ORIGINAL ARTICLE

Liver dysfunction in pregnancy: an important cause of maternal and perinatal morbidity and mortality in Pakistan

N Hossain MBBS FCPS*†, **T Shamsi** MBBS FRC(Path)‡, **E Kuczynski** PhD†, **C J Lockwood** MD† **and M J Paidas** MD†

*Dow University of Health Sciences, Karachi, Pakistan; †Yale Women and Children's Center for Blood Disorders, Department of Obstetrics, Gynecology and Reproductive Sciences, Yale University School of Medicine, New Haven, CT, USA; ‡National Institute of Blood Diseases, Karachi, Pakistan

Summary: The objective of this study was to evaluate the maternal and perinatal outcome of women with liver dysfunction during pregnancy. The study involved a prospective observational study design and was carried out at the Dow University of Health Sciences and Civil Hospital Karachi, Pakistan. A total of 800 women, who delivered during the study period from January 2006 to September 2006, constituted the study population. Pregnant women with liver dysfunction underwent evaluation for the aetiology of their liver dysfunction, including screening for hepatitis E. Thirty-five women were identified with liver dysfunction. Fourteen (40%) presented in the second trimester and 21 (60%) presented in the third trimester. Twenty-two of the 35 women (63%) had isolated acute hepatitis E; five (14%) had HELLP (haemolysis, elevated liver enzymes and low platelet count) syndrome; two (6%) had intrahepatic cholestasis of pregnancy (IHCP), two had acute fatty liver of pregnancy (AFLP) and two women had hepatitis A. A specific diagnosis was not reached in two women who died prior to delivery. In women with hepatitis E, the mean values of bilirubin and alanine transaminase were 12 mg/dL and 675 U/L, respectively. Abnormal coagulation parameters were present in 20 (57%) of the women and in 18 of 22 (82%) with hepatitis E. Fulminant hepatic failure (FHF) was seen in four patients. Seven women (20%) underwent caesarean section, 26 (74%) delivered vaginally and two women died undelivered. There were six maternal deaths in the study population; two were due to hepatitis E, one each from HELLP and AFLP, and two remained undiagnosed. The overall perinatal mortality within the group was 43%. Hepatitis E was the most common cause of FHF and maternal death in pregnant women with liver dysfunction.

Keywords: hepatitis, hepatitis E, maternal mortality, Pakistan

INTRODUCTION

Liver dysfunction complicates as many as 3% of pregnancies[1] and, although rare, rapid progression to fulminant disease may occur. Common causes of liver dysfunction in pregnancy include hyperemesis gravidarum, viral hepatitis, severe pre-eclampsia, HELLP syndrome (haemolysis, elevated liver enzymes and low platelet count), intrahepatic cholestasis of pregnancy (IHCP) and acute fatty liver of pregnancy (AFLP). Liver dysfunction in pregnancy is associated with both maternal and fetal morbidity and mortality. Published case-fatality rate for non-pregnant women with acute hepatitis E is 0.1% in endemic areas.[2]

The increased case-fatality rate in acute viral hepatitis (AVH) in pregnancy is usually seen in third trimester. Acute hepatitis E in pregnancy is of importance as it can assume a fulminant course in pregnant women.[1] In developed countries, this picture is usually seen in women with chronic hepatitis B infection. Increased case-fatality rate in pregnancy is usually seen in the third trimester and is commonly attributed to fulminant hepatic failure (FHF) and disseminated intravascular coagulation (DIC). There are at least five different types of viral hepatitis. These include A, B, D caused by the hepatitis B-associated delta agent, C and hepatitis E. The viruses themselves are not hepatotoxic, but rather the immune response generated is responsible for hepatocellular necrosis. Hepatitis with the 'A' virus results in elevated transaminases, with normal gamma glutamyl transaminase. The disease is self-limiting and is not severe in pregnancy; the management is supportive. Acute infections with both hepatitis B and C may be asymptomatic and occur with or without apparent jaundice. The main issue with hepatitis B and C infection is the risk of vertical transmission to the newborn. Hepatitis E (HE) is an enterically transmitted RNA virus and is responsible for large-scale epidemics in developing countries. The regions susceptible for endemic spread include south-east Asia, central Asia, sub-Saharan Africa and north-west China. Outbreaks of HE virus have been reported from the Middle East, Africa and North America.[2] Although it is non-endemic in the industrialized world, anti-HEV antibodies are detected in the general population. This has led to the hypothesis that an animal reservoir for HEV may exist.[3] Epidemics are caused by

Correspondence to: Nazli Hossain, Associate Professor, Dow University of Health Sciences, Karachi, Pakistan
Email: nazlih1999@gmail.com

contamination of drinking water. Transmission of hepatitis E from one person to another does not occur. Acute HE in pregnancy is of concern as it assumes a fulminating course in the majority of pregnant women.[1,2] Pakistan is situated in a region, where enterically transmitted infection with HEV is endemic.

Here we report a descriptive study of pregnant women presenting with liver dysfunction. We hypothesized that HE infection in pregnancy is associated with increased maternal and perinatal morbidity and mortality. Our aim was to study the spectrum of liver dysfunction in pregnancy, with emphasis on maternal and fetal outcome in women with HE infection.

MATERIALS AND METHODS

Pregnant women with deranged liver function who presented to the High Risk Pregnancy unit or delivery suite of the University Hospital were evaluated, with special emphasis on viral hepatitis. The study period was from January 2006 to September 2006, over a period of nine months. Clinical history, physical examination, labour details and follow-up were recorded on the Standardized Antenatal Hospital Record Sheet and the results are summarized in Table 1. Blood samples were obtained for biochemical and serological tests. Ultrasound was performed to assess gestational age and fetal wellbeing. Admission to the High Risk Pregnancy unit or delivery suite was based on the severity of the liver disease as assessed by clinical and biochemical tests. A conservative and expectant approach was adopted and recommendations regarding delivery were made on maternal or obstetrical grounds.

Preeclampsia with liver dysfunction, haemolysis and low platelets was defined as HELLP syndrome. IHCP was diagnosed in women with elevated bile acids, liver enzymes and bilirubin. Acute fatty liver of pregnancy (AFLP) was diagnosed in women with jaundice, coagulopathy and hypoglycaemia. Criteria for diagnosis of AVH were:

- Recent onset of jaundice, in the absence of prior history of jaundice or chronic liver disease;
- Serum transaminases levels at least three times more than normal value.

Table 1 **Clinical and biochemical profile of patients with hepatitis E**

Age in years at presentation	
20–25 years	6 (27%)
26–29 years	9 (40%)
30–35 years	7 (31%)
Gestational age at presentation	
14–28 weeks of gestation	5 (22%)
>28 weeks of gestation	17 (77%)
Clinical disease	
Fulminant	4 (18%)
Non-fulminant	18 (81%)
Mean total bilirubin levels + 1SD, range	12 mg/dL + 7.019 mg/dL, 1–36
Mean alanine transaminase values + 1SD, range	675 IU/L + 1129 U/L, 75–4015
Mean prothrombin time + SD	29 seconds +10.3 seconds
Mean partial thromboplastin time + SD	42 seconds +6.5 seconds
Hepatic encephalopathy	4 (18%)
Cerebral oedema	8 (36%)

Criteria for diagnosis of fulminant hepatitis were as above plus deranged coagulation profile (prothrombin time [PT] at least four seconds greater than control) and progression to rapid-onset hepatic encephalopathy, within 15 days of onset of jaundice in the absence of chronic liver disease.[4]

During the study period, a total of 35 pregnant women with deranged liver function tests were seen in the high-risk clinic or were admitted in the delivery suite. During the same interval, the total of number of deliveries in thee labour suite were 800, thus giving an overall prevalence of hepatic dysfunction of 4.4% in study population.

In this prospective study, all the eligible patients were evaluated on the basis of history, clinical examination and liver function profile. Serology for hepatitis viruses included serology for markers of hepatitis A virus (IgM anti-HAV), HbsAg (hepatitis B surface antigen), anti-HCV antibodies for hepatitis C and enzyme-linked immunosorbent assay (IgM and IgG anti-HEV) for HE. A comprehensive laboratory evaluation consisted of: hepatic, renal function tests, serum uric acid, complete blood count, prothrombin and partial thromboplastin time. The diagnosis of HE was made when history, clinical findings, ultrasound examination and serology excluded preeclampsia, AFLP, IHCP, HAV along with a positive titre of HE antibodies of IgM variety. No patient had a history suggestive of chronic liver disease. Only two patients gave a history of prior blood transfusion but these two women were serologically negative for both hepatitis B and C. DIC was diagnosed in the presence of thrombocytopaenia ($<100 \times 10^9$, low fibrinogen levels [<2 g/L]) and high fibrin degradation products, along with bleeding from venepuncture sites and mucosal bleeding. We did not perform liver biopsy in any of our patients. A liver transplant facility for FHF was not available in our centre. Those women with severe preeclampsia or HELLP syndrome were managed with antihypertensive drugs, magnesium sulphate in the event of convulsions, and steroids for HELLP syndrome. Pregnancy was terminated if blood pressure continued to rise in patients with severe preeclampsia, or in the event of worsening liver function tests. The management of HE was mainly supportive in the form of intravenous fluids, lactulose, metronidazole, third-generation cephalosporins, antacids and vitamin K supplements. The study design was approved by the institutional review committee of our centre.

RESULTS

Demographic and reproductive characteristics

Thirty five women were identified with liver dysfunction from a total of 800 women delivered during the study period. The mean age of the women in the study was 27 years; 11 were primigravida, eight were second gravida and 16 were multigravid. Fourteen (40%) of the women presented in the second trimester, and 21 (60%) presented in the third trimester. Eight (23%) women were registered for antenatal care, whereas 27 (77%) were unregistered. The majority of cases of HE were seen in the months of June, July and August.

Clinical features

The main clinical features at the time of presentation were yellow discoloration of sclera, low-grade fever, nausea and vomiting, malaise and lethargy.

Twenty-two of the 35 women (63%) had isolated acute HE infection, five (14%) had HELLP syndrome, two (6%) were

diagnosed with IHCP, two with AFLP and two with hepatitis A. In two cases the cause of the jaundice could not be determined. The mean bilirubin level in women with HE was 12 mg/dl and mean alanine transaminase (ALT) was 675 U/L. All but five women were delivered preterm and seven women underwent caeserean section, whilst 26 delivered vaginally. Two women remained undelivered at their time of death. Nine patients had spontaneous onset of labour and the remainder were induced with prostaglandins.

FHF was diagnosed in 11% (4/35). The PT and PTT were abnormal in 57% (20/35) and in 82% (18/22) of those with HE. In the latter, the mean PT was 31 seconds (control 18 seconds) and the PTT 48 seconds (control 33 seconds). Four of the 22 women (18%) with HE had DIC. FHF was seen in 18% (4/35) patients. Prothrombin, partial thromboplastin time of the group was abnormal in 20 (57%) of women, and in 18 of 22 (82%) with HE. The mean prothrombin time was 31 seconds versus a control of 18 seconds, and mean partial thromboplastin time was 48 seconds versus a control of 33 seconds, in women with HE. DIC was seen in 18% (4/22).

Maternal and perinatal mortality

There were six maternal deaths in the group; one each with AFLP and HELLP syndrome, two with HE and two undiagnosed. The maternal mortality from HE was thus 9% (2/22). There were seven intrauterine fetal deaths and two stillbirths in the women with HE giving a fetal mortality rate of 41%. HE was associated with a 36% (8/22) rate of preterm delivery and a neonatal mortality rate of 27% (6/22) for a total perinatal mortality of 64% (14/22).

DISCUSSION

Compared with the specific liver diseases of pregnancy, AVH poses a significant risk to both mother and baby. Of the viral hepatitides, acute infection with E virus carries high risk of maternal and fetal mortality. The reported maternal mortality from HE is between 20% and 25%.[5] Studies from the west have shown that AVH has no special predilection for pregnant women, and the disease has the same course as in non-pregnant women.[2,6,7] This may reflect the different aetiological agents responsible for AVH. In the developing world, HE is the most common cause of AVH during pregnancy. In Egypt, the prevalence of HEV infection is approximately 84% in women of child-bearing age, but has not been found to be associated with increased maternal and perinatal mortality.[8] This has been attributed to the different strains of HEV.

The mean age of women in our study was 27 years. Fourteen (40%) of the women presented in the second trimester, and 21 (60%) presented in the third trimester. The majority of women with HE (17/22) presented in the third trimester, an observation consistent with previous studies.[9,10] HE in later stages of pregnancy is associated with increased maternal mortality.[11] Common clinical symptoms include a short history of low grade fever, dark-coloured urine, discolouration of sclera, malaise and lethargy. Biochemistry shows raised bilirubin levels, mainly conjugated, elevated transaminases and a mild rise in alkaline phosphatase activity. The transaminases are disproportionally raised but this does not reflect hepatic necrosis. Liver enzyme and bilirubin levels usually return to normal within six weeks.

From a total of 35 pregnant women with liver dysfunction, 22 (63%) were found to be positive for HEV antibodies. Four of these women developed FHF and two died giving a maternal mortality rate of 9%. Kumar *et al.*,[1] also reported seven deaths due to FHF, out of 26 women with AVH in pregnancy. Earlier, Khuroo *et al*. reported a 61.8% rate of FHF and 22% rate of DIC in their women with AVH in pregnancy. In our study, four of 22 women with HE developed DIC. The aetiology of DIC in FHF due to AVH is not known, but pregnancy and advanced gestational age have been identified as risk factors. The presence of DIC significantly influences the maternal mortality rate in HE infection.

Recently, immunological mechanisms have been postulated to explain the higher mortality rates associated with HE in pregnancy. Other contributing factors to the poor prognosis may be hormonal changes of pregnancy and malnutrition. During acute HE, IgM antibodies appear and are present for 4–5 months. IgG antibodies develop shortly after the IgM response, but persist for several years. The role of anti-HEV antibodies in re-infection is not clear. The cellular immune response to HE is altered in pregnant women. Studies have shown Th2 helper cell bias in pregnant women with HEV infection.[9] In our study, FHF developed in 18% of women with HEV infection. This is similar to the rate seen in other studies from this region.[14] In developed countries chronic infection with hepatitis B is the most common cause of FHF in pregnancy. In endemic areas, HEV is an important cause of maternal FHF[12] as well as increased fetal morbidity and mortality. The main fetal risks associated with FHF include intrauterine death, prematurity and stillbirth. In our study, there were eight (36%) preterm deliveries, and six (27%) intrauterine deaths in women who were HEV-positive. There were only four (18%) term live births in HEV-positive women. Still-births, abortions and neonatal deaths are increased in women with HE infection. There is also a risk of vertical transmission of HE to the newborn.[1] Studies have reported the rate of vertical transmission ranging from 33% to 50%.[15] Both anti-HEV antibody and HEV RNA have been detected in colostrum.[16] The rate of vertical transmission was not determined in our study. Breast feeding is not contraindicated in women infected with HEV.

HEV does not lead to chronic infection in either pregnant or non-pregnant subjects. The diagnosis of HE depends on a combination of biochemical, serological and molecular features. Most commonly, HE antibodies are measured by enzyme immunoassays (EIA). Both IgG and IgM antibodies are measured with the presence of IgM signifying acute infection. IgG antibodies may persist for 1–4.5 years. In Europe and North America, 1–5% of the population will have antibodies to HEV, although there is a low rate of HE infection in these populations. It is not clear whether this anti-HEV seroreactivity in the developed world reflects sub-clinical infection, serological cross-reactivity with other agents or false positive tests. In America, there may be a significant rate of cross-reactivity with swine HEV.[17] Molecular diagnosis depends upon the identification of virus in stools and urine by reverse transcriptase method. In our patients, we used EIA for both IgM and IgG, molecular diagnosis though available, was not considered to be cost-effective in our patients.

CONCLUSION

This study shows that AVHE in endemic countries contributes significantly towards maternal and perinatal mortality.

Pregnant women travelling to endemic areas should be warned about the possible risks of contacting HEV infection. Similarly, pregnant women returning from such areas and developing hepatic dysfunction should be evaluated for HE infection. Recently, a phase two trial for recombinant HEV vaccine has been completed. Recombinant HEV vaccine for pregnant women is needed in Asian countries to decrease the maternal mortality rate.

REFERENCES

1 Tamizian O, Arulkumaran S. The surgical management of post-partum haemorrhage. *Best Pract Res Clin Obstet Gynaecol* 2002;**16**:81–98
2 Krawczynski K. Hepatitis E vaccine – ready for prime time? *N Engl J Med* (%R 10.1056/NEJMe068311) 2007;**356**:949–51
3 Aggarwal R, Krawczynski K. Hepatitis E: an overview and recent advances in clinical and laboratory research. *J Gastroenterol Hepatol* 2000;**15**:9–20
4 Bernuau J, Rueff B, Benhamou JP. Fulminant and subfulminant liver failure: definitions and causes. *Semin Liver Dis* 1986;**6**:97–106
5 Wilkinson ML. Diagnosis and management of liver disease in pregnancy. *Adv Intern Med* 1990;**35**:289–310
6 Knox TA, Olans LB. Liver disease in pregnancy. *N Engl J Med* (%R 10.1056/NEJM199608223350807) 1996;**335**:569–76
7 Khuroo MS, Kamili S. Aetiology, clinical course and outcome of sporadic acute viral hepatitis in pregnancy. *J Viral Hepat* 2003;**10**:61–9
8 Stoszek SK, Abdel-Hamid M, Saleh DA, *et al.* High prevalence of hepatitis E antibodies in pregnant Egyptian women. *Trans R Soc Trop Med Hyg* 2006;**100**:95–101
9 Shamsi TS, Hossain N, Soomro N, *et al.* Use of recombinant factor VIIa for massive postpartum haemhorrage: case series and review of literature. *J Pak Med Assoc* 2005;**55**:512–15
10 Dahiya M, Kumar A, Kar P, Gupta RK, Kumar A. Acute viral hepatitis in third trimester of pregnancy. *Ind J Gastroenterol* 2005;**24**(3):128–9
11 Sookoian S. Liver disease during pregnancy: acute viral hepatitis. *Ann Hepatol* 2006;**5**:231–6
12 Khuroo MS, Kamili S. Aetiology, clinical course and outcome of sporadic acute viral hepatitis in pregnancy. *J Viral Hepat* 2003;**10**:61–9
13 Pal R, Aggarwal R, Naik SR, Das V, Das S, Naik S. Immunological alterations in pregnant women with acute hepatitis E. *J Gastroenterol Hepatol* 2005;**20**:1094–101
14 Hamid SS, Jafri SM, Khan H, Shah H, Abbas Z, Fields H. Fulminant hepatic failure in pregnant women: acute fatty liver or acute viral hepatitis? *J Hepatol* 1996;**25**:20–7
15 Sookoian S. Liver disease during pregnancy: acute viral hepatitis. *Ann Hepatol* 2006;**5**:231–6
16 Chibber RM, Usmani MA, Al-Sibai MH. Should HEV infected mothers breast feed? *Arch Gynecol Obstet* 2004;**270**:15–20
17 Meng X-J, Halbur PG, Shapiro MS, *et al.* Genetic and experimental evidence for cross-species infection by swine hepatitis E virus. *J Virol* 1998;**72**:9714–21
18 Mousa HA, Walkinshaw S. Major postpartum haemorrhage. *Curr Opin Obstet Gynecol* 2001;**13**:595–603

(Accepted 30 September 2008)