Outcomes of acute liver failure due to acute hepatitis E in pregnant women


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Introduction: Acute liver failure due to acute hepatitis E carries a high mortality. Methods: Clinical and laboratory parameters of 42 pregnant women (median age 25.5 years) with acute liver failure due to acute hepatitis E were retrospectively analyzed. Results: 22 women delivered, whereas pregnancy continued in 20 women. The maternal mortality in these two groups was similar (9/22 [41%] versus 14/20 [70%], p=0.056). However, in patients with grade I, II or III hepatic encephalopathy, delivery of fetus was associated with reduced mortality in those who delivered as against those who continued pregnancy (5/16 [31%] vs. 13/20 [65%], p=0.046). On multivariate analysis, higher grade of encephalopathy at admission was associated with risk of death (p=0.005). Conclusion: Mortality in pregnant women with acute liver failure with acute hepatitis E is high, especially in patients who present with higher grades of encephalopathy. [Indian J Gastroenterol 2007;26:6-10]
sented with a combination of (a) recent-onset jaundice; (b) absence of evidence of chronic liver disease on clinical and biochemical features, or ultrasonography showing evidence of portal hypertension; (C) elevation of serum alanine transaminase above five times upper limit of normal range.

ALF was defined as presence of encephalopathy within 8 weeks of development of clinical illness in the absence of clinical evidence of chronic liver disease. Encephalopathy was graded using the West Haven criteria.

Acute renal failure was diagnosed when urine output fell below 400 mL/24 hour and/or serum creatinine rose above 2 mg/dL. Clinical coagulopathy was diagnosed when there was bleeding from multiple sites (skin, mucosa, venepuncture sites, etc); abnormal prothrombin time was defined if the patient’s value was 4 seconds more than control value.

Thrombocytopenia was defined as platelet count less than 100 x 10⁹/L. Disseminated intravascular coagulation (DIC) was diagnosed when bleeding occurred from multiple anatomical sites (skin, mucosa, venepuncture sites) along with low levels of fibrinogen (<2 g/L), thrombocytopenia (<100 x 10⁹/L), and elevated levels of fibrin degradation products.

Hypoglycemia was diagnosed when patient had deterioration of sensorium, neuroglycopenic or vasomotor symptoms accompanied either by blood sugar <60 g/dL during periodic blood sugar monitoring, or by response to intravenous dextrose. Infections were diagnosed using clinical, radiological or microbiologic findings, and were treated appropriately based on culture and sensitivity reports.

Stillbirth was defined as birth of a dead fetus. Fetal death within 6 hours preceding maternal death was not considered as stillbirth as it was presumed that the fetal death just before or after maternal death is a result of maternal condition and is unlikely to influence maternal outcome.

Serology for hepatitis viruses
IgM anti-HAV, HBsAg, IgM anti-HBc, HCV (anti-HCV second generation) were tested in patient sera using commercially available ELISA (Abbott; North Chicago, IL, USA). Sera from all patients were also tested for IgM anti-HEV using an enzyme immunoassay (Genelabs, Singapore) that detects IgM antibodies against recombinant proteins corresponding to open reading frames 2 and 3 of HEV.

Management
All patients were managed in the intensive care unit and were monitored for clinical, biochemical, and hemodynamic parameters. Intracranial pressure monitoring and liver transplant facilities were not available. Patients were treated conservatively with an expectant attitude. If intrauterine fetal death (IUFD) occurred, PGE2 and oxytocin were used to induce labor.

Case fatality was defined as death of the mother during pregnancy or in the immediate postpartum period due to ALF.

Statistical methods
Inter-group comparisons for categorical variables were done using chi² test with Yates’ correction (for 3 x 2 tables) or Fisher’s exact test, and those for quantitative variables using Wilcoxon’s rank sum test. p value <0.05 was considered significant. Epi Info version 3.3.2 (www.cdc.gov/epiinfo) was used for analysis. Multivariate analysis was done using variables that were significantly associated with maternal mortality.

Results
One hundred and fifty-six pregnant women with liver disease attended the gastroenterology services at our hospital during the study period. Of these, 69 had non-HEV-related disease (13 malaria, 6 dengue fever, 12 sepsis-related, 8 chronic liver disease, 2 acute hepatitis B, 20 pregnancy-induced hypertension, 5 HELLP, 1 acute fatty liver of pregnancy, 2 intrahepatic cholestasis of pregnancy) and 87 had acute hepatitis due to HEV. Forty-eight patients (30.7%) developed ALF. Six patients with non-HEV-related liver disease (4 eclampsia, 1 HELLP, 1 acute fatty liver of pregnancy) developed ALF. Sixty-eight patients (30.7%) developed ALF. Six patients with non-HEV-related liver disease (4 eclampsia, 1 HELLP, 1 acute fatty liver of pregnancy) developed ALF. Forty-two pregnant women who had ALF due to acute hepatitis E constituted the study group.

The median age of patients was 25.5 years (range 18-38). Two patients (4.8%) were in the first trimester of pregnancy, 14 (33.3%) in the second trimester, and 26 (61.9%) in the third trimester. Twelve (28.6%) women were primigravida. None of the patients had history of alcohol abuse, family history of recent jaundice, or contact with jaundiced patient, recent travel, blood transfusions and promiscuous sexual behavior in the preceding two months.
Liver failure following hepatitis E in pregnancy

At the time of admission to the intensive care unit, 3 (7.1%), 17 (40.5%), 16 (38.1%) and 6 (14.3%) patients had with grade I, II, III, and IV hepatic encephalopathy, respectively. Thirty-nine patients had history of altered behavior for median 2 days (range 8 hours to 3 days) before admission to the ICU; three patients developed hepatic encephalopathy after 2, 5 and 6 days of hospital admission, and were shifted to the ICU. Four (9.5%) patients developed generalized tonic-clonic seizures. Two patients had ascites detectable by ultrasound examination alone. Twenty-three (54.8%) had clinical coagulopathy. Four patients developed disseminated intravascular coagulopathy (DIC). Six patients developed bleeding due to gastric erosions. Hypoglycemia was detected in 14 patients during hourly monitoring of blood glucose, in spite of continuous infusion of 50% dextrose at 10 mL per hour. One patient developed acute renal failure during the course of disease.

Twenty-three (54.8%) women died; these included 7 of 17 (41%), 11 of 16 (68.8%) and 5 (83.3%) pregnant women with grade II, III and IV hepatic encephalopathy at admission, respectively. The median duration between development of hepatic encephalopathy and death was 4 (range 2-9) days.

Twenty-two (52.4%) patients delivered, including 4 in the second trimester and 18 in the third trimester of pregnancy. Labor started spontaneously in 13 women. In the remaining 9 women, it was induced because of intra-uterine fetal death (IUFSD). All deliveries were by vaginal route. Fourteen of these 22 women delivered a dead fetus (fetal mortality 63.6%).

Pregnancy continued in 20 women; 14 of them died. Of the 6 women who continued pregnancy and survived, 5 delivered a normal baby at term and one delivered a premature baby seven days after recovery from hepatic encephalopathy. The baby died on the third postnatal day.

Overall, there were 29 (69%) fetal deaths and 23 (54%) maternal deaths. The Table compares clinical and biochemical parameters at admission among mothers who survived and those who did not.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mother survived (19)</th>
<th>All patients</th>
<th>p value</th>
<th>Mother survived (18)</th>
<th>Mother dead (18)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>26 (18-38)</td>
<td>26 (18-35)</td>
<td>0.7</td>
<td>25 (18-35)</td>
<td>25.5 (18-38)</td>
<td>0.4</td>
</tr>
<tr>
<td>Duration of pregnancy (weeks)</td>
<td>28 (16-36)</td>
<td>26 (8-36)</td>
<td>0.1</td>
<td>27 (12-36)</td>
<td>28 (16-36)</td>
<td>0.3</td>
</tr>
<tr>
<td>Primigravida (number [%])</td>
<td>4 (21.1%)</td>
<td>8 (34.8%)</td>
<td>0.2</td>
<td>4</td>
<td>4</td>
<td>0.5</td>
</tr>
<tr>
<td>Duration of jaundice at admission (days)</td>
<td>8 (2-15)</td>
<td>10 (3-16)</td>
<td>0.3</td>
<td>8 (2-15)</td>
<td>10 (3-16)</td>
<td>0.3</td>
</tr>
<tr>
<td>Jaundice to HE interval (days)</td>
<td>6 (1-17)</td>
<td>8 (2-15)</td>
<td>0.3</td>
<td>6 (1-17)</td>
<td>7 (2-15)</td>
<td>0.5</td>
</tr>
<tr>
<td>Ascites (number)</td>
<td>2</td>
<td>0</td>
<td>0.1</td>
<td>2</td>
<td>0</td>
<td>0.2</td>
</tr>
<tr>
<td>Coagulopathy (number [%])</td>
<td>7 (37 %)</td>
<td>16 (70%)</td>
<td>0.03</td>
<td>6</td>
<td>11</td>
<td>0.09</td>
</tr>
<tr>
<td>GI bleed (number [%])</td>
<td>1 (5%)</td>
<td>5 (22%)</td>
<td>0.1</td>
<td>1 (6%)</td>
<td>5 (28%)</td>
<td>0.08</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>6 (31.6%)</td>
<td>8 (34.8%)</td>
<td>0.9</td>
<td>5 (28%)</td>
<td>5 (28%)</td>
<td>0.6</td>
</tr>
<tr>
<td>Renal failure</td>
<td>0</td>
<td>1</td>
<td></td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Seizures</td>
<td>0</td>
<td>4 (17.4%)</td>
<td>0.07</td>
<td>0</td>
<td>3 (17%)</td>
<td>0.1</td>
</tr>
<tr>
<td>Grade of HE (1:2:3:4)</td>
<td>3:10:5:1</td>
<td>0:7:11:5</td>
<td>0.04</td>
<td>3:10:5</td>
<td>0:7:11</td>
<td>0.017</td>
</tr>
<tr>
<td>Delivery of fetus</td>
<td>13 (68.4%)</td>
<td>9 (39.3%)</td>
<td>0.056</td>
<td>13 (72.2%)</td>
<td>7 (38.9%)</td>
<td>0.046</td>
</tr>
<tr>
<td>Hb (g/dL)</td>
<td>7.6 (6-11)</td>
<td>7 (5-11)</td>
<td>0.02</td>
<td>7.8 (6-11)</td>
<td>7 (5-11)</td>
<td>0.06</td>
</tr>
<tr>
<td>TLC (X10/L)</td>
<td>13.2 (8.0-24.0)</td>
<td>13.0 (6.5-32)</td>
<td>0.44</td>
<td>13.1 (8.0-24.0)</td>
<td>12.9 (6.50-32.0)</td>
<td>0.4</td>
</tr>
<tr>
<td>Platelets (X10/L)</td>
<td>118 (26-300)</td>
<td>210 (65-320)</td>
<td>0.09</td>
<td>119 (26-300)</td>
<td>161 (65-320)</td>
<td>0.3</td>
</tr>
<tr>
<td>Serum bilirubin (mg/dL)</td>
<td>11.5 (6.7-18.4)</td>
<td>12 (6-2.26)</td>
<td>0.4</td>
<td>11.2 (6.2-18.4)</td>
<td>12 (6.7-26)</td>
<td>0.4</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>602 (120-4180)</td>
<td>765 (110-3200)</td>
<td>0.5</td>
<td>671 (120-4180)</td>
<td>812 (110-2135)</td>
<td>0.8</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>420 (142-1211)</td>
<td>882 (124-2970)</td>
<td>0.03</td>
<td>467 (142-1211)</td>
<td>901 (124-2442)</td>
<td>0.07</td>
</tr>
<tr>
<td>Alkaline phosphatase (IU/L)</td>
<td>256 (145-515)</td>
<td>257 (120-771)</td>
<td>0.9</td>
<td>240 (145-515)</td>
<td>263 (160-342)</td>
<td>0.8</td>
</tr>
<tr>
<td>Total protein (g/dL)</td>
<td>6.0 (5.1-7.3)</td>
<td>5.9 (5.4-6.8)</td>
<td>0.2</td>
<td>6.05 (5.1-7.3)</td>
<td>5.9 (5.4-6.8)</td>
<td>0.2</td>
</tr>
<tr>
<td>Serum albumin (g/dL)</td>
<td>2.9 (2.2-3.4)</td>
<td>2.9 (2.1-3.2)</td>
<td>0.5</td>
<td>2.95 (2.2-3.4)</td>
<td>2.9 (2.1-3.2)</td>
<td>0.2</td>
</tr>
<tr>
<td>Prothrombin time (seconds above control)</td>
<td>8 (4-36)</td>
<td>24 (8-36)</td>
<td>0.09</td>
<td>7 (4-36)</td>
<td>25 (8-36)</td>
<td>0.8</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>1.2 (0.8-1.9)</td>
<td>1.2 (0.5-2.1)</td>
<td>0.8</td>
<td>1.2 (0.8-1.8)</td>
<td>1.2 (0.6-2.1)</td>
<td>0.8</td>
</tr>
</tbody>
</table>

Values as median (range) unless otherwise indicated.

Table: Comparison of clinical and laboratory parameters in surviving and dead pregnant women with acute liver failure due to acute hepatitis E
Maternal mortality was similar in women who had delivered and in those who had not. However, when women who presented with grade IV hepatic encephalopathy were excluded, maternal mortality was less in those who delivered (7/20, 35%) as against those who continued pregnancy (11/16, 68.75%; p=0.046). Recovery from hepatic encephalopathy took 2-8 days (median 3) in those who had delivered, and 2-5 days (median 3) in those who had not (p=0.70). On multivariate analysis, grade of encephalopathy at admission was the only parameter that was associated with mortality (p=0.017).

The pregnant women who died due to ALF had worse prothrombin time, higher still-birth rate and worse hepatic encephalopathy at time of admission.

**Discussion**

We analyzed the outcome of acute liver failure due to acute viral hepatitis E in pregnant women. Of 48 pregnant women with ALF, 42 had acute hepatitis E. This distribution is different from that in other studies, probably due to referral bias as our hospital caters to the socioeconomically poor section and is also a major referral center from a hospital that caters to infectious diseases.

Recent studies have shown that hepatitis E affects pregnant women more frequently and is associated with high mortality. The frequency of infection and mortality rate increase with the gestational age.

As noticed in other studies, patients were young and were in either second or third trimester of pregnancy, with median gestational age of 28 weeks. ALF was associated with maternal mortality of 54% and fetal mortality of 69%. Similar high mortality was evident in other studies.

Clinical coagulopathy was observed in 23 patients, 4 of whom had DIC. All these 4 patients had intrauterine fetal loss and were observed for spontaneous onset of labor for 8-12 hours. In otherwise normal pregnant women with IUFD, fibrinolysis develops only over several weeks. In four of our patients with ALF and IUFD, DIC was noted as early as 12 hours after fetal death. Though ALF is known to induce fibrinolysis, it is not clear whether IUFD hastened development of DIC in our cases. Singh et al from Agra studied coagulation factors in 30 patients with acute viral hepatitis with or without hepatic encephalopathy. DIC with significant clinical bleeding was seen in 10 of 15 patients with fulminant hepatic failure. The pathogenesis of early DIC in hepatitis E in pregnancy is not known; Khuroo et al suggested Schwartzman-like reaction to viral proteins.

Mortality in our series was associated with higher grade of encephalopathy at admission. In ALF, it is recommended that patients with altered mentation be admitted to an ICU, since the condition may progress rapidly, with changes in consciousness occurring hour-by-hour. In case liver transplantation is available, we suggest that plans for transfer to a transplant center should begin in patients with grade I or II encephalopathy.

There was no difference in maternal mortality in pregnant women who delivered and in those who continued the pregnancy. But when patients with grade 4 encephalopathy at admission were excluded from the analysis, delivery of the fetus appeared to improve survival.

HEV RNA has been demonstrated in fetal umbilical blood sample. Babies born to mothers have also been shown to develop hepatitis. The increased fetal loss and improved survival in patients who delivered support the possibility that intrauterine transmission of hepatitis E and intrauterine fetal hepatitis contribute to worsening of maternal condition.

Patients who underwent spontaneous or induced labor were similar in their clinical and biochemical profile to women who continued pregnancy. Therefore it is likely that only fetal status, and not clinical profile, influenced the decision to induce.

Our study has certain drawbacks. It is a retrospective study. We did not induce labor if the fetus was viable; it is possible that spontaneous deliveries resulted from progressive worsening of liver condition. However, there was no difference in clinical and biochemical parameters amongst those who delivered and those who continued the pregnancy. Third, we did not examine fetuses for presence of HEV. The number of patients in each subgroup was small, with a possibility of type I error.

In conclusion, acute liver failure due to acute hepatitis E in pregnant women has high mortality, especially in those who present with higher grades of encephalopathy. Whether termination of pregnancy is to be considered in this situation has not been resolved.
References


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