

*Observational Study***Retrospective study of feto-maternal outcome in Hepatitis E infection in third trimester of pregnancy at a tertiary care hospital in Western India**Rajal V Thaker¹, Parul T Shah²

To study of Feto-Maternal outcome in Hepatitis E (HEV) infection in third trimester of pregnancy and to suggest measures for its prevention during pregnancy. After due permission, course of disease and feto-maternal outcome was studied from case papers of patients who were infected with Hepatitis E during third trimester of pregnancy. Analysis of data of 38 patients was done. Proportion of Hepatitis E in third trimester of pregnancy was 0.19%. Maximum numbers of patients 6(15.7%) were reported in months of September and November each. Maximum numbers of patients 23(60.5%) were in age group of 20 to 25 years. Majority 33(86.8%) patients were from lower socioeconomic class. Majority 32(84.2%) patients were emergency admissions. Serum bilirubin was more than 5mg/dl in 35(92.1%). Alkaline phosphatase and serum transaminases were raised in 30(79%) and 33(86.9%) respectively. Coagulation tests were altered in 24(63.1%) patients. Preterm normal deliveries were 21(67.7%) and 6(19.3%) were preterm Caesarean Section (CS). Low birth weight (LBW) was reported in 27(87%). Stillbirths were 7 (22.5%). Perinatal mortality was 11(35.4%). Out of all, 25(65.7%) patients had complications. Disseminated Intravascular Coagulation (DIC) was the most common complication encountered in 24(63.1%). Hepatic encephalopathy occurred in 11(28.9%). Blood components were given in 29(76.3%) of patients. Total 8(21%) patients died following fulminant hepatic failure (FHF), Disseminated Intravascular Coagulation (DIC) and Hepatic encephalopathy. Equal number of patients died in antenatal and postnatal period that, is 4 (10.5%) in each period. Hepatitis E infection in third trimester of pregnancy has a worsening course leading to high feto-maternal morbidity and mortality; hence prevention of Hepatitis E infection in pregnancy is very essential.

[J Indian Med Assoc 2018; 116: 43-6]

Key words : Hepatitis E in pregnancy, Jaundice in pregnancy, HEV and pregnancy.

Pregnancy with jaundice is considered as a high risk pregnancy. Viral hepatitis is the most common cause of jaundice in pregnant women. Seven types of virus can cause viral hepatitis; called hepatitis A to G. Incidence of hepatitis varies greatly around the world. In 89,80,000 cases of viral hepatitis with 5,85,800 deaths occur annually in South East Asia. In addition to the loss of more than 0.5 million lives and untold suffering for millions of people, viral hepatitis causes tremendous economic loss to the patients, and their families due to long hospitalization and expensive treatment for chronic patients¹.

Hepatitis E is a single stranded RNA virus (HEV) that leads to an estimated 20 million hepatitis E infections, over three million acute cases of hepatitis E, and 57 000 hepatitis E-related deaths². Four studies from Delhi, India have reported a prevalence of HEV infection in pregnancy as

18%, 37%,47.4% and 60%³⁻⁶ respectively. This infection often occurs in water born epidemics, spread by faecal-oral route and is clinically similar to hepatitis A. The resultant liver disease is usually mild, except in pregnant women, particularly those in the third trimester⁷ where it can be aggressive and patient may develop fulminant hepatic failure (FHF) with high feto-maternal mortality and morbidity.

MATERIAL AND METHODS

This retrospective observational study was conducted after due permission from authorities. Course of disease and feto-maternal outcome were studied from case papers of patients who were infected with Hepatitis E (positive with IgM HEV antibodies detected by Enzyme Linked Immuno Assay - ELISA) during third trimester of pregnancy admitted at a tertiary care hospital, Sheth V S General Hospital affiliated with Smt NHL Municipal Medical College at Ahmedabad, Gujarat in western India during July 2008 to June 2012. Data was collected as per pre-tested structured proforma. Analysis of 38 patients was done regarding age, parity, residential status, education,

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timing and whether registered or emergency admissions. Data regarding pregnancy outcome, Obstetric complications, transfusion of blood and blood products, maternal and perinatal mortality were analyzed.

RESULTS

It was observed that, overall management of HEV during pregnancy is not different from managing jaundice due to other causes of viral hepatitis. All patients were referred to general physician and gastroenterologist. If required, patients were transferred to Medical Intensive Care Unit (MICU). Repeat investigations were carried out as and when required. Those patients who showed worsening of disease were induced and delivered vaginally. Caesarean section was performed if required. Help of neonatologist was also taken and whenever required, babies were admitted at Neonatal Intensive Care Unit (NICU). Patients showing improvements of signs and symptoms and improved laboratory investigations were managed conservatively.

Analysis of data of 38 patients was done. From July 2008 to June 2012, 19,977 deliveries had taken place. Hence, proportion of Hepatitis E at our institute was 0.19%. Maximum numbers of patients 6(15.7%) were reported in months of September and November each, followed by 5(13.5%) in June. In months of May, July, August, October and December, 3(7.8%) patients were reported in each month. Maximum numbers of patients 23(60.5%) were in age group of 20 to 25 years. There were 34(87.1%) patients who belonged to the age group 20-30 years. Patients from urban areas were 29(76.3%). Majority 32(84.2%) patients had at least primary education. Majority 33(86.8%) patients were from lower socioeconomic class. Majority 32(84.2%) patients were emergency admissions. Out of them, 20(52.7%) were Primi, 11(28.9%) were second gravida and 7(18.4%) were multigravida. Most common presenting symptom was abdominal pain in 33(86.8%) patients. This was followed yellowish discoloration of urine in 29(76.3%), by loss of appetite, nausea and vomiting in 28(73.7%), fever in 12(31.5%), itching in 8(21%), irritability and altered sensorium in 6(15.7%). More than one symptom was present in each patient. Icterus was present in all patients. Yellow discoloration of skin and fever were present in 22(57.9%) and 12(31.5%) respectively. Maternal Hepatomegaly was present in 9(23.7%), ascites was present in 7(18.4%) and splenomegaly was present in 5(13.1%). Majority 26(68.42%) patients were anaemic. TLC was raised in 20(52.6%) and 8(21%) had thrombocytopenia. Serum bilirubin was more than 5mg/dl in 35(92.1%) and 8(21%) had more than 15mg/dl. Alkaline phosphatase and serum transaminases were raised in 30(79%) and 33(86.9%) respectively. Tests of coagulation were altered in 24(63.1%) patients. As shown in Table 1, Preterm normal deliveries were 21(67.7%) and 6(19.3%) were preterm Caesarean Section (CS). Full term normal delivery, for-

Outcome of Pregnancy			Number	Percentage (%)
Delivered N = 31 (81.5%)	Preterm	ND	21	67.7
		CS	06	19.3
	Full term 4(12.9%)	ND	02	6.5
		Forceps	01	3.2
		CS	01	3.2
Undelivered N=07 (18.5%)	Expired	04	10.5	
	Discharged and lost for follow up	03	7.9	

ceps and CS were 2(6.5%), 1(3.2%) and 1(3.2%) respectively. Indications of CS were fetal distress in 3, non progress of labor in previous CS in 3, and previous 2 CS in one patient. During antenatal period, 4(10.5%) patients expired undelivered and 3(7.8%) had come in early third trimester who were discharged after complete recovery, that means patients were discharged after they became asymptomatic and after their laboratory indices became normal but then they had not come for follow-up and for delivery at our institute; hence they were lost for follow up of their fetomaternal outcome. Table 2 shows, Outcome of baby. Li-

quor was meconium stained in 16(51.6%). Low birth weight was reported in 27(87%). Stillbirths were 7(22.5%). NICU admissions were

11(35.4%), out of them 4(12.9%) died. Perinatal mortality was 11(35.4%). Out of all, 13(34.2%) patients had no complications, whereas 25(65.7%) patients had complications as shown in Table 3. More than one complication was found in some patients. Disseminated Intravascular Coagulation (DIC) was the most common complication encountered in 24(63.1%). Hepatic encephalopathy occurred in 11(28.9%). Wound complications like hematoma and infection of CS wound occurred

in 4(10.5%) patients. Other significant complications were PPH and renal failure occurred in 2(5.2%) each.

Blood components were given in 29(76.3%) of patients. Packed Cell Volume (PCV), Fresh Frozen Plasma (FFP), Platelet Rich Concentrate (PRC), and cryoprecipitate were

Outcome of Baby N = 31 (81.5%)	Number	Percentage (%)	
Live Birth	24	77.4	
Still Birth	7	22.5	
Weight	< 2 kg	15	48.3
	2.1-2.5 kg	12	38.7
	> 2.5 kg	04	12.9
NICU admission	11	35.4	
Died within 7 days	04	12.9	

Maternal Morbidity N = 25 (65.7%)	Number	Percentage (%)
Disseminated Intravascular Coagulation	24	63.1
Fulminant Hepatic Failure, Hepatic Encephalopathy	11	28.9
Wound complication	4	10.5
Post Partum Hemorrhage	2	5.2
Renal Failure	2	5.2

given in 12(31.5%), 27(71%), 8(21%) and 5(13.1%) of the patients respectively. As shown in Table 4, total 8(21%) patients died following FHF, DIC, Hepatic encephalopathy and Septicemia. Majority of maternal deaths 6(15.7%) occurred due to FHF and Hepatic encephalopathy. Equal number of patients died in antenatal and post-natal period that, is 4 (10.5%) in each period. There were 6(75%) maternal deaths amongst emergency admissions.

Maternal Mortality (N = 8)	Number	Percentage
Fulminant Hepatic Failure, Hepatic encephalopathy	6	15.7
PPH, DIC, Renal Failure	1	2.6
Septicemia	1	2.6
Total	8	21

DISCUSSION

In our study, HEV infection was found almost any time in a year, but more so in months of summer and monsoon season. In our study, 34(87.1%) were below 30 years. In a study by Caro *et al*⁸ more than 2/3 of patients were below 30 years. Early marriages along with unclean, unhealthy and improperly cooked food among these pregnant women may be a cause of the infection. In our study, majority of patients were from lower socioeconomic status. Kumar *et al*⁹ has also reported similar findings. In our study, more than half of patients were primigravida. In a study by Malahat M *et al*¹⁰ 36.3% were primigravida.

In our study, 13(34.2%) patients had no complications and were managed conservatively as there was improvement in clinical and lab indices. In our study, induction of labour or caesarean section was done as and when required.

Therapeutic termination of pregnancy, which has been proved to be beneficial in pregnancy specific disorders like HELLP(Hemolysis, Elevated Liver enzyme, Low Platelet) syndrome and acute fatty liver of pregnancy¹¹ have not been fully, explored in Hepatitis E infection. However in a retrospective study from India¹² in 42 patients with HEV induced liver failure, there was no difference in maternal mortality in pregnant women who delivered and those who did not questioning the role of therapeutic termination. At present, although there is no consensus to treat patients with HEV infection in pregnancy, early delivery of the fetus if possible to prevent maternal mortality should be tried. Randomized studies are required in the future to decide upon the best way of treating patients with HEV infection in pregnancy¹³. It has been observed that among pregnant patients, the decision to continue pregnancy with increasing levels of bilirubin and other liver functions tests, the mortality rate is high¹⁴. Hence conservative management or "wait see" policy should only be followed if the patients show signs of clinical and laboratory indices improvement¹⁵. At our hospital, we also follow the conservative management approach if patient show improvement in clinical and laboratory indices.

In our study, there were 23 (74.1%) vaginal delivery and 8 (25.8%) operative delivery. Generally, cesarean section has higher morbidity compared to vaginal delivery. Hence, vaginal delivery is always preferred in these patients to prevent complications due to cesarean section and in presence of complications like hepatic encephalopathy and hepatic failure. In our study, we found that, stress of labour has no role in deterioration of disease.

Our study revealed that, the liquor was meconium stained in 16(51.6%) and 7(22.5%) were stillbirths. Malahat M *et al*¹⁰ has reported 15% rate of stillbirth with HEV infection. This may indicate the chance of vertical transmission which may cause fetal death.

Our study revealed that there was a high percentage of preterm labour and low birth weight in 27(87%). Kumar *et al*⁹ observed that prematurity in HEV affected fetuses was 84%. Suruchi S *et al*³ has reported 6% of intrauterine death and 41.3% of low birth weight baby in mother having HEV infection. In our study, 11(35.4%) babies were admitted in NICU and out of them 4(12.9%) died. Perinatal mortality was 11(35.4%). With better NICU facility at our hospital neonatal mortality and morbidity is low compared to other studies^{10,16} where it was 47% and 54% respectively.

Our study revealed that, 25(65.7%) patients developed complications. More than one complication was present in some patients. DIC was the most common complication encountered in 24(63.1%). Hepatic encephalopathy occurred in 11(28.9%) and ventilator support was required. Wound complications like hematoma and infection of CS wound occurred in 4(10.5%) patients. Other significant complications were Post Partum Haemorrhage (PPH) and Renal failure seen in 2(5.2%) each. Blood components were given in 29(76.3%) patients. Some patients were given more than one component. Transfusion with PCV, FFP, Cryoprecipitates and Platelets are usually necessary for management of severe anaemia, PPH and Coagulation defects. Patients who developed renal failure were managed with dialysis. Patients who developed FHF were managed at MICU with supportive care. They received 25% Dextrose, Vitamin K, lactulose, antibiotics, refaximine, parenteral intervention if required and ventilator support if and when needed. Thus, Multidisciplinary approach by Gastroenterologist, Nephrologist and availability of blood components at our tertiary care hospital have played a crucial role in management of complications. Several cross-sectional studies where fetomaternal outcome in pregnancy due to Hepatitis A, B, C and E viruses were compared, it was seen that incidence of FHF was highest in patients suffering from Hepatitis E³. Beniwal M *et al*⁵ has reported that, HEV was responsible for 75% cases of FHF and maternal mortality was 39.1%. The cause

of the increased severity of this hepatitis during pregnancy is unknown, but may relate to attenuated cellular immunity during pregnancy.

In our study, equal number of patients that is 4 (10.5%) each, died in antenatal and postnatal period. Out of these, 6(75%) maternal deaths were reported in emergency admissions that were brought in very late stage with altered sensorium. These patients could have been saved if they were brought early. Although, proportion of Hepatitis E was 0.19% during the study period, maternal mortality was 8(21%) following FHF, DIC, Hepatic encephalopathy and septicemia. Of those who died in post natal period, one patient also had Renal Failure following DIC and PPH and other also had Septicemia. According to WHO², pregnant women are at greater risk of obstetrical complications and mortality from hepatitis E, which can induce a mortality rate of 20% among pregnant women in their third trimester.

In our study, higher levels of Serum bilirubin, Alkaline phosphatase and serum transaminases were associated with higher maternal mortality. No Maternal mortality reported when initial serum bilirubin was less than 5 mg%. Prolonged hospital stay contributes to more financial burden either on family or on Government. Feto-maternal mortality is in addition a great loss to family and to society.

Prevention of Hepatitis is very important especially in developing countries. Public health education helps in creating awareness regarding different modes of transmission of hepatitis. Pregnant women are best advised to avoid contact with suspected HEV cases and it can be minimized by adapting hygienic habits like hand washing with safe water. Better sanitation facilities, safe drinking water, avoiding uncooked food and disposing of contaminated clothes and fomites by autoclaving and incineration also helps. Increased availability of antenatal care for early detection and aggressive management of pregnancy with jaundice at tertiary care center with multidisciplinary approach will help in the reduction of maternal and perinatal morbidity and mortality.

CONCLUSION

Hepatitis E in third trimester has a worsening course in pregnancy that affects both fetus and mother. There is high risk of preterm delivery, fetal distress, IUD and meconium aspiration leading to high perinatal mortality and morbidity. HEV also has grave prognosis with high maternal mortality. Conservative management should only be followed if the patients show improvement in clinical signs and laboratory indices. Obstetric management along with NICU facility and multi disciplinary approach at a tertiary care center can help in reduction of maternal and perinatal morbidity and mortality. Prevention of HEV is also necessary. Hence, all antenatal women along with their family

members should be made aware regarding different modes of transmission of hepatitis during their antenatal visits.

ACKNOWLEDGEMENT

We hereby would like to thank Dr ST Malhan, the superintendent of Sheth VS General Hospital, Dr Pankaj R Patel, the dean of Smt NHL Municipal Medical College to allow us to publish this paper. Declarations:

Funding : None

Competing interests : None

Ethical approval : Yes

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