Hepatic encephalopathy in pregnancy

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Hepatic encephalopathy in pregnancy may be related to a wide variety of acute and chronic liver diseases, including acute viral hepatitis, acute fatty liver of pregnancy, pre-eclampsia-related liver injury, etc. Of these, hepatitis E virus infection is a particularly important cause in those developing countries where this infection is endemic. Etiological diagnosis can be made based on epidemiologic, clinical and laboratory findings. Treatment is usually similar to that of hepatic encephalopathy in the absence of pregnancy. Patients with acute fatty liver of pregnancy and pre-eclampsia-related liver injury may benefit from termination of pregnancy; the role of this treatment modality among patients with viral hepatitis has not been studied. [*Indian J Gastroenterol* 2003;22 (Suppl 2):S78-S80]

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Hepatic encephalopathy, or neuropsychiatric alterations that result from liver disease, among pregnant women may be related to a wide variety of acute and chronic liver diseases. Since advanced chronic liver disease adversely affects the ability to conceive, occurrence of hepatic encephalopathy related to chronic liver disease during pregnancy is unusual. Hepatic encephalopathy in most pregnant women is thus related to acute liver disease. These diseases can be classified broadly as diseases unrelated to pregnancy, some of which occur either with increased frequency or increased severity during pregnancy, and diseases specific to pregnancy. The Table lists the major causes of hepatic encephalopathy in pregnant women.

Viral hepatitis in pregnancy

Viral hepatitis is a common cause of liver injury and of hepatic encephalopathy among pregnant women. Though all hepatotropic viruses can affect pregnant women, hepatitis E virus (HEV) is of particular importance in this group in geographical areas where this infection is endemic. Hepatitis A is an unlikely cause of hepatic encephalopathy in pregnant women in our country in view of near universal exposure to this infection (resulting in immunity to reinfection) before reaching reproductive age.

Hepatitis E is usually a self-limiting disease with a low rate of fulminant hepatic failure (FHF). However, this infection appears to have particularly disastrous consequences for pregnant women. Pregnant women, particularly those in the second and third trimesters, are more frequently affected during hepatitis E outbreaks. In addition, among pregnant women, especially those infected in the third trimester, the disease is more severe, with mortality rates between 15% and 25%.[1-4] In an epidemic in Kashmir, attack rates among those in the first, second and third trimesters were 8.8%, 19.4% and 18.6%, respectively, as compared with 2.1% among non-pregnant women and 2.8% among men.[1] Further, FHF developed in 22.2% of the affected pregnant women, in comparison with 2.8% and 0% of affected men and non-pregnant women, respectively. Similarly, during a large epidemic of hepatitis E in Kanpur affecting an estimated 79,000 persons, 13 of 48 deaths were among pregnant women;[5] this suggests an inordinately high mortality rate among pregnant women since such women constitute only around 2% of the total population. The reason for more severe course of hepatitis E among pregnant women is not known. However, in a primate model of HEV infection, infected pregnant females did not have a particularly severe course.[6]

HEV infection adversely affects fetal outcome, with increased frequencies of abortions, stillbirths, and neonatal deaths.[4] HEV infection can also be transmitted vertically from mother to infant. In one study, six of eight babies born to mothers who had either acute uncomplicated hepatitis or FHF due to hepatitis E in the third trimester of pregnancy were found to have evidence of HEV infection.[7] The infected babies frequently had hypoglycemia and biochemical evidence of liver injury.

In a recent study, administration of immune serum globulin to pregnant women during an outbreak was shown to reduce the number of total recent HEV infections, though the number of clinical cases was unchanged.[8] Vaccine against HEV infection, when developed, will find particular application among pregnant women in endemic areas.

Table: Major causes of hepatic encephalopathy in pregnant women

A.	Diseases/conditions unrelated to pregnancy
	Acute liver disease
	Acute viral hepatitis of all types, in particular hepatitis E
	Budd-Chiari syndrome
	Chronic liver disease (cirrhosis) of various etiologies
B.	Diseases/conditions specifically related to pregnancy
	Acute fatty liver of pregnancy
	Pre-eclampsia/eclampsia related liver injury (including HELLP syndrome)
	Tetracycline-induced acute fatty liver

Liver diseases related exclusively to pregnancy[9,10,11]

These diseases include acute fatty liver of pregnancy (AFLP), hepatic involvement in pre-eclampsia/eclampsia of pregnancy, and HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count). The exact pathogenesis of these diseases remains unclear. There is significant overlap in clinical, biochemical and other findings in these syndromes and in some patients features of more than one syndrome coexist. These observations, and occurrence of more than one of these syndromes in consecutive pregnancies in the same person, suggest that these diseases may be pathogenetically related.[11] Since treatment of these diseases is similar, i.e., termination of pregnancy, there may be little to gain by trying to distinguish between various syndromes.

Acute fatty liver of pregnancy (AFLP)

Patients with AFLP typically present in the third trimester of pregnancy with malaise, headache, nausea, poor appetite, and abdominal pain. As the disease progresses, the pregnant woman develops evidence of hepatic failure with jaundice and encephalopathy. Patients usually have moderate elevations in transaminases with minimal elevations in bilirubin. Coagulopathy with elevations in prothrombin time and activated partial thromboplastin time, and disseminated intravascular coagulation (DIC) are common. Thrombocytopenia however is not a prominent feature. Renal impairment is frequently present.

Diagnosis of AFLP depends on a high index of suspicion when malaise, headache, nausea, poor appetite, abdominal pain, and jaundice appear during the third trimester and laboratory data show coagulopathy. Liver biopsy, though diagnostic when oil red O stains of fresh tissue reveal microvesicular fat, is often not possible in view of coagulopathy. There are conflicting data on whether evidence of fatty liver on computed tomography (reduced liver density) or ultrasonography (increased echogenicity) can aid in the diagnosis of AFLP.

Delivery of the fetus often leads to improvement in hepatic symptoms. Sometimes, however, the liver disease continues to progress. Previously thought to be uniformly fatal for both mother and fetus, this condition has, in recent years, been associated with reduced maternal and fetal mortality rates of 20% to 85% each. This improvement is at least partly related to inclusion of milder cases.

Pre-eclampsia/eclampsia-related liver disease

Pre-eclampsia/eclampsia is a syndrome that occurs in the third trimester of 7% of pregnancies and is characterized by hypertension (>15 mmHg rise in diastolic blood pressure or >30 mmHg rise in systolic blood pressure over levels observed in early pregnancy, or blood pressure exceeding 140/90 mmHg during late pregnancy), edema, proteinuria, and hyperreflexia with or without seizures. Biochemical abnormalities include disseminated intravascular coagulation and hyperuricemia.

Liver involvement is usually mild and manifests as abdominal pain, nausea and vomiting. Jaundice, when present, is mild. Serum aminotransferase activities show only mild elevation. Histologic changes in liver are common, are more prominent in periportal areas, and include fibrin deposits in sinusoids and hemorrhages. Fat deposition is infrequent. Hepatic failure is uncommon. Complications include spontaneous liver hematomas and rupture. Treatment consists of early termination of pregnancy.

HELLP syndrome

HELLP syndrome is probably a severe variant of pre-eclampsia/eclampsia. It is characterized by the triad of microangiopathic hemolytic anemia, elevated liver enzymes, and low platelet count. On CT scan, hepatic hemorrhage may be seen. Patients often have abdominal pain but may lack the other features of pre-eclampsia/eclampsia listed above. As with typical pre-eclampsia, treatment of the HELLP syndrome is termination of pregnancy.

Budd-Chiari syndrome in pregnancy

Pregnancy and postpartum state are associated with a hypercoagulable state and predisposition to venous thromboses. Acute hepatic venous thrombosis may occasionally present as acute liver cell failure. Hepatomegaly, abdominal pain, mild jaundice, and ascites represent clinical accompaniments. Ultrasonography is diagnostic.

Diagnosis of nature of liver involvement in a pregnant patient

In practice, the diagnoses that one needs to consider in a pregnant patient with hepatic encephalopathy include acute viral hepatitis, in particular HEV infection, AFLP and liver injury related to pre-eclampsia/eclampsia. Systemic illnesses that cause altered sensorium (unrelated to liver injury) and coexistent jaundice, viz., severe falciparum malaria, septicemia, leptospirosis, severe infection associated with hemolysis, etc., may need exclusion by appropriate investigations.

In the developed world where HEV infection is not endemic, AFLP is the commonest cause of hepatic encephalopathy during pregnancy. However, in HEV-endemic areas like the Indian subcontinent, this virus infection possibly forms the most important cause of hepatic encephalopathy during pregnancy. In a report from Kashmir, 21 of 23 pregnant patients with acute hepatic failure had evidence of HEV infection.[12] Simi-

larly, in Pakistan, two-thirds of a group of pregnant women with FHF had HEV infection.[13]

Diagnosis of etiology of liver injury in a pregnant patient with FHF and hepatic encephalopathy can be a difficult task. Existence of an epidemic of HEV infection in the area of residence of the patient may favor a diagnosis of acute hepatitis E, as may very high alanine aminotransferase activity (>1000 units). Testing for IgM anti-HEV antibodies in serum may be helpful in confirming or excluding the diagnosis. Evidence of fat deposition on imaging studies may favor a diagnosis of AFLP. Ultrasonography and Doppler studies are useful if Budd-Chiari syndrome is suspected.

Treatment of hepatic encephalopathy in pregnancy

Treatment of hepatic encephalopathy in pregnancy, as in the case of all other forms of acute liver failure, is mainly supportive. The drugs commonly used in patients with liver failure, viz., neomycin or ampicillin for decontamination of gut, lactulose, vitamin K and mannitol appear to be safe in pregnancy.

As indicated above, patients with AFLP and pre-eclampsia/eclampsia syndrome may benefit from early induction of delivery. On the other hand, there is no evidence that induction of labor has any role in patients with acute viral hepatitis, including hepatitis E. Decision on termination of pregnancy therefore depends on the diagnosis considered to be more likely. If induction of labor is decided upon or if the patient enters labor spontaneously, vaginal delivery is preferable to cesarean section in view of coagulation disturbances and a high risk of intraoperative and postoperative bleeding. Episiotomy too should be avoided, if possible. It is advisable to routinely use ergometrine in such patients in the immediate postpartum period to reduce the chances of postpartum bleeding. If postpartum bleeding occurs, infusion of fresh frozen plasma may be indicated. Systemic infections are common in these patients, and broad-spectrum antibiotic cover may be useful.

The newborn infant should be carefully evaluated and monitored for occurrence of hypoglycemia and for evidence of liver injury. If the pregnant woman had hepatitis B virus infection, the newborn should be immunized against hepatitis B.

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