Background: Liver disease in pregnancy can have serious consequences. Its prevalence, profile, and effect on outcome of pregnancy have not been documented systematically in India. We prospectively determined the frequency, causes, and outcome of liver disease in pregnant women. Setting: Tertiary-care teaching hospital. Methods: Consecutive pregnant women with liver disease attending the inpatient or outpatient services of the Departments of Gastroenterology and Obstetrics and Gynecology between December 2002 and October 2004 were evaluated and followed up till 2 weeks postpartum or death. Results: Liver disease was found in 107 (0.9%) of 12,061 pregnancies. Of these, fifty six (52.3%) had pregnancy-specific liver disorders (pregnancy-induced hypertension [PIH]-associated liver dysfunction 36 – including HELLP syndrome 22 and pre-eclamptic liver dysfunction 14; intrahepatic cholestasis of pregnancy 10; hyperemesis gravidarum 7; acute fatty liver of pregnancy 3). Liver disorders not specific to pregnancy included hepatitis E (16), hepatitis B, non A-E hepatitis and chronic liver disease (5 each), and others (14); in 6 patients no cause could be found. Ninety-six patients completed follow up. Overall maternal and perinatal mortality rates were 19.7% and 35.4%, respectively. Conclusions: PIH-associated liver dysfunction was the most common cause of liver disease in pregnancy. This is associated with significant maternal and perinatal morbidity and mortality.

Methods
All pregnant women with liver disease attending the indoor or outdoor services of the Departments of Gastroenterology and of Obstetrics and Gynecology between December 2002 and October 2004 were studied prospectively. Women with pre-existing liver disease or those suspected to have liver dysfunction on the basis of clinical or investigative data were included. Informed consent was obtained from all patients. The protocol was approved by the ethics committee of the institute.

After thorough clinical assessment, all patients underwent tests for liver biochemistry, hepatitis viral markers (HBsAg, anti-HCV) and hepatobiliary sonography. When indicated, additional investigations to identify the etiology of liver disease were done.

Patients with acute hepatitis were observed for complications. Patients with intrahepatic cholestasis of pregnancy received ursodeoxycholic acid (10-15 mg/Kg body weight). Patients with serious disease were managed in the intensive care unit. In women with portal hypertension, gastroesophageal varices were looked for and managed using beta-blockers; endotherapy was done in patients with variceal bleeding. Patients with decompensated liver disease received symptomatic treatment.

Patients were prospectively followed up till two weeks postpartum or death.

Definitions
Pregnancy-induced hypertension (PIH)-associated liver dysfunction included HELLP syndrome 22 and pre-eclamptic liver dysfunction.

HELLP syndrome: Complete: elevated AST (>70 IU/L), low platelet count (<100,000/µL), hemolysis (suggestive peripheral smear with increased reticulocytes). Partial: elevated AST (>40 IU/L), low platelet count (<150,000/µL), absence or presence of hemolysis.

Pre-eclamptic liver dysfunction: Elevated transaminases or bilirubin in the presence of hyper-
tension, proteinuria and edema, after 20 weeks of gestation.

**Intrahepatic cholestasis of pregnancy (ICP):** Pruritus without any local or other systemic cause, with elevated transaminases, which disappeared soon after delivery.

**Hyperemesis gravidarum with liver dysfunction:** Elevated transaminases or bilirubin in the presence of persistent vomiting for more than one week during the 1st or 2nd trimester.

**Acute fatty liver of pregnancy (AFLP):** Six or more of the following features in the absence of another explanation: vomiting, abdominal pain, polydipsia or polyuria, encephalopathy, leukocytosis, elevated bilirubin, elevated transaminases, elevated ammonia, hypoglycemia, renal impairment, coagulopathy, elevated urate, ascites or bright liver on ultrasound, and microvesicular steatosis on liver biopsy.

**Results**

During the study period, 107 pregnant women were diagnosed to have liver disease. Ninety-six completed follow up. One patient with non A-E hepatitis underwent medical termination of pregnancy and 10 patients (two with hyperemesis gravidarum, one each with hepatitis E, hepatitis non A-E, hepatitis B, chronic liver disease of unknown etiology, three with others, and one with obscure diagnosis) were either lost to follow up or had incomplete follow up. During this period, there were 12,061 pregnancies; thus liver dysfunction was found in 0.9%.

Hyperemesis gravidarum was the most common cause of liver dysfunction in the first trimester, whereas viral hepatitis and PIH-related liver dysfunction were the commonest liver diseases in the second and third trimesters, respectively (Table 1).

**Pregnancy-specific liver diseases (Table 2)**

All 7 patients with hyperemesis gravidarum presented in the first trimester; only one had jaundice. All recovered with supportive treatment, and liver function tests became normal.

Of 10 patients with ICP, nine had pruritus in the 3rd trimester. Four needed emergency induction of labor for fetal distress, including one who underwent caesarean section. There was no maternal death, but one stillbirth. Pruritus disappeared within 3 days after delivery and liver function tests became normal within 2 weeks.

Patients with PIH-related liver dysfunction (n=36; complete HELLP 9, partial HELLP 13, pre-eclamptic liver dysfunction 14) had right upper quadrant or epigastric pain (23 [64%]) and nausea or vomiting (14 [39%]) as the presenting symptoms. Ten (27.8%), 8 (22.2%), and 7 (19.4%) patients had jaundice, eclampsia and low-protein ascites, respectively. Disseminated intravascular coagulation (DIC; n=16 [44%]), acute renal failure (11 [31%]) and abruptio placentae (6 [17%]) were the common complications in these patients.

Of these 36 women, 24 delivered vaginally, 10 underwent caesarean section, and 2 died before delivery. The maternal mortality in this group

<table>
<thead>
<tr>
<th>Table 1: Distribution of liver disease during antenatal period</th>
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<tr>
<td><strong>Trimester</strong></td>
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<tr>
<td>1st trimester</td>
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<td>2nd trimester</td>
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<td>3rd trimester</td>
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<table>
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<th>Table 2: Maternal and perinatal outcome (n=96)</th>
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<tr>
<td><strong>Disease</strong></td>
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<tr>
<td>Pregnancy-induced hypertension-associated liver dysfunction (36)</td>
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<tr>
<td>Intrahepatic cholestasis of pregnancy (10)</td>
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<tr>
<td>Hyperemesis gravidarum (5)</td>
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<td>Acute fatty liver of pregnancy (3)</td>
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<td>Hepatitis E (15)</td>
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<td>Hepatitis non A-E (3)</td>
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<td>Hepatitis B (4)</td>
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<tr>
<td>Chronic liver disease (4)</td>
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<tr>
<td>Others* (14)</td>
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<td>Diagnosis obscure (5)</td>
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<td>Overall (96)</td>
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*Malaria (3), leptospirosis (2), dengue (1 - lost to follow up), cardiac failure (3, 1-lost to follow up), non-alcoholic steatohepatitis (1), diabetes + anti-phospholipid antibody syndrome (1), anti-tuberculosis drugs-induced hepatitis (1), choledocholithiasis (1), hemangioma in liver (1 - under follow up)
was 25% (9/36), with DIC as commonest proximate cause of death. Of 16 (44%) perinatal deaths, 13 were intrauterine fetal deaths (2 were death of mother with fetus in utero). Maternal mortality (7/22 vs 2/14) and perinatal mortality (12/22 vs 4/14) were similar in those with HELLP syndrome and those with pre-eclamptic liver dysfunction. In all 27 patients who survived, transaminases returned to normal by two weeks and ascites disappeared within 4 weeks of delivery.

All three patients with AFLP had nausea, vomiting and upper abdominal pain preceding jaundice. All developed encephalopathy, renal failure and coagulopathy. Two patients had DIC, hypoglycemia and sepsis. Ultrasonography in one patient showed fatty liver. Two patients died of multiorgan failure. Transaminases remained elevated in the patient who recovered after prolonged hospital stay. There were two intrauterine fetal deaths and one child survived.

Other causes of liver dysfunction (Table 2)
Though viral hepatitis was seen in all trimesters, 11/16 developed acute hepatitis E during the third trimester. Four of the six patients (all hepatitis E) who developed fulminant hepatic failure (FHF), died. Postpartum hemorrhage and DIC occurred in three each whereas sepsis developed in two. Perinatal mortality in patients with hepatitis E was 38% (6/16), including 3 deaths of mother with fetus in utero, one stillbirth, 2 early neonatal deaths.

None of the 5 patients having acute non A-E hepatitis developed FHF. There was no maternal mortality and one perinatal death due to preterm delivery.

Sixteen women tested HBsAg positive, of whom 5 were HBeAg positive (one with cirrhosis, four with elevated transaminases). Markers for acute infection were not done in them, and 6 months’ follow-up information was not available. Two of the 16 had cirrhosis (included among those with chronic liver disease) and another five had elevated liver enzymes (subjects with normal enzyme levels were not included in this study).

Five patients had evidence of chronic liver disease (2 HBV related, 1 chronic Budd-Chiari syndrome, 2 cryptogenic). Four of them had portal hypertension; none had gastrointestinal bleeding during pregnancy. There was no maternal mortality. The perinatal mortality rate was 2/4; one patient was lost to follow up.

The 14 patients with miscellaneous conditions involving the liver included 3 with malaria, 2 leptospirosis, 1 dengue, 3 congestive heart failure, and 1 each with nonalcoholic fatty liver disease, diabetes with antiphospholipid syndrome, antitubercular drug-induced hepatitis, choleodocholithiasis, and liver hemangioma. Of five women with falciparum malaria and leptospirosis, 3 died; 4 of the newborns also died.

In 6 patients in whom no definite etiology could be established for the liver function test abnormality, 3 had acute febrile illness and one was taking NSAIDs. All but one completed pregnancy.

Mortality
The highest maternal mortality was in patients with AFLP (2/3), followed by hepatitis E (4/16) and PIH-related liver dysfunction (9/36). Overall maternal mortality was 20%. The highest perinatal mortality was in AFLP (2/3). Perinatal mortality in PIH-related liver dysfunction and hepatitis E was 16/36 and 6/16, respectively. Overall perinatal mortality was 35%.

Discussion
In the present study, liver disease was found in 0.9% of pregnant women attending our institution. This may be an underestimate since many women came to hospital only for delivery without prior antenatal visits. Also, we did not do biochemical liver function tests in asymptomatic women.

An earlier study from our center identified severe liver disease in 1.4% of deliveries. A prospective study from southern India identified liver disease in 125 (0.34%) of 36,486 pregnancies using evaluation of abnormal liver function tests. Kingston and co-workers found liver dysfunction in 3% of more than 4000 deliveries in a European study.

The reported proportion of pregnancy-specific liver diseases among affected patients has varies from 67% to 89% in previous studies. In our study, 52% of affected patients had pregnancy-specific liver disease and 24% had viral hepatitis.

Liver diseases had specific pattern of association with duration of pregnancy. Thus, most of the patients with liver dysfunction in the first trimester had hyperemesis gravidarum, whereas those in the third trimester most often had PIH-associated liver dysfunction or hepatitis E. Viral
hepatitis and some non-viral infections were common in the second trimester. Leptospirosis, dengue and malaria occurred in all trimesters. In the study from southern India, the commonest causes of liver disease in pregnancy were AFLP (15%) and PIH-associated liver dysfunction (42%), and viral hepatitis was equally distributed in all trimesters.\(^3\)

Hyperemesis gravidarum did not affect the outcome in our study. ICP may remain undiagnosed because itching in pregnancy is often ignored by patients, and jaundice is uncommon in this condition. Sudden-onset fetal distress is common in these patients,\(^4\) and was seen in 40% of our patients (with one stillbirth). A high index of suspicion for this diagnosis, intensive fetal monitoring, and delivery soon after fetal lung maturity may be helpful.\(^5\)

Liver dysfunction is seen in 4% to 12% of patients with pre-eclampsia.\(^6\) The HELLP syndrome is often associated with complications such as acute renal failure and DIC. This increases morbidity and mortality, both in the mother and fetus. In our study, maternal and perinatal mortality were high in PIH-associated liver dysfunction. There are no definite guidelines regarding the timing of induction of labor in these patients.

It has been proposed that AFLP and HELLP are parts of the same spectrum,\(^6\) and both lead to multi-organ involvement and serious complications. Histology often fails to differentiate AFLP from HELLP and may not be done since the patients have liver failure and coagulopathy. The management of both conditions is by early induction of labor. AFLP was seen in 3 of our patients and all had encephalopathy, renal failure and coagulopathy; 2 of them died. Western studies\(^1,7\) have shown maternal mortality of 0%-13% and perinatal mortality of 0%-9% in patients with AFLP; in Indian reports, these have been 31%-54%, and 100%.\(^3,8,9\)

Hepatitis E is known to be the most common cause of acute viral hepatitis during pregnancy in India (58% to 86%).\(^10,11,12\) In our study, hepatitis E was the most common cause (76.2%) of acute hepatitis and was seen predominantly in the third trimester. Hepatitis E in pregnancy is often complicated by FHF and high maternal and perinatal mortality.\(^10,12,13\) Six (37.5%) patients with hepatitis E in the present study developed FHF, all in the third trimester. Perinatal mortality (40%) and maternal mortality (26.7%) in this group were comparable to previous reports from India.\(^10,11,12\)

A higher HBeAg-positivity rate in our patients with HBsAg positivity (5/16) than in previous reports\(^14,15\) is possibly due to referral bias.

Pregnancy is reported to be rare in patients with cirrhosis, due to associated anovulation.\(^16\) We encountered only 5 pregnant women with chronic liver disease. Two patients developed ascites for the first time. Water retention and increased activity of the renin-angiotensin-aldosterone system during pregnancy can lead to development of ascites.\(^5\) No patient had variceal bleed or encephalopathy. Perinatal mortality was high (2 of 4) and there was one pre-term delivery.

Disorders unrelated to pregnancy were not uncommon and could be differentiated by appropriate tests. Three patients had falciparum malaria with multi-organ failure, and 2 patients had perinatal and maternal death.

Maternal mortality in pregnancy with liver disease has dropped to 0%-1.1% in recent studies from the West.\(^1,6\) Pereira et al\(^7\) reported 13% maternal as well as perinatal mortality rate among pregnant women with severe liver disease. Tank et al\(^2\) from our center included patients with only severe liver disease and had found higher maternal and perinatal mortality rates (42% and 62%, respectively). The southern Indian study showed overall maternal mortality of 20.2% and perinatal mortality of 24.6%.\(^3\) In our study population, the overall maternal and perinatal mortality were 20% and 35%, respectively. These differences may reflect differences in referral patterns in various institutions.

In conclusion, our study shows that though liver disease is uncommon in Indian pregnant women, it is associated with high maternal and perinatal mortality, even in a tertiary referral center. PIH-associated liver dysfunction, AFLP and viral hepatitis are serious conditions. A high index of suspicion of liver disease, early diagnosis, prompt referral to a higher center when required, appropriate supportive management, and a proactive policy of early delivery when indicated may improve the maternal and fetal outcomes in pregnant women with liver disease.

References


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