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REVIEW

Update in Liver Diseases with Pregnancy

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ABSTRACT

Liver disease in pregnancy encompasses a spectrum of diseases encountered during gestation and the postpartum period that result in abnormal liver function tests, hepatobiliary dysfunction, or both. It occurs in 3% to 10% of all pregnancies.Several disorders contribute to liver disease in pregnancy. These include diseases induced by the pregnancy such as acute fatty liver of pregnancy (AFLP) and intrahepatic cholestasis of pregnancy (IHCP), diseases that existed before pregnancy that could potentially flare during pregnancy such as autoimmune hepatitis and Wilson's disease, and diseases not related to the pregnancy but that could affect the pregnant woman at any time during gestation such as viral hepatitis.

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Key words: Liver diseases; Pregnancy

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REVIEW

Abnormal liver tests occur in 3%-5% of pregnancies, with many potential causes, including coincidental liver disease (most commonly viral hepatitis or gallstones) and underlying chronic liver disease. However, most liver dysfunction in pregnancy is pregnancy-related and caused by 1 of the 5 liver diseases unique to the pregnant state: these fall into 2 main categories depending on their association with or without preeclampsia. The preeclampsia-associated liver diseases are preeclampsia itself, the hemolysis (H), elevated liver tests (EL), and low platelet count (LP) (HELLP) syndrome, and acute fatty liver of pregnancy. Hyperemesis gravidarum and intrahepatic cholestasis of pregnancy have no relationship to preeclampsia. Although still enigmatic, there have been recent interesting advances in understanding of these unique pregnancy-related liver diseases. Hyperemesis gravidarum is intractable, dehydrating vomiting in the first trimester of pregnancy; 50% of patients with this condition have liver dysfunction. Intrahepatic cholestasis of pregnancy is pruritus and elevated bile acids in the second half of pregnancy, accompanied by high levels of aminotransferases and mild jaundice. Maternal management is symptomatic with ursodeoxycholic acid; for the fetus, however, this is a high-risk pregnancy requiring close fetal monitoring and early delivery. Severe preeclampsia itself is the commonest cause of hepatic tenderness and liver dysfunction in pregnancy, and 2%-12% of cases are further complicated by hemolysis (H), elevated liver tests (EL), and low platelet count (LP)—the HELLP syndrome. Immediate delivery is the only definitive therapy, but many maternal complications can occur, including abruptio placentae, renal failure, subcapsular hematomas, and hepatic rupture. Acute fatty liver of pregnancy is a sudden catastrophic illness occurring almost exclusively in the third trimester; microvesicular fatty infiltration of hepatocytes causes acute liver failure with coagulopathy and encephalopathy. Early diagnosis and immediate delivery are essential for maternal and fetal survival. (HEPATOLOGY 2008.)

Most pregnant women are young and healthy, and physiological changes in pregnancy must not be mistaken for liver dysfunction (Table 1). Abnormal liver tests occur in 3%-5% of pregnancies, with many potential causes (Table 2). Although relatively uncommon, any liver disease can occur coincidentally in the pregnant patient and pregnancy may occur in a patient with underlying chronic liver disease. However, most liver dysfunction in pregnancy is pregnancy-related[1] and due to one of the 5 liver diseases unique to the pregnant state-hyperemesis gravidarum (HG), intrahepatic cholestasis of pregnancy (ICP), preeclampsia, the HELLP syndrome, and acute fatty liver of pregnancy (AFLP). These conditions are complications of pregnancy itself, and each has a characteristic timing in relation to the trimesters of pregnancy: HG in the first trimester, ICP in the second half of pregnancy, and the other 3 in the third trimester.

Liver diseases unique to pregnancy fall into 2 main categories depending on their association with or without preeclampsia. The preeclampsia-associated liver diseases are preeclampsia itself, the HELLP syndrome, and AFLP. HG and ICP have no relationship

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Table 1 Physiological Changes in Liver Tests During Normal Pregnancy.

Test	Normal Range
Bilirubin	Unchanged or slightly decreased
Aminotransferases	Unchanged
Prothrombin time	Unchanged
Alkaline phosphatase	Increases 2 to 4-fold
Fibrinogen	Increases 50%
Globulin	Increases in α and β globulins
α-fetoprotein	Moderate increase, especially with twins
WBC	Increases
Ceruloplasmin	Increases
Cholesterol	Increases 2-fold
Triglycerides	Increases
Globulin	Decreases in gamma-globulin
Hemoglobin	Decrease in later pregnancy

Table 2 Diagnostic Categories of Liver Disease in Pregnancy (Trimester of Occurrence).

Coincidental to Pregnancy	Underlying Chronic Liver Disease (1–3)	Diseases Unique to Pregnancy
*		

Budd-Chiari syndrome, when associated with pregnancy, usually occurs in the postpartum period.

Viral hepatitis (1–3)	Chronic hepatitis B or C	Hyperemesis gravidarum (1)
Gallstones (1–3)	Autoimmune hepatitis	Intrahepatic cholestasis of pregnancy (late 2,3)
-	-	
Drugs (1–3)	Primary sclerosing cholangitis	-
Sepsis (1–3)	-	Preeclampsia (3)
Budd-Chiari*	Wilson disease	HELLP syndrome (3)
-	Primary biliary cirrhosis (rare)	Acute fatty liver of pregnancy (3)
-	-	
-	Cirrhosis (uncommon)	-

to preeclampsia. Although still enigmatic, there have been recent interesting advances in understanding of these unique pregnancy-related liver diseases.

LIVER DISEASES UNIQUE TO PREGNANCY

Hyperemesis Gravidarum

HG, occurring in 0.3% of pregnancies, is intractable vomiting in the first trimester of pregnancy of such severity as to necessitate intravenous hydration. Immunological, hormonal, and psychological factors associated with pregnancy may play an etiologic role and risk factors include hyperthyroidism, psychiatric illness, molar pregnancy, preexisting diabetes, and multiple pregnancies[2, 3].

The diagnosis is clinical-intractable, dehydrating vomiting, typically between 4 and 10 weeks' gestation. Liver dysfunction occurs in 50% patients with aminotransferases up to 20-fold elevation and with occasional jaundice[2]. Uncomplicated vomiting in pregnancy does not cause liver dysfunction. Viral hepatitis must be excluded. Liver biopsy is needed only to exclude more serious disease; the hepatic histological appearance is generally normal or shows bland cholestasis. Hospitalization is necessary for rehydration, nutritional support, and symptomatic measures with antiemetics; occasionally steroids are used.

Intrahepatic Cholestasis of Pregnancy

ICP is defined as pruritus and elevated bile acid levels which appear in the second half of pregnancy and disappear after delivery, typically to recur in subsequent pregnancies. It is second only to viral hepatitis as a cause of jaundice in pregnant women.

Etiology: ICP is associated with abnormal biliary transport across the canalicular membrane, the etiology of which is probably heterogeneous, with hormonal, genetic and exogenous factors exerting different influences on the hepatocyte or canalicular membrane of different individuals. It is related in some way to female sex hormones—the temporal relationship to hormone levels in 3rd trimester, increase in twin pregnancies, precipitation by exogenous progesterone in 3rd trimester. Sex hormones have known cholestatic effects, including inhibition of the bile salt export pump, and an abnormal metabolic response to increased hormones in pregnancy may cause ICP. Impaired sulfation and abnormalities in progesterone metabolism have been found in ICP[4].

The recognition of familial cases and high incidence in certain ethnic groups have long suggested a genetic predisposition to ICP. Pedigree analysis of family members of a child with progressive familial intrahepatic cholestasis has identified a mutation in the MDR3 (ABCB4) gene associated with ICP. MDR3 is the transporter for phospholipids across the canalicular membrane, and mutations may result in loss of function and raised bile acids as a secondary effect[5]. At least 10 different MDR3 mutations have been identified in ICP, and MDR3 mutations may account for 15% of cases of ICP[5–8]. Exogenous factors also may play an etiologic role. ICP recurs in only 45%-70% of pregnancies and with variable intensity, and there is a clear seasonal variability. It has striking geographical variations, and dietary factors such as selenium deficiency have been implicated in some studies from Chile[9].

Fetal complications in ICP are placental insufficiency, premature labor, and sudden fetal death, probably due to elevated fetal levels of bile acids (BA). Fetal BA are normally transported across the placental membrane to the maternal circulation; high maternal levels of BA correlate with fetal morbidity and mortality[10]. Abnormal placental BA transport from fetal to maternal circulation, increased maternal BA levels, and immaturity of fetal transport systems may all contribute to elevated fetal BA levels in ICP.

Clinical Features and Diagnosis: Pruritus typically starts around 25 to 32 weeks of gestation, but occasionally earlier, even in the first trimester. It affects all parts of the body, is worse at night, and in severe cases, the patient may be suicidal. Occasionally the cholestasis is complicated by diarrhea or steatorrhea. Jaundice occurs in 10%-25% of patients, 2-4 weeks after the pruritus. Aminotransferases levels vary from mild to 10-fold to 20-fold elevations; bilirubin is usually less than 5 mg/dL. Alkaline phosphatase will be elevated though diagnostically unhelpful in pregnancy; mildly elevated levels of gamma glutamyltransferase are found in fewer than 30% cases. The most specific and sensitive marker of ICP is serum BA levels of greater than 10 μmol/L and up to 100-fold elevated.

Typical clinical features in the absence of other liver diseases is strongly suggestive of ICP, especially if the pruritus has been present in other pregnancies and then disappeared immediately after delivery. Diagnosis in the first pregnancy is presumptive, made on clinical grounds alone, and can be confirmed only with rapid postpartum resolution. Elevated BA levels add weight to the diagnosis but are not routinely available. Liver biopsy is only needed to exclude more serious liver disease (Table 3). The differential diagnosis of cholestasis in pregnancy is wide and includes viral hepatitis and gall stones; however, pregnancy is a cholestatic and pruritogenic state and may therefore unmask underlying chronic liver disease such as primary sclerosing cholangitis or hepatitis C.

Management: Management of ICP is 2-fold: symptomatic therapy for the mother and close monitoring and early delivery for the fetus. Pruritus and liver dysfunction resolve immediately after delivery, with no maternal mortality. Withdrawal of exogenous progesterone may cause remission of pruritus before delivery. Fat-soluble vitamin supplementation at the time of delivery may be needed with severe steatorrhea.

Ursodeoxycholic acid (UDCA), generally in doses of 10 to 15 mg/

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Table 3 Distinguishing Features of Intrahepatic Cholestasis of Pregnancy (ICP), the HELLP Syndrome and Acute Fatty Liver of Pregnancy (AFLP).

	ICP	HELLP	AFLP
% Pregnancies	0.1% (USA)	0.2%–0.6%	0.005%–0.01%
Onset/trimester	25–32 weeks	3 or postpartum	3 or postpartum
Family history	Often	No	Occasionally
Presence of preeclampsia	No	Yes	50%
Typical clinical features	Pruritus	Hemolysis Thrombocytopenia (<50 000 often)	Liver failure with coagulopathy, encephalopathy hypoglycemia, DIC
-	Mild jaundice	-	-
-	Elevated bile acids	-	-
-	Vitamin K↓	-	-
Aminotransferases	Mild to 10–20-fold elevation	Mild to 10–20-fold elevation	300–500 typical but variable ++
Bilirubin	<5 mg/dL	<5 mg/dL unless massive necrosis	often <5 mg/dL, higher if severe
Hepatic imaging	Normal	Hepatic infarcts	Fatty infiltration
-	-	Hematomas, rupture	-
Histology	Normal–mild cholestasis, no necrosis	Patchy/extensive necrosis and hemorrhage	Microvesicular fat in zone 3
Maternal mortality	0%	1%–25%	7%–18%
Fetal/perinatal mortality	0.4%–1.4%	11%	9%–23%
Recurrence in subsequent pregnancies	45%–70%	4%–19%	α-subunit, long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) defect—yes
-	-	-	No fatty acid oxidation defect—rare

kg body weight, is the treatment of choice for ICP; UDCA, in several small randomized trials, produced relief of pruritus with improvement in liver tests and with no adverse maternal or fetal effects[11]; fetal outcome was improved with less prematurity. High-dose UDCA (1.5-2.0 g/d) reduces abnormal maternal and fetal BA levels and is completely safe for the fetus[12]. UDCA is more effective in reducing pruritus, aminotransferases, and BA levels than cholestyramine, with fewer preterm deliveries and fewer side effects[10]. Dexamethasone (12 mg/d for 7 d) has the advantage of promoting fetal lung maturity, but this therapy, tested in 130 patients, was less effective than UDCA in reducing pruritus and aminotransferase levels[13]. S-adenosyl-L-methionine is also less effective than UDCA but may have an additive effect[14].

The main risk in ICP is to the fetus and necessitates referral to a high-risk obstetrician. Fetal monitoring for chronic placental insufficiency is essential but will not prevent all fetal deaths from acute anoxia, which can be prevented only by delivery as soon as the fetal lungs are mature; 60% of babies are delivered before term. Fetal distress occurs in 20%-40%, with occasional perinatal death; an early onset in the second trimester and severe biochemical abnormalities seem to be risk factors. A recent Swedish population study of more than 45 000 pregnancies with 693 cases of ICP (1.3%) showed that fetal complications correlate with maternal BA levels, with premature delivery, asphyxial events, and meconium staining occurring only in the 19% of cases with maternal BA levels greater than 40 μmol/L[10]. Whether maternal therapy with UDCA will improve fetal outcome is still unknown.

Outcome and Counseling: ICP resolves with fetal delivery to recur in 45%-70% of subsequent pregnancies and occasionally with oral contraceptives. Some rare familial cases of apparent ICP have persisted postpartum, with progression to subsequent fibrosis and cirrhosis, but these cases may represent chronic cholestatic liver disease from the onset. A recent large Finnish population study[15] with more than 10 000 patients showed that patients who have had ICP subsequently have more gallstones and cholecystitis, more nonalcoholic pancreatitis, more hepatitis C, and more nonalcoholic cirrhosis. Therefore, in some patients, ICP may be an indicator of more serious subsequent liver disease.

Preeclampsia

Preeclampsia is the triad of hypertension, edema, and proteinuria in the third trimester of 5%–10% of pregnancies. Liver involvement, although infrequent, always indicates severe preeclampsia with significant perinatal morbidity and mortality; it is the commonest cause of hepatic tenderness and liver dysfunction in pregnancy. Aminotransferases are variable from mild to 10-fold to 20-fold elevations; bilirubin is usually less than 5 mg/dL. No specific therapy is needed for the hepatic involvement of preeclampsia, and its only significance is as an indicator of severe disease with need for immediate delivery to avoid eclampsia, hepatic rupture, or necrosis.

HELLP Syndrome

Severe preeclampsia is complicated in 2%-12% of cases (0.2%-0.6% of all pregnancies) by hemolysis (H), elevated liver tests (EL), and low platelet count (LP)—the HELLP syndrome[16,17]. Though recognized for over 50 years, diagnosis, management, and pregnancy outcome of the HELLP syndrome remain controversial.

Etiology: The HELLP syndrome is a microangiopathic hemolytic anemia associated with vascular endothelial injury, fibrin deposition in blood vessels, and platelet activation with platelet consumption, resulting in small to diffuse areas of hemorrhage and necrosis dissecting from zone 1 to involve the whole lobule, leading to large hematomas, capsular tears, and intraperitoneal bleeding. The precipitating injury is not known[17]. There is some overlap with AFLP and fatty acid oxidation (FAO) defects, but this is much less established than for AFLP. Studies of families with known FAO deficiencies have shown a high incidence of HELLP, but babies of mothers with HELLP do not have a proven increased risk of FAO deficiencies[18,19].

Clinical Features and Diagnosis: There are no diagnostic clinical features to distinguish HELLP from preeclampsia[17,20]; most patients present with upper abdominal pain and tenderness, nausea and vomiting, malaise, headache, edema and weight gain, hypertension, and proteinuria; jaundice is uncommon (5%); some patients have no obvious preeclampsia. Most patients present between 27 and 36 weeks' gestation, but 25% in postpartum period. HELLP is commoner in white patients, multiparous, and older patients but can occur with any parity and age.

The diagnosis of HELLP must be quickly established because of maternal and fetal risk and the necessity for immediate delivery. Diagnosis requires the presence of all 3 laboratory criteria: (1) hemolysis, (2) elevated aminotransferases, and (3) thrombocytopenia (Table 4)[16,17,20], but, unfortunately, diagnostic criteria are used inconsistently[20]. Occasionally, disseminated intravascular coagulation (DIC) may be present. Aminotransferase elevation is variable, from mild to 10-fold to 20-fold, and bilirubin is usually less than 5 mg/dL.

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Computed tomography of the liver may show subcapsular hematomas, intraparenchymal hemorrhage, or infarction or hepatic rupture (Figure 1); these abnormalities correlate with thrombocytopenia of less than 20 000 but not with liver dysfunction. Occasionally the HELLP syndrome must be distinguished from other conditions, especially AFLP, with which it has significant overlap in some cases[17], or from the rare conditions of thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, or antiphospholipid syndrome.

Management: The patient with HELLP must be hospitalized for antepartum stabilization of hypertension and DIC, for seizure prophylaxis, and fetal monitoring[17]. Transfer to a tertiary referral center should be effected if possible and a hepatic computed tomography (limited views) obtained.

Table 4 Diagnostic Criteria for HELLP Syndrome.

H	EL	LP
Hemolysis *	Elevated liver tests	Low platelets
HELLP syndrome may be subdivided, based on platelet count, into severe/Class 1 (platelets <50 000), moderate/Class 2 (50–99 000), and mild/Class 3 (100–150 000).		
Abnormal blood smear	AST > 70 U/L	< 150,000*
LDH >600 U/L Elevated ↑indirect bilirubin	-	-

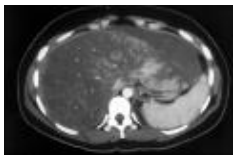

Figure 1 Computed tomography of abdomen of 28-year-old woman with severe HELLP syndrome at 39 weeks' gestation. A large subcapsular hematoma extends over the left lobe; the right lobe has a heterogeneous, hypodense appearance because of widespread necrosis, with "sparing" of the areas of the left lobe (compare perfusion with the normal spleen).

Delivery is the only definitive therapy, and for patients with severe HELLP there is progressive and often sudden maternal deterioration[20]. At greater than 34 weeks' gestation or if there is any evidence of multiorgan dysfunction, DIC, renal failure, abruptio placentae, or fetal distress, there is consensus that immediate delivery should be effected. Well-established labor should be allowed to proceed in the absence of obstetric complications or DIC, but many patients (40%-50%) will require caesarean section, especially a primigravida remote from term. Patients may require blood or blood products to correct hypovolemia, anemia, and coagulopathy, and prophylactic antibiotics are recommended.

Management remote from term with fetal lung immaturity and a stable maternal condition without DIC is controversial, as is the use of corticosteroids[16,17,20,21]. In the absence of randomized trials, a National Institutes of Health Consensus Development Panel suggests that perinatal outcome at less than 34 weeks' gestation is better when corticosteroids (betamethasone or dexamethasone, which cross the placenta) are used for 24 to 48 hours, with delivery thereafter; the main benefit of this therapy is fetal lung maturity but it also improves the maternal platelet count in some cases. There are some advocates for giving dexamethasone to all cases, starting before delivery but completed postpartum with no delay in delivery; they may also aid maternal stability during the transfer time to a tertiary referral center. Most cases with longer conservative therapy will deteriorate in 1 to 10 days after diagnosis, with a high risk of fetal loss.

Most patients have rapid, early resolution of HELLP after delivery with normalization of platelets by 5 days. Persistence of thrombocytopenia or hemolysis for more than 72 hours, worsening hepatic or renal failure, or life-threatening complications are taken as an indication for specific therapy. Many different treatment modalities have been used—plasmapheresis, plasma volume expansion, antithrombotic agents, steroids, plasma exchange with fresh-frozen plasma, dialysis—but no clinical trials have been done. Heparin therapy has increased bleeding complications and is not recommended. In about 25% of cases, HELLP will develop in the postpartum period, and therapy is the same as antepartum.

Complications of the HELLP Syndrome: Serious maternal complications are common[16,17,20]—DIC, abruptio placentae, acute renal failure, eclampsia, pulmonary edema, acute respiratory distress syndrome, severe ascites, subcapsular hematoma, hepatic failure, and wound hematomas. Indications to proceed with liver transplantation are very limited—persisting bleeding from a hematoma or hepatic rupture or liver failure from extensive necrosis[22] Perinatal mortality is 11%, due to prematurity, dysmaturity due to placental insufficiency, or the consequences of severe maternal complications.

Hepatic hemorrhage without rupture is managed conservatively in a hemodynamically stable patient with close hemodynamic monitoring in an intensive care unit, correction of coagulopathy, immediate availability of large-volume transfusion of blood products, immediate intervention for rupture or rapid expansion of hematoma, on diagnostic hepatic imaging. Exogenous trauma must be avoided—abdominal palpation, convulsions, emesis, and unnecessary transportation.

Liver rupture is a rare, life-threatening complication of HELLP, usually preceded by an intraparenchymal hemorrhage progressing to a contained subcapsular hematoma in the right lobe in patients with severe thrombocytopenia. Survival depends on rapid, aggressive supportive care and immediate laparotomy. The best surgical management is still controversial; most successful is evacuation of the hematoma with pressure packing and drainage, followed by consideration of hepatic artery embolization or ligation, partial hepatectomy, or oversewing of the laceration. In the rare hemodynamically stable patient with contained hepatic rupture or a rapidly enlarging hematoma, angiographic embolization may be considered. Maternal mortality from hepatic rupture remains very high at 50%, and perinatal mortality rates are 10%-60%, mostly from placental rupture, intrauterine asphyxia, or prematurity.

Recurrence of HELLP: Subsequent pregnancies in patients with HELLP syndrome carry a high risk of complications—pre-eclampsia, recurrent HELLP, prematurity, intrauterine growth retardation, abruptio placentae, and perinatal mortality[16]. However, no long-term effect on renal function has been noted.

Acute Fatty Liver of Pregnancy

Acute fatty liver of pregnancy (AFLP) is a sudden catastrophic illness occurring almost exclusively in the third trimester, where microvesicular fatty infiltration results in encephalopathy and hepatic failure[23,24]. It carries significant perinatal and maternal mortality and requires early diagnosis and intervention to prevent maternal and fetal death (Table 3).

Etiology: In some cases the etiology of AFLP involves abnormalities in intramitochondrial FAO[18]. Beta-oxidation of fatty acids in hepatic mitochondria is a complex process requiring several essential enzymes; mitochondrial trifunctional protein and its α-subunit, long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD), are the 2 enzymes of this metabolic process, whose autosomally inherited genetic mutations are most closely associated with AFLP, especially the G1548C mutation of LCHAD[22]. Of 24 babies with defects in FAO, 62% of their mothers had maternal liver disease, either AFLP or HELLP syndrome[18]. Further study showed that in 83 pregnancies in families with known FAO deficiencies, 24 pregnancies had maternal liver disease, with AFLP in 20 cases, all with the G1528C mutation

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of LCHAD. A separate study showed an 18-fold increase in incidence of maternal liver disease, both HELLP syndrome and AFLP, in the mothers of 50 infants with FAO defects[19].

Babies of mothers with AFLP have been screened for FAO defects: 5 of 27 pregnancies with AFLP revealed fetuses with LCHAD deficiencies but no affected babies in 81 pregnancies with HELLP[18]. LCHAD deficiency has been identified in about 20% of babies of mothers with AFLP. Speculation is that maternal heterozygosity for LCHAD deficiency reduces the maternal capacity to oxidize long-chain fatty acids both in liver and placenta, and this, together with the metabolic stress of pregnancy and fetal homozygosity for LCHAD deficiency, causes accumulation in the maternal circulation of potentially hepatotoxic LCHAD metabolites[18]. Perhaps external factors, such as carnitine deficiency or other dietary factors, exacerbate this situation[19]. There are reports of maternal liver disease associated with defects of other enzymes involved in FAO, but the role of these other enzymes in causing AFLP remains controversial.

Clinical Features and Diagnosis: Unlike HELLP, 40%-50% of patients with AFLP are nulliparous, with an increased incidence in twin pregnancies[23,24]. AFLP occurs almost exclusively in the third trimester from 28 to 40 weeks, rarely in late second trimester. In a few patients, it presents as jaundice in the postpartum period. The presentation can vary from asymptomatic to fulminant liver failure. The typical patient has 1 to 2 weeks of anorexia, nausea and vomiting, headache, and right upper quadrant pain, and is ill-looking with jaundice, hypertension, edema, ascites, a small liver, and hepatic encephalopathy. Intrauterine death may occur. About 50% of patients with AFLP have preeclampsia, and there is some overlap with the HELLP syndrome.

In AFLP, aminotransferases vary from near-normal to 1000, usually about 300 to 500; bilirubin is usually less than 5 mg/dL but higher in severe or complicated disease. Other typical abnormalities are normochromic, normocytic anemia, high white blood cell count, normal to low platelets, coagulopathy with or without DIC, metabolic acidosis, renal dysfunction (often progressing to oliguric renal failure), hypoglycemia, high ammonia, and biochemical pancreatitis[24].

The presumptive diagnosis of AFLP is made on compatible clinical and laboratory features, the need for expeditious therapy and presence of coagulopathy precluding biopsy. A definitive diagnosis is histological—microvesicular fatty infiltration (free fatty acids) predominantly in zone 3 with lobular disarray and mild portal inflammation with cholestasis (Figure. 2). Occasionally the histological picture, although usually diagnostic, cannot be differentiated from viral hepatitis or preeclampsia. The main differential diagnoses of acute liver failure in the third trimester are AFLP, HELLP, and fulminant viral hepatitis. In comparison with those with HELLP syndrome, patients with AFLP are more likely to show liver failure with coagulopathy, hypoglycemia, encephalopathy, DIC, and renal failure (Table 3).

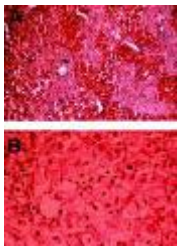

Figure 2 Histological appearance of the liver of a 32-year-old primigravida with acute fatty liver of pregnancy. (A) Sudan stain (low power) shows diffuse fatty infiltration (red staining) involving predominantly zone 3, with relative sparing of periportal areas. (B) Hematoxylin-eosin stain (high power) shows hepatocytes stuffed with microvesicular fat (free fatty acids) and centrally located nuclei.

Management: Early recognition and diagnosis of AFLP with immediate termination of pregnancy and intensive supportive care is essential for both maternal and fetal survival. There are no reports of recovery before delivery. Immediate hospital admission allows maternal stabilization, fetal monitoring, and confirmation of diagnosis. Delivery is effected usually by caesarean section, but the type of delivery should be based on obstetric assessment of likelihood of rapid controlled vaginal delivery in less than 24 hours. Vaginal delivery will reduce the incidence of major intra-abdominal bleeding but is best effected with an international normalized ratio of less than 1.5 and platelet count of greater than 50 000. Prophylactic antibiotics are recommended to prevent uterine infections[24].

By 2 to 3 days after delivery, the aminotransferases and encephalopathy will improve, but intensive supportive care is needed to manage the many complications of liver failure until this recovery occurs. Patients who are critically ill at the time of presentation, who develop complications (encephalopathy, hypoglycemia, coagulopathy), or who continue to deteriorate despite emergency delivery, should ideally be transferred to a liver center. Most patients improve in 1 to 4 weeks postpartum, although a cholestatic phase with rising bilirubin and alkaline phosphatase may persist. Recovery can occur in days or be delayed for months but is complete with no signs of chronic liver disease. With advances in supportive management of these patients, the maternal mortality is now 7%-18% and fetal mortality 9%-23%. Infectious and bleeding complications remain the most life threatening. Liver transplantation has a very limited role here because of the great potential for recovery with delivery but should be considered in patients whose clinical course continues to deteriorate with advancing fulminant hepatic failure after the first 1 to 2 days postpartum without signs of hepatic regeneration.

Recurrence and Screening: Many patients do not become pregnant again after AFLP, either by choice due to the devastating effect of the illness or by necessity due to hysterectomy to control postpartum bleeding. Women who are carriers of LCHAD mutation have an increased risk of recurrence of AFLP in 20%-70% of pregnancies. All babies of mothers with AFLP are tested for defects of FAO because presymptomatic diagnosis and appropriate early management will reduce morbidity and mortality in these babies. Expanded newborn screening in many states will include this, but, in its absence, the appropriate clinical and biochemical testing must be done for all these babies[26,27]. For mothers with previous AFLP, liver tests, glucose, and carnitine levels and plasma acylcarnitine profile may help identify the obligate carrier to allow closer fetal and maternal monitoring[19]. Future options may involve genetic testing for the carrier state. For mothers without identifiable abnormalities of FAO, AFLP does not tend to recur in subsequent pregnancies, though rare cases have been reported.

AFLP, acute fatty liver of pregnancy; BA, bile acids; DIC, disseminated intravascular coagulation; FAO, fatty acid oxidation; HELLP, hemolysis (H), elevated liver tests (EL), and low platelet count (LP); HG, hyperemesis gravidarum; ICP, intrahepatic cholestasis of pregnancy; LCHAD, α-subunit, long-chain 3-hydroxyacyl-CoA dehydrogenase; UDCA, ursodeoxycholic acid.

LIVER DISEASES OCCURRING COINCIDENTALLY IN A PREGNANT PATIENT

Viral Hepatitis

Viral hepatitis, due to hepatitis A, B, C, D, E, herpes simplex, cytomegalovirus, and Epstein-Barr viruses, accounts for 40% of jaundice in pregnant women in the United States[28]. Hepatitis A, B, and C have the same frequency in the pregnant and nonpregnant populations and during each of the 3 trimesters of pregnancy. Acute hepatitis A occurs in 1 per 1000, acute hepatitis B in 2 per 1000

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pregnant women, and hepatitis D is rare. The clinical and serologic course of acute hepatitis in the Western world is generally the same as in the nonpregnant patient, nor does the hepatitis appear to affect the pregnant state adversely, although hepatitis A during the second or third trimesters may increase gestational complications. Hepatitis E is extremely rare in the United States but is endemic to large areas of Asia, Africa, and Central America, where, in the third trimester of pregnancy, it becomes fulminant with a high mortality (up to 25%), probably influenced by malnutrition. Herpes simplex hepatitis is rare but must be diagnosed because antiviral therapy with acyclovir or vidarabine is life-saving; these patients present with a severe or fulminant "anicteric" hepatitis in the third trimester. Management of the patient with acute viral hepatitis is supportive, and viral hepatitis is not an indication for termination of pregnancy, caesarean section, or discouragement for breastfeeding[28]. Congenital malformations in the fetus occur only with early cytomegalovirus infection.

All pregnant women are tested for hepatitis B on first antenatal visit; for those who are without immune antibodies and at high risk for HBV infection during pregnancy (for example, multiple sex partners, intravenous drug use), vaccine can be given in pregnancy with little risk to the fetus. Perinatal transmission of hepatitis B is highest in those with acute hepatitis, especially with hepatitis B e antigen positivity in the third trimester (50%-80%), lower in mothers with anti-HBe (25%), and lowest in carriers (5%); 80%-90% of these babies have persistent hepatitis B surface antigen positivity. Transmission of hepatitis B is not transplacentally but at delivery and is preventable in more than 95% of cases by passive-active immunoprophylaxis of the babies at birth with hyperimmune B immunoglobulin and hepatitis B virus vaccine (3 doses: in first 2 days, at 1 month, and at 6 months) Antiviral therapy in the third trimester may reduce vertical transmission in patients with a high viral load who are most at risk of vertical transmission to their babies[29]. Vertical transmission of hepatitis A and D is rare and occurs only with high viral levels at the time of delivery. Mother-to-infant transmission of hepatitis C is 1% to 5%, with maternal risk factors being human immunodeficiency virus co-infection, history of intravenous drug abuse, and maternal viremia of greater than 106 copies/mL; transmission is unaffected by mode of delivery or breastfeeding. Newborns of mothers with hepatitis A in the third trimester should be given passive immunoprophylaxis with immune globulin within 48 hours of birth.

Gallstones and Biliary Disease

Cholesterol secretion increases in the second and third trimesters compared to bile acids and phospholipids, leading to supersaturated bile; in addition, fasting and postprandial gallbladder volumes are greater, with reduced rate and volume of emptying. This large residual volume of supersaturated bile in the gallbladder of the pregnant patient leads to the retention of cholesterol crystals and eventual gallstones. The formation of biliary sludge and stones is strongly associated with frequency and number of pregnancies. Up to 10% of patients develop stones or sludge over the course of one pregnancy, with obesity and serum leptin being risk factors[30]. Despite their prevalence in 5%-12% of pregnant women, symptomatic gallstones occur in only 0.1%-0.3% of pregnancies, and symptoms usually follow multiple pregnancies rather than during gestation. The commonest clinical presentations are biliary colic (5% jaundice in pregnancy), gallstone pancreatitis, and, least commonly, acute cholecystitis. The clinical features of biliary disease and pancreatitis are the same as in the nonpregnant patient, can occur at any time of gestation, and may recur during the pregnancy and into the postpartum period[31].

For patients presenting with intractable biliary colic, severe acute cholecystitis not responding to conservative measures or acute gallstone pancreatitis, cholecystectomy is indicated despite the pregnant state. However, with uncomplicated acute biliary colic or acute cholecystitis, conservative therapy with bed rest, intravenous fluids, and antibiotics is successful in more than 80%, with no fetal or maternal mortality and is indicated during the first and third trimesters. Surgery is avoided in the first trimester because of the abortion risk with anesthesia and in the third trimester, due to an increased risk of premature labor. But, because biliary colic will recur in 50% of pregnant patients before delivery, symptomatic patients presenting in the first or second trimester, should undergo cholecystectomy, ideally laparoscopic, in the second trimester, with better pregnancy outcome compared with medical therapy[32,33]. An impacted common bile duct stone and worsening gallstone pancreatitis are indications to proceed to endoscopic retrograde cholangiopancreatography, sphincterotomy, and stone extraction under antibiotic coverage; minimization of fluoroscopy and ionizing radiation to the fetus is essential.

The Pregnant Patient with Chronic Liver Disease

Women with chronic liver disease (Table 2) may be of childbearing age, and an uncomplicated pregnancy with no disease flare is expected in those with mild or inactive disease. In hepatitis C, aminotransferases may fall and viral RNA increase during pregnancy, with the reverse in the postpartum period. The course of autoimmune hepatitis in pregnancy is highly variable, and stable immunosuppression should be continued throughout pregnancy; a flare of activity may occur during pregnancy or, more likely, in the postpartum period[34]. A flare is treated by increased steroids and azathioprine as necessary. Patients with Wilson's disease must be adequately treated before pregnancy and continue on therapy throughout to prevent the risk of fulminant Wilson disease[35]. The safety of drugs for chronic liver disease is shown in table 5[36].

Unfortunately, the optimal management of pregnancy with cirrhosis and portal hypertension in the modern era of obstetrics is undefined.

Table 5 Drug Therapy During Pregnancy for Chronic Liver Disease.

Drug	FDA Pregnancy Category	Uses and Safety
Prednisone	C	Low risk: increased cleft palate, adrenal insufficiency
Azathioprine	D	Data suggest low risk
Cyclosporine	C	Most safety data of immunosuppressants
Tacrolimus	C	Probably safe—use as needed
Mycophenylate mofetil	C	Not recommended—limited data
Sirolimus	C	Not recommended
Lamivudine	C	Low risk
Adefovir	C	Few data—minimal toxicity
Entecavir	C	Few data—not recommended
Interferon	C	Not recommended
Ribavirin	X	Contraindicated—severe fetal toxicity Embryopathy but need to maintain
Penicillamine	D	therapy for Wilson disease
Trientine	C	Limited data—potential toxicity
Ursodeoxycholic acid	B	Low risk; use in ICP
Beta blockers	C (1st trimester) D (2/3rd trimesters)	Fetal bradycardia; risk of intrauterine growth retardation
Octreotide	B	Probably safe—limited data
Vasopressin	X	Contraindicated, uterine ischemia

Most patients with advanced cirrhosis are amenorrheic and infertile due to hypothalamic-pituitary dysfunction, but successful pregnancy may be completed in those with well-compensated disease and only mild portal hypertension. However, increased maternal and fetal problems can be expected in about 50% cases with increased fetal loss, and all patients with cirrhosis should be followed by a high-risk obstetrician as well as a hepatologist. The main risk to the

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mother is from variceal bleeding (20%-25%), especially during the second trimester or during labor. Other maternal risks are hepatic decompensation, jaundice, thrombocytopenia, and rupture of splenic aneurysms. Patients with known esophageal varices should be considered for endoscopic therapy, shunt surgery, or even liver transplantation before pregnancy. In addition, all patients, even if no varices before pregnancy, should undergo upper endoscopy for assessment of varices in the second trimester and, if large varices are present, then beta blocker therapy is introduced despite occasional fetal effects (Table 5). Whether prophylactic endoscopic therapy for esophageal varices in early pregnancy is beneficial has not been tested. Acute variceal bleeding is managed endoscopically, as in the nonpregnant, though vasopressin is contraindicated; little is known about the use of octreotide in pregnancy. Ascites and hepatic encephalopathy are treated in the standard way.

Vaginal deliveries with assisted, short second stage are preferable, as abdominal surgery is avoided. But in patients with known large varices, avoidance of labor by caesarean section is recommended to avoid increases in portal pressure and risk of variceal bleeding. Postpartum hemorrhage and bacterial infections are reduced by correction of coagulopathy and prophylactic antibiotics.

The pregnant liver transplant recipient represents a unique clinical situation[37]. With the success of liver transplantation, more pregnancies are being reported in liver recipients, and a carefully planned pregnancy in a stable healthy patient, beyond the first 2 years after orthotopic liver transplantation, can have excellent outcome for fetus, mother, and graft. However, this is still a high-risk pregnancy with increased fetal prematurity and dysmaturity; also, there is some risk to the allograft from acute cellular rejection or recurrent viral hepatitis; as a result, it is imperative to closely monitor immunosuppression with adjustment in calcineurin inhibitor doses as needed for the increased blood volume in the second half of pregnancy. Liver function must be monitored regularly and all liver abnormalities investigated and treated as aggressively as in the nonpregnant, especially acute cellular rejection.

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