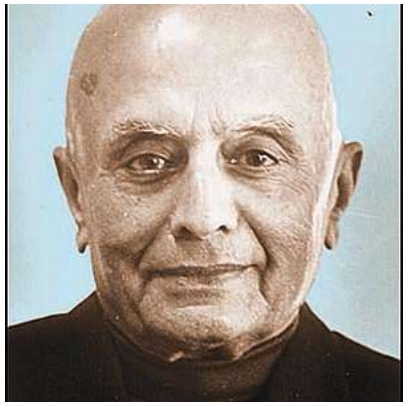


Dr P.N. Chauttani Oration

VIRAL HEPATITIS DURING PREGNANCY

Dr. Premashis Kar

MD, DM, PhD, FRCP, FACG, FAMS

Former Director Professor of Medicine, MAMC

NAMS Emeritus Professor

Senior Director & Medical Advisor,

Department of Gastroenterology and Hepatology,

Max Super Speciality Hospital, Vaishali

Dr. P. N. Chuttani Oration

- Named in honor of **Dr. P. N. Chuttani**
- One of the founding pillars of Gastroenterology in India
- Former Director, All India Institute of Medical Sciences (AIIMS)
- Pioneer in:
  - Hepatology & GI endoscopy in India
  - Development of academic gastroenterology training programs
- Established modern Gastroenterology as a superspeciality in India
- Instrumental in:
  - Early adoption of **GI endoscopy**
  - Advancing liver disease management
- Mentored multiple generations of gastroenterologists
- Strong advocate for research-based clinical practice

📌 *This oration recognises excellence, innovation, and lifetime contribution in Gastroenterology & Hepatology*

HEPATITIS E VIRUS

- Enterically transmitted non-A, non-B hepatitis
- Caused by a non-enveloped single stranded RNA virus.
- Initially classified in Caliciviridae family
- Currently classified into separate genus Hepatitis E-like viruses.

Arch Virol 2000; 145: 1421-1436

INTRODUCTION

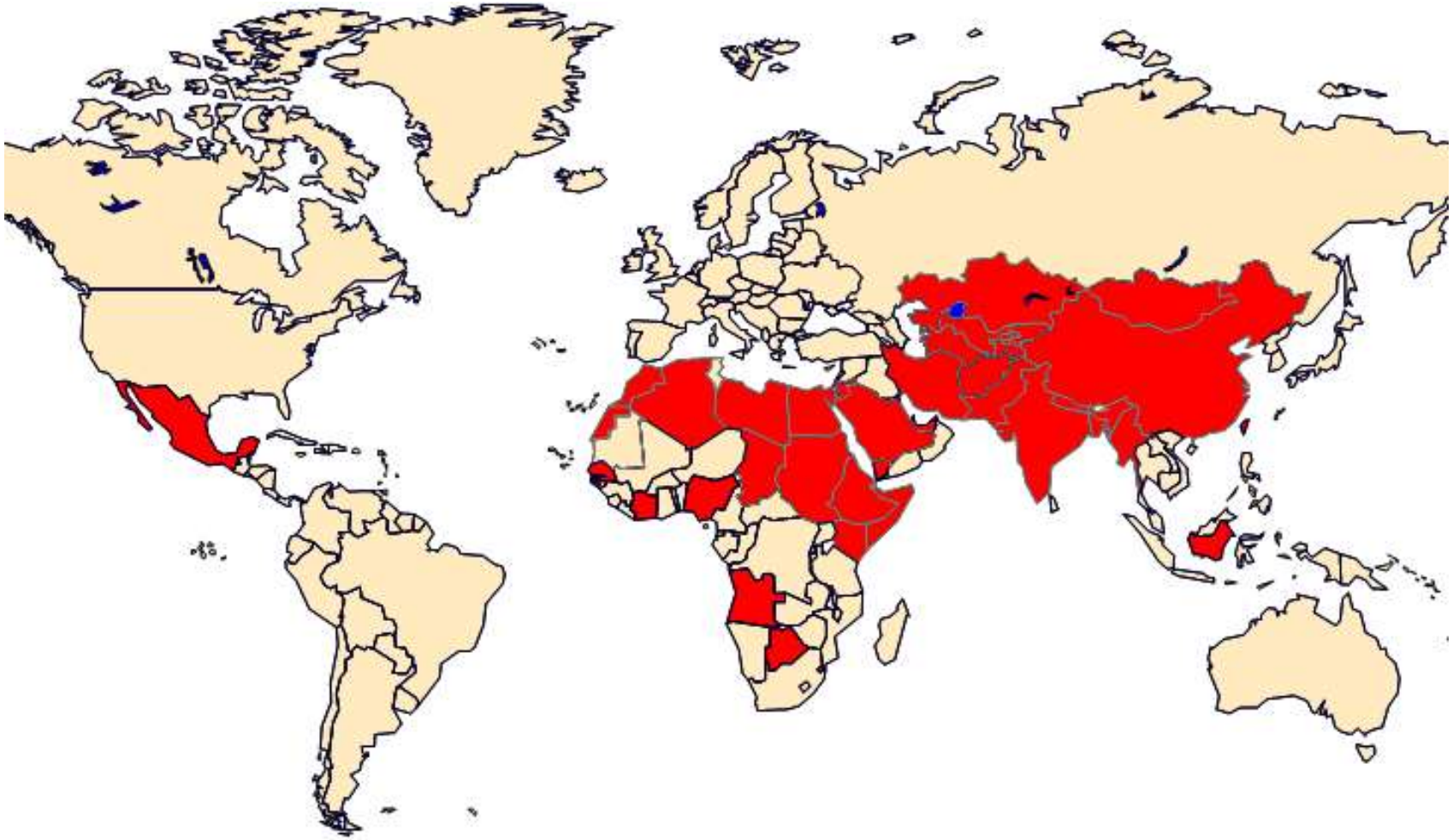
- **Hepatitis E is an acute disease endemic in many countries throughout developing parts of the world, particularly in Africa, Asia (Khuroo, et al., 1981, Nayak *et al*., 1989)**

- **HEV infection is not associated with chronicity, but a fraction of the patients progress to acute liver failure (Nanda *et al*., 1994, Lau, 1995)**

- **High mortality rates of 20-30% have been reported for HEV infection during pregnancy, where FHF account for maximum severity in the third trimester (Khuroo *et al*., 1981)**

- **HEV is the most common cause of sporadic AVH (40%) in India (Khuroo & Kamili, 2002). The prevalence of HEV in pregnant women in first trimester (76%), second trimester (88.9%), third trimester (83.8%), Khuroo, 2002.**

GEOGRAPHIC DISTRIBUTION OF HEPATITIS E



Caption

HEPATITIS E
Epidemiological features

- Most outbreaks associated with fecally contaminated drinking water
- Minimal person to person transmission
- Nosocomial transmission has been reported to occur
- Some studies has shown the possibility of post transfusion hepatitis E
- Not transmitted by sharing utensils, cigarettes, kissing

J hepatol 20 : 567, 1994
Lancet 339 : 1424,1992
J Viral Hepat 1999; 6: 161-164

Different Phases of HEV infection

A. Prodromal Phase

3 - 4 days

Serum transaminases elevated

Anicteric, gastrointestinal (influenza like) symptoms

B. Icteric Phase

Development of jaundice

Lasts 1 – 4 weeks

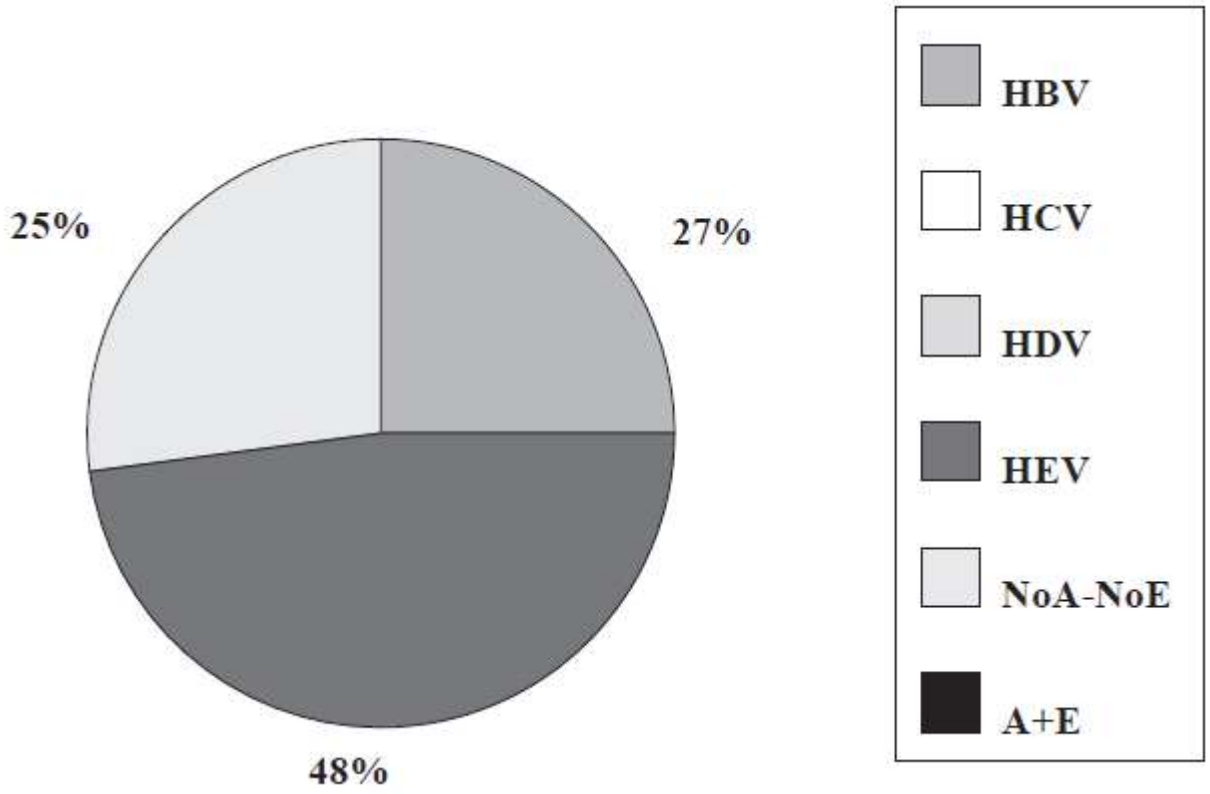
C. Recovery Phase

Clinical & biochemical recovery after 6 weeks of onset

Viremia

- **Clayson et al (1995)** - 2 weeks to 39days
- **Nanda et al. (1995)** - 45 to 112 days
- **Ruan et al. (1997)** - 20.6 days (on avg.)
- **Aggarwal et al. (2000)** - 45 days
- **Zhang et al. (2002)** - 17 days
- **Takahashi et al. (2007)** - 17-48 days

ACUTE VIRAL HEPATITIS



Ref- Jaiswal et al ; International Journal of Gynecology & Obstetrics 72 2001. 103-108

LOKNAYAK HOSPITAL :5 YEARS EXPERIENCE

Prevalence of hepatotropic viruses in AVH

Viral Markers	AVH Pregnant (411)	AVH-Non-Pregnant (357)	
HAVIgM	13 (3.16%)	44 (12.32%)	<0.001
HBsAg	39 (9.48%)	77 (21.56%)	<0.001
Anti-HCV	11 (2.67%)	7 (1.96%)	0.67
HEV IgM	340 (82.72%)	155 (43.41%)	<0.001
Non A-E	8 (1.94%)	74 (20.72%)	<0.001

Prevalence of hepatotropic viruses in ALF

Viral Markers	ALF-Pregnant (139)	ALF Non-Pregnant (181)	
HAVIgM	5 (3.6%)	5(2.76%)	0.91
HBsAg	13 (9.35%)	28(15.47%)	0.14
Anti-HCV	1 (0.72%)	2(1.10%)	0.81
HEV IgM	102 (73.38%)	111 (61.32%)	0.03
nonA-E	18 (12.94%)	35 (19.34%)	0.17

HEV in ALF

Kar et al, 2000	India	41.3%(42/104)
		87.6 (42/46) in NANB
Acharya et al, 2000	India	68.4% (130/190)
Nanda et al, 1994	India	62%
HEV is a major cause of ALF in India		

Viral Hepatitis - etiology

International Journal of Gynecology and Obstetrics 85 (2004) 240–244

International Journal of GYNECOLOGY & OBSTETRICS

www.elsevier.com/locate/ijgo

Article

Hepatitis E in pregnancy

A. Kumar[a,*], M. Beniwal[a], P. Kar[b], J.B. Sharma[a], N.S. Murthy[c]

	HEV (%)	Non HEV (%)					Total (%)
		HAV (%)	HBV *	HCV	A+B	Non A-E **	
AVH	19 (37.2)	0 (0)	3 (5.9)	0 (0)	1 (1.9)	28 (54.9)	51
FHF	9 (81.8)	0 (0)	0 (0)	0 (0)	0 (0)	2 (18.2)	11
Total	28 (45.2)	0 (0)	3 (4.8)	0 (0)	1 (1.6)	30 (48.4)	62

* All cases were found to be positive for IgM anti-Hbc and HbeAg

** HbsAg positive only.

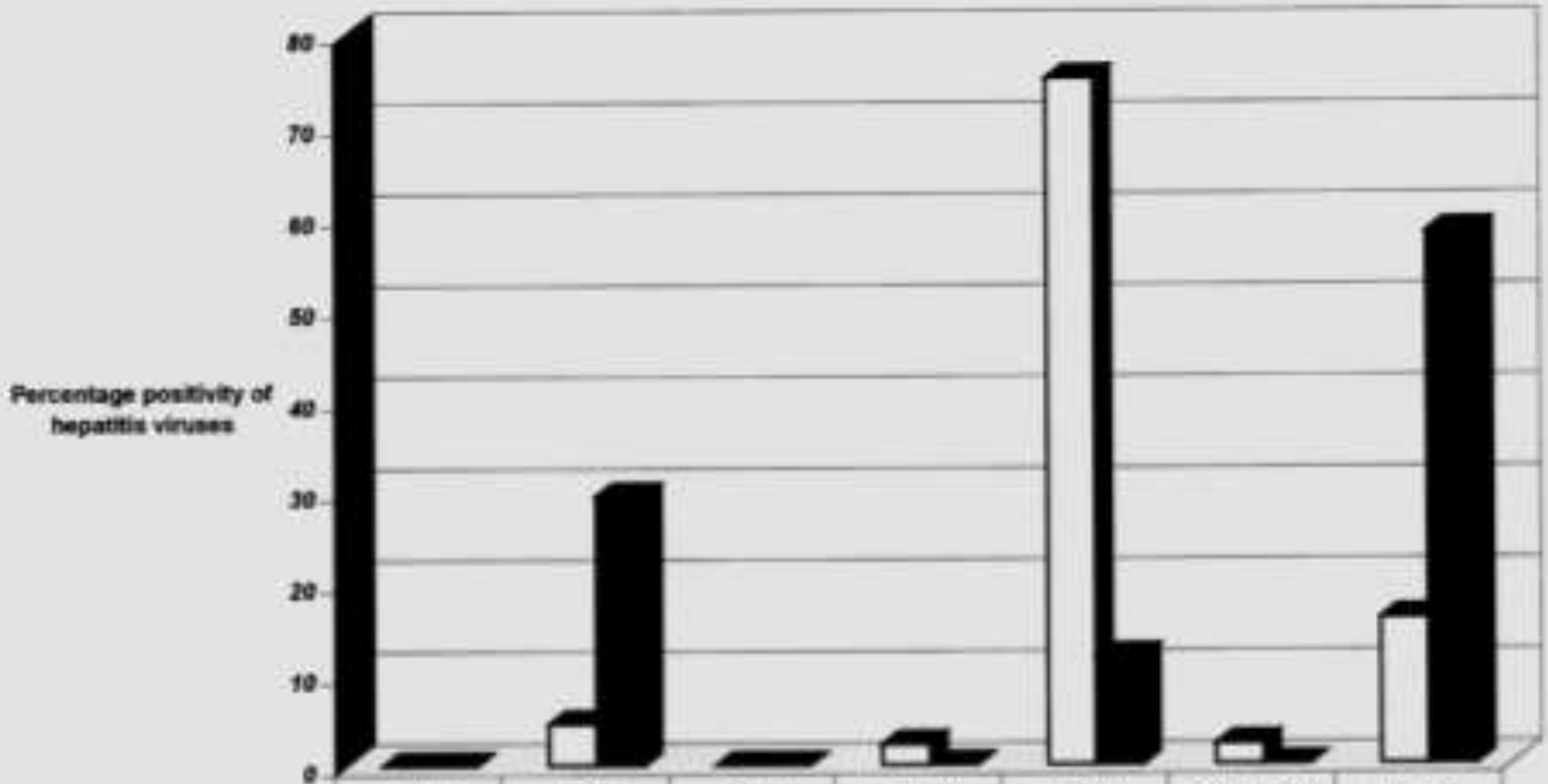
Viral hepatitis-etiology

Subjects	Gestation period in trimester	No of cases	Etiological agent						
			HAV	HBV	HCV	HDV	HEV	A+E	nA-nE
Pregnant females with AVH (Group A)	First	20	0 (0)	7 (35)	0 (0)	0 (0)	10 (50)	0 (0)	3 (15)
	Second	33	0 (0)	8 (24.24)	0 0	0 0	12 (36,36)	0 (0)	13 (39.39)
	Third	30	0 (0)	7 (23.23)	0 (0)	0 (0)	18 (60)	0 (0)	5 (16.66)
	All	83	0 (0)	22 (26.5)	0 (0)	0 (0)	40 (48,19)	0 (0)	21 (25.38)
Pregnant females with FHF (Group B)	First	2	0 (0)	0 (0)	0 (0)	0 (0)	2 (100)	0 (0)	0 (0)
	Second	15	0 (0)	1 (6.6)	0 (0)	0 (0)	12 (180)	0 (0)	2 (13.33)
	Third	27	0 (0)	1 (3.7)	0 (0)	1 (3.7)	19 (70,3)	1 (3.7)	5 (18.5)
	All	44	0 (0)	2 (4.5)	0 (0)	1 (2.27)	33 (75)	1 (2.27)	7 (15.9)
Total pregnant females		127	0 (0)	24 (18.89)	0 (0)	1 (0.78)	73 (57.48)	1 (0.78)	28 (22.04)
Non-pregnant females with AVH (Group C)		129	2 (1,5)	21 (16.27)	0 (0)	0 (0)	65 (50.38)	2 (1.5)	39 (30.23)
Non pregnant females with FHF (Group D)		17	0 (0)	5 (29.41)	0 (0)	0 (0)	2 (11,76)	0 (0)	10 (58.82)
Total non-pregnant females		146	2 (1.36)	26 (17.8)	0 (0)	0 (0)	62 (45.89)	2 (1.36)	49 (33.56)

*Values in parentheses are percentage positivity rate.

International Journal of Gynecology & Obstetrics 72(2001)103-108

Pregnant Vs Non-pregnant - etio



	HAV	HBV	HCV	HDV	HEV	HAV+HEV	nA-nE
Series1	0	4,5	0	2,27	75	2,27	15,9
Series2	0	29,41	0	0	11,76	0	58,12

S1= Pregnant females S2= non-pregnant females

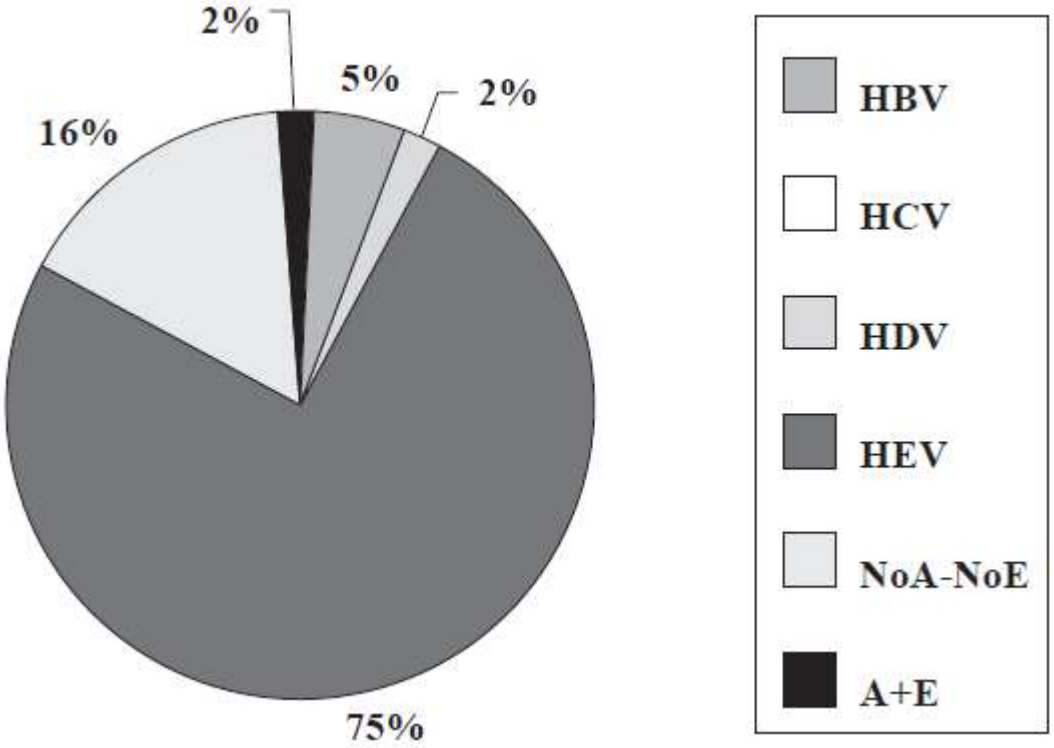
Fig. 1. Incidence of hepatitis viruses among pregnant and non-pregnant fulminant females.

HEV IN PREGNANCY

Study, Year	Patients, n	Prevalence of Hepatitis E Virus Infection, %	Patients with Fulminant Hepatic Failure, %	Mortality Rate, %
Medhat et al., 1993	55	30	43	100
Tsega et al., 1993	32	59	-	42
Jaiswal et al., 2001	127	58	58	45
Singh et al., 2003	60	37	64	64
Khuroo and Kamili, 2003	76	86	69	55
Strand et al., 2003	20	40	-	30
Kumar et al., 2004	65	45	32	73
Present study, 2007	220	60	55	41

Ann Intern Med. 2007;147:28:33

FHF IN PREGNANCY DUE TO VIRAL HEPATITIS



Ref- Jaiswal et al ; International Journal of Gynecology & Obstetrics 72 2001. 103-108

Mortality rates among pregnant females with AVH and FHF

Period pregnancy in trimester	No of AVH pregnant females expired (Group A)				No of FHF pregnant females expired (Group B)			
	HBV	HEV	nA-nE	Total	HBV	HEV	nA-nE	Total
I	0/7	0/10	0/3	0/20	0/0	1/2	0/0	1/2
II	0/8	0/12	1/13	1/33	0/1	4/12	1/2	5/15
III	0/7	1/18	1/5	2/30	2/2	10/19	3/5	15/27
All periods	0/22	1/40	2/21	3/83	2/3	15/33	4/7	21/43

Etiology of Maternal mortality in AVH and ALF pregnant cases.

	AVH (13)	ALF (116)	P value
HAV	1 (7.69%)	5 (4.31%)	0.88
HBV	2 (15.38%)	7 (6.03%)	0.49
HCV	0 (0%)	1 (0.86%)	0.18
HEV	9 (69.23%)	89 (76.72%)	0.79
Non A-E	1 (7.69%)	14 (12.06%)	0.99

Comparison between HEV and Non-HEV associated mortality.

	PREGNANCY Mortality (129)				NON-PREGNANCY Mortality(30)			
	AVH (13)	ALF (116)	Total	P Value	AVH (0)	ALF (30)	Total	P Value
HEV	9	89	98	<0.001	0	21	21	<0.001
Non-HEV	4	27	31		0	9	9	

5 years Unpublished data.
Submitted to Hepatology

Viral hepatitis in pregnancy

- **Viral hepatitis in pregnancy has been a subject of continuing interest and controversy.**

- **Reports from Europe and United States have shown the course of viral hepatitis during pregnancy to be in no way different from non pregnant women.**

- **However, studies carried out in India, Iran, Africa and Middle East have found the incidence of fulminant hepatitis to be higher in pregnancy.**

- **Females constitute more than half of the cases worldwide, irrespective of etiology of ALF.**

- **In a study by Khuroo and Kamili, ratio of male to female was 1:1.6 with higher prevalence of females in HEV (79.7%) than those in the non-E group (47.5%).**

- **Twenty-five to 30 per cent of the women patients are pregnant, whereas the frequency of pregnancy among women in the general population at any time in India is 3%.**

- **The prevalence of HEV in pregnant women with ALF was 95.8% as against 41.2% in non-pregnant women ($P < 0.001$).**

Acharya SK. Acute Hepatic Failure in India: A Perspective from the East. J Gastroenterol Hepatol. 2000;15:473-479.
Khuroo MS. Acute liver failure in India. *Hepatology* 1997;26: 244–6.
Khuroo MS. Aetiology and prognostic factors in acute liver failure in India. J Viral Hepat. 2003 May;10(3):224-31.

HEV in Pregnancy

- **Hepatitis E has both a high incidence and severe course in pregnant women.**

- **Fulminant hepatic failure was more common among HEV-infected women (55%) who were 2.7 times at higher risk than non-HEV infected women (20%); maternal mortality was also higher secondary to fulminant hepatic failure in the HEV infected group (41%) vs. 7% in the non-HEV group**

Ann Intern Med 2007;147:28–33.

- **In contrast, in Egypt, where prevalence of anti-HEV in rural communities is very high, severe HEV infection cause AVH in pregnant women has not been reported.**

- **In one study of 2428 pregnant women, the anti-HEV prevalence was 84.3%. No patients with AVH were reported.**

- **Reasons for the differences in the outcome of HEV in different geographical areas remain unclear but could be the result of**

  - **early childhood HEV exposures, producing long-lasting immunity and/or modify subsequent responses to exposure to the virus**

  - **alternatively, the predominant HEV genotype(s) in Egypt could be less virulent than those in Asia**

Liver injury due to HEV infection during pregnancy

- **Immune system changes**
  - **suppression of T cell mediated immunity.**
  - **definite skew towards Th2 cells**
  - **levels of most cytokines are depressed particularly during the initial 20 weeks of pregnancy**
- **hormonal factor**
  - **Progesterone, estrogen and human chorionic gonadotropin *increase with pregnancy***
  - ***In animal studies, these hormones have suppressive effect on the cell-mediated immunity***
- **the genetic and environmental factors with its occurrence in certain developing countries.**

Viral Hepatitis - etiology

- **Of the 97 pregnant women in the third trimester**
- **69(71.1%) presented as AVH and 28 (28.9%) presented as FHF.**
- **The spectrum with regard to etiological agent**
  - **HAV 5/97 (5.2%),**
  - **HBV 7/97 (7.2%) ,**
  - **HCV 0%,**
  - **HEV 46/97 (47.4%)**
  - **non A-E 46/97 (47.4%)**

- **Co- infection was noted with HAV +HBV in 1/97(1.03%), HBV+HEV in 4/97 (4.1%) and HAV+HEV in 3/97 (3.1%) cases.**

Beniwal M, Kumar A, Kar P, Jilani N, Sharma JB. Indian J Med Microbiol 2003;21:184-5

Does ALF in pregnancy have a worse prognosis

- 3 studies
- Bhatia et al. New Delhi: no difference
- Jilani et al: New Delhi: higher mortality
- Khuroo, Kashmir: ALF prognosis better

Bhatia. Hepatology 2008
Jilani. J GH 2007;22:676
Khuroo. JVH 2003;10:224

Author	Year	Pregnant	Nonpregnant
Bhatia	2008	134/249	195/341
	Mortality	53.8%	57.2%
Khuroo	2003	25/47	25/34
	Mortality	53.2%	69.5%
Jilani	2007	25/38	4/15
	Mortality	65.8%	23.5%

Bhatia. Hepatology 2008
Jilani. JGH 2007;22:676
Khuroo. JVH 2003;10:224

Indian J Med Res 130, December 2009, pp 709-713

Seroprevalence of subclinical HEV infection in pregnant women from north India: A hospital based study

Nargis Begum[*,**,†], Salam Gyaneshwori Devi[*,**,†], Syed A. Husain[**], Ashok Kumar[†] & P. Kar[*]

Table II. Seroprevalence of anti-hepatitis E virus IgG in India

Author	Year	Place	Total samples studied	Prevalence (%)	Population
Khuroo *et al*[5]	1994	Kashmir	40	5	Asymptomatic healthy children
Arankalle *et al*[16]	1995	Pune	1602	23.62	Healthy general population
Aggarwal *et al*[15]	1997	Lucknow	95	59.25	General population asymptomatic or with mild symptoms
Das *et al*[4]	2000	New Delhi	500	35.6	General population sporadic AVH
Mathur *et al*[3]	2001	New Delhi	2070	26.25	Children with minor, non-hepatic illnesses
Mohanavalli *et al*[21]	2003	Chennai	185	9.2	Healthy children
Daniel *et al*[6]	2004	Vellore	600	5.62	Blood donors, antenatal women, and individuals who were screened pre-operatively and found to be negative for hepatitis B surface antigen and hepatitis C virus
Present study	2008	New Delhi	300	33.67	Asymptomatic healthy pregnant women

The overall prevalence of seropositive HEV IgG was 33.67 per cent among the pregnant women.

In the present study, exposure to HEV during pregnancy was higher in urban (slum areas) than rural population. Socio-economic status was a risk factor for anti-HEV IgG in pregnant women.

Maternal and fetal outcome

- Maternal outcome
  - –One-third patients develop fulminant hepatic failure
    - Ref-Kumar et al;Int. j Gynecol Obstet 2004;85(3):240-244
  - –Maternal mortality may be as high as 25%
    - Ref- Krawczynski et al;Infect Dis Clin North Am 2000; 14(3):669-687
- Fetal outcome
  - –High rate of preterm labor and still born
  - –Mother to child transmission may be as high as 33.3% and 50%
    - Ref-Singh Set al;Indian J Pediatr 2003;70(1): 37-39

Maternal and fetal complications

- **Two thirds of the HEV-positive women had preterm deliveries.**
- **Intrauterine fetal death, preterm delivery, and perinatal mortality are reported to be higher in pregnant women with HEV infection**
- **in a prospective series of 220 pregnant women with jaundice and acute viral hepatitis, HEV infec- tion caused 60% of cases and was associated with an in- crease in maternal mortality, obstetric complications, and poor fetal outcomes.**

Khuroo MS, Teli MR, Susan Skidmore S, Sofi MA, Khuroo MI. Am J Med 1981;70:252–255.
Mirghani OA, Saeed OK, Basama FM. East Afr Med J 1992;69:445–449.
Ann Intern Med. 2007;147:28-33.

Obstetric and fetal outcomes of HEV infection

Obstetric complications	
1. Tonic PPH	16 (18.6)
2. Intrauterine fetal death	12 (14)
Fetal complications	
1. Preterm delivery	18 (21)
2. Spontaneous abortions	9 (10.5)
3. Death in the hospital	10 (11)

Ref- Coimbatore Azeez Rasheeda et al; European Journal of Gastroenterology & Hepatology 2008, 20:362–366

Hepatitis E virus infection and fulminant hepatic failure during pregnancy

- **CD4 counts were lower ($P < 0.05$), while CD8 counts were higher ($P < 0.05$), and their ratio (CD4/CD8) in HEV positive pregnant FHF patients was significantly lower ($P < 0.01$) when compared to that of HEV negative pregnant FHF women or controls**

- **Levels of estrogen, progesterone and β-HCG were also found to be higher ($P < 0.001$) in HEV positive pregnant FHF patients when compared to HEV negative patients or controls. HEV infected pregnant FHF patients had a significantly higher mortality rate of 65.8% (25/38) compared to 23.5% (4/15) in HEV positive non-pregnant women ($P < 0.001$).**

Jilani and Kar, Journal of Gastroenterology and Hepatology. Volume 22, Issue 5, pages 676–682, May 2007

Does Hepatitis E Viral Load and Genotypes Influence the Final Outcome of Acute Liver Failure During Pregnancy?

Table : Viral Load Quantification and Genotype in AVH and FHF Patients With and Without Pregnancy

Group	Viral Load IU/mL	Genotype
AVH PREG (N = 7)	343.29 ± 216.44	1
AVH NON-PREG (N = 6)	13.83 ± 7.8∗	1
FHF PREG (N = 14)	$5.87 \times 104 \pm 1.5 \times 10^5$	1
FHF NON-PREG (N = 3)	199.2 ± 225.5∗	1

- ∗$P < 0.05$ (significant). Statistical analysis by Mann-Whitney U test.

- **HEV viral load was found to be significantly higher ($P < 0.05$) in pregnant patients compared to the nonpregnant. Pregnancy appears to be a risk factor for viral replication.**

- **The viral copies of HEV in FHF pregnant women were comparatively higher when compared to AVH pregnant women, which may be related to the severity of the disease in these patients.**

- **We could detect only one genotype (genotype 1) in our study population.**

Kar and Jilani, Am J Gastroenterol 2008;103:2495–2501

- 163 patients with HEV related ALF - 105 pregnant, 46 non-pregnant women and girls and 12 men
- 730 patients with HEV related acute viral hepatitis - 220 pregnant women; 282 non-pregnant women and girls and 228 men were included
- Viral load was measured by real-time PCR
- HEV RNA was detectable in 265 patients (142 pregnant, 75 non-pregnant and 48 men) and 104 patients with ALF (64 pregnant, 34 non-pregnant and 6 men).
- Viral load of HEV in pregnant women with ALF and acute viral hepatitis was significantly higher compared to the non-pregnant women ($P < 0.0001$)
- Viral load of HEV was also significantly higher in the pregnant patients with ALF compared to the pregnant women with acute viral hepatitis and also men ($P < 0.0001$).

Borkakoti J, Kar P, et al. Does high viral load of hepatitis E virus influence the severity and prognosis of acute liver failure during pregnancy? J Med Virol. 2013 Apr;85(4):620-6.

Fulminant hepatitis in Asian pregnant women is generally caused by hepatitis E virus infection, and extremely high mortality is most common in them.

expression and DNA binding activity of NF-kB p50 and NF-kB p65 in pregnant fulminant hepatic failure (FHF) patients was compared with their nonpregnant counterparts.

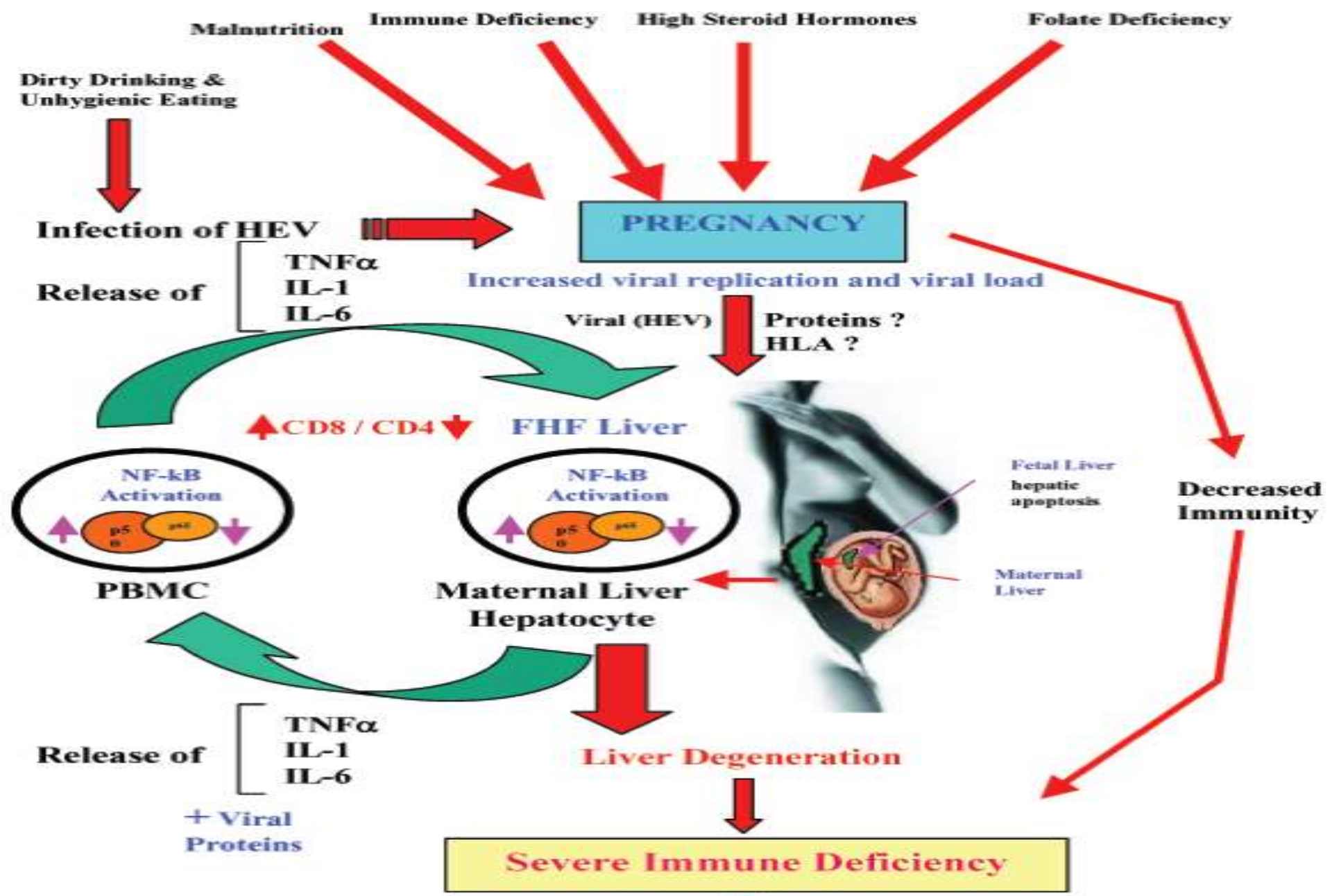
In both PBMC and postmortem liver biopsy specimens the DNA-binding activity of NF-kB was very high in samples from pregnant FHF patients compared with those from nonpregnant women.

Western blotting and immunohistochemical analysis of the expression of p50 and p65 proteins both showed higher levels of p50 expression and a complete absence or a minimal expression of p65, indicating its nonparticipation in NF-kB-dependent transactivation in pregnant FHF patients.

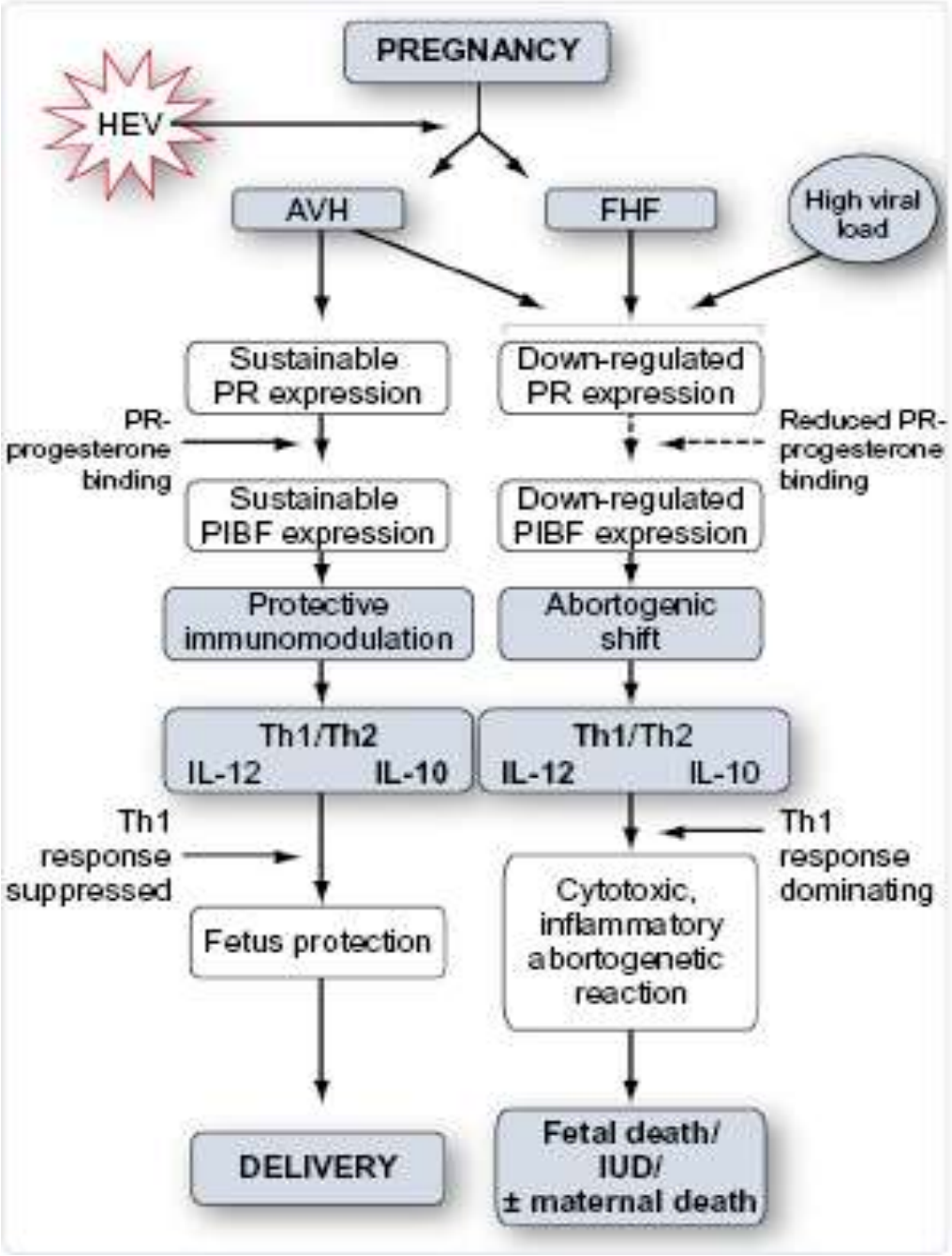
exclusion of p65 from the NF-kB transactivation complex seems to be a crucial step that may cause deregulated immunity and severe liver damage, leading to the death of the patient. Our findings provide a molecular basis, for developing novel therapeutic approaches.

Selective suppression of NF-kBp65 in hepatitis virus-infected pregnant women manifesting severe liver damage and high mortality.

Mol Med. 2007 Sep-Oct;13(9-10):518-26.



Selective suppression of NF-kBp65 in hepatitis virus-infected pregnant women manifesting severe liver damage and



Model depicting the pathways of HEV modulated pregnancy outcome

❑**normal outcome of pregnancy mediated by progesterone receptors and associated proteins are affected by HEV infection via the modulation of the host immune system, which in turn leads to pregnancy-related mortalities in patients.**

❑**PROGINS carriers and lower expression of PR and PIBF, as well as high viral load influences Hepatitis E disease severity and outcomes in pregnancy.**

❑**Higher IL-12 to IL-10 ratio (Th1 bias) in FHF indicates that after crossing the period when there was a lower IL-12 to IL-10 ratio and after the completion of HEV incubation period (i.e. 15–64 days), when the virus has started causing damage to the cells, cytotoxic immunity rises (Th1 immunological state).**

❑**This immunity rises up to a particular level where the body can fight against virally infected cells but during the process, lower PIBF expression and higher NK cell activity results in reduced fetal protection and eventually fetal death occurs because of immunological injury.**

High viral load and deregulation of the progesterone receptor signaling pathway: association with hepatitis E-related poor pregnancy outcome.

J Hepatol. 2011 Jun;54(6):1107-13. Epub 2010 Nov 13

- 142 pregnant women with HEV infection and 142 pregnant controls were included.
- Quantification of estrogen, and its receptors ESR1α and ESR2β done using commercially available third generation ELISA kits
- The levels of estrogen, ESR1α and ESR2β were considerably higher in HEV infected pregnant women than pregnant controls ($p<0.0001$).
- Estrogen levels were significantly higher in pregnant women infected with HEV who had preterm delivery, low birth weight babies and fetal loss than who had full term delivery, average birth weight babies and live babies ($p<0.05$).
- A significant negative correlation was observed between baby birth weight and estrogen levels in HEV infected pregnant women

Singh S, Kar P et al. Role of estrogen and its receptors in HEV associated feto-maternal outcomes. Submitted to **Journal of Viral Hepatitis.**

Role of TNF alpha

- Cases- 262 pregnant and 158 non-pregnant women with jaundice
- Controls - 160 healthy asymptomatic pregnant women and 124 healthy asymptomatic non-pregnant women
- Higher level of TNF-α was observed in HEV-infected pregnant women than non-HEV pregnant women ($P < 0.001$)
- Higher TNF-α level in AVH and FHF of HEV-infected pregnant women vs AVH and FHF of HEV infected non-pregnant women ($P = 0.036$ and $P = 0.010$)
- Pregnant FHF expired group had significantly higher levels of TNF-α than the non-pregnant FHF expired group ($P = 0.025$)
- TNF-α levels were significantly higher in AVH of HEV-infected pregnant women than healthy pregnant controls ($P < 0.001$)
- Higher TNF-α levels were observed in HEV-infected women having preterm delivery and low birthweight newborns.
- **Higher serum concentration of TNF-α observed in HEV infected AVH and FHF pregnant cases shows that pregnancy with HEV infection increases TNF-α secretion. TNF-α may be an important factor in the outcomes of pregnancy due to HEV infection.**

Salam GD, Kar P et al. . Serum tumor necrosis factor-alpha level in hepatitis E virus-related acute viral hepatitis and fulminant hepatic failure in pregnant women**. Hepatol Res**. 2013 Aug;43(8):826-35.

- There are evidences of extrahepatic replication of HEV in animal models.

- Detection of positive strand HEV RNA in variety of tissues after viremia is cleared and occurrence of high titre of HEV genome in feces than in bile in human HEV infected pigs suggests that HEV may replicate in sites other than hepatocytes.

- By experimentally infecting chickens with an avian HEV strain, Billam *et al* has shown sites of extrahepatic HEV replication in chickens.

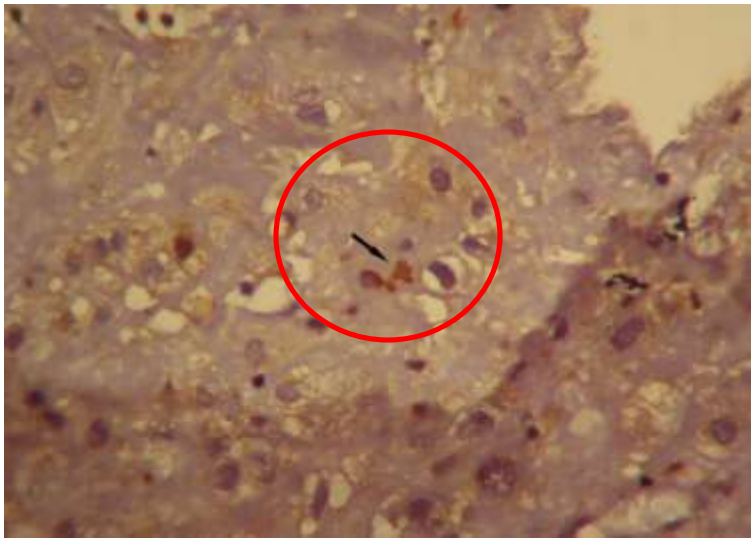
We detected replicating HEV RNA in the placenta of HEV infected pregnant women with Acute viral hepatitis and fulminant hepatic failure who successfully progress to labour using the Negative strand specific RT-PCR in placental tissue

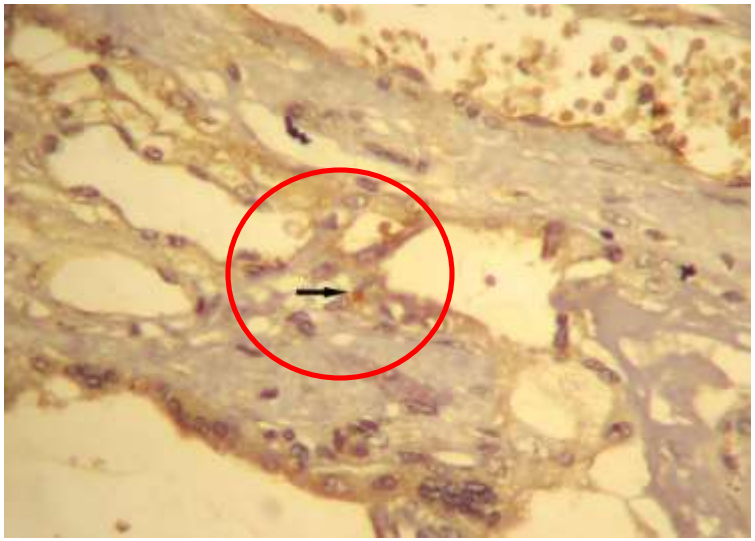
Detection of replicative HEV RNA in placental tissue:

HEV RNA positive placental tissues of 22 AVH patients and 5 FHF patients were tested and all were found positive for the replicative negative strand HEV RNA.

All the patients were found negative for replicative HEV RNA in their blood cells and thus it was confirmed that the replicative HEV RNA in placental tissue was not contaminated with that of circulating blood and also that the blood cells are not the site for HEV replication.

The fetal loss due to IUD or still birth was 50% (7/14) in AVH patients who were positive for HEV RNA, both in the serum as well as placenta, while it was comparatively less in patients who were positive for serum HEV RNA and negative for tissue HEV RNA, 8/30 (26.66%).





IHC Hep E 40x-2. Section of placental tissue stained with Hep E virus antibody. A well defined focus of positive staining (arrow) is identified in the syncytiotrophoblast tissue. (IHC x 40x)

OUR experiment establishes the fact that extrahepatic site of HEV replication exists in placenta of AVH and FHF during pregnancy, which may contribute to the severity of the disease.

Vertical Transmission

- **Six of 18 (33.3%) babies born to HEV- infected mothers tested positive for hepatitis E virus infection. All were sporadic cases of Hepatitis E. A. Kumar et al. / International Journal of Gynecology and Obstetrics 85 (2004) 240–244**

- **In the pioneering study by Khuroo et al. vertical transmission was observed in five newborns**
  - **One was icteric at birth and had elevated trans- aminase levels,**
  - **four had anicteric hepatitis,**
  - **two were born with hypoglycemia and died within 24 hours, and**
  - **one had massive hepatic necrosis.**

  Khuroo MS, Kamili S, Jameel S. Vertical transmission of hepatitis E virus. Lancet 1995;315:1025–1026.

- **Vertical transmission was also noted in all 26 cases of HEV-RNA–positive women by detecting HEV- RNA in cord blood or newborn blood.**

  Kumar RM et al Eur J Obstet Gynecol Reprod Biol 2001;100:9–15.

Public Health Implications

- Effective tool for **outbreak control**, camps, floods, endemic hotspots
- Consider **targeted vaccination** where licensed or authorized by national programs
- Special focus needed for high-risk groups (especially **pregnant women**)
- Global rollout dependent on **WHO-PQ + manufacturing scale-up**

Key Takeaway

- Hecolin is the only licensed/reliable hepatitis-E vaccine with strong trial evidence & real-world utility.
- Scaling access + WHO-PQ + data in special populations = next global priority.

Surveillance and control

- Surveillance and control procedures should include
- provision of safe drinking water and proper disposal of sanitary waste
- monitoring disease incidence
- determination of source of infection and mode of transmission by epidemiologic investigation
- detection of outbreaks
- spread containment

Prevention

- As almost all HEV infections are spread by the faecal-oral route, good personal hygiene, high quality standards for public water supplies and proper disposal of sanitary waste have resulted in a low prevalence of HEV infections in many well developed societies.

- For travelers to highly endemic areas, the usual elementary food hygiene precautions are recommended. These include avoiding drinking water and/or ice of unknown purity and eating uncooked shellfish, uncooked fruits or vegetables that are not peeled or prepared by the traveler.

SUMMARY

- *Hepatitis E has both a high incidence and severe course in pregnant women.*
- *Acute liver failure occurring during 2nd/3rd trimester of pregnancy has a high mortality.*
- *HEV infection during pregnancy is vertically transmitted , leading to increase in maternal mortility, obstetric complication and poor fetal outcome.*
- *The liver injury due to HEV infection during pregnancy is influenced by immune system changes, hormonal factors and genetic and environmental factors.*
- *High viral load and deregulation of the progesterone receptor signaling pathway: association with hepatitis E-related poor pregnancy outcome.*
- *Extrahepatic site of HEV replication exists in placenta of AVH and FHF during pregnancy, which may contribute to the severity of the disease.*

- *FHF patients show Th 1 biasness in terms of higher IL-12/IL-10 ratio. Thus, this shift of Th2 biasness, which is a characteristic of normal pregnancy, in the HEV infected pregnant women, is suggestive of the role of immunological shift during hepatitis E related FHF in pregnancy.*

- *This immune alteration in turn may lead to reduced fetal protection which is probably due to higher activity of NK cells leading to fetal death.*

- *Viral load is comparatively higher in FHF than AVH and also higher in patients with fetal morality in both AVH and FHF, suggesting its role with the disease severity.*

- *High viral load and Th1 immunological state together may attribute to the poor pregnancy outcome in hepatitis E.*

- *The availability of HEV vaccine in future raises a ray of hope for the pregnant mothers.*

- J Hepatol. 2011 Jun;54(6):1107-13. Epub 2010 Nov 13.
  "*High viral load and deregulation of the progesterone receptor signaling pathway: association with hepatitis E-related poor pregnancy outcome*."

- Arch Virol. 2010 Aug;155(8):1227-33. Epub 2010 Jun 2.
  "Surveillance of hepatitis E virus in sewage and drinking water in a resettlement colony of Delhi: what has been the experience? "

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  "Seroprevalence of subclinical HEV infection in pregnant women from north India: a hospital based study."

- Int J Gynaecol Obstet. 2010 Mar;108(3):207-10. Epub 2009 Nov 22.
  "Duration of hepatitis E viremia in pregnancy."

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  "Does hepatitis E viral load and genotypes influence the final outcome of acute liver failure during pregnancy?"

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  "Hepatitis E virus infection and fulminant hepatic failure during pregnancy."

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  "*Hepatitis E in pregnancy*."

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  "*Role of hepatitis E and other hepatotropic virus in etiology of sporadic acute viral hepatitis: a hospital based study from urban Delhi*."

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Other areas of academic contributions in the field of viral hepatitis

PROFILE OF ACUTE LIVER FAILURE – NORTHEAST INDIA

Authors: Anup K Das, Tarjina Begum, **Premashish Kar**, Anupam Dutta

Citation: Eurasian J Hepatogastroenterol 2016

- 255 ALF patients
- Common causes:
  - Non-viral
  - HAV & HEV
- HBV rare
- Herbal drugs significant factor
- INR strongest predictor of mortality

CHANGING EPIDEMIOLOGICAL PATTERN OF HEPATITIS A IN URBAN INDIA

Authors: K Das, A Jain, S Gupta, S Kapoor, R K Gupta, A Chakravorty, **P Kar**

Citation: PMID: 11049092

- Study of 500 urban subjects (Delhi)
- Overall HAV immunity: **71.2%**
- Age-wise decline:
  - 35 yrs: **92%**
  - <35 yrs: **57%**
- Indicates shift from high → intermediate endemicity
- Increasing adult susceptibility to HAV
- Comparable to European epidemiological pattern

IMMUNOLOGICAL PROFILE OF ACUTE & FULMINANT HAV

Authors: Zahid Hussain, Syed A Husain, Fahad N Almajhdi, **Premashish Kar**

Citation: PMID: 21605420

- 1009 patients analyzed
- Fulminant HAV:
  - ↑ CD8 T cells
  - ↓ CD4/CD8 ratio
- Higher viral load in severe disease
- Genotype IIIA dominant
- Suggests immune-mediated injury

INCREASING TREND OF ACUTE HEPATITIS A – NEED FOR VACCINATION

Authors: Zahid Hussain, Bhudev C Das, Syed A Husain, Nandagudi S Murthy, **Premashish Kar**

Citation: PMID: 16677154

- **3495 liver disease patients analyzed**
- Acute HAV: **11.4%**
- Rising incidence:
  - Children: **10.6% → 22%**
  - Adults: **3.4% → 12.3%**
- Chronic liver disease patients largely immune (**98% IgG**)
- Recommends **selective vaccination strategy**

VIROLOGICAL COURSE OF HAV (RT-PCR STUDY)

Authors: Zahid Hussain, Bhudev C Das, Syed A Husain, **Premashish Kar**

Citation: PMID: 16937439

- HAV RNA quantified using RT-PCR
- Severe disease:
  - ↑ viral load
  - Prolonged viremia
- ↓ CD4/CD8 ratio
- Genotype not linked to severity
- Emphasizes host immune response

HBV EPIDEMIOLOGY & PHYLOGENETIC ANALYSIS – NORTHEAST INDIA

Authors: Premashish Kar, B Goswami, J Mahanta et al.

Citation: PMID: 35068784

- Multicentric study (**15,546 subjects**)
- HBV prevalence: **9.9%**
- DNA positivity: **49.5%**
- Genotype:
  - D: **74%**
  - C, A less common
- Significant mutation diversity
- Highlights high disease burden in NE India

HBV GENOTYPES IN ACUTE & FULMINANT HEPATITIS – NORTH INDIA

Authors: Saket Chattopadhyay, Bhudev C Das, Zahid Hussain, **Premashish Kar**

Citation: PMID: 16621685

- Study of 160 patients (AHB, FHB, carriers)
- Genotype D predominant (>90%)
- Genotype A minor but linked to **chronicity**
- No major clinical difference between genotypes
- Establishes genotype distribution in India

HBV PRECORE MUTATIONS IN CHRONIC LIVER DISEASE

Authors: Premashish Kar, Sunil K Polipalli, Saket Chattopadhyay et al.

Citation: PMID: 17211692

- Study in 115 CLD patients
- HBV DNA+: **43.5%**
- Precore mutations: **22%**
- Genotype D predominant in all
- Associated with persistent infection
- Explains HBeAg-negative hepatitis

PREVALENCE OF HCV ANTIBODIES IN VOLUNTARY BLOOD DONORS (DELHI)

Authors: A Jain, S S Rana, P Chakravarty, R K Gupta, N S Murthy, M C Nath, S Gururaja, N Chaturvedi, U Verma, **P Kar**

Citation: PMID: 12952145

- Large study: 15,898 blood donors
- HCV prevalence: **1.57%**
- Highest in **20–29 years**
- No difference by:
  - Gender
  - Donor type
- Suggests significant hidden reservoir
- Higher prevalence vs developed countries

HCV INFECTION IN TRIBAL NORTHEAST INDIA

Authors: Subhash Medhi, B Goswami, A K Das, **Premashish Kar**

Citation: PMID: 22791109

- Study of **700 subjects**
- HCV prevalence: **13.7%**
- High RNA positivity (**73%**)
- Genotype diversity (1–6)
- Risk factors:
  - IV drug use
  - Unsafe barber practices
- Highlights regional variation

HCV DETECTION: SERUM VS LIVER TISSUE

Authors: Umapada Das, **Premashish Kar**, V Gopalakrishna et al.

Citation: PMID: 11856264

- Study in 35 CLD patients
- HCV detection:
  - Serum: **23.3%**
  - Liver tissue: **33.3%**
- Occult HCV present
- Liver PCR more sensitive
- Single test → inadequate diagnosis

SEROPREVALENCE OF HEPATITIS D VIRUS IN HBV-RELATED LIVER DISEASE

Authors: Praloy Chakraborty, Uma Kailash, Anil Jain, Rohit Goyal, Ram K Gupta, Bhudev C Das, **Premashish Kar**
Citation: PMID: 16251784

- Study evaluated HDV prevalence in 123 HBV-related liver disease patients
- HDV infection detected in **10.6%**
- Higher prevalence in:
  - Cirrhosis (**15.2%**)
  - HCC (**33.3%**)
- Majority had past infection (IgG positive)
- Suggests declining HDV epidemiology in India
- Highlights HDV as important cofactor in advanced liver disease

DELTA INFECTION IN FULMINANT HEPATIC FAILURE

Authors: A Narang, P Gupta, **P Kar**, A Chakravarty

Citation: PMID: 9251394

- Study in 31 FHF patients
- HDV positivity: **35.8%**
- Higher liver injury (↑SGOT/SGPT)
- Mortality:
  - HDV+: **91%**
  - HDV–: **65%**
- HDV acts as severity amplifier

DETECTION OF HCV & HEV IN ACUTE & FULMINANT HEPATITIS

Authors: K Madan, V Gopalakrishna, **P Kar**, J K Sharma et al.

Citation: PMID: 10221812

- Study in 50 AVH/FHF patients
- HEV:
  - AVH: **64.7%**
  - FHF: **50%**
- HCV rare as sole cause
- Co-infection: **10%**
- Establishes HEV as dominant etiology

CHANGING ETIOLOGY OF ACUTE VIRAL HEPATITIS – NORTHEAST INDIA

Authors: Anup Kumar Das, Sakir Ahmed, Subhash Medhi, **Premashish Kar**

Citation: IJCRR 2014

- Study in 591 AVH patients
- HAV dominant etiology
- Complications: **16%**, mortality **9%**
- Significant non-viral causes
- Herbal drug use common
- Shows dynamic epidemiology


thank you