Original Article

Evaluation of Maternal and Perinatal Outcome in Hepatitis E during Pregnancy

J B Sharma[1], Vikas Yadav[2], Alka Kriplani[3], Garima Kachhawa[4], Rajesh Kumari[4], Isha Kriplani[2]

Hepatitis E is a single stranded Ribonucleic Acid (RNA) virus transmitted through feco-oral route. The infection usually occurs in young adults and is a mild and self limiting disease. It is of severe degree during pregnancy causing hepatic encephalopathy and even maternal mortality. There is increased obstetric and fetal complications in Hepatitis E Virus (HEV) infection during pregnancy. The present study was conducted to know the maternal and perinatal outcome in hepatitis E infection during pregnancy. A total of 60 patients of hepatitis E who delivered in the tertiary referral centre of Delhi, AIIMS, India were included in this retrospective study. The blood was taken for viral markers, liver function tests, bleeding and coagulation factors. Obstetric and fetal outcomes were observed. The mean age was 27.65±4.81 years. There were 30 primigravida and 30 multigravida patients. Preterm delivery rate, intrapartum fetal distress, meconium stained liquor and postpartum complications was 26.66%,13.33%, 20% and 21.66% respectively. Caesarean section rate was 63.33% in study group. There were 2 maternal deaths in hepatitis E patients. Derangement of liver function, coagulopathy and encephalopathy was seen in significant number of cases. Mean fetal birth weight was 2134.22±625.47gm. Fetal respiratory distress rate was 10%. Hepatitis E in pregnancy is associated with adverse maternal and perinatal outcome.

[*J Indian Med Assoc* 2019; **117(12):** 18-21]

Key words **: Hepatitis E, Pregnancy, Maternal mortality, Liver function tests.**

Hepatitis E is a single stranded RNA virus which causes both sporadic as well as epidemic cases of acute viral hepatitis especially in developing countries[1]. It is mainly transmitted through feco-oral route with mean incubation period of 40 days (range 3 to 8 weeks)[2,3]. The infection usually occurs in young adults and is a mild and self limiting disease[4]. However it is of severe degree during pregnancy usually second and third trimester of pregnancy, causing hepatic encephalopathy and even maternal mortality[5,6]. Incidence varies in different countries and even different parts of the same country. The incidence is much higher in North India where it can cause case fatality rate of 1-2% and even upto 10-20% in pregnant women[7]. Hepatitis E virus has 5 genotypes with genotype 1 and 2 being more virulent in humans. There is increased obstetric complications in HEV infection during pregnancy such as spontaneous abortion, premature rupture of membrane, intrauterine growth restriction, intrauterine fetal death and postpartum hemorrhage[8]. There is increased incidence of fetal complications like prematurity and low birth weight babies and fetal mortality.

The present study was conducted to know the maternal and perinatal outcome in hepatitis E infection during pregnancy.

Department of Obstetrics and Gynaecology, All India Institute of Medical Sciences, New Delhi 110029
[1]MD, FRCOG, FAMS, Professor and Corresponding Author
[2]MD, Senior Resident
[3]MD, FRCOG, Professor and Head
[4]MD, Associate Professor

Materials and Methods

A total of 60 patients of hepatitis E who delivered in a tertiary referral centre over last 10 years were enrolled in this retrospective study. The maternal and perinatal factors were assessed in all cases. Serum was tested for IgM Anti HEV by rapid immunochromatographic assay and only Anti HEV IgM positive cases during pregnancy were included in the study. Patients of jaundice due to other causes (Hepatitis A, B, C, HELLP syndrome, drug induced hepatitis etc) were excluded from the study. No patient had chronic liver disease. The antenatal history, need of medication (ursodeoxycholic acid, N-acetyl cysteine, tenofovir) were noted in all cases. Any antenatal, intrapartum or postpartum obstetric events were noted in all cases. Particular attention was made to preterm delivery, intrapartum fetal distress, maternal mortality. Mode of delivery and need and indication of caesarean section was noted in all the cases.

The fetal outcome was noted in all cases and controls especially mean birth weight, small for gestation age fetus, still birth rate, APGAR<8 and respiratory distress syndrome. Perinatal mortaliy rate was calculated in all cases. Fulminant hepatic failure was defined as occurrence of hepatic encephalopathy (altered sensorium) with grossly deranged Liver Function Tests (LFT) with jaundice. Coagulopathy

was defined as deranged prothrombin time (prolonged to >15 seconds).

Statistical Analysis

Data analysis was carried out using statistical software STATA version 12.0. Continuous variables were tested for normality assumptions using appropriate statistical tests. For the variables that were approximately to normal distribution descriptive statistics such as mean, standard deviation and the range values were calculated. Categorical variables were expressed in terms of frequency and percent values.

Results

A total of 60 cases of Hepatitits E (Group 1) with pregnancy over last 10 years in a tertiary referral centre were enrolled in this retrospective study. Maternal and perinatal outcome was compared in the two groups. Table 1 shows baseline characteristics in the study group. The mean age was 27.85±4.81 years. There were 30 primigravida and 30 multigravida patients. Associated medical problems are shown in Table 1. Table 2 shows obstetric complications and mode of delivery in the study group. Incidence of anemia, preeclampsia, oligoamnios, gestational Diabetes mellitus, premature rupture of membrane, fetal growth restriction and pretern delivery rate was 21.66%, 21.66%, 3.33%, 20%, 13.33%, 13.33% and 26.66% respectively.

Similarly intrapartum fetal distress was seen in significantly higher number of cases of Hepatitis E patients 8(13.3%). Meconium stained liquor was seen in 20% of cases. Postpartum complications were seen in 21.6% (13/60) cases. There were 2(3.33%) maternal deaths in study group. The mode of delivery is shown in Table 2. Vaginal delivery could be achieved in 22(36.67%) cases in study. Cesarean section rate was significantly higher in study cases(63.33%). Emergency cesarean rate was significantly higher (43.33%) in study group.

Table 3 shows abnormalities of liver function tests (LFTs) and use of antiviral drugs. As expected LFTs were severely deranged in hepatitis E in pregnancy. Thus mean aspartate amino transferase (SGOT) and Alanine amino transferase (SGPT) levels were 120.13 ±192.99U/L and 129.29 ±208.42U/L respectively. Total serum bilirubin was 2.49±4.64 mg/dl. Coagulopathy defined as prothrombin time of more than 15 seconds was seen in [8(13.33%)] cases. Hepatic encephalopathy was also seen in [5(8.33%)] cases. Use of medications like ursodeoxycholic acid, N acetyl cysteine and tenofovir was also seen in 60%, 4% and 10% cases respectively.

Most fetal parameters were poorer in hepatitis E patients. Mean birth weight was 2134±625.47 gm in study group. Small for date was seen in 12(20%) cases. Apgar <8/10 at one minute was also seen [12(20%)] cases in study group. Still birth was seen in 4(6.67%) cases. Respiratory distress was seen in 6(10%) cases (Table 4).

Table 1 — *Baseline Characteristics in Two Groups*

Outcome	HEV during Pregnancy N=60 (%)
Mean Age	27.65±4.81
18-35	57(95)
>35	3(5)
Obstetric History :	
Primigravida	30(50)
Multigravida	30(50)
Previous Abortions	30(50)
Associated Medical Problems :	
Anemia	8(13.33)
Hypothyroidism	8(13.33)
Chronic Kidney Disease	2(3.33)
Rheumatic Heart Disease	2(3.33)

Table 2 – *Obstetric Complications and Mode of Delivery in Two Groups*

Outcome	HEV during Pregnancy N=60 (%)
Obstetric events :	
Anemia	13(21.66)
PIH	13(21.66)
Oligoamnios	2(3.33)
GDM	12(20)
PROM	8(13.33)
FGR	8(13.33)
Preterm Delivery	16(26.66)
Intrapartum Fetal Distress	8(13.33)
MSL at delivery	12(20)
Postpartum complication	13(21.66)
Maternal mortality	2(3.33)
Mode of Delivery :	
Vaginal	22(36.67)
Spontaneous	10(16.66)
Induced	12(20)
LSCS	38(63.33)
Elective	12(20)
Emergency	26(43.33)

PIH : Pregnancy Induced Hypertension
GDM : Gestational Diabetes Mellitus,
PROM : Premature Rupture of Membrane
FGR : Fetal Growth Restriction

Discussion

Hepatitis E is an acute viral infection caused by single stranded non enveloped RNA virus[1,8]. The first outbreak of hepatitis E in India came in 1953-56 and was described retrospectively[8,9]. The main source of infection of HEV is through contaminated drinking water. Usually the infection has

Table 3 — *LFT Abnormality and use of Antiviral Medication*

Outcome	HEV during Pregnancy N=60 (%)
LFT Abnormality :	
Mean SGOT (in IU/l)	120.13±192.99
Mean SGPT (in IU/l)	129.27±208.42
Mean ALP (in IU/l)	365.23±203.16
Mean T. Bilirubin (in mg%)	2.49±4.64
Coagulopathy	8(13.33)
Hepatic Encephalopathy	5(8.33)
Use of Medications :	
Ursodeoxycholic acid	36(60)
NAC	4(6.67)
TENOFOVIR	6(10)

LFT : Liver Function Test
SGOT : Serum Glutamine Oxaloacetic Acid Transaminase
SGPT : Serum Glutamate Pyurvate Transaminase
ALP : Alkaline Phosphatase
NAC : N Acetyl Cysteine

Table 4 — *Fetal outcome in two groups*

Outcome	HEV during Pregnancy N=60 (%)
Fetal Outcome :	
Mean Birth Weight (in gram)	2134.22±625.47
Small For Dates	12(20)
Large For Dates	4(6.67)
APGAR<8	12(20)
Still Birth	4(6.67)
Congenital Anomaly	3(5)
Respiratory Distress	6(10)

an incubation period of 3-8 weeks with a mild and self limiting illness resolving within 6 weeks with no chronic sequlae[8]. Fulminant hepatitis and case fatality is rare in men and in non pregnant women[8]. However HEV infection during pregnancy causes a serious illness with risk increasing with progress of pregnancy and there is risk of fulminant hepatic failure and death which may be seen in upto 30-100% patients[10]. Infact one of the most distinctive features of the epidemic and endemic hepatitis E is higher occurrence and mortality of diseased patients in pregnancy[11,12]. The obstetric complications like miscarriages, premature rupture of membrane, intra uterine growth restriction and death occurs with greater frequency in women with HEV infection during pregnancy. Infact in a study 58% of death in pregnant women with acute liver disease in hepatitis were due to HEV infection[13].

In the present study, we observed increased obstetric complication like preterm delivery (26.6%), intrapartum fetal distress (13.33%), meconium stained liquor (20%) in pregnant patients infected with HEV infection. We observed 2 maternal deaths (3.33%) in 60 cases of HEV which corresponds to maternal mortality rate (MMR) of 3333 per lac live births which is 33 times higher than our hospitals average MMR of 110 per lac births during this period (hospital statistics, unpublished data). Shinde *et al*[8] also observed a very high maternal mortality of 32% in their study on acute HEV infection in pregnancy. We also observed a higher fetal complications like lower mean birth weight, small for dates fetuses, increased chances of low APGAR babies, still births and respiratory distress rate in our study. Results are similar to Prasad *et al*[4] who observed 80% risk of prematurity in their study. Shinde *et al*[8] observed 23.5% preterm delivery, 48.15% poor fetal outcome in their study. Beniwal *et al*[14] also observed adverse maternal and fetal outcome with high mortality rate, increased frequency of abortion, preterm delivery, still birth and neonatal death in their study. Other authors have also observed increased preterm delivery rate, increased fetal and maternal death in their studies on HEV infection during pregnancy[15,16,17]. Hepatitis E infection during pregnancy was also most important medical condition presenting in obstetric critical care[18]. In a chinese study Xu *et al*[19] also observed adverse maternal and perinatal outcome with HEV infection during pregnancy. Hepatitis E can also cause vertical transmission causing fetal and neonatal morbidity and mortality[20,21,22].

Prevention and control of hepatitis E in developing countries is a daunting task and mainly rests on provision of supply of clean portable drinking water, adequate sanitation, proper hygiene, proper sewage disposal[21]. Clean India campaign, a Government of India campaign 2014 is a 10 billion US dollar project meant to clean environment, construct toilets in most homes and schools and a plan to have 1.2 billion Indians to have access to public latrines in next 5 years[23]. It will go long way in reducing incidence of various water borne disease in india including hepatitis E. Hepatitis E vaccine-239, marketed in China has shown high efficacy with sustained protection for over four years but is still not available and used in India.

Conclusion :

Hepatitis E infection in second and third trimester and during labor is a serious disease causing higher incidence of obstetric complications, maternal morbidity and maternal mortality, increased chances of caesarean section, hepatic encephalopathy, coagulopathy, poor perinatal outcome (low mean birth weight babies, still birth and respiratory distress rate). Hence all pregnant women with HEV infection should be treated on tertiary referral centres with facilities for intensive care unit. As HEV is transmitted by feco-oral route, sanitation, adequate disposal of excreta and provision for safe drinking water can go long way in preventing this menace.

Acknowledgement

Author is thankful to all residents of Department of Obstetrics and Gynaecology, AIIMS, Delhi for their support.

Referrences

1 Khuroo MS — Acute liver failure in India (Letter). *Hepatology* 1997; **26(1):** 244-6.
2 Krawczynski K, Aggarwal R, Kamili S — Hepatitis E. *Infect Dis Clin North Am* 2000; **14(3):** 669-87.
3 Tsarev SA, Tsareva TS, Emerson SU, Yarbough PO, Legters LJ, Moskal T, *et al* — Infectivity titration of a prototype strain of Hepatitis E virus in cynomolgus monkeys. *J Med Virol* 1994; **43(2):** 135-42.
4 Prasad GY, Prasad S, Bhupali A, Patil AN, Parashar K — A Study of Hepatitis E in Pregnancy: Maternal and Fetal Outcome. *J Obstet Gynecol India* 2016; **66(Suppl1):** S18-S23.
5 Purcell RH, Emerson SU — Hepatitis E: an emerging awareness of an old disease. *J Hepatol* 2008; **48(3):** 494-503.
6 Aggarwal R — Hepatitis E and pregnancy. *Indian J Gastroenterol* 2007; **26(1):** 3-5.
7 Kasper L, Fauci J — Acute viral hepatitis. *Harrison's Principles of Internal Medicine* 2015; **2(18):** 2537-55.
8 Shinde NR, Patil TB, Deshpande AS, Gulhane RV, MB Patil, YV Bansod — Clinical profile, maternal and fetal outcomes of acute hepatitis E in pregnancy. *Ann Med Health Sci Res* 2014; **4(Suppl 2):** S133-S139.
9 Teshale EH, Hu DJ, Holmberg SD — The two faces of hepatitis E virus. *Clin Infect Dis* 2010; **51(3):** 328-34.
10 Navaneethan U — Seroprevalence of hepatitis E infection in pregnancy - more questions than answers. *Indian J Med Res* 2009; **130(6):** 677-9.
11 Khuroo MS, Teli MR, Skidmore S, Sofi MA, Khuroo MI — Incidence and severity of viral hepatitis in pregnancy. *Am J Med* 1981; **70(2):** 252-5.
12 Khuroo MS, Kamili S — Aetiology, clinical course and outcome of sporadic acute viral hepatitis in pregnancy. *J Viral Hepat* 2003; **10(1):** 61-9.
13 Gurley ES, Halder AK, Streatfield PK, Sazzad HM, Huda TM, Hossain MJ, *et al* — Estimating the burden of maternal and neonatal deaths associated with jaundice in Bangladesh:

Possible role of hepatitis E infection. *Am J Public Health* 2012; **102(12):** 2248-54.
14 Beniwal M, Kumar A, Kar P, Jilani N, Sharma JB — Prevalence and severity of acute viral hepatitis and fulminant hepatitis during pregnancy: A prospective study from north India. *Indian J Med Microbiol* 2003; **21(3):** 184-5.
15 Shrestha P, Bhandari D, Sharma D, Bhandari BP — A study of viral hepatitis during pregnancy in Nepal Medical College Teaching Hospital. *Nepal Med Coll J* 2009; **11(3):** 192-4.
16 Banait VS, Sandur V, Parikh F, Murugesh M, Ranka P, Ramesh VS, *et al* — Outcome of acute liver failure due to acute hepatitis E in pregnant women. *Indian J Gastroenterol* 2007; **26(1):** 6-10.
17 Patra S, Kumar A, Trivedi SS, Puri M, Sarin SK — Maternal and fetal outcomes in pregnant women with acute hepatitis E virus infection. *Ann Intern Med* 2007; **147(1):** 28-33.
18 Bhadade R, De' Souza R, More A, Harde M — Maternal outcomes in critically ill obstetrics patients: A unique challenge. *Indian J Crit Care Med* 2012; **16(1):** 8-16.
19 Xu B, Yu HB, Hui W, He JL, Wei LL, Wang Z, *et al* — Clinical features and risk factors of acute hepatitis E with severe jaundice. *World J Gastroenterol* 2012; **18(48):** 7279-84.
20 Krain LJ, Atwell JE, Nelson KE, Labrique AB — Fetal and neonatal health consequences of vertically transmitted hepatitis E virus infection. *Am J Trop Med Hyg* 2014; **90 (2):** 365-70.
21 Khuroo MS, Khuroo MS, Khuroo NS — Hepatitis E: Discovery, global impact, control and cure. *World J Gastroenterol* 2016; **22(31):** 7030-45.
22 Khuroo MS, Kamili S, Jameel S — Vertical transmission of hepatitis E virus. *Lancet* 1995**; 345(8956):** 1025-6.
23 Khuroo MS, Kamili S, Khuroo MS — Clinical course and duration of viremia in vertically transmitted hepatitis E virus (HEV) infection in babies born to HEV-infected mothers. *J Viral Hepat* 2009; **16(7):** 519-23.
24 Khuroo MS — Sanitation and sewage disposal in India.2014.Available from :URL:http://www.researchgate.net/publication/269411584
25 Zhu FC, Zhang J, Zhang XF, Zhou C, Wang ZZ, Huang SJ, *et al* — Efficacy and safety of a recombinant hepatitis E vaccine in healthy adults: a large-scale, randomised, double-blind placebo-controlled, phase 3 trial. *Lancet* 2010; **376 (9744):** 895-902.