Original Article

# Acute Liver Failure in Pregnancy: Causative and Prognostic Factors

Shweta Sahai, Ravi Kiran[1]

Department of Medicine, GR Medical College, Gwalior, Madhya Pradesh, [1]Department of Gastroenterology, MS Ramaiah Medical College and Hospitals, Bangalore, Karnataka, India

**Address for correspondence:**
Dr. Shweta Sahai, Department of Medicine, GR Medical College, Gwalior, Madhya Pradesh, India.
E-mail: sahay.shweta2@gmail.com

## ABSTRACT

**Background/Aims:** Acute liver failure (ALF) in pregnancy is often associated with a poor prognosis. In this single-center observational study we aim to study the incidence, causes, and factors affecting mortality in pregnant women with ALF. **Patients and Methods:** Sixty-eight pregnant women reporting with clinical features of liver dysfunction were enrolled as "cases." Their clinical course was followed and laboratory studies were performed. The presence of ALF was defined as the appearance of encephalopathy. The results were compared with a "control" group of 16 nonpregnant women presenting with similar complaints. The cases were further subdivided into two groups of "survivors" and "nonsurvivors" and were compared to find out the factors that contribute to mortality. **Results:** ALF was seen in significantly more number of pregnant women than the controls ($P = 0.0019$). The mortality rate was also significantly higher ($P = 0.0287$). Hepatitis E virus (HEV) caused jaundice in a higher number of pregnant women ($P < 0.001$). It also caused ALF in majority (70.3%) of pregnant women, but HEV infection was comparable between the survivors and nonsurvivors ($P = 0.0668$), hence could not be correlated with mortality. **Conclusions:** Pregnant women appear to be more susceptible for HEV infection and development of ALF. The mortality of jaundiced pregnant women increased significantly with appearance of ALF, higher bilirubin, lower platelet count, higher international normalized ratio, and spontaneous delivery.

**Key Words:** Acute liver failure, HEV infection, pregnancy

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Acute liver failure (ALF) is defined as the rapid development of hepatocellular dysfunction, specifically coagulopathy and encephalopathy in a patient without known hepatic disease.[1] Encephalopathy is the defining condition for ALF. ALF usually results because of an acute insult, most frequently a virus, or a drug such as paracetamol. Worldwide and especially in developing world, the most common cause of ALF is viral hepatitis.[2] In India, 95% of ALF is virus-related, with 40% due to hepatitis E virus (HEV) and nearly 30% due to hepatitis B virus.[3-5]

The relationship between pregnancy and hepatic function is complex. Pregnancy induces certain physiological changes in the liver, which, if exaggerated, may result in pregnancy-associated acute liver disease (PAALD). PAALD may occur as a result of pre-eclampsia, acute fatty liver of pregnancy, or due to the HELLP (Hemolysis, Elevated Liver Enzymes, Low Platelet Count) syndrome. PAALD has been proved to be associated with a worse prognosis and may require termination of pregnancy.[6]

HEV infection has been found to be one of the most common causes for ALF among pregnant women in North India,[1] and has been associated with variable outcomes.[2-4] Although few authors found a poor prognosis when HEV infection occurs in pregnancy, many say that pregnancy *per se* is not to be regarded as a poor prognostic factor for a patient with ALF.[5,6] The difference in outcome among different studies has been attributed to the change in genotype of the virus or the nutritional status of these women. The incidence, causes, clinical course, and outcome of ALF in pregnant women has never been studied in Central India. With this back ground, we carried out this study with these aims:

- To find out the incidence of ALF among jaundiced pregnant women

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- To find out the most common causes of ALF in pregnant women
- To find out the prognostic factors predicting poor outcome in jaundiced pregnant women.

## PATIENTS AND METHODS

Sixty-eight pregnant women with symptoms and signs of hepatic dysfunction, presenting to our hospital during the period May 2007 to July 2009, were enrolled in the study. The course of their pregnancy was closely followed and the end point of observation was the discharge or death of the woman. ALF was defined by the presence of encephalopathy. The biochemical investigations included liver and kidney function tests. Hematology investigations included complete blood count and prothrombin time. The viral studies included anti–hepatitis A IgM, hepatitis B surface Ag, anti–hepatitis C IgM and IgG, and anti–hepatitis E IgM. Testing for hepatitis A and B was done using the equipment "Biomereus" VIDAS and testing for hepatitis C and E was done using Open ELISA method on ELx MS 800. Ultrasound of abdomen was done for all cases, using the apparatus TWT Vision 400 SSA 3.25.

These results were compared with a cohort of age-matched 16 nonpregnant women. The liver function tests and virologic profile of the surviving neonates was recorded for vertical transmission. A comparison was also done between the "survivor" and "nonsurvivor" cases regarding the type of viral hepatitis, biochemical, and hematological picture. This was done to find out the factors responsible for maternal mortality.

Unpaired Student's *t* test, Z test calculator, and Chi-square test were used by the online SPSS calculator to compare the results. A difference of $<0.05$ was considered statistically significant.

## RESULTS

The women in the cases and controls were well matched in age and were between 21 and 25 years of age. All the women belonged to the poor socio-economic strata of the society. The most common presenting symptoms in cases and controls were jaundice, nausea, vomiting, and abdominal pain. Nausea was seen in a significantly higher number of cases in comparison to the controls ($P = 0.0354$). The presentation of jaundice and abdominal pain was comparable between the two groups [Table 1].

ALF was seen in 27 cases, whereas no woman in the control group presented with ALF. This difference was found to be statistically highly significant ($P = 0.0019$).

**Table 1: Comparison of clinical and laboratory parameters in two groups**

| | Cases (*n*=68 ) | Controls (*n*=16) | *P* |
|---|---|---|---|
| Jaundice | 58 | 10 | 0.07 |
| Nausea/vomiting | 50 | 7 | 0.0354 |
| Pain abdomen | 43 | 9 | 0.7755 |
| Encephalopathy (acute liver failure) | 27 | 0 | 0.0019 |
| Hemoglobin (gm/dL) | 7.87±2.36 | 8.13±2.28 | 0.698 |
| Total leukocyte count (cells/mm$^3$) | 38236.36±3450 | 12478.69±2257 | 0.028 |
| Serum bilirubin (mg/dL) | 8.52±6.11 | 6.38±4.39 | 0.191 |
| AST (IU/mL) | 335.95±566.87 | 406.13±449.09 | 0.646 |
| ALT (IU/mL) | 453.29±591.09 | 575.85±594.17 | 0.459 |
| SAP (IU/mL) | 324.72±285.59 | 290.02±165.49 | 0.63 |
| Protein (g/dL) | 9.72±11.08 | 7.19±1.00 | 0.503 |
| AG ratio | 1.13±1.73 | 0.88±0.31 | 0.663 |
| Prothrombin time (s) | 26.19±23.02 | 27.69±26.20 | 0.832 |
| International normalized ratio | 3.03±4.95 | 2.31±2.30 | 0.614 |
| Urea (mg/dL) | 55.81±43.60 | 31.69±21.60 | 0.24 |
| Serum creatinine (mg/dL) | 1.45±2.16 | 1.24±1.45 | 0.838 |
| Mortality | 13 (19.11%) | 0 (0.00%) | 0.0287 |

AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, SAP: Serum alkaline phosphatase, AG ratio: Albumin to Globulin ratio

Most of the cases and controls were anemic but the average hemoglobin concentration was not significantly different between the two groups.

The mean total leukocyte count was much higher in the cases compared with that of the controls, and this difference was statistically significant ($P = 0.028$).

The levels of serum bilirubin, liver enzymes, serum proteins, prothrombin time, blood urea, and creatinine levels were comparable between the cases and controls.

Hepatitis E infection was found in 53 (77.9%) pregnant women and 4 (25%) controls [Table 2]. This difference was highly significant ($P < 0.001$). This could indicate a predilection of the hepatitis E virus for pregnant women.

No virus could be detected in 9 cases (13.2%) and 8 controls (50%). This difference was also significant ($P = 0.003$), suggesting a higher incidence of hitherto unknown/undetected hepatotropic virus or drug-induced hepatitis in nonpregnant women. Absence of viral infection in 9 pregnant women could be a result of PAALD, or an undetected virus such as Herpes Simplex virus (HSV) or Cytomegalovirus (CMV).

Maternal mortality rate was very high (19.1%) in the cases [Table 3]. Fetal wastage was also found to be very

high (42.6%). Vertical transmission of hepatitis E virus was noted in 3 out of the 10 neonates studied.

Among the cases, there were 13 deaths, whereas there were no deaths in the controls group. Mortality was significantly higher in the cases ($P = 0.0287$) compared with controls.

The cases were further divided into two groups of "survivors" and "nonsurvivors." The clinical and laboratory findings in both groups were compared to find out the factors responsible for maternal mortality [Table 4]. Among the biochemical parameters, the average serum bilirubin was significantly higher among the nonsurvivors (16.08 ± 6.12) as compared with the survivors (11.57 ± 5.11); ($P = 0.0076$). The average international normalized ratio (INR) value was significantly higher in the nonsurvivor group (2.40 ± 2.00) as against the survivor group (1.12 ± 1.0); $P = 0.0023$.

The average platelet count was significantly lower in the nonsurvivors ($P = 0.0001$). However, only 3 patients could satisfy the criteria of partial HELLP syndrome, of whom 2 survived and 1 died.

None of the patients presented in the first trimester. Among the survivors, 41 women presented in the second trimester and 14 presented in the third trimester of pregnancy. Among the nonsurvivors, 7 presented in the second trimester and 6 in the third trimester. The trimester of pregnancy was not a significant factor for prediction of mortality.

**Table 2: Comparison of type of hepatitis in controls and cases**

| Type of viral hepatitis | Cases (*n*=68) (%) | Controls (*n*=16) (%) | *P* |
|---|---|---|---|
| HAV | 0 | 1 (6.3) | 0.19 |
| HBV | 5 (7.4) | 3 (18.8) | 0.173 |
| HCV | 1 (1.5) | 1 (6.3) | 0.347 |
| HEV | 53 (77.9) | 4 (25.0) | <0.001** |
| No virus detected | 09 (13.23) | 08 (50) | 0.003* |
| Co-infection of two or more viruses | 0 | 0 | 0 |

HAV: Hepatitis A virus, HBV: Hepatitis B virus, HCV: Hepatitis C virus, HEV: Hepatitis E virus. *Statistically signifi cant. **Statistically very signifi cant

**Table 3: Maternal and fetal outcome**

| | Number of patients (*n*=68) | Percentage |
|---|---|---|
| Maternal outcome | | |
| Survived | 55 | 80.89 |
| Died | 13 | 19.11 |
| Fetal outcome | | |
| Survived | 39 | 57.39 |
| Fetal Wastage | 29 | 42.61 |

Twenty-seven women presented with features of encephalopathy (ALF), of whom 13 died. The presence of encephalopathy at the time of admission correlated with maternal mortality ($P = 0.0001$). All women in the nonsurvivor group had presented with varying grades of hepatic encephalopathy.

Spontaneous delivery occurred in 20 survivors (36.36%) and 8 nonsurvivors (61.53%). Hence, spontaneous delivery was associated with a worse outcome ($P = 0.048$).

Ultrasound (US) of the abdomen was done in all the cases and controls. The chief findings were hepatomegaly, gall bladder sludge, gall bladder (GB) thickening, GB collapse, and ascites. A comparison between the US findings of cases against controls and survivors against nonsurvivors showed that there was no significant difference in the US findings.

HEV was the most common cause of hepatitis among both survivors and nonsurvivors, but there was no statistically

**Table 4: Comparison between survivors and nonsurvivors**

| Parameter | Survivors *N*=55 | Nonsurvivors *N*=13 | *P* |
|---|---|---|---|
| Hb (g%) | 7.60±2.36 | 7.27±2.28 | 0.6497 |
| Total leukocyte count (cells/mm$^3$) | 11,624±4,015 | 15,576±5,642 | 0.6521 |
| Platelet count (cells/mm$^3$) | 1,60,430±49,640 | 1,03,430±39,680 | 0.0001** |
| Bilirubin (mg%) | 11.57±5.11 | 16.08±6.12 | 0.0076* |
| Aspartate transaminase (IU/mL) | 305.46±506.87 | 316.60±409.09 | 0.9149 |
| Alanine transaminase (IU/mL) | 457.48±581.09 | 310.69±504.17 | 0.3824 |
| SAP (IU/mL) | 214±167.49 | 329±285.69 | 0.0594 |
| International normalized ratio | 1.12±1.0 | 2.40±2.00 | 0.0023* |
| Urea (mg/dL) | 34±29.04 | 32±28.10 | 0.8395 |
| Creatinine (mg/dL) | 0.82±0.78 | 0.94±0.87 | 0.6271 |
| Type of virus-hepatitis E virus | 40 (72.70%) | 12 (92.30%) | 0.0668 |
| Type of virus-others | 15 (27.27%) | 1 (07.69%) | 0.13362 |
| Time lag to hospitalization (days) | 05±02 | 06±03 | 0.1481 |
| Pregnancy trimester | | | |
| Second | 41 (74.54%) | 07 (53.84%) | 0.0707 |
| Third | 14 (25.45%) | 06 (46.15%) | |
| Features of encephalopathy on admission | 14 (25.45%) | 13 (100%) | 0.0001** |
| Spontaneous delivery/ abortion | 20 (36.36%) | 08 (61.53%) | 0.0484* |

SAP – Serum alkaline phosphatase, *Statistically significant. **Statistically highly significant

significant difference in the rate of HEV infection among the survivors and nonsurvivors.

## DISCUSSION

The occurrence of ALF in pregnancy has been studied by various authors across the world. To our knowledge, this study is the first of its kind from Central India.

In an epidemic in Kashmir, India, 22.2% of pregnant women presented with ALF compared with only 2.8% of nonpregnant women.[7] Beniwal *et al*. have reported an incidence of 28.9% of ALF during pregnancy.[8] ALF occurred in 27 out of 68 pregnant women in our study (39.70%). The incidence of ALF was found to be significantly higher among pregnant women compared with nonpregnant women ($P = 0.0019$).

HEV was found to be the causative factor for hepatic dysfunction in 77.9% of pregnant women versus 25% of nonpregnant women ($P < 0.001$). The highest incidence of hepatitis E in pregnancy was reported by Khuroo and Kamili in 2003 from North India (86%),[9] and the least was reported by Singh *et al*. (37%), also from North India in 2003.[10] Thus, predilection of the HEV for pregnant women is also emphasized in our study.

No virus was detected in 50% of nonpregnant women, which was significantly more than in pregnant women (13.23%), $P = 0.003$. This may suggest the possibility of cryptogenic hepatitis or a hitherto unknown/undetected organism affecting nonpregnant women. The pregnant women in whom no virus was detected could be suffering from PAALD (acute fatty liver, HELLP) or an infection from an unknown/undetected hepatotropic virus. It is very difficult to differentiate between viral hepatitis and acute fatty liver of pregnancy on initial presentation. This was the observation of Hamid *et al*.,[11] who observed that out of 12 pregnant women with ALF, 10 had hepatitis E, 1 patient had Hepatitis A, whereas only 1 had acute fatty liver of pregnancy. The prognosis was worse with acute fatty liver of pregnancy.

In our study, there was a high rate of maternal mortality (19.1%). The high mortality rate was comparable to most of the other studies conducted in North India, ranging from 12% to 64%. But, it was in variance from other studies done in other parts of the world such as the one from Egypt,[12] which revealed a very high rate of hepatitis E infection (84.3%), but there was no case of maternal mortality. Similarly, a study carried out in South India[13] showed a very high infection rate with hepatitis E, but the mortality rate was very low (3.4%). The high seroprevalence of hepatitis E IgG antibody was probably protective in Egypt and South India. The seroprevalence of hepatitis E IgG antibody was found to be low (33.67%) in New Delhi by Begum *et al*.,[14] probably leading to higher rates of clinical disease and maternal mortality.

Mortality among pregnant women of 19.1% was significantly higher than the nonpregnant controls ($P = 0.0287$). This finding is different from that of Bhatia *et al*.[15] In a large study lasting 20 years, Bhatia *et al*. found that the mortality of pregnant women with hepatitis E is comparable to that of nonpregnant women and men.

Banait *et al*.[16] found a much higher maternal mortality rate of 54.76%. The reason for this was that they included only women with ALF in their study. When we analyzed the causes of mortality of pregnant women, it was found that hepatitis E infection rate was comparable between the women who survived (72.70%) and the women who died (92.30%). This difference was statistically not significant $P = 0.0668$. Hence, hepatitis E infection *per se* could not be blamed for mortality. This finding correlated well with that of Bhatia *et al*.,[15] who found that the outcome of HEV-associated ALF was comparable in pregnant women, nonpregnant women, and men. In fact, Khuroo and Kamili[9] have found a worse outcome when ALF in pregnancy occurred as a result of non-HEV etiology. Hamid *et al*.[11] have also found that ALF in pregnancy has a better outcome whenever it is a result of HEV infection. They found a mortality rate of 16% with HEV-associated ALF and 68% with acute fatty liver of pregnancy. This finding was at variance with the study conducted by Patra *et al*.[17] who found that ALF was more common and maternal mortality was higher in HEV-infected pregnant women than those women in whom jaundice was caused by other factors.

The presence of encephalopathy on admission was closely related to mortality, with about 25.45% of the survivors and 100% of the nonsurvivors presenting with encephalopathy ($P = 0.0001$). This was similar to the findings of Banait *et al*.,[16] who also found a higher mortality with higher grade of encephalopathy.

The average serum bilirubin was significantly higher among the nonsurvivors as compared with the survivors ($P = 0.0076$). This correlated well with the Sequential Organ Failure Assessment (SOFA) score,[18] which takes into consideration a single parameter to define the prognosis of a critically ill patient. This finding is similar to that of Bhatia *et al*.,[15] who found a higher bilirubin to be predictive of mortality.

The average INR value was also found to be significantly higher in the nonsurvivor group versus the survivors, indicating a higher occurrence of coagulopathy among the nonsurvivors. The average platelet count was significantly lower in the nonsurvivors as compared with the survivors ($P = 0.0001$). This also correlated well with theSOFA score.[18] Low platelet

counts could be a feature of the HELLP syndrome. However, only 3 cases fulfilled the criteria of partial HELLP syndrome.

Spontaneous delivery/abortion occurred in 20 survivors (36.36%) and 8 nonsurvivors (61.53%). Hence, spontaneous delivery was associated with a worse outcome ($P = 0.048$). In our study, elective induction of labor was not attempted in any case. Worse outcome after delivery in our study is contrary to the findings of Banait *et al*.,[16] who found that after excluding the women in encephalopathy, spontaneous/induced delivery improved the survival of women. Beniwal *et al*.[8] found that a majority of the pregnant women in ALF who died were undelivered (87.5%). In a study conducted by Devarbhavi *et al*.[6] at St. John's Hospital, Bangalore, suggested means to clearly differentiate between PAALD and viral hepatitis in pregnancy. They recommended that PAALD should prompt early delivery.[6]

Trimester of pregnancy was not a significant factor for mortality in our study. This correlates well with the finding of Khuroo and Kamili,[9] who found that duration of gestation did not affect the maternal outcome.

Vertical transmission was seen in 3 out of the 10 newborns studied (transmission rate of 30%). This correlated very closely with the finding of Singh *et al*.[10] and Beniwal *et al*.[8] who found a vertical transmission rate of 33.33%.

## CONCLUSION

Our study reemphasizes the fact of the predilection of HEV for pregnant women without necessarily increasing the mortality. However, the predictors of mortality in these patients included presence of encephalopathy, coagulopathy, and low platelet count at admission.

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