adverse relationship. The epidemics caused by HEV-gt1 and not by HEV-gt2 show adverse relationship with pregnancy. The pathogenesis of the unholy alliance is complex and at present not well understood. Possibly multiple factors play a role in causing severe liver disease in the mother including: infection, replication and damage to the maternal-foetal interface by HEV-gt1; vertical transmission of HEV to foetus causing severe foetal/neonatal hepatitis; and combined viral and hormone related immune dysfunction of diverse nature in the mother promoting viral replication. Management is multidisciplinary and needs a close watch for the development and management of ALF. Preliminary data suggest beneficial maternal outcomes by early termination of pregnancy in patients with lower grades of encephalopathy.

Key words: Hepatitis E, Hepatitis E virus, Genotypes, Pregnancy, Epidemic hepatitis, Sporadic hepatitis, Acute liver failure, Foetus, Neonate, Delivery, Hepatitis E vaccine.

Abbreviations used: NANBH=non-A, non-B hepatitis, ETNANBH=Enterically-transmitted non-A, non-B hepatitis, ENANBH=Epidemic non-A, non-B hepatitis, ALF=Acute liver failure, gt=genotype, ORF=Open Reading Frame, CFR=Case fatality rate, DIC=Disseminated intravascular coagulation, VLP=Virus like particles.

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"*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].*"

1. Historical Background

The association between epidemics of jaundice and pregnancy has had a historical past. 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 them were pregnant. All the dead pregnant women delivered stillborn babies. None of the jaundiced soldiers in the nearby garrison had died. Another notable epidemic of jaundice occurred in Paris in 1871. Deaths occurred exclusively in gestating mothers and autopsies revealed acute yellow atrophy of the liver as the cause of deaths [3]. Over the ensuing decades till 1946, Europe had recorded several epidemics of jaundice with high deaths in pregnant women [1]. Also, these epidemics reported high rates of fetal and neonatal deaths as a result of abortions, premature deliveries, miscarriages, and stillbirths in both dead and surviving mothers.

2. Controversy over Data from the West versus East

In the latter part of the last century, viral hepatitis and pregnancy had been a matter of investigation and controversy [4]. The data published from Industrialized countries namely Europe, Australia, and the United States had indicated that pregnancy does not increase the severity of disease and /or susceptibility to infection [5-9]. However, several reports from developing countries especially India, Iran, and the Middle East had shown that pregnancy increases severity and mortality from viral hepatitis [10-14]. These reports were based on retrospective analysis of hospital admissions and were seen by the West as a reflection of biased hospital based data collection [15].

3. Unmasking the Unholy Alliance

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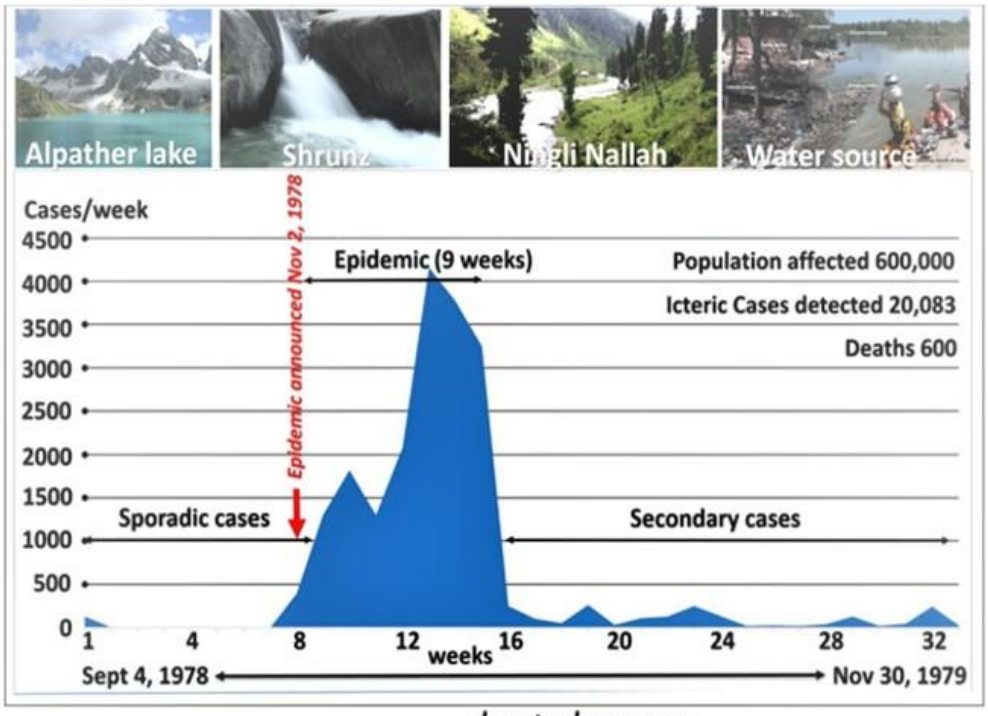
The true face of the unholy alliance between viral hepatitis and pregnancy was unmasked with the discovery of hepatitis E virus from an epidemic of viral hepatitis in Kashmir, India [16] and defining the true incidence and the severity of disease in pregnancy based on a prospective door-to-door study [17] (Fig 1).



door-to-door survey

Survey results 1 2 3 4

	No.	HEV-AVH (%)	HEV-ALF (%)
Men (15-45 yr.)	3822	107 (2.8)	3 (2.8)
NPF (15-45 yr.)	2350	72 (2.1)	0
PF	208	36 (17.3)$^{\alpha}$	8 (22.2)$^{\alpha}$

Fig 1. Gulmarg Kashmir Epidemic, 1978–1979. The epidemic curve with the weekly occurrence of hepatitis E cases. The region had an open-source water supply from a canal (*Ningli Nallah*) which originates from '*Alpather Lake*' situated at the foot of '*Apharwat Peaks'*, Gulmarg. After passing through mountains with a world-famous '*Sharanz waterfall*', the stream crosses the valley to join the Wular lake. The canal along its route is used for multiple purposes including drinking water, linen washing, swimming, fishing, and sewage

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and garbage disposal, and thus stays highly polluted. The data on incidence and severity of viral hepatitis in pregnancy were collected by four door-to-door surveys done at 4 to 6 weeks intervals during the epidemic.

3.1. Discovery of hepatitis E

HEV discovery started with studies done on a large-scale epidemic of viral hepatitis in Gulmarg-Kashmir, India in November 1978 [16]. Investigating an epidemic of the size had posed problems of harsh weather, primitive healthcare facilities, highly compressed period, lack of funding, and hesitancy of medical manpower to join the team due to fear of personal health risks. To face the challenges, Mohammad Khuroo with a team consisting of 500 healthcare workers (local inhabitants) opted to reside in the epidemic region, support the primitive healthcare facilities, offer care to the needy at the doorstep, and record every case of hepatitis from the community. Over 9 weeks, 20,083 cases of AVH with 600 fatalities were recorded. The epidemic curve was highly compressed with the occurrence of up to 4,000 icteric cases per week. The disease selectively affected young adults and presented as acute hepatitis syndrome with cholestatic features in around 20%. Liver histology showed portal and lobular hepatitis with necrosis and ballooning degeneration and Kupffer cell hyperplasia (AVH) with a subset of patients showing distinctive features in form of intracanalicular bile stasis and rosette formation of hepatocytes as a dominant feature. All patients who survived recovered and none developed chronic liver disease [18]. IgG anti-HAV, as a marker for past exposure to HAV, was reactive in all patients, while none was seropositive for IgM anti-HAV, HBsAg, and IgM anti-HBc. It was announced that this epidemic was caused by an agent, different from NANBH following transfusions (later identified as HCV). Following self-experimentation, Balayan et al identified VLP in his stool samples from an outbreak of hepatitis that occurred in Soviet troops in Afghanistan [19]. Reyes et al isolated a cDNA from the virus responsible for ETNANBH [20]. Tam et al cloned and sequenced the full length of

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HEV [21] and Yarbough et al developed a serological test for diagnosis of HEV infection [22].

After these developments, of the 114 sera collected during the Gulmarg Kashmir epidemic 1978-79, 71 percent tested positive for IgG anti-HEV and 75 percent of these were reactive for IgM anti-HEV, confirming the HEV as the causative agent of the epidemic [23]. From 1978 to 2013, ten epidemics of viral hepatitis were reported from Kashmir, India [24]. Sera from all the ten epidemics were tested for IgG anti-HEV, IgM anti-HEV and HEV PCR and the epidemics were confirmed to be caused by HEV. HEV was transmitted to rhesus monkeys (Macaca mulata) by intravenous administration of fecal extracts of patients from 2 epidemics (the Jammu epidemic 1988 and Pinglina epidemic 1993), which had shown VLP on IEM [25,26]. VLP's (IEM) and HEV RNA (PCR) were detected in faces, bile, and liver biopsies samples from infected animals. HEV genome 2.2 kb from ORF2 and ORF3 was cloned from Jammu 1988 epidemic and sequenced which revealed homology of 96.8% to Burmese strain [27]. Partial genomic sequencing representing 326 nucleotides (nt. 4420-4745) of the non-structural region of the HEV from the Pinglina 1993 epidemic and showed 94.6 homology with Burmese strain of HEV [26].

3.2. **Incidence and Severity of Hepatitis E in Pregnancy**

During the Gulmarg-Kashmir epidemic of 1978, a prospective study was done to define the incidence and severity of hepatitis E in pregnant women and compared with non-pregnant women of child-bearing age and men (15-45 years) [17]. The data were collected in Block Sopore consisting of 15 villages with a population of 16,620. The four door-to-door surveys were conducted at 4 to 6 weeks intervals to identify every next case of hepatitis. A total of 275 cases of hepatitis E were recorded. Thirty-six (17.3 percent) of the 208 pregnant women were infected with HEV as compared to 71 (2.1 percent) of 3350 nonpregnant women and 107 (2.8 percent) of 3350 men. The incidence of disease in the first trimester (3/34; 8.8

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percent), second trimester (15/77; 19.2 percent), and third trimester (18/97; 18.6 percent) was higher when compared to those in nonpregnant women and men. Acute liver failure (ALF) developed in 22.2 percent (8/36) of pregnant women with HEV infection, as compared to 2.8 percent (3/107) of men and none (0/71) of nonpregnant women. Nine deaths had occurred, 6 in pregnant women and 3 in men. The case fatality rate of HEV infection was 16.6 percent (6/36) in pregnant women and 2.8 percent (3/107) in men. None of the nonpregnant women with HEV infection died. None of the 18 pregnant women with HEV infection in their first and second trimester developed ALF, while 8 (44.4 percent) of 18 pregnant women with HEV infection in the third trimester developed acute hepatic failure with 6 deaths. The case fatality rate of HEV infection in the third trimester of pregnancy was 33.3 percent (6/18). These data were conclusive that during epidemics, HEV infection had increased incidence and severity in pregnancy. The incidence was higher in all three trimesters, while, the increased severity of disease was restricted to the third trimester of pregnancy.

4. Hepatitis E

Hepatitis E is one of the five main viral hepatitis and is caused by infection with HEV [28]. HEV is a group of viruses in the family *Hepeviridae [29]*. These viruses are non-enveloped, have an icosahedral shape with 20 faces, spherical geometry with surface spikes and indentations, and T=1 symmetry. Genomes are linear, non-segmented, 7.2 kb in length, and have 3 ORFs (ORF1, ORF2 & OR3) [30]. HEV has marked genetic heterogeneity and divided into two 2 genera namely *Orthohepevirus* and *Piscihepevirus [31]*. A possible third genus *Insecthepevirus* from the giant freshwater prawn has recently been identified [32]. *Orthohepevirus* has four species A, B, C & D. *Orthohepevirus A* has eight genotypes (gt): HEV-gt1 & HEV-gt2 infect humans alone. An additional ORF4, spanning nt2835-3308 and overlapping ORF1 is present in HEV-gt1 alone and its protein expression is regulated via an IRES-like RNA element (nt2701-2787) [33,34] (Fig 2). As C-terminal 19 amino acids are

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absent in around half of the genomes, the N-terminal 124 amino acids of pORF4 can alone interact with other viral and host proteins. This protein functions to enhance viral polymerase activity and promote viral replication and is indispensable for HEV-gt1 life cycle [35]. HEV-gt3 and HEV-gt4 are highly divergent and have been isolated from several animals including pig, wild boar, deer, mongoose, rabbit, goat, horse, bottlenose dolphin, and sheep (HEV-gt3) and pig, wild boar, cattle, cow, sheep, goat, and yak (HEV-gt4). HEV-gt5 and HEV-gt6 infect wild boar in Japan and HEV-gt7 and HEV-gt8 infect dromedary and Bactrian camels respectively. HEV-gt3 & HEV-gt4 from pigs and possibly rabbits are zoonotic and isolated cases of HEV-gt7 infection in humans have been reported. *Orthohepevirus B* has four genotypes, infects birds primarily chicken, and causes hepatitis-splenomegaly syndrome and big liver-spleen disease in chicken. *Orthohepevirus C* causes infection in rats and ferret and *Orthohepevirus D* infects bats. Cases of rat HEV infection in humans have been reported [36,37]. Genus *Piscihepevirus* includes a single species and comprises the closely related cutthroat trout virus [31]. Isolates from moose, fox, kestrel, and little egret have yet remained unassigned [29,31].

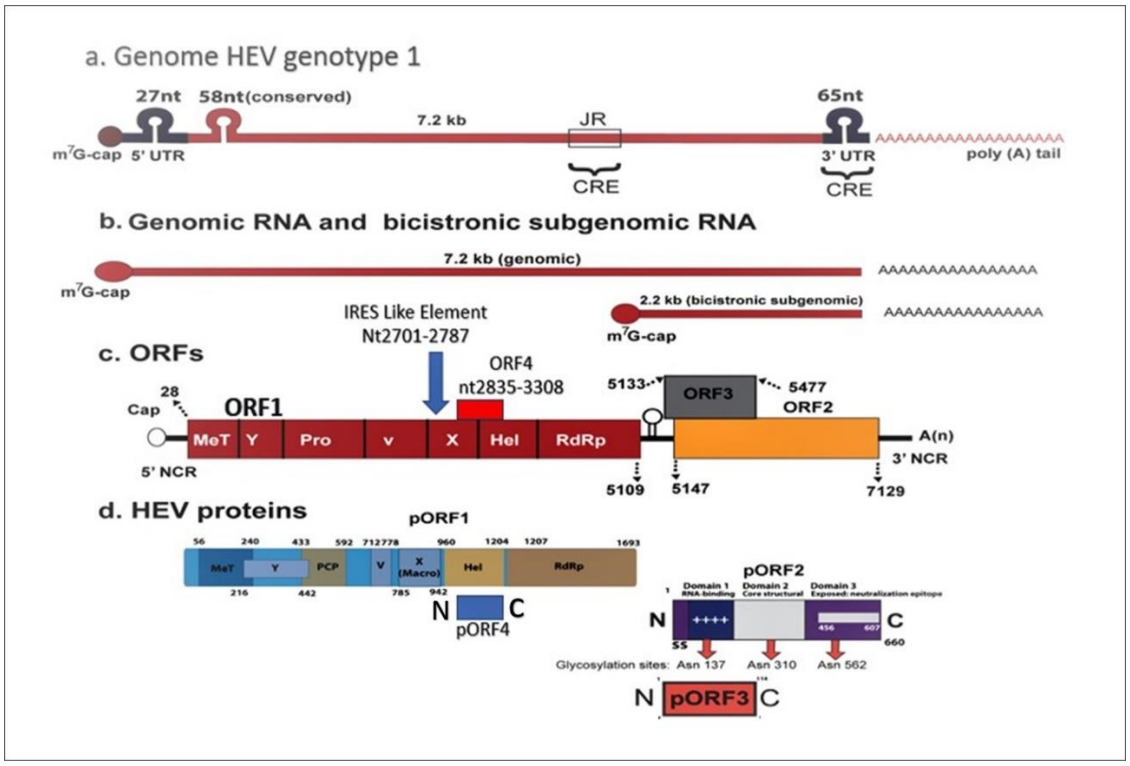

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Fig 2. Hepatitis E virus Genotype 1. Genomic organization. A: The hepatitis E virus genome; B: Genomic RNA and bicistronic subgenomic RNA; C: Four Open reading frames (ORFs) and (D): Four encoded proteins (pORF1, pORF2, pORF3, and pORF4). ORF4, spanning nt2835-3308 and overlapping ORF1 in present in HEV genotype 1 alone, and its protein expression is regulated via an IRES-like RNA element (nt2701-2787). ORF4 encodes a protein (pORF4) of 124 aa, which functions to enhance viral polymerase activity and promote viral replication and is indispensable for the HEV genotype 1 life cycle.

Hepatitis E is a global disease and estimated to cause 20.1 million incident infections in the year 2005, out of which approximately 3.4 million infections were symptomatic with around 70,000 deaths and 3000 stillbirths [38]. Hepatitis E has distinctive epidemiological and clinical characteristics in developing countries, which contrast sharply with those in the industrialized world [39,40]. Based on disease pattern and prevalence and genotype distribution, four hepatitis E epidemiological patterns are seen [41]. The Hyperendemic zone encompasses many countries in the Indian subcontinent, Southeast Asia, Central Asia, many regions in Africa and Mexico. Here HEV-gt1 and HEV-gt2 present as an epidemic and endemic disease. Hepatitis E is endemic in several countries in the Middle East and South America and some regions of Southeast Asia (Singapore). HEV-gt1 causes one-fourth of sporadic hepatitis and acute liver failure in these countries. Epidemics of hepatitis E do not occur. Hepatitis E in Egypt is caused by HEV-gt1 and has a distinctive epidemiological pattern with disease occurring at young age similar to hepatitis A. HEV-gt3 and HEV-gt4 cause sporadic autochthonous zoonotic food borne infection in Industrialized countries. HEV-gt3 has been reported from many European countries, North and South America, Russia, Japan, and Australia; while HEV-gt4 is prevalent in many regions of China, several Southeast Asian countries, Japan, and few countries in Europe.

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5. Epidemic hepatitis E and pregnancy

After the description of 1978-79 Gulmarg-Kashmir epidemic non-A, non-B hepatitis [16], several large-scale water-borne epidemics of hepatitis have been reported from many regions of the developing world [1] (Table 1). Initially, these epidemics were designated empirically as ENANBH based on serological testing for HAV and HBV. Later once serological testing for HEV was available, most of such epidemics in India were found to be caused by HEV. HEV strains once characterized were all of HEV-gt1 [42,43]. 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.

Table 1. Epidemics of hepatitis E with number of recorded cases, case fatality rate (overall and in pregnant women) and relationship with hepatitis E virus genotypes.

Region year	Cases	CFR (%)		HEV genotypes
		Overall	Pregnancy	
Kashmir 1978-2013	55,563	3.19	22.0	HEV-gt-1,
New Delhi 1956	29,300	0.9	10.5	HEV
Kanpur 1991	79,091	0.06	27.0	HEV
Azamgarh 1982	152	12	39.0	ENANBH
Kolhapur 1981	1169	0.25	8.33	HEV-gt1A
Islamabad 1997	3827	0.2	11.4	HEV-gt1B
Rangoon 1985	399	3.5	12.0	HEV-gt1
Kathmandu 1981	12000	-	21.0	HEV-gt1
Kathmandu 1987	7405	0.41	24.65	HEV-gt1
Bangladesh 2008	4198	0.47	19.0	HEV-gt1
Bangladesh 2010	2162	0.55	25	HEV-gt1
Turkmenistan 1985	16,175	0.12	27.4	HEV-gt1
Uzbekistan 1985	12,000	-	7.1	HEV-gt1
Xinjiang 1986	120,000	0.59	13.3	HEV-gt1
Indonesia 1991	1688	1.78	26.3	HEV
Algeria 1980	788	1.39	100	HEV-gt1
Sudan 2006	253	13.5	31.1	HEV-gt1
Djibouti 1998	42	9.5	33.3	HEV-gt1
Central African Republic 2002	715	0.55	14.28	HEV-gt1
Somalia1993	11,413	2.9	13.8	HEV-gt1
Kenya 1991	1702	3.70	14.28	HEV-gt1
Sudan 2004	2621	1.71	31.14	HEV-gt1
Uganda 2007	4789	1.50	6.87	HEV-gt1
Mexico 1986	223	1.35	0	HEV-gt2
Namibia 1995	>600	0.50	1 death [β]	HEV-gt2
Namibia 1983	201	3.48	85.7	HEV-gt1
Nigeria 2018	146	1.37	8	HEV-gt1 & HEV-gt2
Central African Republic 2008	222	1.8	20	HEV-gt1
Chad 2004	989	3.0	-	HEV-gt1 & HEV-gt2
Namibia 2017	7247	0.80	6.00	HEV
Chad 2016	1293	0.69	3.16	HEV-gt1

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Table 1. Epidemics of hepatitis E with number of recorded cases, case fatality rate (overall and in pregnant women) and relationship with hepatitis E virus genotypes.

Region year	Cases	CFR (%)		HEV genotypes
		Overall	Pregnancy	

CFR= Case fatality rate, gt=genotype, ENANBH=Epidemic non-A, non-B hepatitis, β=number of pregnant women not mentioned to calculate CFR.

From 1978 to 2013, 10 large-scale water-borne epidemics of hepatitis E were recorded in Kashmir [24]. A total of 55,563 persons had contracted the disease and 1775 had 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 1955-56 revealed that the epidemic was caused by HEV [44-46]. This epidemic had affected an estimated 29,300 patients with 266 deaths. Overall CFR was 0.9% and CFR in pregnancy was 8.5 percent. A massive epidemic of hepatitis E involving estimated 79,000 cases visited Kanpur, UP, India in 1992, with a CFR of 27 percent in pregnant women [47]. Several other outbreaks have been reported from other parts of India [48-51], Pakistan [52-55], Burma [21,56], Nepal [57-59], and Bangladesh [60,61], and all of these showed high CFR in pregnant women [42]. Several regions in Central Asia namely Turkmenistan [62], Uzbekistan [63], Tajikistan [64], and Kirgizstan [65] have been hit by epidemics of viral hepatitis caused by HEV-gt1. These epidemics affected between 10,000 and 30,000 persons and had high mortality in pregnant women with CFR ranging from 7 to 27%. Xinjiang region 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% [66]. The outbreak was later confirmed to be caused by HEV-gt1 [67]. Few regions of South-East Asia regions namely Indonesia [68] and Vietnam [69] have reported several epidemics of hepatitis E with a high fatality rate of up to 26% in pregnant women. Several circumscribed outbreaks caused by HEV-gt1 have been reported from many regions of Africa including Somalia [70,71], Algeria [72,73], Côte d'Ivoire [74], Botswana [75], Djibouti [71,76], Central African Republic [71,77], with higher fatality in pregnant women. Of late,

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outbreaks of hepatitis E in refugee camps among displaced people in several African countries including Somalia [78], Kenya [79], Sudan [80] and Uganda [81,82]. have occurred. All these epidemics have reported higher deaths in pregnant women.

HEV-gt2 was the incriminating agent for 2 Outbreaks of hepatitis that occurred in two villages 70 km south of Mexico City in 1986 [83]. Of the 223 cases, 3 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 [84]. However, a previously reported epidemic from Namibia in 1983 was caused by HEV-gt1 [85,86] and of the 201 cases 6 of the 7 deaths were seen in pregnant women. Epidemics of hepatitis in Nigeria [87], Central African Republic [88], and Chad [89] were caused by HEV-gt1 and HEV-gt2 and all had 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 [90,91]. An HEV-gt3 outbreak on a cruise ship causing 33 infections did not cause higher mortality in pregnant women [92]. HEV-gt3 and HEV-gt4 are prevalent in industrialized countries and have not been associated with higher mortality in pregnant women [93]. 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.

6. Sporadic Hepatitis E and Pregnancy

In 1983, we reported on 293 patients of acute sporadic viral hepatitis from Kashmir, India, of whom 155 patients were of NANBH (later confirmed as HEV by serology) [26,94]. The mode of transmission was enteric, mostly based on person-to-person contact. The disease occurred in young adults with relative sparing of children. The clinical profile resembled acute viral hepatitis with cholestasis in a subset of patients. The disease was self-limiting and none of the patients developed chronic hepatitis or cirrhosis on follow-up. All these features

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resembled ENANBH described from Kashmir [16]. The disease occurred in 19 pregnant women. The overall CFR was 12.3 percent and CFR in pregnant women was 35.6 percent. After this, we studied the etiology, clinical course, and outcome of AVH in 76 pregnant women and 337 non-pregnant women of childbearing age [95]. The prevalence of HEV in pregnant women was 85.5 (65/76 patients) percent, as against 41.5 percent (140/337) in nonpregnant women. The prevalence of HEV infection was 76.9 percent (4/13), 88.9 percent (12/18), 83.8 percent (23/37), and 100 percent (8/8) in first, second, third trimesters, and puerperium respectively. The CFR of HEV infection in pregnant women was 69.2 percent (45/65) as against 10.0 percent (14/140) nonpregnant women. The CFR was 40 percent (4/10) in the first trimester as against 74.5 percent (41/55) percent in the second trimester and beyond. A north Indian study reported HEV as the cause of acute sporadic hepatitis in 82 percent, 49 percent, and 57 percent of pregnant women, nonpregnant women, and men respectively [96]. Several other studies done on acute sporadic viral hepatitis showed a higher prevalence of HEV infections and higher CFR in pregnant women [97-101] (Table 2).

Table 2. Prevalence of HEV infection among pregnant women with acute sporadic viral hepatitis.

Author, yr.	Study Material		HEV-AVH (%)		HEV-ALF (%)		HEV status
	PF	Others	PF	Others	PF	Others	
Khuroo et al 1983	27	266α	19 (70.4)	136 (51.1)	6 (31.6)	13 (9.6)	ETNANBH
Nayak et al 1989	169	70β	138 (81.6)	34 (48.6)	21 (28.5)		ETNANBH
Psega et al 1993	32	34β	19 (59.4)	7 (20.6)	8 (42.1)	0	HEV
Jaiswal et al 2001	127	146β	83 (65.4)	129 (88.4)	44 (53.0)	17 (13.2)	HEV
Khuroo et al 2003	76	337β	65 (85.5)	140 (41.5)	46 (70.8)	14 (10)	HEV
Beniwal et al 2003	97	-	46 (47.4)	-	18 (39.1)	-	HEV
Patra et al 2007	220	-	132 (60)	-	73 (55.3)	-	HEV

PF=Pregnant females, α = all age groups, β = nonpregnant women of childbearing age.

Regarding HEV genotypes prevalent in acute sporadic hepatitis in India, Arankalle et al [46] studied 17 HEV isolates (both epidemic and sporadic) from India and found all to be related to various subtypes of HEV-gt1. In another study, Indian swine were found to be infected by HEV-gt4, while all Indian humans isolated studied were HEV-gt1 [102]. Gupta et al [43] studied sequences of 74 patients with acute sporadic hepatitis E from North India

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and found all the isolates were related to HEV-gt1a. Thus, HEV circulating in India and causing acute sporadic viral hepatitis with higher mortality in pregnancy is also genotype-specific and associated with HEV-gt1.

7. **HEV-ALF and pregnancy**

Several large series of ALF and its relation with pregnancy have been reported from India. We studied 180 patients with ALF from Kashmir, India [103]. Forty-nine of the 111 females with ALF were pregnant. Seventy-nine patients were related to HEV and the remaining 101 patients were caused by HAV (4 cases), HBV (25 cases), HCV (13 cases), HDV (2 cases), drug (1 case), and non-A-E agents (56 cases). HEV was the cause of ALF in 47 of the 49 pregnant women as against 14 of the 34 nonpregnant women of childbearing age. Acharya et al [104] from AIIMS, New Delhi reported 423 patients with ALF. Of the 223 females, 53 were pregnant. The etiology included HAV (7 cases), HBV (117 cases), HDV (16 cases), NANBH (264 cases), and drugs (19 cases). Thirty-one of the 50 cases from the NANBH group were caused by HEV. Subsequently, 1015 patients with ALF were reported from the same center. 249 of the 647 females were pregnant. HEV was the etiological cause in 342 patients while 651 patients had non-HEV etiology [105]. 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. In another study, HEV was the cause of ALF in 102 of the 139 pregnant women as against 111 of the 181 nonpregnant women ($p<0.03$) [106]. Kar et al studied 100 patients with ALF, 50 of whom were pregnant and another 50 nonpregnant women of childbearing age. ALF was caused by HEV in 28 pregnant women against 7 of the 50 nonpregnant women. [107] . Sequencing data of all HEV positive sera detected HEV-gt1. These data point out the fact that a substantial proportion of ALF in India are seen in pregnant women and HEV is the dominant etiology in pregnant women.

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HEV-ALF in pregnant women starts with prodrome followed by other features of acute viral hepatitis [108]. 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 [103,104,109]. In addition, the occurrence of "Disseminated intravascular coagulation (DIC)" is a distinctive feature of HEV-ALF during pregnancy [110], resembling a Schwartzmann phenomenon.

The prognosis of HEV-ALF in pregnant women has been studied by us and others [103,105]. The investigators from AIIMS, New Delhi questioned the worse prognosis of HEV-ALF during pregnancy [105,111]. The authors compared the mortality rates in 249 pregnant women, 341 non-pregnant women, and 425 men 15 to 45 years of age. The mortality rates in the three groups were 53.8 percent, 57.2 percent, and 57.9 percent respectively (p=0.572). Earlier we prospectively studied 180 pregnant women with ALF; 79 with HEV-ALF and 101 with non-HEV-ALF [103]. The prognosis in patients with HEV-ALF was better than those with non-HEV-ALF (CFR 51.9% in HEV-ALF versus 84.2% in non-HEV-ALF). Factors predictive of poor prognosis included non-HEV etiology, prothrombin time >30 sec, 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 HEV did not mean that such patients will have higher mortality [112].

8. Proposed Hypothesis on Pathogenesis of the Unholy Alliance

The pathogenesis of higher morbidity and mortality of HEV infection in pregnancy is complex and ill-understood as of today. Rhesus monkey (Macaca mulata) is an established animal model for HEV infection [25]; however, the transmission of HEV to pregnant monkeys has not documented HEV-ALF [182,183] and thus, are not good to study the

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pathogenesis of the disease. However, several important facts have recently emerged to explain the complex relationship between HEV and pregnancy (Fig 3).

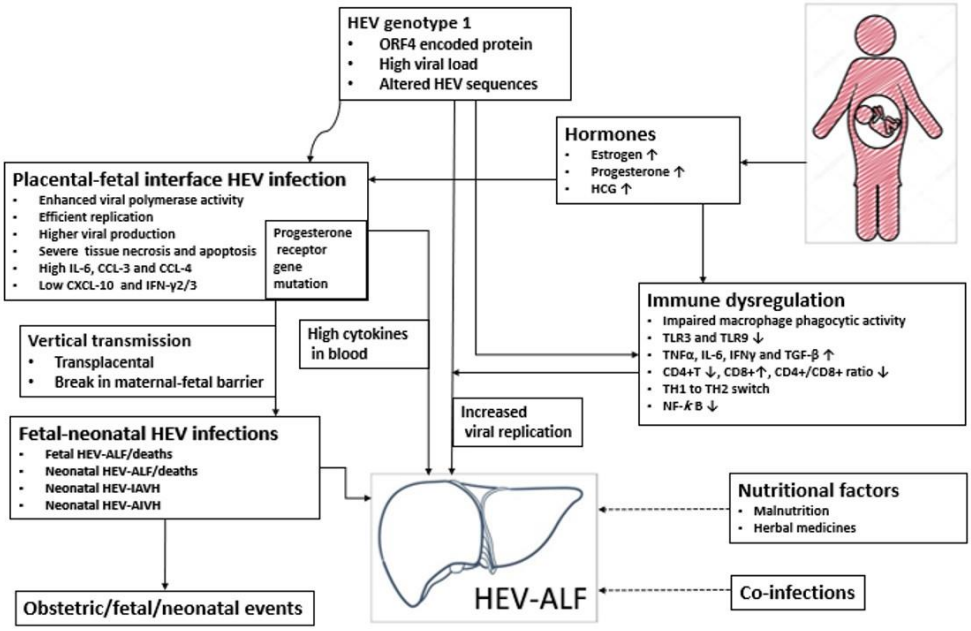

Fig 3. Pathogenesis of hepatitis E virus-related acute liver failure in pregnancy. IAVH=icteric acute viral hepatitis, AIAVH=Anicteric acute viral hepatitis.

8.1. HEV Genome, Heterogeneity and variants in pregnancy

The data available from epidemic and sporadic HEV indicate that pregnant women acquire HEV and develop ALF more often than others and this phenomenon is limited to infection with HEV-gt1. Other hepatitis viruses (HAV, HBV & HCV) and other HEV genotypes (HEV-gt2 and HEV-gt3) do not cause higher deaths in pregnant women. Among the HEV family, HEV-gt1 alone has ORF4 which encodes ORF4 protein of 124 aa. The encoded pORF4 by the HEV-gt1 genome interact with other viral and host proteins, enhance viral polymerase activity and promote viral replication. HEV-gt1 and not HEV-gt3 causes necrosis and apoptosis in the maternal-fetal interface possibly caused by mitochondrial damage and activation of caspene family membranes. This leads to alterations of the placental barrier architecture and promotes vertical transmission. High viral load related to HEV-gt1

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has been correlated with increased severity of disease in pregnant women [147,149]. HEV sequences in patients with HEV-ALF (5 patients) were compared with those of HEV-AVH (5 patients) and showed 150 nucleotide substitutions [150] and included six in ORF-1 namely F179S, A317T, T735I, L1110F, V1120I, and F1439. Two of these (L1110F and V11201) occurred in the helicase domain pointed to its role in determining the outcome of HEV.

8.2. Immune Response in HEV infected pregnant women

The immunological alterations in pregnancy are complex, showing immune tolerance to an allogenic fetus and host defense against pathogen. This is accomplished by the maternal-fetal interface (decidua) consisting of decidual stromal cells, decidual immune cells, and trophoblast cells [131]. The maternal-fetal interface contains natural killer (NK) cells, macrophages, dendritic, and T cells which interact with invading fetal extravillous trophoblast for placentation, fetal growth, and pregnancy outcome [132]. Pregnancy suppresses cell-mediated immunity at the maternal-fetal interface to tolerate fetal antigens and maintains a normal humoral immune response against pathogens [133]. Pregnancy causes a shift from a Th1 to a Th2 cytokine response, allowing maternal-fetal tolerance for fetus development.

HEV-gt1 infection in pregnant women causes several alterations in innate and adaptive immune response, which help virus replication and increase the severity of disease in the mother [134]. Pregnant women with HEV-ALF have impaired macrophage phagocytic activity and downregulation of TLR3 & TLR9 expression impeding MyD88-mediated IFN production [135,136]. This may lead to inadequate triggers for the innate immune response which in turn could lead to enhanced viral replication and severe liver injury. HEV-gt1 (but not HEV-gt3) in pregnant women was shown to evade early antiviral response and cause adverse consequences due to poor IFN response in placental cells [137]. Pregnant women with HEV-ALF have significantly higher levels of pro-inflammatory cytokines (TNF-alpha, IL-6, IFN-gamma, and TGF-beta) and this had a significant positive correlation with viral

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load, serum bilirubin, and prothrombin time. Increased severity of disease in pregnant women with HEV-ALF may be mediated through cytokines [138]. Pregnant women with HEV-ALF have lower CD4+ T cell counts, higher CD8+ T cell counts, and lowered CD4/CD8 ratio than women with HEV-negative ALF [139]. Pregnant women with HEV-ALF have excessive Th2 switching, that dysregulates balance between tolerance and immunity [140,141]. Pregnant women with HEV-ALF shows higher DNA-binding activity of NF-κB and absence of p65 expression, leading to deregulated immunity and severe liver damage [142].

8.3. Hormones and HEV in Pregnancy

Hormones of pregnancy may enhance HEV viral replication. Women experience a sudden and marked increase in estrogen and progesterone during pregnancy [143]. Estrogen helps the fetus to develop and mature. Progesterone suppresses the maternal immune response by stimulation of Th2 and reduction of Th1 cytokines, thereby preventing maternal rejection of the trophoblast [143-145]. Pregnant women with HEV infection have higher levels of estrogen, progesterone, and HCG than those without HEV infection. Higher hormone levels are apt to further dampen the immune response and help viral replication [131,144]. Estradiol has been shown to facilitate HEV replication in an in vitro experiment in A546 cells [146]. High estrogen in pregnancy causes placental dysfunction and lead to preterm delivery, low birth weight infants and fetal mortality. Bose et al [147] studied deregulation of the progesterone receptor signaling pathway in pregnant women with HEV-ALF, HEV infection, and healthy controls. Patients with HEV-ALF show progesterone receptor gene mutations and a high IL-12/IL-10 ratio and are associated with a poor maternal outcome.

8.4. Nutritional Status and HEV in Pregnancy

Malnutrition had been proposed to explain the reports of higher deaths with viral hepatitis in pregnancy from developing countries. However, the nutritional assessment of pregnant women in these reports had not been evaluated [11]. During the 1981 Gulmarg-

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Kashmir HEV epidemic, we evaluated calories and protein intake as well as estimation of serum protein as an index of nutritional status in pregnant women and compared it with nonpregnant women (15-45 yr.). The caloric and protein intake and serum protein in pregnant women were within normal ranges (3242+551 cal/day, 60+20g/day, and 3.3+0.4 g/dl respectively) and did not differ from those seen in nonpregnant women (300+450 cal/day, 50+15 g/day, and 3.2+0.6 g/dl; p>0.50). The caloric and protein intake and serum proteins were well in acceptance with those recommended for Indian women [148]. Of significance was the observation that pregnant women who developed HEV-ALF had excellent nutritional status. Thus, malnutrition contributing to severe disease in pregnant women in developing countries was not collaborated by these data.

8.5. Fetal HEV Infections and Maternal Mortality, Obstetric Events and Neonatal Outcome

Morbidity and mortality among pregnant women and their neonates and obstetric events may be a reflection of the severity of the HEV infection in the mother [17,95,97]. However, there is growing evidence that vertically transmitted HEV infections causing fetal HEV infections may directly contribute to maternal mortality, obstetric events, and neonatal outcome [113]. Several investigators from India and the Middle East ([110,114-123] have reported vertical transmission of HEV and resultant peri-natal morbidity and mortality (Table 3).

Table 3. Vertical transmission of HEV and maternal and obstetric events and Neonatal outcome.

Author yr.	HEV-PF	Maternal & obstetric Events	HEV-Fetus status		Neonatal Disease	Follow up
			Babies	HEV +ve		
Khuroo et al 1995	10	ALF 6, died 3 (dud 2), ftnd 7, PD 1.	8	6 (RNA 5, IgM 3, IgG 8: passive 7, seroconversion 1).	HEV-ALF 2, icteric HEV 1, anicteric HEV 4.	died 24 hr. 2, liver biopsy x 1 massive hepatic necrosis; ; recovered 6; RNA 1 mon. 2.
Khuroo et al 2003	26	ALF-15, died 9 (dud 5), ftnd 15, ab 2, pd 4.	19	15 (RNA 10, IgM 12, IgG15).	HEV-ALF 6, icteric HEV 1, anicteric HEV 5, prematurity 1.	died 7 (HEV-ALF 6, liver biopsy x 1-massive hepatic necrosis with HEV RNA in liver tissue, prematurity 1);

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						recovered 9; RNA 32 wk. 1; IgM 8 wk.; IgG 32 wk. 1.
Khuroo et al 2006	36	ALF 16 (DIC 9, died 10), ab 3, pd7, ftnd 26.	36	25 (RNA 20, IgM 24).	HEV-ALF 14, icteric HEV 9, anicteric HEV 2.	died first wk. 14 (HEV ALF, liver biopsies-massive hepatic necrosis). Recovered 19.
Kumar et al 2004	93	ALF 6 (dud 2), pd 2.	91	26 (RNA 26)	HEV-ALF 2, icteric HEV 3, anicteric HEV 1.	HEV-ALF died 48hr. 2, RNA -ve 9 mon. all others.
Singh et al 2003	22	ALF 14 (died 14).	NK*, 6	3 (RNA 3).	icteric HEV 1.	-
Kumar et al 2004	28	ALF 9 (died 7), pd 18.	NK*, 18	6 (RNA 4, IgM 3).	-	-
Chibber et al 2004	92	FTND 92 (vaginal 8, cs 12)	92	4 (RNA 4, IgM 4).	icteric HEV***	-
El Sayed Zaki et al 2014	29	29**	29	9 (RNA 9).	RDS with icterus 5, icteric HEV 3, sepsis 1.	-
Sharma et al 2017	144	ALF 41 (dud 6)	128	59 (RNA 15, IgM 59).	-	-
Bonney et al 2012	3	ALF 2 (dud 1), pd 1, ab 1.	1	1 (RNA 1, IgM 1).	Icteric HEV 1.	recovery, RNA -ve 3 wk., IgM -ve 4 wk.
Pradhan et al 2012	1	Fetal HEV-AVH 15 wk.	1	1 (IgM cord blood, amniotic fluid & serum at birth).	Fetal ascites at 15 wk. pregnancy, resolved to follow up	healthy Baby delivered 38 wk., LFT normal, IgM +ve.
ALF= acute liver failure, DIC= disseminated intravascular coagulation, ftnd=full term normal delivery, dud=mother died with baby undelivered, ab=abortion, pd=premature delivery, cs=caesarean section, RNA=HEV RNA +ve, IgM=IgM anti-HEV +ve, IgG= IgG anti-HEV +ve, RDS=respiratory distress syndrome.						
*= total babies born not know, **= all deliveries had complicated clinical course, ***= baby developed icterus at 6 weeks of birth.						

In a seminal study, we studied mother-to-child transmission of HEV in 10 pregnant women [114]. Two mothers died with babies undelivered. Six of the eight live-born babies showed evidence of HEV infection at birth. HEV RNA was detected in cord and birth blood samples in 5; IgM anti-HEV in 3 and IgG anti-HEV seroconversion in 4 babies. Two babies died within 24 hours from hypothermia and hypoglycaemia. A liver biopsy in one baby revealed massive hepatic necrosis. Of the remaining six, one baby had icteric hepatitis and the other 3 had anicteric hepatitis. In another study, we detected vertical transmission of HEV

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in 15 of the 19 babies born to HEV-infected pregnant women [115]. Seven of these died within the first week of life. The remaining 8 babies survived and 5 showed HEV RNA for varying intervals lasting up to 32 weeks. All surviving babies recovered and none developed chronic liver disease. Recently we studied the relationship of severity of disease in the 36 pregnant women (HEV-AVH 20 & HEV-1LF 16) with the severity of HEV infection in foetuses/new-borns fetus [110]. Babies born to HEV-ALF mothers were more often HEV infected, viremic, and borne with severe disease than those with HEV-AVH. DIC in mothers with HEV-ALF occurred exclusively in pregnant women who delivered babies with HEV-ALF. All the six mothers who survived had delivered babies within 4 days (2.3±1.0 days) of onset of encephalopathy. Based on these data, it was postulated that severe fetal disease is the likely cause of increased severity of HEV infection in the mother, akin to mirror syndrome of pregnancy and delivery of baby performed early in the course of the disease may reverse the severe maternal disease [124-126].

Vertically transmitted fetal HEV infections and the HEV infections in such new-born babies have a wide spectrum of manifestations (Fig 4). Severe fetal disease results in intrauterine fetal death and often the mother also had severe disease with DIC and died undelivered. Autopsies of such foetuses have shown massive hepatic necrosis. A significant proportion with severe disease present with hypothermia, hypoxia, and hypoglycaemia at birth and die within 24 to 48 hours of birth. Liver biopsies in such patients also show massive hepatic necrosis. Babies born with HEV infection may be asymptomatic, show mild abnormality of liver tests (anicteric HEV), and present with jaundice with elevated live tests (Icteric HEV). The disease is self-limiting and serial follow-up clinical, serological and virological recovery in few weeks. Few babies show prolonged viremia lasting for up to 32 weeks with eventual recovery.

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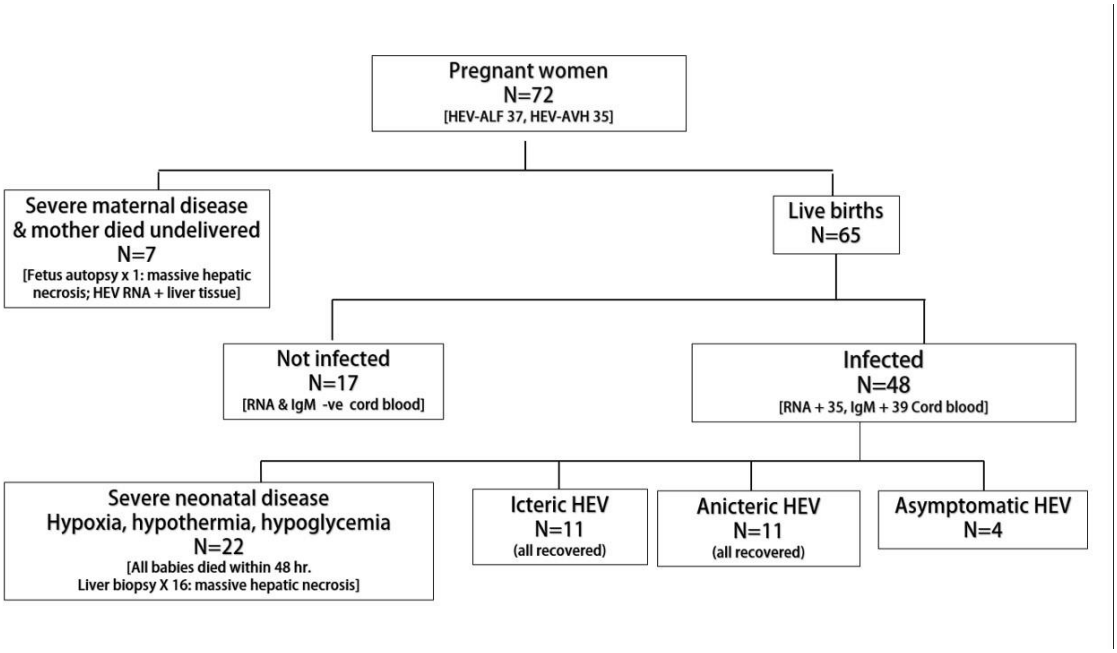

Fig 4. Fetal-neonatal hepatitis E virus infection recorded in foetuses and neonates from 72 pregnant women with hepatitis E virus infection seen at Sher-I-Kashmir Institute of Medical Sciences, Srinagar Kashmir, India from Dec 1993 onwards. ALF=acute liver failure, RNA= HEV RNA, IgM= IgM anti-HEV.

8.6. Maternal-fetal Interface HEV Infections

The role of HEV-gt1 is increasingly being recognized in causing infection and dysregulation at the maternal-fetal interface which leads to vertical transmission and increased systemic inflammation and consequent severe maternal disease [127]. Based on HEV transplacental transmission to the fetus, Bose et al [128] studied placental HEV replication in 90 pregnant women (HEV-AVH 68 & HEV-ALF 22) and detected replicative HEV RNA and HEV RNA staining by ORF3, which correlated with fetal and maternal mortality in HEV-ALF patients. El-Mokhtar et al [129] found HEV-gt1 replicated more efficiently with a higher degree of inflammatory response in non-decidualized primary human endometrial stromal cells than HEV-gt3. The authors believed this infection mediates vertical transmission of HEV to the fetus. Recently, Gouilly et al [130] infected ex vivo maternal-fetal interface with HEV-

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gt1 and HEV-gt3 and showed HEV-gt1 was more efficient than HEV-gt3 in viral replication and production and showed more severe tissue damage (necrosis and apoptosis) with upregulated IL-6, CCL-3, and CCL-4 and downregulated CXCL-10 and IFN-γ2/3. The authors concluded that HEV placental replication is genotype-specific and HEV-1 tropism at the maternal-fetal interface with the extent of tissue damage, pro-inflammatory cytokines, and chemokines might be responsible for the severe maternal disease.

9. Management

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

HEV-AVH is usually a self-limiting disease and would need 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 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, however, it 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 acute liver failure 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,

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hypoglycaemia, 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 [103,104,131,132]. Unfortunately, as of today, only isolated case reports of liver transplantation in pregnant women with HEV-ALF are published in the literature [133-135]

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 like abortions, preterm labour, 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 [97]. Therapeutic termination of pregnancy and its beneficial effects on the liver disease in the mother needs serious consideration [28,136], as events in the maternal-fetal interface and the fetus are involved are being incriminated in the severity of the maternal disease [124,130]. Therapeutic termination has proved effective in other two clinical syndromes namely HELP syndrome and acute fatty liver of pregnancy, wherein fetal events drive the maternal disease [137,138]. Several investigators do not recommend termination of pregnancy in pregnant women with HEV-ALF [139,140]. This is based on the results of a retrospective study, in which 42 patients with HEV-ALF were studied [141]. Nine of the 22 women who delivered had died and 14 of the women who continued their pregnancy had died. 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 [142] from Mumbai, Maharashtra, India showed promising results of induction of labour in a pregnant woman with HEV-ALF with grade 2 hepatic encephalopathy and DIC. Patient after induced vaginal delivery made an eventual recovery. The authors recommended therapeutic termination of pregnancy in HEV-

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ALF with lower grades of encephalopathy for a better maternal outcome. We showed that of the 16 pregnant women with HEV-ALF and DIC (10 patients), all the six mother (DIC in 3) who delivered babies within 4 days (mean±1SD 2.3±1.0 days) from onset of encephalopathy and with lower grades of encephalopathy (mean±1SD 3.0±0.89) survived. In contrast, all the 10 mothers (DIC in 6) who died had delivered babies after 4 days (mean±1SD 9.6±3.0 days) and with higher grades of encephalopathy (mean±1SD 3.5±0.53) (p=0.02). The results of such an endeavour are striking in sick patients with severe metabolic problems and DIC (Fig 5). Thus, therapeutic or spontaneous termination of pregnancy done in pregnancy with HEV-ALF early in course of disease with lesser grades of encephalopathy was recommended [110]. We believe randomized trials on the therapeutic role of termination in pregnancy HEV-ALF need to be done. However, till the results of such trials are not available, it is a safe practice to induce labour early in the course of disease with lower grades of encephalopathy for a better maternal outcome.

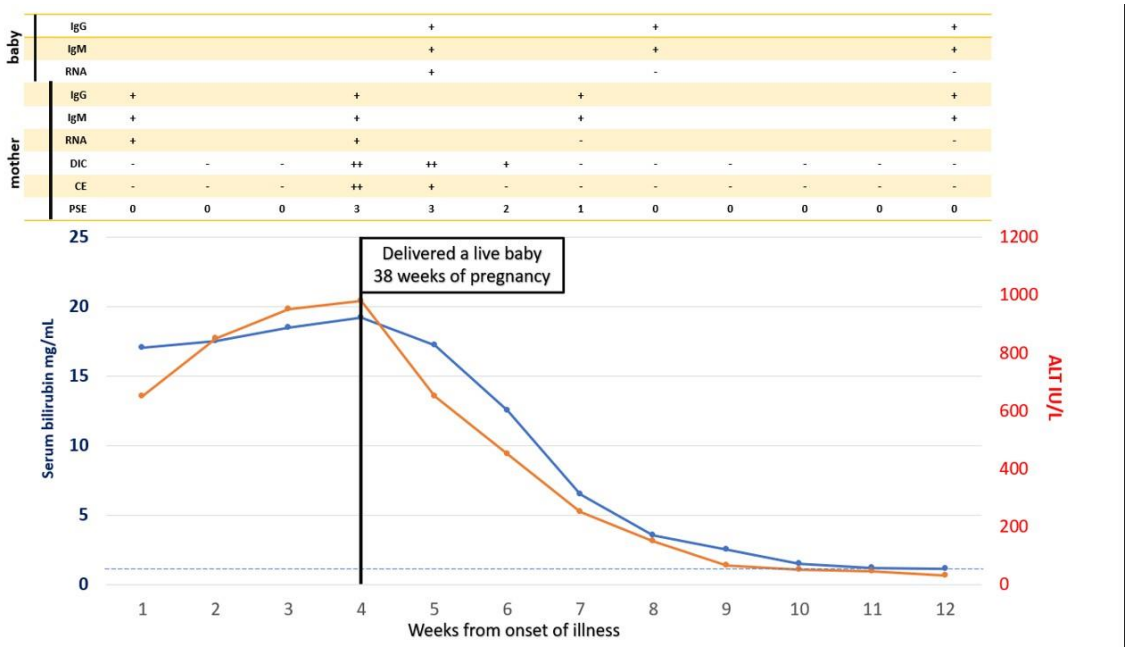

Fig 5. Spontaneous Vaginal Delivery in pregnancy with HEV-ALF and the outcome on maternal disease. A 30 yr. old pregnant woman presented with features of icteric hepatitis E virus infection. On the 24th of her illness, she had rapid deterioration with encephalopathy,

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 [115].

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 [41]. Recently ribavirin has been successfully used to treat HEV ACLF and severe HEV infection in nonpregnant states [143]. Ribavirin is teratogenic and is contraindicated during pregnancy and there are no reports of ribavirin therapy in HEV-AVH and HEV-ALF.

10. Vaccination

The development of the HEV vaccine is seen as a breakthrough in the control of hepatitis E [144,145]. Vaccination against HEV in pregnant women and women of childbearing age in endemic regions may be the most important management strategy [146]. The Chinese vaccine, HEV 239 marketed as Hecolin [147] and is protective against HEV-gt1. The vaccine is safe in pregnant women [148] and protects against HEV infection and HEV-related adverse outcomes in pregnant rabbits [149]. 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 [150]. Availability of the vaccine in developing countries is being watched with great interest [151].

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