Liver Disease Associated with Pregnancy*

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ABSTRACT

Pregnancy is associated with altered liver function, particularly in serum enzymes. Anabolic steroids are responsible to some degree in mediating the physiologic and biochemical changes that occur during an uncomplicated pregnancy. However, several liver disorders are unique to pregnancy and include intrahepatic cholestasis of pregnancy, acute fatty liver of pregnancy, and hepatic dysfunction associated with pre-eclampsia and eclampsia. It is imperative for the clinician to diagnose these liver disorders in a timely manner and to institute appropriate management as maternal and fetal outcome are affected in an adverse manner if these conditions are left untreated.

Introduction

Acute and chronic forms of liver disease occur during pregnancy, including a group of liver disorders unique to pregnancy (table I). These may present special difficulties in diagnosis as the implications for the fetus and mother depend on appropriate identification and management. The purpose of this paper is to review the effects of pregnancy on liver function and to discuss diseases of the liver specifically related to pregnancy.

Liver Function Changes in Normal Pregnancy

While no significant anatomical or histological changes occur in the liver during the course of a normal human pregnancy, several alterations in liver function have been documented as shown on Table II.6 Alterations in the synthesis, catabolism, and serum concentration of various plasma proteins occur during gestation. Although a certain portion of the decrease in total serum protein and albumin may be accounted for by simple dilution caused by an increased total blood volume, this mechanism cannot account for the variable changes in the several globulin fractions.

Alterations in serum enzymes also occur during the course of an uncomplicated pregnancy. Of note, total serum alkaline phosphatase rises minimally in the first trimester to a two to four fold increase above normal values by term gestation. It has been shown that the placenta accounts for over 50 percent of the rise in alkaline phosphatase, with a further increase during labor.10 Levels of
TABLE I
Liver Disease Specifically Related to Pregnancy

<table>
<thead>
<tr>
<th>Condition</th>
</tr>
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<tbody>
<tr>
<td>Intrahepatic cholestasis of pregnancy (ICP)</td>
</tr>
<tr>
<td>Acute fatty liver of pregnancy (AFLP)</td>
</tr>
<tr>
<td>Eclampsia and spontaneous rupture of the liver</td>
</tr>
</tbody>
</table>

serum gamma glutamyl-transpeptidase (GGTP), lactic dehydrogenase, and ornithine transcarbamylase are also increased near term. However, serum aspartate aminotransferase (AST) and serum alanine aminotransferase (ALT) are only slightly increased near term with values usually within the range of normal. Substantial increases in serum triglyceride and serum cholesterol levels also occur during the last trimester of pregnancy.

Serum bilirubin may be slightly elevated in approximately five percent of otherwise normal pregnancies with clinical jaundice occurring in approximately one in 1,500 gestations. However, a significant rise in serum bilirubin level should alert the clinician to consider either liver or hematologic disease.

SEX HORMONE EFFECTS ON LIVER FUNCTION

The role that anabolic steroids, estrogens and progestins play in mediating the physiologic and biochemical alterations during an uncomplicated pregnancy is not entirely clear. Anabolic steroids, particularly those containing a methyl or ethyl group in the C-17 position, are known to cause cholestasis and result in an increased serum level of alkaline phosphatase, 5'-nucleotidase, GGTP, bile acids, and bilirubin. Estrogens increase hepatic rough endoplasmic reticulum and accelerate the synthesis of proteins. Further, estrogenic compounds can reduce lipoprotein lipase activity and accelerate hepatic triglyceride biosynthesis, leading to an elevation of serum lipids.

Intrahepatic Cholestasis of Pregnancy

This syndrome, consisting of pruritis and mild jaundice occurring in the last trimester of pregnancy, was originally described by Thorling in Swedish women. Intrahepatic cholestasis of pregnancy (ICP) is second only to viral hepatitis in causing jaundice during pregnancy and accounts for approximately 20 percent of all cases of clinical jaundice. The frequency of ICP varies in different racial groups and may complicate as many as 2.4 percent of pregnancies in Scandinavian and Chilean women. Approximately 50 percent of women may suffer from ICP in subsequent pregnancies. Although the mechanism of cholestasis is uncertain, substantial evidence suggests an unusual sensitivity to estrogenic steroids is important in the pathogenesis of ICP. This is suggested by the observation that individuals with this syndrome develop similar clinical symptoms and biochemical changes while taking oral contraceptives.

TABLE II
Alterations in Liver Function Tests in Normal Pregnancy

<table>
<thead>
<tr>
<th>Elevated</th>
<th>Period of Maximum Change (Trimester)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactic dehydrogenase</td>
<td>Third</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>Third</td>
</tr>
<tr>
<td>Cholesterol and lipids</td>
<td>Third</td>
</tr>
<tr>
<td>Ceruloplasmin</td>
<td>Third</td>
</tr>
<tr>
<td>Transferrin</td>
<td>Third</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>Third</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Decreased</th>
<th>Period of Maximum Change (Trimester)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein</td>
<td>Second</td>
</tr>
<tr>
<td>Albumin</td>
<td>Second</td>
</tr>
<tr>
<td>Gamma globulin</td>
<td>Third</td>
</tr>
</tbody>
</table>
tive medications containing estrogens. Genetic factors may also be involved as a familial occurrence of ICP has been shown and provides evidence that the inheritance is Mendelian dominant. An occasional but major complication of ICP on the mother is postpartum hemorrhage, presumably owing to a prolongation of prothrombin time as a result of vitamin K deficiency. There also seems to be an increased risk of premature labor (60 percent) and perinatal mortality owing to prematurity.

CLINICAL FEATURES

The characteristic feature of ICP is onset of pruritis at the beginning of the third trimester followed in one to two weeks by the onset of mild jaundice, dark urine, and light colored stools. Rarely, the pruritis may present as early as the sixth week of pregnancy. There is an increased incidence of emesis in early pregnancy in women with ICP, thus suggesting the existence of an underlying metabolic disorder throughout pregnancy. Pruritis can involve any area of the body and is more severe at night. The insomnia owing to itching can lead to irritability and fatigue. Shortly after delivery, the pruritis resolves within 24 hours, with jaundice resolving subsequently.

BIOCHEMICAL CHANGES

Although the physical exam is unremarkable in ICP, the laboratory findings are consistent with cholestasis with marked elevation of serum alkaline phosphatase (7 to 10 fold), and 5'-nucleotidase. Total serum bilirubin is usually less than five mg per 100 ml and rarely above 10 mg per 100 ml, with the major fraction being conjugated. Serum bile acid levels are markedly increased (10 to 100 fold) with a rise in cholic as well as in chenodeoxycholic and deoxycholic acids. Presumably, the pruritis in ICP is secondary to the deposition of bile acids in the skin. Serum amino transferases are usually only moderately elevated with values of AST and ALT comparable to those seen in uncomplicated pregnancies. Occasionally, prothrombin time may be prolonged because of malabsorption of Vitamin K when jaundice appears early in pregnancy.

HISTOLOGIC FEATURES

Histologically, the liver in ICP shows characteristic features of cholestasis with canalicular bile plugs which are most prominent around the central veins. Mild Kupffer cell proliferation and periodic-acid Schiff (PAS)-positive granules are seen in macrophages. However, the architecture of the liver remains intact, and the portal areas are normal. There is little evidence of parenchymal necrosis, although in some areas enlarged and irregular mitochondria may be seen in parenchymal cells.

MANAGEMENT

Generally, therapy of ICP is directed at treating the pruritis coagulopathy and observing for onset of premature labor. The drug of choice for lowering serum and skin bile acid levels is cholestyramine with doses as high as 20 g per day occasionally required for relief. Prothrombin time should be monitored as cholestyramine adds to the malabsorption of vitamin K already present in cholestasis. Vitamin K in a dose of 10 mg orally per day may prevent the abnormality of prothrombin time.

ACUTE FATTY LIVER OF PREGNANCY

Acute fatty liver of pregnancy (AFLP) is a potentially fatal, uncommon disorder.
that may complicate the last trimester of pregnancy.\textsuperscript{3,20} It was first recognized in 1934\textsuperscript{17} and is estimated to occur in roughly 1 per 13,000 deliveries. It usually occurs after the 35th week of pregnancy but has been noted as early as the 30th week and most often affects primiparas, particularly those carrying twins or male fetuses. The cause of AFLP is unknown, but it clearly is not an infectious process. Increased levels of fatty acids have been found in the livers of patients, suggesting a toxic effect of these compounds. Marked abnormalities of the structure of the mitochondria, as well as abnormalities in the urea cycle enzymes suggest a resemblance to Reye's syndrome. However, in contrast to the findings in Reye's syndrome, the mitochondrial matrix does not expand in fatty liver of pregnancy, nor does it become thickened, flocculent, or granular.\textsuperscript{21}

**Clinical Features**

The syndrome is characterized by the sudden onset of nausea, severe recurrent vomiting followed by abdominal pain, and headache.\textsuperscript{16} The abdominal pain may be epigastric, suggesting a worsening of reflux esophagitis that commonly occurs in pregnancy. Jaundice follows shortly, as well as bleeding from puncture sites and hematemesis. Many patients have mild hypertension and peripheral edema, suggestive of preeclampsia. The abdomen may be tender, but the liver is small and not palpable. Seizures and frank coma are later, more ominous manifestations.

Spontaneous labor frequently occurs with the delivery of a dead fetus. Following delivery, there is significant improvement in the patient's status.

**Laboratory Changes**

Early diagnosis of acute fatty liver of pregnancy is critical as it leads to prompt treatment, improving both maternal and fetal survival. Liver aminotransferase levels should be measured immediately in any woman in the third trimester of pregnancy who has the symptoms noted previously. Elevated serum aminotransferase, at levels in the range of 300 to 500 units per ml, should prompt further laboratory evaluation. The peripheral blood smear shows thrombocytopenia and normoblasts, as well as burr cells, fragmented red cells, and Howell-Jolly bodies, indicating microangiopathic hemolysis.\textsuperscript{1,2}

There is evidence of disseminated intravascular coagulopathy as fibrinogen levels are below the normal values for pregnancy and fibrin split products are present. Prothrombin time is markedly prolonged at greater than 25 seconds. Serum bilirubin is usually less than 10 mg per dl but alkaline phosphatase is markedly elevated. Other abnormal laboratory values include, an elevated blood ammonia level, decreased blood glucose level, increased white cell count, often above $20 \times 10^9$ per L, an increased blood urea nitrogen, uric acid and creatinine levels. The maternal mortality rate is extremely high, varying between 65 to 90 percent with fetal mortality somewhat less.

**Histologic Changes**

The liver is small and pale on gross examination in AFLP. Microscopically, hepatocytes, particularly those in the pericentral area, are swollen and pale with centrally located nuclei. The pale, vacuolated appearance of hepatocytes is due to the fat-filled microvesicles which can be demonstrated using fat stains such as oil red O on fresh-frozen biopsy specimens. The portal triad is unaffected, but bile thrombi are often seen in the central areas.\textsuperscript{4,6} Lobular disarray is commonly seen, as well as patchy hepatocellular necrosis, lobular inflammation, and reticulin condensation.
Prompt diagnosis is essential to appropriate therapy. Once the diagnosis of AFLP is suspected, the patient should be managed with fluid and electrolyte solutions and maintenance of normal serum glucose. Fresh frozen plasma should be used to correct the clotting abnormalities and blood transfusion for controlling hemorrhage. As soon as the mother's clinical condition has stabilized, the infant should be delivered either by induction or cesarian section. Patients who survive have a rapid normalization of liver function tests, and those who have undergone subsequent pregnancies have not suffered a recurrence of this disorder.

Pre-Eclampsia and Eclampsia

In approximately 50 percent of pregnancies classified as eclampsia or pre-eclampsia, there is evidence of liver involvement as part of the general vascular disorder. If disseminated intravascular coagulation accompanies the pre-eclampsia or eclampsia (approximately 10 percent of cases), liver injury is common and known by the mnemonic HELLP syndrome (hemolysis, elevated liver enzymes, low platelets).

Clinical Features

Following the onset of hypertension and proteinuria, patients will present in the last trimester of pregnancy with nausea, vomiting, as well as moderate to severe epigastric pain and occasionally jaundice. In addition to the physical findings common to pre-eclampsia and eclampsia, patients will exhibit tender hepatomegaly.

Biochemical Changes

Changes in liver function associated with pre-eclampsia and eclampsia include a markedly elevated alkaline phosphatase and rise in AST to levels as high as 1,000 IU per ml. There is good correlation between the degree of abnormal liver function and clinical course. The bilirubin elevation that accompanies this disorder is usually mild at levels <6 mg per dl. Hemolysis which accompanies the disseminated intravascular coagulation is a major contributing factor of the jaundice.

Histologic Changes

Microscopically, the changes in the liver of patients with pre-eclampsia or eclampsia differ from those of fatty liver of pregnancy. Characteristically, there are fibrin thrombi in the hepatic sinusoids associated with surrounding focal necrosis of the hepatocytes. Diffuse hemorrhagic necrosis, as well as centrilobular necrosis, is seen in severe cases, particularly when shock occurs.

Management

As the predisposing condition of this disorder is pre-eclampsia or eclampsia of pregnancy, treatment should be first directed at stabilizing this disorder. Where there is disseminated intravascular coagulation, prompt delivery of the fetus is recommended. By 12 to 24 hours following delivery, there is reversal of hypertension and liver derangement.

Summary

A careful physical examination and performance of liver function tests are essential in evaluating the pregnant patient who presents with symptoms that include gastrointestinal complaints, pruritis, abdominal pain, edema, and icterus. Measurements of excretory and synthetic functions of the liver should include determination of serum total protein, albumin and globulin; direct
and total bilirubin; alkaline phosphatase or 5'-nucleotidase; ALT and AST; cholesterol; and prothrombin time.

A timely diagnosis of the major hepatic disorders associated with pregnancy will lead to appropriate management, with improved health and survival in both the mother and fetus.

References