Acute fatty liver in pregnancy

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ABSTRACT

When confronted with liver abnormalities during the third trimester of pregnancy, one should consider acute fatty liver of pregnancy. The differential diagnosis with (pre-)eclampsia and HELLP syndrome is sometimes difficult. In these cases a liver biopsy is helpful though rarely performed during pregnancy. After delivery of the child the liver test abnormalities will ultimately disappear. Recent publications reveal that a dysfunction in β-oxidation of mitochondrial fatty acids may contribute to the aetiology of this rare disorder. We describe a case of acute fatty liver in pregnancy, with liver dysfunction (decreased albumin, prolonged prothrombin time) slowly returning to normal after delivery. Testing for disorders in β-oxidation of mitochondrial fatty acids did not reveal abnormalities in mother or child.

INTRODUCTION

Liver function abnormalities during pregnancy can be due to pre-existent liver diseases or to newly developed liver diseases. In the latter group, liver diseases occurring coincidentally during pregnancy (i.e. viral hepatitis) have to be distinguished from liver diseases occurring exclusively during pregnancy, such as pre-eclampsia or the HELLP (haemolysis elevated liver enzymes low platelet count) syndrome. Other less frequent causes should also be kept in mind, including acute fatty liver in pregnancy and intra-hepatic cholestasis of pregnancy. The timing of the onset, specific clinical symptoms and if necessary a liver biopsy can differentiate between these disorders. We describe a patient with a rare disorder of liver failure during pregnancy.
of liver insufficiency, although glucose was borderline normal (3.6 mmol/l). A direct Coombs test was negative, again there were no fragmentocytes. Fibrinogen was 1880 (normal 1600-3200 E) and D-dimer count was 900 (normal <500 U). Viral serology (hepatitis B, C, E, CMV, EBV) was negative. There were no signs of autoimmune or metabolic liver diseases (ANA, antismooth muscle antibody, antiliver kidney cell antigen, antimicrosomal antibody were all negative, γ-globulin was 8.4 g/l, α-1-antitrypsin, ceruloplasmin, serum copper and iron were normal). Clinically there were no signs of encephalopathy although the ammonia content was initially 67 µmol/l, and later decreased to 45 µmol/l. Echography of the liver showed normal liver parenchyma and a normal flow in both the portal and hepatic veins. Blood pressure was normal (130/80 mmHg) and repeat urine analysis did not reveal proteinuria. Puncture of ascites fluid showed a leukocyte count of 100 x 10⁶/l, albumin 1 g/l and lactic dehydrogenase of 88 U/l. Cytologically there was no suspicion of malignancy. The liver abnormalities gradually improved. Using diuretics, the ascites disappeared. Seventeen days after birth a liver biopsy was performed showing microvesicular steatosis (figures 1 and 2). This fits into the diagnosis of acute fatty liver during pregnancy. Later, the child was investigated for disturbances of the mitochondrial β-fatty acid oxidation: urine analysis for organic acids did not show any abnormalities. Acylcarnitine analysis was normal, as was the enzyme activity of the long chain fatty acid dehydrogenase. Acylcarnitine and tetradeccenic acid blood levels were also found to be normal in the mother.

**DISCUSSION**

Liver diseases occurring exclusively during pregnancy are intrahepatic cholestasis of pregnancy, pre-eclampsia, the HELLP syndrome, and acute fatty liver.1,2 When pain is a predominant symptom, rupture of the liver capsule should be considered. Towards the end of pregnancy pre-eclampsia, the HELLP syndrome and acute fatty liver of pregnancy are most probable. After delivery of the child, liver function abnormalities return to normal. Table 1 on page 372 shows some clinical characteristics of liver diseases in pregnancy. In our patient, there were no signs or symptoms of a pre-existing liver disease. Laboratory results were negative for viral hepatitis or autoimmune liver disease. The occurrence during late third trimester, the absence of itching and the relatively low levels of serum bilirubin did not point to intrahepatic cholestasis of pregnancy. There were no signs of hypertension, proteinuria, persisting renal failure or thrombopenia (suggesting pre-eclampsia or HELLP syndrome). Plasma glutathione S-transferase alpha values (often elevated in these conditions) were normal.3 In view of these findings, the clinical diagnosis in our patient was acute fatty liver of pregnancy. This diagnosis was confirmed by the results of the liver biopsy, which showed predominantly steatosis. There was mild ballooning of liver cells, cholestasis and cell death. These features are fairly typical for fatty liver and argue against autoimmune hepatitis (no plasma cells, too much steatosis) or viral hepatitis (too little inflammation and necrosis). There are several causes for fatty liver and the clinical history suggests here a diagnosis of fatty liver of pregnancy rather than a drug-induced fatty liver; moreover, more severe cholestasis and inflammation often accompany drug effects. The clinical course and the complete recovery of liver function abnormalities are in agreement with this diagnosis.

Acute fatty liver during pregnancy is a poorly understood disease that occurs during the third trimester of pregnancy.4 The frequency varies from 1:6600 to 1:13,000 pregnancies.5 In comparison, the incidence of the HELLP syndrome is 0.1 to 0.6%. Sheehan first described acute fatty liver of pregnancy in 1940.6 It can occur during the first as well as during subsequent pregnancies. Its predominant symptoms

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**Figure 1**

*Liver biopsy: an overview showing a central hepatic vein surrounded by regular hepatocytes with partial steatosis.*

There are no signs of fibrosis or inflammation.

**Figure 2**

*Liver biopsy showing a larger image of the same area as seen in figure 1.*

In the cytoplasm of the hepatocytes, a micro and macrovesicular steatosis is shown. In some hepatocytes the yellow-green bile is seen as a sign of cholestasis. There are only few lymphocytes and acidophilic bodies.
Table 1

Clinical characteristics of liver diseases specific to pregnancy and viral hepatitis

<table>
<thead>
<tr>
<th>TRIMESTER</th>
<th>SYMPTOMS</th>
<th>TYPICAL LABORATORY ABNORMALITIES</th>
</tr>
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<tbody>
<tr>
<td>Hyperemesis gravidurum</td>
<td>1 or 2</td>
<td>Nausea, vomiting</td>
</tr>
<tr>
<td>Intrahepatic cholestasis of pregnancy</td>
<td>2 or 3</td>
<td>Pruritus</td>
</tr>
<tr>
<td>Acute fatty liver of pregnancy</td>
<td>3</td>
<td>Upper abdominal pain, nausea, vomiting</td>
</tr>
<tr>
<td>Pre-eclampsia/ eclampsia</td>
<td>3 (late 2)</td>
<td>Upper abdominal pain, oedema, hypertension</td>
</tr>
<tr>
<td>HELLP syndrome</td>
<td>3 (late 2)</td>
<td>Upper abdominal pain, Nausea, vomiting, Hypertension</td>
</tr>
<tr>
<td>Viral hepatitis</td>
<td>All</td>
<td>Nausea, vomiting, fever, jaundice, Increased mortality with hepatitis E</td>
</tr>
</tbody>
</table>

APH = alkaline phosphatase, DIC = diffuse intravascular coagulation. In normal pregnancy, a slight increase in APh is normal.

are nausea and vomiting, epigastric pain, anorexia and jaundice. Itching is a rare symptom. The liver is usually small. Ascites can occur due to portal hypertension. Elevated liver transaminases are the predominant liver abnormalities. Liver synthesis can be severely disturbed as shown in our patient. Hepatic encephalopathy and diffuse intravascular coagulation can occur. Echography of the liver can show increased echogenicity due to steatosis. Histologically, a microvesicular fatty infiltration of the hepatocytes mainly in the central part of the liver lobules is observed. Often a mild inflammation with cholestasis is seen. Severe hepatocellular necrosis (as in fulminant viral hepatitis) is seldom seen. Analysis of the intrahepatic lipids shows an accumulation of mainly free fatty acids. The differential diagnosis with pre-eclampsia and the HELLP syndrome can be very difficult on clinical symptoms. In acute fatty liver a slight hypertension and oedema with proteinuria and intravascular coagulation may occur. In some cases only liver biopsy can solve the differential diagnosis. Liver biopsy, however, is seldom performed during pregnancy because of its associated morbidity. Furthermore, treatment for these syndromes is symptomatic and mainly aimed at stabilising the condition of the mother until delivery can be safely performed. If necessary, liver biopsy can be carried out, preferably under ultrasonographic control (after checking and correction of coagulation disorders).

The final treatment is induction of labour. Liver abnormalities return to normal, though this may take some time as was the case in our patient. There is no known medication for acute fatty liver. Conservative measures should be taken to minimise liver damage and prevent further maternal morbidity. These include correction of coagulation and electrolyte disorders and treating reflux oesophagitis (due to the intense vomiting) with proton pump inhibitors. Blood sugar levels need to be monitored and corrected. Encephalopathy and seizures should be treated appropriately (lactulose and antibiotics, magnesium or benzodiazepines and phenytoin). Acute fatty liver can deteriorate suddenly and progress rapidly to fulminant hepatic failure requiring admission to an intensive care unit. Once the diagnosis is made likely, immediate delivery should always be considered to reduce maternal mortality and morbidity, even if this means sacrificing the foetus. Rare cases have been reported of patients whose condition did not improve after delivery and liver transplantation was necessary.

Before 1970, maternal mortality was very high (70 to 80%). As a result of early diagnosis and termination of pregnancy the mortality is now less than 15%. The aetiology of acute fatty liver is still unknown. The histological abnormalities have similarities with disorders of the intramitochondrial oxidation of fatty acids. Recent literature shows a predominance of acute fatty liver in mothers who are heterozygous for a genetic abnormality in long chain 3-hydroxyacyl-coenzyme A dehydrogenase (LCHAD), which is an important enzyme in the β-oxidation of fatty acids in mitochondria. In children with LCHAD deficiency, the mother more often experienced an acute fatty liver or HELLP syndrome during pregnancy. All of these children had a specific mutation in the gene coding for LCHAD. This association between the heterozygous mother and the specific mutation in the child probably somehow contribute to the development of acute fatty liver syndrome. The co-occurrence of the HELLP syndrome may point to a common pathophysiological pathway. In view of these abnormalities, both mother and child should be screened for disorders in the mitochondrial β-oxidation.

In our patient, however, neither mother nor child had these abnormalities. In conclusion, when encountering liver function abnormalities during the third trimester of pregnancy, acute fatty liver should be considered. This rare disorder has a benign course when the diagnosis is considered at an early stage and delivery is initiated.
REFERENCES


Tan, et al. Acute fatty liver in pregnancy.

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