PRACTICE GUIDELINES

Liver Disease in the Pregnant Patient

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PREAMBLE

Guidelines for clinical practice are intended to suggest preferable approaches to particular medical problems as established by interpretation and collation of scientifically valid research, derived from extensive review of published literature. When data are not available that will withstand objective scrutiny, a recommendation may be made based on a consensus of experts. Guidelines are intended to apply to the clinical situation for all physicians without regard to specialty. Guidelines are intended to be flexible, not necessarily indicating the only acceptable approach, and should be distinguished from standards of care that are inflexible and rarely violated. Given the wide range of choices in any health care problem, the physician should select the course best suited to the individual patient and the clinical situation presented. These guidelines are developed under the auspices of the American College of Gastroenterology and its practice parameters committee. These guidelines are also approved by the governing boards of the American Gastroenterological Association, the American Society for Gastrointestinal Endoscopy, and the American Association for the Study of Liver Diseases. Expert opinion is solicited from the outset for the document. Guidelines are reviewed in depth by the committee, with participation from experienced clinicians and others in related fields. The final recommendations are based on the data available at the time of the production of the document and may be updated with pertinent scientific developments at a later time.

INTRODUCTION

The cause of liver disease in pregnancy can be difficult to diagnose. Making the correct diagnosis is of paramount importance, as failure to do so can result in morbidity or mortality for not only the mother, but also for her fetus. Many practitioners are unfamiliar with the normal physiology of pregnancy. In addition, the practitioner in this setting is faced with disorders unique to pregnancy and thereby unfamiliar, and with disorders that commonly occur outside of pregnancy but that can be altered in their course by the pregnancy.

Pregnancy causes very few alterations in the results of standard liver tests. The aminotransferases (AST and ALT), γ-glutamyl transeptidase (GGTP), total bilirubin, and serum bile acid level remain within the normal range. The alkaline phosphatase rises modestly in the third trimester. The albumin level is lower than in nonpregnant women, and the cholesterol level higher. Thus, elevations in aminotransferases or GGTP signify pathology, and should prompt a search for disease.

RECOMMENDATIONS

Use the gestational age of the pregnancy as the best guide to the differential diagnosis of liver disease in the pregnant woman.

Hyperemesis gravidarum has its onset in the first trimester. Cholestasis of pregnancy usually begins in the second trimester. The disorders associated with preeclampsia occur in the second half of pregnancy, usually in the third trimester toward term. Acute viral hepatitis in pregnancy can occur in any trimester of pregnancy, but can be more severe in the third trimester. In patients with portal hypertension, variceal bleeding usually occurs in the second trimester as the intra-vascular volume expands, or occurs at delivery.

Disorders Unique to Pregnancy

Hyperemesis gravidarum should be considered in the differential diagnosis of abnormal liver tests presenting in the first trimester.

Nausea is so common in early pregnancy that “morning sickness” is taken as a typical early symptom of pregnancy. In extreme cases, this leads to intractable nausea and vomiting, with dehydration and ketosis. As a rule, hyperemesis gravidarum resolves by wk 20 of gestation, but in some patients it may persist for the entire gestation. It may be accompanied by transient hyperthyroidism. The pathogenesis is unknown. In the modern era, the outcome is good, with no ill effects for the mother or fetus and with no increase in prematurity or birth defects.

Involvement of the liver is common but not invariable. The aminotransferases are abnormal in 50% of patients, usually <1000 U. Jaundice may occur rarely in severe cases. The liver biopsy shows minor, nonspecific changes. The differential diagnosis should include liver diseases associated with nausea, such as viral hepatitis, and gastrointestinal diseases such as gastric outlet obstruction from peptic ulcer disease. Viral serologies and upper endoscopy may be useful in ruling out these other disorders.

Management is empiric, aimed at alleviating the vomiting, and includes gut rest and i.v. fluids. No comparative
trials exist, but antiemetics such as promethazine, odanestrone, or droperidol have been reported to be useful (5, 6). Rare patients will require enteral or parenteral feeding (7). Corticosteroids have been reported to be effective (8).

*Cholestasis of pregnancy is common, and should be considered in the differential diagnosis of abnormal liver tests presenting initially in the second trimester. Affected pregnancies are at increased risk for prematurity and stillbirth, and early delivery should be considered when possible.*

The prevalence of cholestasis of pregnancy varies from 0.7% in the United States (9) to 6.5% in Chile (10). Itching is the cardinal symptom. The clinical spectrum is broad, ranging from modest pruritus to intractable itching associated with jaundice (11). The symptoms usually begin in the second trimester, but may start either earlier or later. The pruritus may vary in intensity during pregnancy, and it resolves within days after delivery. The pathogenesis is unclear, but it is known that affected patients are sensitive to the cholestatic effects of estrogen (12). Progesterone may be involved in the pathogenesis (13). Ethnicity and inheritance play a role (14, 15).

Laboratory tests may suggest hepatitis rather than cholestasis, as the GGTP is normal and the aminotransferases may be quite elevated (≤1000 U) (16). The most useful laboratory test is the serum bile acid level, which may be measured as cholyglycine (16). Liver biopsy shows only bland cholestasis, and generally is not warranted.

Effective treatment is limited. Initial therapy is aimed at symptomatic improvement of the pruritus with sedatives and antipruritics. Ursodeoxycholic acid in a dose of 13–15 mg/kg/day, divided twice a day, has shown in small controlled trials to be partially effective (13, 17). No adverse effects on the fetus have been reported, but this drug has not yet been proven to be safe in pregnancy. Cholestyramine has been used, but aggravates the fat malabsorption associated with this condition. Care should be taken in patients treated with cholestyramine to give supplementary vitamin K, which may be further depleted by the resin. S-adenosyl-methionine has been advocated as treatment, but with inconsistent results (10, 18). No data exist in the literature to support the benefit of using rifampin or grapefruit juice. The only completely effective therapy is delivery.

Several studies demonstrate an increase in prematurity and sudden intrauterine death in affected pregnancies (19, 20). Unfortunately, in one study, prospective monitoring of the fetus was not effective in preventing these adverse events. Consideration should be given to early delivery, at 38 wk in most cases, and at 36 wk in severe cases if fetal lung maturity has been reached (21, 22). The only long term sequela for the mother is a modest increase in risk for gallstones (23).

**HELLP (hemolysis, elevated liver tests, low platelets) syndrome and acute fatty liver of pregnancy should be considered in the differential diagnosis of abnormal liver tests in the second half of pregnancy, usually in the third trimester.**

In HELLP syndrome, patients have signs of pre-eclampsia as well as thrombocytopenia. Pre-eclampsia affects 3–10% of pregnancies, and HELLP syndrome occurs in 20% of patients with severe pre-eclampsia (24). The most common symptom is abdominal pain, but it occurs in only 65% of affected patients. Many patients have no specific symptoms, and the condition is diagnosed when laboratory tests are done on patients with pre-eclampsia. Renal failure or seizures (eclampsia) may complicate the pre-eclampsia. As many as 30% of patients with HELLP present, or are diagnosed, after delivery (24). As with pre-eclampsia, the pathogenesis of this condition is unknown (25).

Aminotransferase elevations are the hallmark of this syndrome, with AST elevations ranging from 70 to 6,000, with a mean of 250 in a large series (24). This is not a true hepatic failure, and the prothrombin time is normal except in the most severe cases complicated by disseminated intravascular coagulation. The thrombocytopenia may be modest to very severe. Most patients are not jaundiced, and the hemolysis is manifested as schistocytes and buff cells on peripheral smear. The liver biopsy shows the findings typical of pre-eclampsia: periportal hemorrhage and fibrin deposition. The severity of this histological changes is not uniformly reflected in the laboratory abnormalities (26), and biopsy is not usually needed for diagnosis. The differential diagnosis includes viral hepatitis or, rarely, ITP. Viral serologies are useful.

Management is obstetrical, with careful fetal monitoring and prompt delivery. Temporizing management has been advocated by some (27), but caution is advisable. HELLP syndrome is presumed to be the initial pathology that leads, in rare cases, to subcapsular hemorrhage with hepatic rupture, often resulting in death of both the mother and fetus. Such patients present with shock and hemoperitoneum, and are best managed surgically by a trauma team experienced in liver lacerations (28). HELLP syndrome may also underlie hepatic infarction, associated with very high levels of aminotransferase (>5000), and anemia. The infarctions are best seen on CT or MRI scanning, and resolve spontaneously (29). HELLP syndrome and hepatic hematoma may recur in subsequent pregnancies (30, 31). Once delivered, the infants have no liver involvement or thrombocytopenia and have an outcome appropriate for gestational age (32). There are no long term hepatic sequelae for the mother.

**Patients with acute fatty liver of pregnancy have true hepatic dysfunction, and may, or may not, have signs of pre-eclampsia and HELLP syndrome.**

Acute fatty liver of pregnancy (AFLP) is rare, reported to occur in 1/13,000–16,000 deliveries (33, 34). Like the HELLP syndrome, it may present postpartum. This may be an underestimate, as the spectrum of clinical involvement is broad, ranging from asymptomatic elevations in aminotransferases to fulminant hepatic failure with jaundice,
profound coagulopathy, hepatic coma, and hypoglycemia, requiring maximum supportive care (35). Nephrogenic diabetes insipidus may complicate the course (36).

The pathogenesis remains unclear. Preeclampsia is present in 50% of cases (37). However, the hepatic histology is distinct from that of HELLP syndrome, and involves a microvesicular fatty infiltrative disorder similar to that in Reye’s syndrome. Recent studies document that infants born of affected pregnancies can be deficient in one of the enzymes of mitochondrial beta oxidation of fatty acids, long chain 3-hydroxyl-acyl CoA dehydrogenase (LCHAD) (38). Affected infants are at risk for developing nonketotic hyperglycemic coma, often with death, when stressed and fasted. Some women affected with AFLP have been shown to be heterozygous deficient for LCHAD, and it appears that many cases of AFLP are due to an inherited partial deficiency in beta oxidation of fatty acids, brought out in susceptible women by a fetus that is fully deficient, or by the stress of preeclampsia (39). Not all workers have been able to demonstrate such abnormalities (40). DNA testing in now available for several known defects in LCHAD (41).

Laboratory tests in AFLP demonstrate a long prothrombin time and low fibrinogen. The aminotransferases are usually elevated but <1000 U. Hypoglycemia and hyperammonemia may complicate the course. The liver biopsy shows hepatic vacuolization and pallor in the central zone, confirmed on special stains or electron microscopy to be microvesicular fat. Because of the hepatocyte unrest and portal infiltrate, the biopsy may be misread as showing viral hepatitis (35). The differential diagnosis includes fulminant hepatic failure of other etiologies, especially viral, such as hepatitis E in endemic areas (42), or herpes simplex (43). HELLP syndrome may be in the differential diagnosis, if the platelet count is low because of attendant severe liver disease with disseminated intravascular coagulation. Given the clinical setting, liver biopsy usually is not indicated.

Management consists of prompt delivery with maximal support as the liver recovers. Liver transplantation has been done for AFLP (44), but should not be necessary with early diagnosis and delivery. Because of the association with LCHAD deficiency, consideration should be given to testing both the mother and child for this disorder.

Liver Disorders Coincidental With Pregnancy
Consider viral or drug-induced hepatitis, gallstone disease, or malignancy in the differential diagnosis of abnormal liver tests in any of the trimesters of pregnancy.

Pregnant women may be affected by intercurrent diseases during pregnancy, and some of these are exacerbated by the underlying pregnant state. Viral hepatitis is the most common liver disease, and acute viral hepatitis can present problems in the pregnant woman. The natural course of acute hepatitis A or B is not altered in the pregnant woman, and interruption of the pregnancy or early delivery is not indicated. But acute hepatitis B in the second or third trimester may pose a risk for transmission to the baby, and immunoprophylaxis with hepatitis B hyperimmune globulin as well as the standard vaccination program is indicated for the neonate. For unclear reasons, both herpes simplex and hepatitis E, which is endemic in the Middle East and in Asia but has not been reported in the United States except in travelers, can cause fulminant hepatic failure with a high maternal mortality when affecting the pregnant woman, particularly during the third trimester (42, 43). Hepatitis serologies are useful in the differential diagnosis of possible viral hepatitis in pregnancy. A history of potential exposure should be sought. Typically, patients with herpes simplex have marked elevations of aminotransferases (3000–6000 U) but are not jaundiced. Such patients usually have a rash and can be effectively treated with intravenous acyclovir, thus not requiring early delivery (43).

Pregnancy predisposes to gallstone disease, and the biliary sludge and gallstones that form during pregnancy may resolve after delivery with the return to nonpregnant physiology (45, 46). If possible, acute cholecystitis is best managed medically in the first and third trimesters, when the risk of premature delivery prompted by surgery is greater than in the second trimester. Choleodocholithiasis can be managed with endoscopic retrograde cholangiography, which may be necessary in the management of symptomatic common bile duct stones leading to cholecystitis or pancreatitis (47).

Pregnancy is associated with a heightened procoagulant state, and patients who have an underlying procoagulant state, such as an inherited deficiency in protein C or protein S, or the presence of an anticardiolipin or antiphospholipid antibody, may be at an increased risk for thromboses during pregnancy (48, 49). This may take the form of Budd-Chiari syndrome, thrombosis of the major hepatic outflow tract, leading to painful hepatomegaly, often with liver failure, and portal hypertension with ascites. Liver transplantation may be necessary in this setting (50). Life-long anticoagulation is indicated in patients who survive.

Malignancy with metastases to the liver may occur in pregnancy, and there may be some permissive effect of pregnancy promoting tumor growth (51). The presence of a palpable liver during pregnancy, when the liver is usually forced up under the rib cage, is ominous, and should prompt investigation with laboratory tests and imaging (52).

Chronic hepatitis B or C requires no therapy in pregnancy, but poses a risk of transmission to the offspring.

Pre-existing liver disease, when severe, usually is not compatible with pregnancy, and such patients are anovulatory and infertile. However, most patients who are chronically infected with hepatitis B or hepatitis C are well, and can conceive and carry the gestation with no increased risk to themselves. There is, however, a risk to their offspring. For women with hepatitis B who are hepatitis Be antigen–positive, the risk of transmission of the virus to the baby is 90% (53). Because of this risk, all pregnant women are now screened for the presence of hepatitis Bs antigen (54, 55). If positive, the infant is passively immunized at birth with
hepatitis B hyperimmune globulin along with the hepatitis B vaccine that is now given as a standard to all newborns. The risk of transmission of hepatitis C is substantially lower (6–10%) and depends on the mother’s level of viremia (56). For example, the risk of hepatitis C transmission is higher for mothers with HIV, who have high levels of hepatitis C viremia. Unfortunately, no effective immunoprophylaxis is available for lowering this risk, and gamma globulin does not prevent transmission. Breast feeding is safe for the offspring of mothers with hepatitis B, once appropriately immunized, and with hepatitis C (57).

Patients with autoimmune hepatitis or with Wilson’s disease improve on therapy, regain their fertility, and can conceive. Such patients should continue their therapy during the pregnancy (58, 59). Like all patients with chronic liver disease, they are at increased risk for preeclampsia and premature delivery (60).

Many survivors of liver transplantation are young women, who return to normal fertility after the transplant. Like the patients with chronic liver disease, they are at increased risk for pregnancy complications such as hypertension or prematurity, but their infants do not have an increased risk for birth defects (61).

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References

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