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RESEARCH ARTICLE

Predictors of poor maternal outcome in pregnant women with acute viral hepatitis

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ABSTRACT

Background: Acute viral hepatitis is the most common cause of jaundice in pregnancy. Various criteria have been devised to determine early indices of poor prognosis in patients with fulminant hepatic failure (FHF) but no such criteria exist for pregnancy related liver failure. **Aim:** To determine the predictors of poor maternal outcome in pregnant women with acute viral hepatitis. **Methodology:** This prospective observational study was conducted in Lady Hardinge Medical College, New Delhi from January 2009 to April 2010. In present study, 50 pregnant women with acute viral hepatitis with or without FHF were included and closely followed with daily clinical assessment and subjected to serial investigations. **Results:** In our study, amongst the 50 pregnant women, 40 were survivors and 10 were non survivors. 94% of the patients were infected with hepatitis E. All patients (100%) had jaundice. There was a statistically significant difference between the mean TNF α in patients with acute viral hepatitis without fulminant hepatic failure (FHF) (59.80 ± 65.95 pg / ml) and in patients with acute viral hepatitis with FHF (322 ± 231.2 pg / ml) which was raised. 80% of the non survivors had coagulopathy (d-dimers >16 µg/ml) as compared to 10% of the survivors. **Conclusions:** In this study we have ascertained few poor prognostic factors for maternal outcome in acute viral hepatitis in pregnancy. Further studies need to be done among pregnant women with acute viral hepatitis with larger study population in order to develop criteria for selection and timely referral of pregnant women with FHF for orthotopic liver transplantation to improve maternal survival.

Keywords: Encephalopathy, jaundice, laboratory parameters, liver failure, pregnancy.

There are many types of viral hepatitis, both acute and chronic, which may affect an individual, but pregnancy can exacerbate this condition[1]. Pregnant women with acute viral hepatitis have a poorer outcome than pregnant women with chronic viral hepatitis.[2]

Various criteria have been devised to determine the early indices of poor prognosis in patients with fulminant hepatic failure but no such criteria exists for pregnancy related liver failure.[3] ,[4] Incidence of hepatitis in developed countries is around 0.1% whereas in developing countries it is 3-20% or even higher.[5] Hepatitis E (HEV) is the commonest cause of hepatitis in pregnancy in developing countries and the reported prevalence of HEV infection in pregnant women with acute viral hepatitis varies from 49.6% to as high as 85.5%.[6-9] Increased feto-maternal mortality has been reported from the developing countries.[10] The reasons for increased maternal and perinatal morbidity and mortality in pregnant women with hepatitis are not clear. It is possible that in utero fetal transmission of HEV results in fetal hepatitis and similar to patients with acute fatty liver of pregnancy; the added load of toxins from the fetal circulation may result in increased severity of the disease and hepatic encephalopathy in the mother and intrauterine fetal death.[11-14]

Various criteria have been devised to determine the early indices of poor prognosis in patients with fulminant hepatic failure but no such criteria exists for pregnancy related liver failure.[3] Pregnancy is associated with profound hemostatic

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changes in the form of increased levels of fibrinogen, clotting factors and decreased fibrinolytic activity which predisposes pregnant women to disseminated intravascular coagulation (DIC).[15-17] Therefore, we closely followed the clinical presentation and progress of acute viral hepatitis in pregnant women and studied its relationship with laboratory parameters and maternal outcome and we describe here the factors predicting the prognosis in these patients.

Materials and methods

This prospective observational study was conducted in the Department of Obstetrics and Gynecologyof Lady Hardinge Medical College and Shrimati Sucheta Kriplani Hospital, New Delhi from January 2010 to April 2011. All the patients admitted to the hepatitis ward of the Department of Obstetrics and Gynecology were screened by detailed history and clinical examination.

Detailed history with special emphasis on history of yellow discoloration of sclera and or urine, fever, malaise, loss of appetite, vomiting, irritability, alteration in sleep pattern, seizures, bleeding from any site, drug intake, toxin ingestion, promiscuous sexual behavior, recent contact with a patient with jaundice, tattooing, piercing, transfusion of blood or blood component or alcohol abuse was taken. This was followed by detailed clinical examination. Level of consciousness and grade of encephalopathy (if present) was assessed.

All the patients were subjected to investigations like complete blood count, liver function tests, kidney function tests, random blood sugar (RBS), detailed coagulation profile and viral markers for hepatitis. For each investigation, the worst value over the entire hospital stay was used for analysis. Tumor necrosis factor α (TNFα) was done for all the patients on the day of admission.

A total of 50 pregnant women with acute viral hepatitis, with or without fulminant hepatic failure, were included. These patients were managed as per standard hospital protocol. Their data was collected according to a proforma.

Statistical analysis: The t test and the Mann–Whitney U test were used to compare normally distributed data and non-normally distributed data, respectively in the study groups. Chi-square test was used to compare discrete values between groups. A p value less than 0.05 was considered significant. Statistical analysis was done by using SPSS, version 13.0 (SPSS, Chicago, Illinois).

Results

A total of 50 pregnant women suffering from acute viral hepatitis were included in the study. Of these 40 women (80%) survived (group A) and 10 women (20%) died (group B) during the study.

Table 1: Distribution of patients according to demographic characters

Demographic characters		Survivors (n=40)	Non survivors (n=10)	P value
Age (maximum – minimum)		24.3 ± 3.7 yrs (19 - 35)	24.2 ± 5.5 yrs (19 - 35)	>0.05
Gravidity		1.9 ± 0.8 (1 - 3)	2 ± 1.3 (1 - 5)	>0.05
Low socioeconomic status		37 (92.5%)	9 (90%)	>0.05
Period of gestation	<28 weeks	12 (30%)	2 (20%)	>0.05
	>28 weeks	28 (70%)	8 (80%)	>0.05

Various parameters like demographic profile, symptomatology and laboratory investigations were compared in two groups: group A (survivors) and group B (non-survivors). Table 1 shows the distribution of patients according to demographic profile. It was observed that there was no statistical difference in two groups as regards age, gravidity, socioeconomic status and period of gestation.

Table 2: Distribution of patients according to signs and symptoms

Signs & symptoms	Survivors		Non-Survivors		P
	N =40	%	N=10	%	Value
Yellow discolouration of sclera/urine	40	100%	10	100%	-
Vomiting	12	30%	4	40%	0.54
Malaise	22	55%	10	100%	0.006
Loss of appetite	21	52.5%	9	90%	0.03
Abnormal bleeding from any site	1	2.5%	5	50%	<0.001
Irritability	3	7.5%	10	100%	<0.001
Sleep alteration	4	10%	10	100%	<0.001
Altered sensorium	4	10%	10	100%	<0.001
Seizures	0	0%	2	20%	0.03
Fever	7	17.5%	8	80%	0.0003
Pedal edema	7	17.5%	8	80%	0.0003
Ascites	3	7.5%	2	20%	0.25
Hepatomegaly	5	12.5%	2	20%	0.42

In our study, majority of patients (94%) had acute viral hepatitis due to hepatitis E virus both in survivors [(38/40) 95%] and non-survivor groups [(9/10) 90%]. Very few patients were found to be infected with hepatitis B (2 / 50) and hepatitis C (1 / 50). One patient in the non-survivor group had acute viral hepatitis due to hepatitis B.

The distribution of patients according to various symptoms and signs is as shown in table 2. The frequency of occurrence of symptoms like loss of appetite, malaise, irritability, sleep alteration, altered sensorium, seizures and abnormal bleeding from any site was statistically significantly higher in non survivors compared to survivors, whereas symptoms like vomiting, yellow discoloration of sclera and urine were comparable among survivors and non survivors.

As regards laboratory parameters mean total leucocyte count, bilirubin, prothrombin time (PT), activated partial thromboplastin time (APTT) and international normalized ratio (INR) were all found to be statistically significantly higher in the non-survivor group compared to survivor group.

It was observed that mean TNF α in patients with acute viral hepatitis without FHF was 59.80 ± 65.95 pg / ml (0 – 320 pg / ml) whereas in patients with acute viral hepatitis with FHF it was 322 ± 231.2 pg / ml (56 – 918 pg / ml). The difference was found to be statistically highly significant ($p<0.001$). Majority of non survivors (80%) had d-dimer >16 µg/ml as compared to only 10% in the survivors and the difference was statistically highly significant ($p<0.001$). All the non survivors had coagulopathy as compared to only 60% amongst survivors. The difference was statistically significant.

Amongst survivors 82.5% patients delivered as compared to 80% patients amongst non survivors and the difference was statistically insignificant indicating that delivery did not influence the maternal outcome. All the patients delivered vaginally except two patients in the survivor group who had lower segment cesarean section (LSCS).

Complications like coagulopathy, upper gastrointestinal bleed, seizures, hypoglycemia, and intrauterine death were more common in non survivors and the difference was statistically significant.

Table 3: Distribution of patients according to laboratory parameters

Laboratory parameters	Total survivors (N=40)	Non survivors (N=10)	P value
Hemoglobin (11-14 gm%)	10.1 ± 2.4 (2.4 – 13.8)	10.8 ± 2.4 (8.4 – 16)	0.47
TLC (5,000-12,000/mm^3)	12,328 ± 728.24 (4,500 – 25,600)	23,025 ± 7,589 (14,400 – 35,780)	< 0.001
Platelet count (1,50,000-4,00,000/mm^3)	1,98,800 ± 82,827.66 (4,000 – 432,000)	2,41,600 ± 13,9679.16 (19,000 – 442,000)	0.214
S. Bilirubin (total) (0.3-1 mg%)	10.9 ± 6.4 (2.6 - 24.8)	18.8 ± 8.4 (8.0 - 33.0)	0.002
S. Bilirubin (direct) (0.0-0.3 mg%)	7.8 ± 4.9 (1.3 – 20.7)	13.0 ± 6.5 (5.5 – 25)	0.007
ALT (0-35 u/ml)	727.5 ± 735 (118 – 2195)	320 ± 180 (106 -725)	0.091
AST (0-35 u/ml)	838 ± 1089 (112 – 4430)	260 ± 146.4 (67 – 504)	0.103
ALP (60-200 u/ml)	541.3 ± 57.3 (135 – 3648)	507.7 ± 310(85 -1248)	0.861
Total protein (5.5-8.0 mg%)	5.9 ± 0.6 (5 – 7.8)	5.1 ± 0.5 (4 – 6)	<0.001
Total albumin (2.5-4.5 mg%)	2.7 ± 0.5 (1.9 - 4.5)	2.1 ± 0.23 (1.6 - 2.4)	0.002
Blood urea (15-50 mg%)	23.2 ± 12.6 (14 – 84)	54.9 ± 70.7 (11 – 238)	0.224
Serum creatinine (0.8-1.2 mg%)	0.8 ± 0.3 (0.4 – 2.5)	1.5 ± 2 (0.4 – 7.1)	0.511
APTT (32.27±2.43 secs)	44.9 ± 19.3 (29 – 120)	98.7 ± 25.9 (53.6-120)	<0.001
INR (1-1.3)	2.6 ± 2.6 (0.98 – 10.55)	8.5 ± 2.93 (1.55-10.55)	<0.001
Fibrinogen (3-6 g/l)	2.8± 1.2 (0.56 – 6.35)	1.05 ± 0.5(0.53 – 1.83)	<0.001

TLC - total leucocyte count, ALT - Alamine transaminase, AST - Aspartate transaminase, ALP - alkaline phosphatase, APTT - Activated plasma thromboplastin time, INR - International normalized ratio.

Discussion

Average age of the patients in our study was 24.2 years. In the study, majority (72%) of pregnant patients with acute viral hepatitis were in their third trimester. In our study, although the mortality rate of the patients in their third trimester (22.22%) was higher, compared to second trimester (15.38%), but the difference was statistically insignificant. This compares well with studies conducted by Khuroo [18] et al and Singh [19] et al where trimester of pregnancy was not found to affect the survival among FHF patients. However, Jaiswal [10] et al reported that mortality among pregnant women presenting with FHF progressively increased with the gestation period and was maximum during the third trimester.

Majority of acute viral hepatitis patients included in the study were due to hepatitis E virus (95% in survivors and 90% in non survivors). Our findings correlate well with various studies which have reported HEV as the most common cause of acute viral hepatitis in pregnancy and the prevalence of HEV ranging between 49.6 - 85.5% [7-11, 20, 21].

Other reason for high prevalence of HEV in our study can be that our hospital is a tertiary care referral center. As the course of hepatitis E is more severe in pregnancy as compared to other types of viral hepatitis; such patients are usually referred. Overall mortality rate of pregnant women with acute hepatitis E in our study was 19.2%. Our results were comparable to studies conducted by Kumar [21] et al, Hamid [22] et al and Tsega [23] et al who have reported mortality rates ranging between 15 - 26.9%.

In our study, fever was documented in 80% of non survivors as compared to 17.5% in survivors and the difference was statistically highly significant ($p \leq 0.001$). The mean leucocyte count was 12,328 ± 728.2 /mm^3 in survivors whereas 23,025 ± 7,589 /mm^3 in non survivors and the difference was found to be statistically highly significant. Acharya [24] et al reported presence of infection (diagnosed by presence of fever with neutrophilic leukocytosis and any other evidence of infection) to be a significant factor adversely influencing the survival in patients with FHF.

In our study, mean total bilirubin was significantly higher among non survivors (18.8 ± 8.4 mg%) as compared to

survivors (10.9 ± 6.4 mg%). Our findings were like Singh [19] et al who had reported bilirubin to be significantly raised in non survivors compared to survivors. Acharya [24] et al, Huo et al [25] reported total bilirubin levels to be an independent predictor of non-survival.

Mean prothrombin time (PT), activated partial thromboplastin time (APTT) and international normalized ratio (INR) were all found to be statistically significantly higher in the non-survivor group compared to survivor group. In various studies conducted by Acharya [24] et al, Ke et al [26] PT was reported to be an independent predictor of survival in patients with FHF. The mean fibrinogen among non survivors (1.05 ± 0.474 g/l) was significantly lower compared to survivors (2.81 ± 1.15 g/l). Although Adams [17] et al have reported lower mean fibrinogen in pregnant patients with hepatitis but it has not been studied as a prognostic marker. Significantly lower fibrinogen levels in non survivors as compared to survivors might be due to more severe synthetic dysfunction of liver and possibly degradation of fibrinogen to fibrinogen-degradation products consequent to consumptive coagulopathy in non-survivor group.

On analyzing d-dimer value amongst survivors it was observed that majority (13/16; 81.25%) of survivors without coagulopathy had d- dimer value < 2 µg/ml. Most of survivors with coagulopathy (17/24; 70.83%) had d-dimer ranging from > 2 µg/ml to <16 µg/ml whereas most of non survivors (8/10; 80%) had d-dimer levels >16 µg/ml. Deranged coagulation profile manifested by prolonged PT, APTT in our study, in the presence of significantly raised d-dimers, decreased fibrinogen and normal platelet count could be explained by a combination of low grade well compensated DIC and decreased synthesis of coagulation factors by the liver in patients of acute viral hepatitis. Release of thromboplastin from a severely damaged liver or presence of dead fetus might explain markedly raised d-dimer, severe derangement in coagulation profile and bleeding complications in fatal cases.[17, 27]

It was observed that mean TNF α in patients with acute viral hepatitis with FHF (322 ± 231.2 pg / ml) was significantly raised as compared to patients with acute viral hepatitis without FHF (59.80 ± 65.95 pg / ml). Similar results have been reported by Nagaki [28] et al and Seikayama [29] et al. Our study included patients with acute viral hepatitis with or without FHF. At admission 60% (6/10) of non survivors had encephalopathy as compared to 7.5% (3/40) of survivors. Eventually, during the study 100% (10/10) of non survivors and 10% (4/40) of survivors developed encephalopathy. This difference was statistically significant. Delivery of the fetus did not appear to affect the maternal outcome in our study. Similar observations had been made by Banait [14] et al.

Intrauterine death was documented in 20% (10/50) of all patients included in our study. It was observed in 12.5% of survivors as compared to 50% of non survivors and the difference was found to be statistically significant (p=0.018). Our findings are comparable to Yuel [8] et al who reported intrauterine death as a complication in 28% of pregnant patients with acute hepatitis E. HEV RNA has been demonstrated in umbilical blood sample and some of the babies born to mothers with HEV infection have been shown to develop hepatitis subsequently [11, 30]. Beniwal [21] et al suggested the possibility of intrauterine transmission of hepatitis E and intrauterine fetal hepatitis as a cause for increased fetal loss and worsening of maternal condition [14].

Conclusion

To conclude, the knowledge of poor prognostic factors as regards maternal outcome is important as orthotopic liver transplantation has become an established treatment option in patients with fulminant hepatic failure (FHF) and is increasingly becoming available in developing nations like India. Hence there is a need for a prognostic model in patients with FHF for facilitating timely referral of patients needing liver transplant. In our study, clinical features like presence of encephalopathy, abnormal bleeding from any site, fever and pedal edema were associated with poor maternal outcome. Laboratory parameters like high serum bilirubin, high total leucocyte count, prolonged prothrombin time, raised D-dimer, low serum protein, low serum albumin, low fibrinogen high TNF α and low blood sugar levels affected the maternal outcome adversely. Development of complications like upper gastrointestinal bleed, seizures and intrauterine death indicated poor prognosis. Further studies need to be conducted among pregnant women with acute viral hepatitis with larger study population to develop guidelines for selection and timely referral of pregnant patients with FHF for orthotopic liver transplantation to improve maternal survival.

Conflict of interest: None. **Disclaimer:** Nil.

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