Ann Natl Acad Med Sci (India), **54(1):** 54-61, 2018

HEV-related Liver Disease in India : Why is the Disease Stormy?

Premashis Kar
Department of Gastroenterology and Hepatology,
Max Super Specialty Hospital, Ghaziabad.

ABSTRACT

Hepatitis E virus (HEV) is an important cause of epidemic and sporadic acute viral hepatitis (AVH) in many developing countries, including India. Hepatitis E, a positive-sense single-stranded RNA virus approximately 7.2 kb in length had been classified provisionally into the Caliciviridae family from 1988 to 1998 but HEV is currently placed in the genus Hepevirus and is the only member of the family Hepeviridae. Pregnant women with jaundice and AVH caused by HEV infection have worse fetal and obstetric outcome and higher maternal mortality compared to other types of viral hepatitis. Studies from various developing countries have shown that the incidence of HEV infection in pregnancy is high and a significant proportion of pregnant women can progress to fulminant hepatitis with a mortality rate varying from 30% to 100%. The incidence of hepatitis B virus (HBV) related acute liver failure is known widely in comparison to hepatitis C virus (HCV) infection in which acute liver failure (ALF) is rare. But the severe course of HEV infection causing ALF during pregnancy is unique to this virus with chronicity occurring in recipients of solid organ transplants.

Various factors have been suggested to be associated with the mortality rate of the HEV in pregnant women along with the abortion of the fetus. Steroid hormones play a significant role in the viral replication through their effects on viral regulatory elements. The NF-κB signaling pathway regulating at the transcriptional level through p50 subunits has been suggested to correlate with the severe liver damage, leading to multiple organ failure and the death of both the mother and the fetus. Pregnant women in Asia suffer from folate deficiency reducing the immunocompetence to greater risk of multiple viral infections and higher viral load. The viral load of HEV was found to be significantly higher ($P < 0.05$) in pregnant patients compared to the non-pregnant and the viral copies of HEV with fulminant hepatic failure (FHF) in pregnant women were comparatively higher when compared to the pregnant women with AVH, which may be related to the severity of the disease in these patients. Besides, reduced expression of progesterone and progesterone induced-blocking factor and the high viral load of HEV have been regarded as a cause of poor pregnancy outcome in hepatitis E infection. Vertical transmission of the HEV infection has been reported. There are published reports of abortion, death of the fetus in utero, premature delivery or death of the baby soon after birth in patients with icteric hepatitis or with ALF caused by HEV. However, studies in Europe and United States have shown the course of viral hepatitis during pregnancy resembling with the non-pregnant women. In contrast, various reports carried out in India, Iran, Africa, and Middle East have reported the incidence of ALF to be higher during pregnancy.

Correspondence: Dr. Premashis Kar, Former Director Professor & Head, Department of Medicine, Maulana Azad Medical College, New Delhi. Presently Director & HOD, Department of Gastroenterology and Hepatology, Max Super Specialty Hospital, W-3 Sector-1, Vaishali, Ghaziabad-201012. Mob : 09811042164.

DR. R.V. RAJAM ORATION delivered during NAMSCON 2017 at Sri Guru Ram Das Institute of Medical Sciences & Research, Sri Amritsar, Punjab.

Data on the viral load of HEV during pregnancy are limited. The study was designed to determine the viral load of HEV and its association with the disease severity in patients with ALF. A total HEV related 163 patients with ALF which included 105 pregnant, 46 non-pregnant women and girls, 12 men, and 730 patients with AVH which comprised of 220 pregnant women; 282 non-pregnant women and girls, and 228 men were included. Viral load was measured by real-time PCR. Comparison was made between the pregnant and non-pregnant women. 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). The viral load of HEV in pregnant women with ALF and AVH was significantly higher 129,984.0±103,104.17 and 768.92±1,105.40 copies/ml, respectively compared to the non-pregnant women which was 189.2±225 and 12.73±7.8 copies/ml ($P < 0.0001$). The viral load of HEV was also significantly higher in the pregnant patients with ALF compared to the pregnant women with AVH and also men ($P < 0.0001$). High viral load of HEV during pregnancy could be one of the factors responsible for the severity of the infection during pregnancy.

Keywords: Immunocompetence, HEV during pregnancy, acute liver failure, acute viral hepatitis.

Introduction

Viral hepatitis, caused by various hepatotropic viruses A through E, constitutes a major healthcare burden in India (1). Several epidemics of viral hepatitis have been reported (2-8). Both hepatitis A virus (HAV) (9) and hepatitis E virus (HEV) are transmitted by fecal-oral route and highly endemic in India.

HEV has a positive-stranded, 7.5 kb, RNA genome with 3 open reading frames (ORFs) (10, 11). HEV has been accountable for most of the epidemics of viral hepatitis in India (2-8, 12-19). HEV infection is responsible for 30-70% of cases of acute sporadic hepatitis and is the leading cause of acute liver failure (ALF) in India (20-23). HEV infection is a common cause of super infection leading to acute on chronic liver failure in patients with chronic liver disease due to various etiologies (24, 25). It is transmitted majorly by fecal contamination of water and food (2-8, 26). Thus, it is important to understand the epidemiology of HEV infection and take preventive measures against the propagation of the virus.

The first extensively studied epidemic of HEV infection in Delhi affected 29300 people between December 1955 and January 1956 (1) and much of the epidemiological information on HEV had been collected from this epidemic. A number of epidemics reported subsequently had identical epidemiological features (2-8, 12, 14). In most of the epidemics, fecal contamination of the source of drinking water was the culprit.

During epidemics of HEV infection, secondary attack rates in household contacts are 0.7-2% (10, 18, 27-29). Person-to-person transmission is uncommon in the course of sporadic HEV infection (28). However, a few studies have reported the possibility of parenteral transmission (28-35).

The incubation period of HEV infection is 2–9 weeks (mean 6 weeks) (2-8). In epidemics of HEV infection, clinical hepatitis occurs more frequently in adults than children below 15 years of age, and in men than women (2-8). Anicteric hepatitis is more common than icteric hepatitis during epidemics (2-5). Icteric sporadic hepatitis has been reported in children (28, 35).

In India, HEV infection has also been associated with severe liver disease. During epidemics, pregnant women (second and third trimester) are infected more frequently (12-20%) than men and non-pregnant women (2-4%) (2-8, 18, 19, 22). The incidence of ALF is

higher among pregnant women (10-22%) with HEV infection than among men and non-pregnant women (1-2%) (2-8, 18, 19). Therefore, mortality is considerably higher among pregnant women (10-39%) than in the general population (0.06-12%) who develop acute hepatitis during epidemics (2-8, 18, 19). HEV infection has been detected in 30-45% of patients with ALF in sporadic cases (22). Combined HAV and HEV infection is associated with ALF in children (36). Superinfection with HEV has been found to cause decompensation of compensated liver disease (24, 25). However, no chronic sequelae have been reported after HEV infection (37).

Hepatitis and Pregnancy

Pregnancy appears to be a potential risk factor for viral replication and leads extreme low immune status of Indian/Asian pregnant women. Mortality rates among pregnant women, especially those infected in the 3rd trimester, have ranged between 5% and 25%, much higher that men and non-pregnant women (38). It has been reported that a significant proportion of pregnant women with acute viral hepatitis E (AVH-E) (up to 70%) progress to ALF with a short pre-encephalopathy period, rapid development of cerebral edema and high occurrence of disseminated intravascular coagulation (39).

Vertical transmission of HEV infection from mother to infant, although rare, has been reported. Babies born to HEV-RNA positive mother had evidence of hepatitis E infection (40-42). Fulminant HEV infection in pregnancy contributes to highest mortality rate of the fetus and mother. The fatality rate among pregnant women with ALF is reported to be high in India at 22.2%, with the maximum severity occurring during the 3rd trimester (44.4%) (38, 43, 44). Hepatitis E in pregnancy is also associated with high rates of spontaneous abortion, intrauterine death, and preterm labour (38). Worse maternal and fetal outcome of Hepatitis E compared to other types of viral hepatitis has been observed in pregnant women with HEV infection (45). Greater morbidity and mortality, particularly during epidemics of hepatitis, has been noted among pregnant females in developing countries.

Association of HEV and viral hepatitis with pregnancy has been reported earlier in many studies. Jaiswal and colleagues (46) and Borkakoti *et al* (47) from India and Aziz and associates (48) from Pakistan have reported that HEV is responsible for 58-62% of cases of AVH in pregnant women, respectively. Two studies from New Delhi (42, 43) reported slightly lower prevalence (45% and 37%, respectively), and a study of sporadic HEV infection in the context of multiple HEV epidemics in Kashmir reported a prevalence of 86% among pregnant patients with AVH (40). Patra and colleagues in a study on pregnant women with jaundice and AVH caused by HEV infection concluded that, they had a higher maternal mortality rate and worse obstetric and fetal outcomes than did pregnant women with jaundice and AVH caused by other types of viral hepatitis (45).

HEV infection during pregnancy leads to severe complications which may result in fetal and/or maternal mortality, abortion, premature delivery, or death of a live-born baby soon after birth depending on the severity of the infection which is stratified as AVH or ALF (most severe form of AVH). HEV infection is one of the predominant causes of pregnancy-related complications in the developing countries including India (38, 49).

HEV infection accounts for 50-70% of all patients with sporadic viral hepatitis in India (50). The reason for it may be that pregnancy is associated with high levels of steroid hormones. These steroid hormones may promote viral replication. It also has a direct inhibition on hepatic cells, which may predispose to hepatic

dysfunction/failure when exposed to infectious pathogens (51). Steroid hormones are immunosuppressive (52) and mediate lymphocyte apoptosis through NF-κB. NF-κB is a eukaryotic dimeric transcription factor which has a multiple cellular effects, including liver development and regeneration and its implications on the immune response (53).

Jilani *et al* found that HEV infected pregnant women with fulminant hepatic failure (FHF) had lower CD4 count and higher CD8 counts, they also observed that the levels of estrogens, progesterone and beta-HCG were significantly higher in the above-mentioned group when compared to HEV negative patients or control healthy pregnant females (54). Although the levels of hormones were physiologically high in the normal control population; patients with HEV infection seemed to have significantly higher levels than controls, which probably explain the direct interaction of HEV with the immune system. In another interesting study, Pal *et al* studied the cellular immune response in both pregnant and non-pregnant women with acute hepatitis E and the control population (55); they found that pregnant women with HEV had generalized immune suppression characterized by decrease in lymphocyte response to phytohemagglutinin (PHA) with a predominant Th2 bias as compared to non-pregnant women with hepatitis E and normal healthy controls. This was contradictory to the earlier hypothesis that normal pregnancy is associated with systemic immune suppression with an increased risk of infections (56-59).

Higher viral load of HEV has been reported to be associated with FHF during pregnancy; this was reported in a study by Kar *et al*, where a comparatively higher HEV viral load was observed in FHF patients (139994.0±103104.17 copies/ml) than AVH patients (768.92±1105.40 copies/ml). However, HEV genotype could not be correlated with the disease outcome as only single genotype (genotype1) was detected in both the disease groups (60). High fetal mortality has been explained in AVH and FHF cases which showed vertical transmission of HEV from HEV infected mothers to their infants (41).

In a recent study by Deka *et al*, 2010 it was shown that PROGINS, i.e. anti-progesterone monoclonal antibodies carriers and lower expression of progesterone receptor (PR) and progesterone-induced blocking factor (PIBF), as well as high HEV load influences the Hepatitis E disease severity and outcome 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) up to a particular level where body can fight against the virus infected cells but in the due process, lower PIBF expression and higher NK cell activity results in reduced fetal protection and eventually fetal death occurs because of immunological injury (61).

HEV Genotypes and Severity of Hepatitis E during Pregnancy

There are 4 mammalian genotypes of HEV found to have unique geographic distributions. Genotype 1 includes Asian and African HEV strains, genotype 2 includes the single Mexican HEV strain and few variants identified from industrialized countries and genotype 4 includes human and sine HEV strains from Asia, particularly China, Taiwan and Japan. HEV with genotype 1 is most frequently recovered from patients in developing countries (Asia, North Africa). This genotype and genotype 2 appear to be more virulent than genotypes 3 and 4 (62). It has been discussed earlier that the course and severity of hepatitis E in pregnant women is not different from that in non-pregnant women in Europe and United States. This can be explained by the viral genotypes with lesser virulence

found in those areas. In the United Kingdom, HEV genotype 3 is most common, like genotype 4 in China (63, 64).

When HEV infection occurs, a cytotoxic Th1 immune response is likely to be elicited in the Th2 biased pregnant women. FHF is always associated with high HEV load. For that a strong Th1 response is required. This elevated Th1 immune response if still remains insufficient to fight with such a high HEV load, there is a possibility that Th1 response goes on increasing but in the due process, the cytotoxic immune response may result in reduced fetal protection and eventually fetal death.

Opinions differ over the maternal and fetal outcome of pregnancies associated with viral hepatitis. The studies from West opinions differ over the maternal and fetal outcome of pregnancies associated with viral hepatitis. The studies from the developed countries conclude that the pregnancy state, per se, has no adverse effect on the course of hepatitis, provided the nutrition is adequate. However, increased maternal and fetal mortality has been reported by many groups, mainly from the developing countries. Poor prenatal care and maternal nutrition appear to have contributed significantly to the increased severity of infection.

HEV infection in pregnancy leads to poor maternal and fetal outcome. FHF patients show Th1 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 mortality 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.

References

1. Viswanathan R (1957). Infectious hepatitis in Delhi (1955–56): a critical study-epidemiology. *Indian J Med Res* **45**:1–29.
2. Dhamdhere MR, Nadkarni MG (1962). Infectious hepatitis at Aurangabad: report of an outbreak. *Indian J Med Sci* **16**:1006–1015.
3. Bhattacharji LM, Saha AL, Sampathkumaran MA, De SK (1963). Investigation of an outbreak of infectious hepatitis in a small town in West Bengal during July–October, 1960. *Indian J Med Res* **51**:550–562.
4. Pattanayak S, Singha P, Pal SC, Rao CK, Shrivastav JB (1968). An outbreak of infectious hepatitis in Siliguri, 1966. *Indian J Med Res* **56**:1605–1616.
5. Khuroo MS (1980). 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* **68**:818–824.
6. Naik SR, Aggarwal R, Salunke PN, Mehrotra NN (1992). A large waterborne viral hepatitis E epidemic in Kanpur, India. *Bull WHO* **70**:597–604.
7. Ray R, Talwar GP, Aggarwal R, Salunke PN, Naik SR, Mehrotra NN (1991). Hepatitis E virus genome in stools of hepatitis patients during large epidemic in north India. *Lancet* **338**:783–784.
8. Wong DC, Purcell RH, Sreenivasan MA, Prasad SR, Pavri KM (1980). Epidemic and endemic hepatitis in India: evidence for a non-A, non-B hepatitis virus aetiology. *Lancet* **2**:876–879.

9. Acharya SK, Batra Y, Bhatkal B, *et al* (2003). Seroepidemiology of hepatitis A virus infection among school children in Delhi and north Indian patients with chronic liver disease: implications for HAV vaccination. *J Gastroenterol Hepatol* **18**:822–827.

10. Skidmore SJ, Yarbough PO, Gabor KA, Tam AW, Reyes GR (1992). Hepatitis E virus: the cause of a waterborne hepatitis outbreak. *J Med Virol* **37**:58–60.

11. Tam AW, Smith MM, Guerra ME, *et al* (1991). Hepatitis E virus (HEV): molecular cloning and sequencing of the full-length viral genome. *Virology* **185**:120-131.

12. Sreenivasan MA, Banerjee K, Pandya PG, *et al* (1978). Epidemiological investigations of an outbreak of infectious hepatitis in Ahmedabad city during 1975–76. *Indian J Med Res* **67**:197–206.

13. Khuroo MS, Duermeyer W, Zargar SA, Ahanger MA, Shah MA (1983). Acute sporadic non-A, non-B hepatitis in India. *Am J Epidemiol* **118**:360–364.

14. Tandon BN, Joshi YK, Jain SK, Gandhi BM, Mathiesen LR, Tandon HD (1982). An epidemic of non-A, non-B hepatitis in North India. *Indian J Med Res* **75**:739-744.

15. Sreenivasan MA, Arankalle VA, Sehgal A, Pavri KM (1984). Non-A, non-B epidemic hepatitis: visualization of virus-like particles in the stool by immune electron microscopy. *J Gen Virol* **65**:1005–1007.

16. Arankalle VA, Ticehurst J, Sreenivasan MA, *et al* (1988). Aetiological association of a virus-like particle with enterically transmitted non-A, non-B hepatitis. *Lancet* **1**:550–554.

17. Panda SK, Datta R, Kaur J, Zuckerman AJ, Nayak NC (1989). 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* **10**:466–472.

18. Datta R, Panda SK, Tandon BN, *et al* (1987). Acute sporadic non-A, non-B viral hepatitis of adult in India: epidemiological and immunological studies. *J Gastroenterol Hepatol* **2**:333–345.

19. Chauhan A, Dilawari JB, Jameel S, *et al* (1992). Common aetiological agent for epidemic and sporadic non-A, non-B hepatitis. *Lancet* **339**:1509–1510.

20. Nanda SK, Yalcinkaya K, Panigrahi AK, Acharya SK, Jameel S, Panda SK (1994). Etiological role of hepatitis E virus in sporadic fulminant hepatitis. *J Med Virol* **42**:133–137.

21. Madan K, Gopalkrishna V, Kar P, Sharma JK, Das UP, Das BC (1998). Detection of hepatitis C and E virus genomes in sera of patients with acute viral hepatitis and fulminant hepatitis by their simultaneous amplification in PCR. *J Gastroenterol Hepatol* **13**:125–130.

22. Acharya SK, Panda SK, Saxena A, Gupta SD (2000). Acute hepatic failure in India: a perspective from the East. *J Gastroenterol Hepatol* **15**:473–479.

23. Tandon BN, Gandhi BM, Joshi YK (1984). Etiological spectrum of viral hepatitis and prevalence of markers of hepatitis A and B virus infection in north India. *Bull WHO* **62**:67–73.

24. Tandon BN, Gupta H, Irshad M, Joshi YK, Chawla TC (1984). Associated infection with non-A, non-B virus as possible cause of liver failure in Indian HBV carriers. *Lancet* **2**:750–751.

25. Monga R, Garg S, Tyagi P, Kumar N (2004). Superimposed acute hepatitis E infection in patients with chronic liver disease. *Indian J Gastroenterol* **23**:50–52.

26. Bradley DW (1990). Enterically-transmitted non-A, non-B hepatitis. *Br Med Bull* **46**:442–461.

27. Aggarwal R, Naik SR (1994). Hepatitis E: intrafamilial transmission versus waterborne spread. *J Hepatol* **21**:718–723.

28. Panda SK, Acharya SK (1998). Hepatitis E virus infection: where are we? *Natl Med J India* **11**:56–58.

29. Arankalle VA, Chadha MS, Mehendale SM, Tungatkar SP (2000). Epidemic hepatitis E: serological evidence for lack of intrafamilial spread. *Indian J Gastroenterol* **19**:24–28.

30. Khuroo MS, Kamili S, Yattoo GN (2004). Hepatitis E virus infection may be transmitted through blood transfusions in an endemic area. *J Gastroenterol Hepatol* **19**:778–784.

31. Wang JT, Lin JT, Sheu JC, Wang TH, Chen DS (1994). Hepatitis E virus and posttransfusion hepatitis. *J Infect Dis* **169**:229–230.

32. Aggarwal R (2004). Hepatitis E: is it a blood-borne pathogen? *J Gastroenterol Hepatol* **19**:729–731.

33. Robson SC, Adams S, Brink N, Woodruff B, Bradley D (1992). Hospital outbreak of hepatitis E. *Lancet* **339**:1424–1425.

34. Arankalle VA, Chobe LP (1999). Hepatitis E virus: can it be transmitted parenterally? *J Viral Hepat* **6**:161–164.

35. Mathur P, Arora NK, Panda SK, Kapoor SK, Jailkhani BL, Irshad M (2001). Sero-epidemiology of hepatitis E virus (HEV) in urban and rural children of North India. *Indian Pediatr* **38**:461–475.

36. Arora NK, Nanda SK, Gulati S, *et al* (1996). Acute viral hepatitis types E, A, and B singly and in combination in acute liver failure in children in north India. *J Med Virol* **48**:215–221.

37. Chuttani HK, Sidhu AS, Wig KL, Gupta DN, Ramalingaswami V (1966). Follow-up study of cases from the Delhi epidemic of infectious hepatitis of 1955–56. *Br Med J* **2**:676–679.

38. Khuroo MS, Teli MR, Skidmore S, Sofi MA, Khuroo MI (1981). Incidence and severity of viral hepatitis in pregnancy. *Am J Med* **70**:252-255.

39. Khuroo MS, Kamili S (2003). Aetiology, clinical course and outcome of sporadic acute viral hepatitis in pregnancy. *J Viral Hepat* **10**:61-69.

40. Khuroo MS, Kamili S, Jameel S (1995). Vertical transmission of hepatitis E virus. *Lancet* **345**:1025-1026.

41. Kumar RM, Uduman S, Rana S, Kochiyil JK, Usmani A, Thomas L (2001). Sero-prevalence and mother-to-infant transmission of hepatitis E virus among pregnant women in the United Arab Emirates. *Eur J Obstet Gynecol Reprod Biol* **100**:9-15.

42. Singh S, Mohanty A, Joshi YK, Deka D, Mohanty S, Panda SK (2003). Mother-to-child transmission of hepatitis E virus infection. *Indian J Pediatr* **70**:37-39.

43. Kumar A, Beniwal M, Kar P, Sharma JB, Murthy NS (2004). Hepatitis E in pregnancy. *Int J Gynecol Obstet* **85**:240–244.

44. Dahiya M, Kumar A, Kar P, Gupta RK, Kumar A (2005). Acute viral hepatitis in third trimester of pregnancy. *Indian J Gastroenterol* **24**:128–129.

45. Patra S, Kumar A, Trivedi SS, Puri M, Sarin SK (2007). Maternal and fetal outcomes in pregnant women with acute hepatitis E virus infection. *Ann Intern Med* **147**: 28-33.

46. Jaiswal SP, Jain AK, Naik G, Soni N, Chitnis DS (2001). Viral hepatitis during pregnancy. *Int J Gynaecol Obstet* **72**:103-108.

47. Borkakoti J, Hazam RK, Mohammad A, Kumar A, Kar P (2013). Does high viral load of hepatitis E virus influence the severity and prognosis of acute liver failure during pregnancy. *J Med Virol* **85**: 622-626.

48. Aziz AB, Hamid S, Iqbal S, Islam W, Karim SA (1997). Prevalence and severity of viral hepatitis in Pakistani pregnant women: a five year hospital based study. *J Pak Med Assoc* **47**:198-201.

49. Purcell RH, Emerson SU (2001). Hepatitis E virus. In: Fields Virology, 4th edn. Knipe DM, Howley PM, eds. Philadelphia: Lippincott Williams & Wilkins, 3051–3061.

50. Aggarwal R, Krawczynski K (2000). Hepatitis E: an overview and recent advances in clinical and laboratory research. *J Gastroenterol Hepatol* **15**:9-20.

51. McGovern BH, Diteberg JS, Taylor LE, *et al* (2006). Hepatic Steatosis is associated with fibrosis, nucleoside analogue use, and hepatitis C virus genotype 3 infection in HIV-seropositive patients. *Clin Infect Dis* **43**:365–372.

52. Mellor AM, Munn DH (1999). Tryptophan catabolism and T-cell tolerance: immunosuppression by starvation? *Immunol Today* **20**:469–473.

53. Siebenlist U, Franzoso G, Brown K (1994). Structure, regulation and function of NF-kappa B. *Ann Rev Cell Biol* **10**:405–455.

54. Jilani N, Das BC, Husain SA, *et al* (2007). Hepatitis E virus infection and fulminant hepatic failure during pregnancy. *J Gastroenterol Hepatol* **22**:676–682.

55. Pal R, Aggarwal R, Naik SR, Das V, Das S, Naik S (2005). Immunological alterations in pregnant women with acute hepatitis E. *J Gastroenterol Hepatol* **20**:1094–1101.

56. Fried M, Duffy PE (1996). Adherence of Plasmodium falciparum to chondroitin sulfate A in the human placenta. *Science* **272**:1502–1504.

57. Morell V (1995). Zeroing in on how hormones affect the immune system. *Science* **269**:773–775.

58. Singh N, Shukla MM, Sharma VP (1999). Epidemiology of malaria in pregnancy. *Bull WHO* **77**:567-572.

59. Matthiesen L, Berg G, Ernerudh J, Hakansson L (1996). Lymphocyte subsets and mitogen stimulation of blood lymphocytes in normal pregnancy. *Am J Reprod Immunol* **35**:70–79.

60. Kar P, Jilani N, Husain SA, *et al* (2008). Does hepatitis E viral load and genotypes influence the final out- come of acute liver failure during pregnancy? *Am J Gastroenterol* **103**:2495-2501.

61. Bose PD, Das BC, Kumar A, Gondal R, Kumar D, Kar P (2011). High viral load and deregulation of the progesterone receptor signaling pathway: association with hepatitis E-related poor pregnancy outcome. *J Hepatol* **54**: 1107-1113.

62. Purcell RH, Emerson SU (2008). Hepatitis E: an emerging awareness of an old disease. *J Hepatol* **48**:494-503.

63. Zhu G, Qu Y, Jin N, *et al* (2008). Seroepidemiology and molecular characterization of hepatitis E virus in Jilin, China. *Infection* **36**:140-146.

64. Ijaz S, Arnold E, Banks M, *et al* (2005). Non-travel-associated hepatitis E in England and Wales: demographic, clinical, and molecular epidemiological characteristics. *J Infect Dis* **192**:1166-1172.