Acute fatty liver of pregnancy

Authors: Richard H Lee, MD, Tram T Tran, MD
Section Editors: Keith D Lindor, MD, Charles J Lockwood, MD, MHCM
Deputy Editors: Kristen M Robson, MD, MBA, FACG, Vanessa A Barss, MD, FACOG

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INTRODUCTION

Acute fatty liver of pregnancy (AFLP) is an obstetric emergency characterized by maternal liver dysfunction and/or failure that can lead to maternal and fetal complications, including death. Prompt delivery and supportive maternal care are important for achieving a full recovery for the mother.

The clinical features, diagnosis, and management of AFLP will be reviewed here. A general approach to the patient who develops liver disease during pregnancy is presented separately and has also been addressed in a guideline issued by the American College of Gastroenterology [1]. (See "Approach to liver disease occurring during pregnancy".)

EPIDEMIOLOGY AND RISK FACTORS

Acute fatty liver of pregnancy (AFLP) is rare, with an approximate incidence of 1 in 7000 to 20,000 pregnancies [2-5]. Potential risk factors for AFLP include [1,3]:

- Fetal long-chain 3-hydroxyacyl CoA dehydrogenase deficiency.
- Prior episode of AFLP [6].
- Multiple gestation [3,7].
- Preeclampsia or hemolysis, elevated liver enzymes, and a low platelet count syndrome [4].
- Male fetal sex.
- Low body mass index (BMI <20 kg/m^2 [3]).

PATHOGENESIS

The pathogenesis of acute fatty liver of pregnancy (AFLP) is unclear, but defects in fatty acid metabolism during pregnancy appear to play a role. Free fatty acids normally increase in pregnancy, particularly late in gestation, to fuel fetoplacental growth and development. If maternal-fetal fatty acid

metabolism is defective, intermediate products of metabolism can accumulate in maternal blood and hepatocytes, with deleterious effects on maternal hepatocytes [8].

An overview of fatty acid oxidation disorders including the clinical manifestations is presented separately. (See "Overview of fatty acid oxidation disorders" and "Specific fatty acid oxidation disorders".)

Fetal long-chain 3-hydroxyacyl CoA dehydrogenase (LCHAD) deficiency — Approximately 20 percent of AFLP is associated with LCHAD deficiency [1]. LCHAD is one of the enzymes involved in fatty acid oxidation; it catalyzes a step in beta-oxidation of mitochondrial fatty acids in which 3-ketoacyl-CoA is formed from 3-hydroxyacyl-CoA. In fetuses homozygous for LCHAD deficiency, the fetoplacental unit cannot perform this step, so levels of intermediate products of fatty acid metabolism increase and enter the maternal circulation [9,10]. Because the mother is heterozygous for LCHAD deficiency, these long-chain metabolites can accumulate in maternal blood and hepatocytes and have toxic effects on the maternal liver.

However, not all mutations that lead to LCHAD deficiency result in AFLP [11,12]. The homozygous G1528C mutation, which alters amino acid 474 from glutamic acid to glutamine on the protein (E474Q), appears to be the most common genotype associated with development of AFLP [8,9]. The heterozygous and wild-type fetal genotype are not associated AFLP [13].

The G1528C mutation has also been associated with development of hemolysis, elevated liver enzymes, and a low platelet count syndrome [8,9,13] and preeclampsia [13], which share several phenotypic features with AFLP [14].

Other enzyme deficiencies — The following deficiencies of fetoplacental mitochondrial oxidation have also been associated with development of AFLP, but are less common than the G1528C mutation [15]:

- Short-chain acyl-CoA dehydrogenase deficiency [16].
- Medium-chain acyl-CoA dehydrogenase deficiency [17].
- Carnitine palmitoyltransferase deficiency [18].

(See "Specific fatty acid oxidation disorders", section on 'Medium- and short-chain fatty acid oxidation disorders'.)

PATIENT PRESENTATION

Acute fatty liver of pregnancy (AFLP) typically presents between the 30th and the 38th week of gestation, but the diagnosis has been made as early as 22 weeks and as late as four days after delivery [3,19].

The initial symptoms of AFLP are often nonspecific (eg, nausea, vomiting, abdominal pain, malaise, headache, and/or anorexia). Many patients have hypertension, with or without proteinuria, possibly due to co-existent hemolysis, elevated liver enzymes, and low platelet count syndrome or preeclampsia.

Signs and symptoms of acute liver failure, including jaundice, ascites, encephalopathy, disseminated intravascular coagulopathy, and hypoglycemia rapidly develop. Most patients develop acute kidney injury, and often progress to multiorgan failure [4].

Central diabetes insipidus may occur and is thought to be caused by decreased levels of arginine vasopressin secondary to reduced clearance of vasopressinase by the impaired liver [20]. Acute pancreatitis, which can be severe, is rare and generally occurs in the setting of hepatic and renal dysfunction [21].

LABORATORY, IMAGING, AND HISTOLOGIC FINDINGS

Laboratory findings — All women with acute fatty liver of pregnancy (AFLP) have elevations in aminotransferases (aspartate aminotransferase or alanine aminotransferase), usually ranging from 5 to 10 times the upper limit of normal, but not exceeding 500 int. unit/L (table 1) [22]. Other laboratory findings that may be present include:

- Elevated serum bilirubin levels
- Low serum glucose
- Elevated serum creatinine
- Elevated white blood cell count
- Elevated ammonia level
- Elevated uric acid level
- Prolonged prothrombin time, international normalized ratio, activated partial thromboplastin time
- Increased thrombin time
- Reduced levels of coagulation inhibitors (eg, antithrombin)
- Low platelet count
- Low fibrinogen
- Fragmented red blood cells and burr cells
- Proteinuria

Note: In normal pregnancy, the mean platelet count is slightly lower than in nonpregnant women, but usually remains within the normal range. Pregnancy is also associated with leukocytosis: The neutrophil count begins to increase in the second month of pregnancy and plateaus in the second or third trimester, at which time white blood cell counts range from 9000 to 15,000 cells/microL. The physiologic increase in the glomerular filtration rate during pregnancy results in a decrease in serum creatinine concentration, which falls by an average of 0.4 mg/dL (35 micromol/L) to a normal range of 0.4 to 0.8 mg/dL (35 to 70 micromol/L) (table 2).

Imaging — Radiologic findings thought to be characteristic of AFLP have been described in small case series and reports. Ultrasound of the liver may show nonspecific changes, including fatty infiltration or brightness [22,23]. In one report of five patients with AFLP, serial magnetic resonance imaging (MRI) showed a transient increase in detectable fat (ie, >5 percent MRI-proton density fat fraction) that resolved within two weeks after delivery [24]. In a retrospective study of 19 patients with AFLP who

underwent at least one imaging study, fatty infiltration of the liver was found on ultrasound in three of 11 patients, on computed tomography (CT) in five of 10 patients, and on MRI in none of five patients; three patients with normal ultrasound scans subsequently had fatty filtration seen on CT [25].

Histologic findings — Microvesicular fatty infiltration of the hepatocytes is suggestive of AFLP [26]. The fat droplets surround centrally located nuclei, giving the cytoplasm a foamy appearance. The fatty infiltration is prominent in central and mid zonal parts of the lobule and usually spares a sharply defined rim of cells around the portal tracts [27]. Tissue should be set aside at the time of the procedure for special stains (oil red O on frozen section, or electron microscopy) for confirmation of diagnosis in patients without evident vacuolization (picture 1) [28,29].

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of acute fatty liver of pregnancy (AFLP) (table 1) primarily involves hemolysis, elevated liver enzymes, and a low platelet count (HELLP) syndrome and preeclampsia with severe features (table 3 and table 4) [30]. There is a large clinical overlap between AFLP, HELLP syndrome, and severe preeclampsia [31]. Sometimes it is difficult, or even impossible, to differentiate among them. Adding to the complexity, a patient may have both AFLP and HELLP or preeclampsia with severe features. (See "HELLP syndrome" and "Preeclampsia: Clinical features and diagnosis".)

Hypertension is present in essentially 100 percent of patients with preeclampsia, 85 percent of patients with HELLP, and up to about 50 percent of patients with AFLP. Severe symptoms and signs of hepatic insufficiency such as nausea/vomiting, malaise, hypoglycemia, and disseminated intravascular coagulation/coagulopathy are more consistent with AFLP than HELLP or severe preeclampsia, and transaminase and bilirubin levels are almost always higher in AFLP. Hypertension and proteinuria are often more severe in HELLP and severe preeclampsia. (See "HELLP syndrome", section on 'Differential diagnosis' and 'Laboratory findings' above.)

In addition, non-pregnancy-related causes of abnormal liver chemistries need to be assessed, such as hepatitis (viral, autoimmune), gallstone disease, and drug-induced liver injury; these disorders can usually be excluded by clinical setting.

DIAGNOSTIC EVALUATION

Pregnant women in the second half of pregnancy who present with nausea, vomiting, abdominal pain, malaise, hypertension, headache, and/or anorexia should be evaluated for acute fatty liver of pregnancy (AFLP), severe preeclampsia, and hemolysis, elevated liver enzymes, and a low platelet count syndrome, as well as other disorders associated with these nonspecific symptoms (eg, hepatitis and other viruses, acetaminophen poisoning), when clinically appropriate.

The initial work-up includes maternal vital signs and:

- Complete blood count

- Creatinine
- Glucose
- Alanine aminotransferase and aspartate aminotransferase
- Lactate dehydrogenase
- Bilirubin
- Uric acid
- Urine protein (protein:creatinine ratio or 24-hour urine protein)

Coagulation studies (prothrombin time, partial thromboplastin time, fibrinogen) are not routinely obtained, but are indicated as part of the evaluation of patients who are acutely ill, found to have liver dysfunction, and those with additional complications, such as abruptio placentae or severe bleeding.

Role of liver biopsy — Liver biopsy is not necessary for the diagnosis of AFLP in nearly all patients. It is reserved for rare cases in which the diagnosis is in doubt and the results will affect patient care (eg, for patients with persistent liver failure postpartum who are being evaluated for liver transplantation). Stabilization of the mother and emergency delivery of the fetus should not be delayed for liver biopsy in patients whose clinical presentation and laboratory findings are compatible with AFLP [19]. If liver biopsy is performed in a patient with coagulopathy, a transjugular approach is used because it carries a lower risk of bleeding compared with percutaneous liver biopsy [22]. (See "Transjugular liver biopsy".)

DIAGNOSIS

A presumptive diagnosis of acute fatty liver of pregnancy (AFLP) is usually made clinically based upon the presence of characteristic symptoms (nausea, vomiting, abdominal pain, malaise, and/or anorexia) in a pregnant woman with significant hepatic dysfunction in the second half of pregnancy, after other potential causes of these findings have been excluded. There is a large clinical overlap between AFLP, HELLP syndrome, and severe preeclampsia, and it is sometimes impossible to differentiate among them. Multisystem involvement, including acute kidney injury, encephalopathy, coagulopathy, pancreatitis, pulmonary edema, and/or adult respiratory distress syndrome, strengthens the diagnosis of AFLP [32-34]. (See 'Laboratory findings' above and 'Differential diagnosis' above.).

Findings on imaging may support the diagnosis, but imaging is not required. (See 'Imaging' above.)

Swansea criteria — The Swansea criteria, which include symptoms, laboratory findings, and imaging, are a diagnostic model for AFLP that have been validated in a cohort study where the incidence of AFLP was 5.0 cases per 100,000 births [3,35].

The Swansea criteria are [3,22,36]:

- Vomiting
- Abdominal pain
- Polydipsia/polyuria
- Encephalopathy
- Elevated bilirubin (>0.8 mg/dL or >14 micromol/L)

- Hypoglycemia (<72 mg/dL or >4 mmol/L)
- Leukocytosis (>11,000 cells/microL)
- Elevated transaminases (AST or ALT) (>42 international unit/L)
- Elevated ammonia (>47 micromol/L)
- Elevated uric acid (5.7 mg/dL or >340 micromol/L)
- Acute kidney injury, or creatinine 1.7 mg/dL or >150 micromol/L
- Coagulopathy or prothrombin time >14 seconds
- Ascites or bright liver on ultrasound scan
- Microvesicular steatosis on liver biopsy

The number of criteria needed for a positive diagnosis has varied from six to nine in research studies, and the criteria are intended for use in women without hemolysis, elevated liver enzymes, and a low platelet count syndrome or preeclampsia, which limits their clinical utility [22,37]. When the Swansea criteria were applied to a cohort of 24 women with suspected pregnancy-related liver disease who underwent biopsy, the presence of ≥6 abnormal variables had positive predictive value of 85 percent and negative predictive value of 100 percent for finding microvesicular steatosis [35].

INITIAL MANAGEMENT

Initial management of the patient with acute fatty liver of pregnancy (AFLP) includes prompt delivery of the fetus, regardless of gestational age, because delivery initiates resolution of this life-threating disease. Medical treatment is provided to stabilize the mother while the liver recovers. Although it may not be possible to distinguish between AFLP, HELLP syndrome, and preeclampsia with severe features, the clinical management is the same (prompt delivery, maternal support) for the three diagnoses and delivery should not be delayed while attempting to ascertain the underlying disorder.

Components of pregnancy management include:

- **Assessing for multi-organ dysfunction and severity of liver dysfunction** – After a presumptive diagnosis of AFLP is made, close laboratory monitoring is important because these patients are at risk for multi-organ failure:
  - Complete blood count
  - Comprehensive metabolic panel (which should include transaminases, bilirubin, creatinine, blood urea nitrogen, electrolytes, glucose)
  - Ammonia
  - Prothrombin time, partial thromboplastin time, fibrinogen
  - Amylase, lipase
- **Critical care support** – The care of these patients requires a multidisciplinary team including maternal-fetal medicine, obstetric anesthesia, hepatology, neonatology, and a blood bank. Patients may require monitoring in an intensive care unit with close attention to their fluid status because aggressive fluid replacement in the setting of low plasmatic oncotic pressure can lead to pulmonary edema, which was reported in 14 percent of patients in one study [4]. We monitor

patients by physical examination, pulse oximetry, and by following urine output and fluid balance. We avoid invasive hemodynamic monitoring if possible because of the increased risk for bleeding in the setting of coagulopathy. However, if central venous access is necessary, use of an internal jugular approach with ultrasound guidance may decrease the risk of complications. The indications for central venous access and the approach to patients with coagulopathy and/or thrombocytopenia who require catheter placement are discussed separately. (See "Overview of central venous access".)

Mental status should be evaluated since they are at risk of encephalopathy. Mechanical ventilation may be needed for management of acute respiratory distress syndrome.

- **Monitoring for and treatment of hypoglycemia** – We monitor plasma glucose concentration every six to eight hours if the initial serum glucose is normal. If the glucose concentration is trending downward, we check values more frequently, even hourly, until liver function improves [2]. A continuous infusion of a 10 percent dextrose solution is administered, as needed to maintain a plasma glucose concentration above 65 mg/dL (3.6 mmol/L). (See "Acute liver failure in adults: Management and prognosis", section on 'Metabolic abnormalities'.)

- **Monitoring for and treatment of coagulopathy** – We generally monitor platelet count, international normalized ratio, partial thromboplastin time, and fibrinogen levels every four to six hours; more frequently if we suspect rapid deterioration and less frequently when the patient stabilizes and begins to improve. Management of disseminated intravascular coagulation in pregnancy is described in detail separately. (See "Disseminated intravascular coagulation during pregnancy", section on 'Replace blood, platelets, and coagulation factors'.)

- **Fetal monitoring** – The fetal heart rate should be monitored continuously; abnormal fetal heart rate patterns would impact the urgency of delivery. (See "Management of intrapartum category I, II, and III fetal heart rate tracings".)

- Magnesium sulfate – In pregnancies <32 weeks of gestation, magnesium sulfate is administered until delivery to reduce the risk of cerebral palsy and severe motor dysfunction in offspring. Magnesium sulfate is also administered in women with preeclampsia with severe features to prevent eclampsia regardless of gestational age. Dosing should be adjusted in patients with renal insufficiency. (See "Neuroprotective effects of in utero exposure to magnesium sulfate" and "Preeclampsia: Management and prognosis", section on 'Dosing'.)

DELIVERY

Once a patient is diagnosed with acute fatty liver of pregnancy, plans should be made to proceed with delivery. The route of delivery is contingent on the rate and degree of maternal/fetal decompensation and the probability of successful vaginal birth.

Labor induction is a reasonable option if vaginal birth is likely to be accomplished within 24 hours and the disease is not rapidly progressing within that time frame. Cervical ripening agents can be used if the

cervix is unfavorable. (See "Techniques for ripening the unfavorable cervix prior to induction".)

If accomplishing a successful vaginal birth within 24 hours is unlikely, and there is concern about rapidly progressing maternal/fetal decompensation, then performing a cesarean delivery rather than induction is reasonable. However, the mother should be stabilized before surgery, with special attention given towards correcting any coagulopathy. (See "Disseminated intravascular coagulation during pregnancy".)

POSTPARTUM MANAGEMENT

Maternal monitoring and course — Over the past several decades, maternal mortality rates have decreased from >75 percent to <5 percent [3,4,29,38,39]. This improvement has been attributed to multiple factors: earlier diagnosis of acute fatty liver of pregnancy (AFLP), prompt delivery, and advances in critical care [22].

In most patients, AFLP usually resolves completely after delivery, with return of normal liver function within 7 to 10 days in many cases [4]. The liver function tests and coagulopathy typically begin to improve within two days after delivery. In some patients, a transient worsening of liver and renal functions and coagulopathy may be observed during the first few days after delivery, followed by a definitive improvement [4].

We check liver chemistries, creatinine, and coagulation tests every six hours until we observe a clear downward trend, at which point the frequency of testing is reduced. Some patients have a prolonged course with multi-organ failure, requiring supportive management in an intensive care unit, including mechanical ventilation because of hepatic encephalopathy, dialysis for acute renal failure, nutritional support because of associated pancreatitis, or transfusion of blood for ongoing hemolysis or postpartum hemorrhage from atony or incisional bleeding [1]. If bleeding is related to coagulopathy, blood products may be needed. Management of these patients is the same as other adult patients with acute liver failure or postpartum hemorrhage, and is discussed in detail separately. (See "Acute liver failure in adults: Management and prognosis" and "Postpartum hemorrhage: Medical and minimally invasive management".)

Liver transplantation for fulminant hepatic failure caused by AFLP has been reported, but transplantation is unlikely to be needed with early diagnosis and prompt delivery of the fetus [19,40,41]. There are also reports of plasma exchange being used following delivery in patients who fail to improve with delivery and supportive care within two to eight days [42].

Long-term maternal consequences of AFLP are uncertain as most studies have not followed women beyond the immediate postpartum phase of the illness, and the disease is rare [22]. Limited data suggest that there are no sequelae of the liver disease itself [4,22,43].

Genetic testing — Children born to mothers with AFLP should undergo molecular testing for long-chain 3-hydroxyacyl CoA dehydrogenase (LCHAD) because early diagnosis of LCHAD deficiency in the newborn can be life-saving [44,45]. Testing should be coordinated with a metabolic or genetic

specialist. If the newborn has a positive test for LCHAD deficiency, the mother and father are screened. If they are positive, we suggest that they notify their siblings so that the siblings can be screened.

At a minimum, testing for the G1528C mutation should be performed since it is most common. If the patient tests negative for this mutation, LCHAD deficiency is still possible since it may be caused by a number of other mutations. In this setting, we suggest testing for other defects in fatty acid oxidation (eg, medium-chain acyl CoA dehydrogenase, short-chain acyl-CoA dehydrogenase) [15,16]. (See "Overview of fatty acid oxidation disorders" and "Specific fatty acid oxidation disorders".)

A list of laboratories that provide genetic testing is available at Genetic Testing Registry.

Perinatal outcome — AFLP is associated with an increased risk of perinatal mortality and morbidity [3,4]. It is likely then that the majority, if not all, fetal and neonatal deaths are secondary to maternal decompensation and/or preterm birth. Maternal acidosis is associated with a reduction in uterine blood flow, which can result in fetal hypoxia, and ultimately fetal asphyxia. In the setting of LCHAD deficiency, the unoxidized fatty acids are transferred to the mother through the placenta, rather than accumulating in the fetus, and thus are not a direct cause of fetal demise.

If no fatty acid oxidation defect is identified in the infant, offspring of mothers with AFLP appear to have no long-term adverse effects from the disorder itself. If a fatty acid oxidation defect is identified in the infant, long-term prognosis depends upon the clinical manifestations of the defect, which can range from mild to severe (table 5) [15,22,46]. Clinical presentation and prognosis of disorders of fatty acid oxidation are discussed separately. (See "Overview of fatty acid oxidation disorders".)

Recurrence in subsequent pregnancies — AFLP has been reported in subsequent pregnancies, even if testing for LCHAD deficiency mutation is negative; however, the exact risk of recurrence is unknown [11,37,47-51].

Affected women should be counseled about the possibility of recurrence if they are considering future pregnancy. Such patients should be co-managed with a maternal-fetal medicine specialist.

Women with a history of AFLP should be closely monitored in a subsequent pregnancy. They should be advised to seek medical attention if they develop any signs or symptoms of AFLP (eg, malaise, new onset nausea and vomiting, headache, upper abdominal pain, jaundice). In addition to routine prenatal care (weight, blood pressure, urine dipstick), they should be asked about signs and symptoms of AFLP, examined for jaundice, and undergo frequent laboratory screening. If AFLP previously occurred in the third trimester, we obtain labs (eg, aspartate aminotransferase, alanine aminotransferase, blood urea nitrogen/creatinine, prothrombin time/activated partial thromboplastin time) at the initial prenatal visit, once again in the second trimester, then at every visit in the third trimester. In the third trimester, visits are scheduled every one to two weeks and weekly after 34 weeks. If AFLP previously occurred in the second trimester, we begin this surveillance approximately one month before the gestational age of the previous diagnosis.

SUMMARY AND RECOMMENDATIONS

- Acute fatty liver of pregnancy (AFLP), characterized by maternal liver dysfunction and microvesicular fatty infiltration of hepatocytes, is rare, with an approximate incidence of 1 in 7000 to 20,000 deliveries. Risk factors include multiple gestation, prior history of AFLP, and male sex of the fetus. (See 'Epidemiology and risk factors' above.)

- Acute fatty liver of pregnancy typically presents between the 30th and the 38th gestational week, although it is not always diagnosed prior to delivery. The initial symptoms of AFLP may be nonspecific (eg, nausea, vomiting, abdominal pain, malaise, and/or anorexia). However, patients may develop manifestations of acute liver failure including jaundice, encephalopathy, coagulopathy and/or hypoglycemia. (See 'Patient presentation' above.)

- The diagnosis of AFLP is usually made clinically, based upon the presentation and compatible laboratory results. Laboratory tests that support the diagnosis include the following (see 'Diagnostic evaluation' above and 'Laboratory findings' above):

  - Elevated aminotransferases (5 to 10 times the upper limit of normal)
  - Elevated serum bilirubin
  - Elevated prothrombin time
  - Elevated uric acid level
  - Elevated ammonia level
  - Elevated creatinine
  - Elevated white blood cell count
  - Low serum glucose
  - Low fibrinogen

- For women with AFLP, initial management includes prompt delivery of the fetus, regardless of gestational age. Treatment is otherwise largely supportive with the goals of maternal stabilization and recovery of liver dysfunction. (See 'Initial management' above.)

- An enzyme deficiency associated with AFLP is fetal long-chain 3-hydroxyacyl CoA dehydrogenase (LCHAD) deficiency that results in fetal fatty oxidation defects. LCHAD catalyzes a step in beta-oxidation of mitochondrial fatty acids that forms 3-ketoacyl-CoA from 3-hydroxyacyl-CoA. Homozygous deficient offspring cannot perform this step and unmetabolized, long-chain fatty acids enter the maternal circulation. The accumulation of long-chain 3-hydroxyacyl metabolites produced by the fetus or placenta is toxic to the liver and may be the cause of maternal liver disease. (See 'Pathogenesis' above.)

- We suggest that all women with AFLP and their children undergo molecular testing for LCHAD, at least for the most common G1528C mutation. Additional testing for other defects in fatty acid oxidation can be pursued if this mutation is not detected. A list of laboratories that provide genetic testing is available at Genetic Testing Registry, and testing should be coordinated with a metabolic or genetic specialist. (See 'Genetic testing' above.)

- Acute fatty liver can recur in subsequent pregnancies, even if testing for LCHAD mutation is negative. Women with a history of AFLP who are contemplating another pregnancy should be co-

managed with a maternal-fetal medicine specialist. (See 'Recurrence in subsequent pregnancies' above.)

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Topic 3619 Version 23.0

GRAPHICS

Clinical characteristics of liver diseases in pregnancy

Disease	Symptoms	New onset hypertension	Gestational age at diagnosis	Laboratory findings	
				Aminotransferase levels	Other findings
Hyperemesis gravidarum	Persistent vomiting accompanied by weight loss exceeding 5% of pre-pregnancy body weight and ketonuria unrelated to other causes.	No	Onset in the first trimester. Often continues into the early second trimester, but usually resolves by 20 weeks of gestation.	Abnormal liver chemistries occur in approximately 50% of patients who are hospitalized because of the disease. Alanine aminotransferase (ALT) is typically elevated to a greater degree than aspartate aminotransferase (AST). Values for both are typically only mildly elevated.	▪ Bilirubin usually normal. Rarely exceeds 4 mg/dL.
HELLP syndrome (Hemolysis, Elevated Liver chemistries, and Low Platelets)	Most common symptom is abdominal pain and tenderness in the midepigastrium, right upper quadrant, or below the sternum. Many patients also have nausea, vomiting, and malaise. Headache, visual changes, and jaundice may occur but are uncommon. Liver rupture is rare.	Yes, in 85% of cases	Onset in the second half of pregnancy, usually in the third trimester. First recognition of disease may be postpartum, usually within 48 hours of delivery.	AST >2 times upper limit of normal for local laboratory (usually >70 international units/L). Marked elevations in the setting of hepatic infarction.	▪ Platelets <100,000/mm^3. ▪ LDH >600 international units/L. ▪ Total bilirubin ≥1.2 mg/dL (20.52 micromol/L). ▪ Random protein:creatinine ratio ≥0.3 mg protein/mg creatinine common. ▪ Elevated uric acid.
Preeclampsia with severe features	New-onset cerebral or visual disturbance (eg, severe headache, photopsia [flashes of light], scotomata [dark areas or gaps in the visual field],	Yes, in 100% of cases	Onset in the second half of pregnancy, usually in the third trimester. Can also present postpartum, usually within 48 hours of delivery.	Transaminase levels ≥2 times upper limit of normal for a specific laboratory.	▪ Platelets <100,000/mm^3. ▪ Serum creatinine >1.1 mg/dL [97.3 micromol/L] (or twice the baseline value). ▪ Random protein:creatinine ratio ≥0.3 mg protein/mg

	altered mental status) and severe, persistent right upper quadrant or epigastric pain are most common symptoms. Pulmonary edema may occur.				creatinine common. ▪ Elevated uric acid.
Intrahepatic cholestasis of pregnancy	Pruritus is the cardinal sign, and ranges from mild to intolerable. It is often generalized, but typically starts and predominates on the palms and soles and is worse at night. Right upper quadrant pain, nausea, poor appetite, sleep deprivation, or steatorrhea may occur.	No	Onset typically in the late second or the third trimester. Transient first trimester symptoms have been linked to ovarian hyperstimulation syndrome.	Serum aminotransferases are elevated in 60% of cases, and usually less than two times the upper limit of normal, but may reach values greater than 1000 international units/L.	▪ Elevated serum bile acid levels. ▪ Total and direct bilirubin concentrations are elevated in 25% of cases; in over 90% of cases, total bilirubin levels rarely exceed 6 mg/dL.
Acute fatty liver of pregnancy	Initial symptoms may be nonspecific (eg nausea, vomiting, abdominal pain, malaise, and/or anorexia), but patients may develop manifestations of acute liver failure including jaundice, encephalopathy, coagulopathy and/or hypoglycemia.	Yes, on occasion	Onset usually in third trimester, but the diagnosis has been made as early as 22 weeks of gestation and as late as four days after delivery.	Modest elevations, up to 500 international units/L.	▪ Elevated WBC count. ▪ Elevated serum creatinine. ▪ Elevated uric acid level. ▪ Elevated ammonia level. ▪ Prolonged PT/PTT. ▪ Decreased platelets. ▪ Decreased glucose. ▪ Decreased antithrombin level. ▪ Decreased fibrinogen.

HELLP syndrome likely represents a form of preeclampsia with severe features.

ALT: alanine aminotransferase; AST: aspartate aminotransferase; LDH: lactate dehydrogenase; WBC: white blood cell.

Graphic 57913 Version 6.0

Normal reference ranges in pregnant women

	Nonpregnant woman*	First trimester	Second trimester	Third trimester	References
Hematology					
Erythropoietin[¶] (units/L)	4 to 27	12 to 25	8 to 67	14 to 222	1-3
Ferritin[¶] (ng/mL)	10 to 150[Δ]	6 to 130	2 to 230	0 to 116	1-8
Folate, red blood cell (ng/mL)	150 to 450	137 to 589	94 to 828	109 to 663	6, 9, 10
Folate, serum (ng/mL)	5.4 to 18.0	2.6 to 15.0	0.8 to 24.0	1.4 to 20.7	1, 6, 9-13
Haptoglobin (mg/mL)	25 to 250	130 ± 43	115 ± 50	135 ± 65	93
Hemoglobin[¶] (g/dL)	12 to 15.8[Δ]	11.6 to 13.9	9.7 to 14.8	9.5 to 15.0	2, 3, 6, 7, 13
Hematocrit[¶] (percent)	35.4 to 44.4	31.0 to 41.0	30.0 to 39.0	28.0 to 40.0	1, 2, 5, 6, 13-15
Iron, total binding capacity[¶] (mcg/dL)	251 to 406	278 to 403	Not reported	359 to 609	7
Iron, serum[¶] (mcg/dL)	41 to 141	72 to 143	44 to 178	30 to 193	2, 7
Mean corpuscular hemoglobin (pg/cell)	27 to 32	30 to 32	30 to 33	29 to 32	5
Mean corpuscular volume (xm^3)	79 to 93	81 to 96	82 to 97	81 to 99	5, 6, 13, 14
Platelet ($x10^9$/L)	165 to 415	174 to 391	155 to 409	146 to 429	5, 6, 14, 16, 17
Mean platelet volume (mcm^3)	6.4 to 11.0	7.7 to 10.3	7.8 to 10.2	8.2 to 10.4	5
Red blood cell count ($x10^6/mm^3$)	4.00 to 5.20[Δ]	3.42 to 4.55	2.81 to 4.49	2.71 to 4.43	5, 6, 13, 14
Red cell distribution width (percent)	<14.5	12.5 to 14.1	13.4 to 13.6	12.7 to 15.3	5
White blood cell count ($x10^3/mm^3$)	3.5 to 9.1	5.7 to 13.6	5.6 to 14.8	5.9 to 16.9	5, 6, 13, 14, 18
Neutrophils ($x10^3/mm^3$)	1.4 to 4.6	3.6 to 10.1	3.8 to 12.3	3.9 to 13.1	5, 14, 16, 18
Lymphocytes ($x10^3/mm^3$)	0.7 to 4.6	1.1 to 3.6	0.9 to 3.9	1.0 to 3.6	5, 14, 16, 18
Monocytes ($x10^3/mm^3$)	0.1 to 0.7	0.1 to 1.1	0.1 to 1.1	0.1 to 1.4	5, 14, 18
Eosinophils ($x10^3/mm^3$)	0 to 0.6	0 to 0.6	0 to 0.6	0 to 0.6	14, 18
Basophils ($x10^3/mm^3$)	0 to 0.2	0 to 0.1	0 to 0.1	0 to 0.1	14, 18
Transferrin (mg/dL)	200 to 400	254 to 344	220 to 441	288 to 530	4, 5
Transferrin, saturation without iron (percent)	22 to 46[¶]	Not reported	10 to 44	5 to 37	3
Transferrin, saturation with iron (percent)	22 to 46[¶]	Not reported	18 to 92	9 to 98	3
Coagulation					

Antithrombin, functional (percent)	70 to 130	89 to 114	78 to 126	82 to 116	17, 19, 20
D-dimer (mcg/mL)	0.22 to 0.74	0.05 to 0.95	0.32 to 1.29	0.13 to 1.7	17, 20-24, 87
Factor V (percent)	50 to 150	75 to 95	72 to 96	60 to 88	25
Factor VII (percent)	50 to 150	100 to 146	95 to 153	149 to 211	17
Factor VIII (percent)	50 to 150	90 to 210	97 to 312	143 to 353	17, 25
Factor IX (percent)	50 to 150	103 to 172	154 to 217	164 to 235	17
Factor XI (percent)	50 to 150	80 to 127	82 to 144	65 to 123	17
Factor XII (percent)	50 to 150	78 to 124	90 to 151	129 to 194	17
Fibrinogen (mg/dL)	211 to 496	244 to 510	291 to 538	301 to 696	5, 17, 20, 21, 23, 24, 87
Homocysteine (mmol/L)	4.4 to 10.8	3.34 to 11	2.0 to 26.9	3.2 to 21.4	6, 9, 10-12
International Normalized Ratio	0.9 to 1.04◇	0.86 to 1.08	0.83 to 1.02	0.80 to 1.09	19, 24
Partial thromboplastin time, activated (seconds)	26.3 to 39.4	23.0 to 38.9	22.9 to 38.1	22.6 to 35.0	5, 17, 19, 24
Plasminogen activator inhibitor-1 (PAI-1) antigen (pg/mL)	17.3 ± 5.7	17.7 ± 1.9	Not reported	66.4 ± 4.9	87
Plasminogen activator inhibitor-1 (PAI-1) activity (arbitrary units)	9.3 ± 1.9	9.0 ± 0.8	Not reported	31.4 ± 3.0	87
Prothrombin time (seconds)	12.7 to 15.4	9.7 to 13.5	9.5 to 13.4	9.6 to 12.9	5, 17, 24
Protein C, functional (percent)	70 to 130	78 to 121	83 to 133	67 to 135	19, 25, 26
Protein S, total (percent)	70 to 140	39 to 105	27 to 101	33 to 101	17, 25, 26
Protein S, free (percent)	70 to 140	34 to 133	19 to 113	20 to 65	25, 26
Protein S, functional activity (percent)	65 to 140	57 to 95	42 to 68	16 to 42	25
Tissue plasminogen activator (ng/mL)	1.6 to 13§	1.8 to 6.0	2.36 to 6.6	3.34 to 9.20	17, 19, 87
Tissue plasminogen activator inhibitor-1 (ng/mL)	4 to 43	16 to 33	36 to 55	67 to 92	17
von Willebrand measurements					
von Willebrand factor antigen (percent)	75 to 125	62 to 318	90 to 247	84 to 422	20, 27, 28
ADAMTS-13, von Willebrand cleaving protease	40 to 170¥	40 to 160	22 to 135	38 to 105	20, 28
Blood chemical constituents					
Alanine transaminase (units/L)	7 to 41	3 to 30	2 to 33	2 to 25	4, 5, 8, 29
Albumin (g/dL)	4.1 to 5.3Δ	3.1 to 5.1	2.6 to 4.5	2.3 to 4.2	29-32
Alkaline phosphatase (units/L)	33 to 96	17 to 88	25 to 126	38 to 229	4, 5, 8, 29, 30

Alpha-1 antitrypsin (mg/dL)	100 to 200	225 to 323	273 to 391	327 to 487	5
Alpha-fetoprotein (ng/mL)	—	—	Approximately 130-400	Approximately 130-590	95
Ammonia (microM)	31 ± 3.2	—	—	27.3 ± 1.6	94
Amylase (units/L)	20 to 96	24 to 83	16 to 73	15 to 81	4, 5, 33, 34
Anion gap (mmol/L)	7 to 16	13 to 17	12 to 16	12 to 16	5
Aspartate transaminase (units/L)	12 to 38	3 to 23	3 to 33	4 to 32	4, 5, 8, 29
Bicarbonate (mmol/L)	22 to 30	20 to 24	20 to 24	20 to 24	5
Bilirubin, total (mg/dL)	0.3 to 1.3	0.1 to 0.4	0.1 to 0.8	0.1 to 1.1	4, 29
Bilirubin, unconjugated (mg/dL)	0.2 to 0.9	0.1 to 0.5	0.1 to 0.4	0.1 to 0.5	5, 29
Bilirubin, conjugated (mg/dL)	0.1 to 0.4	0 to 0.1	0 to 0.1	0 to 0.1	29
Bile acids (micromol/L)	0.3 to 4.8‡	0 to 4.9	0 to 9.1	0 to 11.3	29, 35
CA-125 antigen (units/mL)	7.2 to 27.0	2/2 to 268	12 to 25.1	16.8 to 43.8	88, 89, 90
Calcium, ionized (mg/dL)	4.5 to 5.3	4.5 to 5.1	4.4 to 5.0	4.4 to 5.3	5, 31, 36, 37
Calcium, total (mg/dL)	8.7 to 10.2	8.8 to 10.6	8.2 to 9.0	8.2 to 9.7	4, 5, 30, 32, 36-38
Ceruloplasmin (mg/dL)	25 to 63	30 to 49	40 to 53	43 to 78	5, 39
Chloride (mEq/L)	102 to 109	101 to 105	97 to 109	97 to 109	4, 5, 40
Creatinine (mg/dL)	0.5 to 0.9Δ	0.4 to 0.7	0.4 to 0.8	0.4 to 0.9	4, 5, 46
Gamma-glutamyl transpeptidase (units/L)	9 to 58	2 to 23	4 to 22	3 to 26	4, 5, 8, 29
Lactate dehydrogenase (units/L)	115 to 221	78 to 433	80 to 447	82 to 524	4, 5, 32, 8
Lipase (units/L)	3 to 43	21 to 76	26 to 100	41 to 112	33
Magnesium (mg/dL)	1.5 to 2.3	1.6 to 2.2	1.5 to 2.2	1.1 to 2.2	4, 5, 30-32, 36, 38
Osmolality (mOsm/kg H20)	275 to 295	275 to 280	276 to 289	278 to 280	38, 41
Phosphate (mg/dL)	2.5 to 4.3	3.1 to 4.6	2.5 to 4.6	2.8 to 4.6	4, 5, 30, 31, 42
Potassium (mEq/L)	3.5 to 5.0	3.6 to 5.0	3.3 to 5.0	3.3 to 5.1	4, 5, 15, 31, 32, 38, 40
Prealbumin (mg/dL)	17 to 34	15 to 27	20 to 27	14 to 23	5
Protein, total (g/dL)	6.7 to 8.6	6.2 to 7.6	5.7 to 6.9	5.6 to 6.7	5, 31, 32
Sodium (mEq/L)	136 to 146	133 to 148	129 to 148	130 to 148	4, 5, 15, 31, 32, 38, 41
Urea nitrogen (mg/dL)	7 to 20	7 to 12	3 to 13	3 to 11	4, 5, 40
Uric acid (mg/dL)	2.5 to 5.6Δ	2.0 to 4.2	2.4 to 4.9	3.1 to 6.3	4, 5, 41
Metabolic and endocrine tests					
Aldosterone (ng/dL)	2 to 9	6 to 104	9 to 104	15 to 101	43, 44, 45
Angiotensin converting enzyme (units/L)	9 to 67	1 to 38	1 to 36	1 to 39	39, 46

Alpha-fetoprotein (ng/mL)	0 to 8.5	Not reported	50 to 425	50 to 590	84, 86
Cortisol (mcg/dL)	0 to 25	7 to 19	10 to 42	12 to 50	5, 45
Hemoglobin A_{1C} (percent)	4 to 6	4 to 6	4 to 6	4 to 7	36, 47, 48
Parathyroid hormone (pg/mL)	8 to 51	10 to 15	18 to 25	9 to 26	30
Parathyroid hormone-related protein (pmol/L)	<1.3[†]	0.7 to 0.9	1.8 to 2.2	2.5 to 2.8	30
Renin, plasma activity (ng/mL/hour)	0.3 to 9.0[†]	Not reported	7.5 to 54.0	5.9 to 58.8	40, 44
Thyroid-stimulating hormone (milli-int. units/mL)	0.34 to 4.25	0.60 to 3.40	0.37 to 3.60	0.38 to 4.04	4, 5, 49
[American Thyroid Association recommendation]**		0.1 to 2.5	0.2 to 3.0	0.3 to 3.0	85
Thyroxine-binding globulin (mg/dL)	1.3 to 3.0	1.8 to 3.2	2.8 to 4.0	2.6 to 4.2	5
Thyroxine, free (ng/dL)	0.8 to 1.7	0.8 to 1.2	0.6 to 1.0	0.5 to 0.8	5, 49
Thyroxine, total (mcg/dL)	5.4 to 11.7	6.5 to 10.1	7.5 to 10.3	6.3 to 9.7	5, 32
Triiodothyronine, free (pg/mL)	2.4 to 4.2	4.1 to 4.4	4.0 to 4.2	Not reported	49
Triiodothyronine, total (ng/dL)	77 to 135	97 to 149	117 to 169	123 to 162	5
Vitamins and minerals					
Copper (mcg/dL)	70 to 140	112 to 199	165 to 221	130 to 240	50, 51, 5
Selenium (mcg/L)	63 to 160	116 to 146	75 to 145	71 to 133	5, 50
Vitamin A (retinol) (mcg/dL)	20 to 100	32 to 47	35 to 44	29 to 42	5
Vitamin B12 (pg/mL)	279 to 966	118 to 438	130 to 656	99 to 526	6, 10
Vitamin C (ascorbic acid) (mg/dL)	0.4 to 1.0	Not reported	Not reported	0.9 to 1.3	52
Vitamin D, 1,25-dihydroxy (pg/mL)	25 to 45	20 to 65	72 to 160	60 to 119	30, 36
Vitamin D, 24,25-dihydroxy (ng/mL)	0.5 to 5.0[†]	1.2 to 1.8	1.1 to 1.5	0.7 to 0.9	53
Vitamin D, 25-hydroxy (ng/mL)	14 to 80	18 to 27	10 to 22	10 to 18	30, 53
Vitamin E (α-tocopherol) (mcg/mL)	5 to 18	7 to 13	10 to 16	13 to 23	5
Zinc (mcg/dL)	75 to 120	57 to 88	51 to 80	50 to 77	5, 13, 50
Autoimmune and inflammatory mediators					
C3 complement (mg/dL)	83 to 177	62 to 98	73 to 103	77 to 111	5
C4 complement (mg/dL)	16 to 47	18 to 36	18 to 34	22 to 32	5
C-reactive protein (mg/L)	0.2 to 3.0	Not reported	0.4 to 20.3	0.4 to 8.1	54
Erythrocyte sedimentation rate	0 to 20[Δ]	4 to 57	7 to 47	13 to 70	55

(mm/hour)					
Immunoglobulin A (mg/dL)	70 to 350	95 to 243	99 to 237	112 to 250	5
Immunoglobulin G (mg/dL)	700 to 1700	981 to 1267	813 to 1131	678 to 990	5
Immunoglobulin M (mg/dL)	50 to 300	78 to 232	74 to 218	85 to 269	5
Sex hormones					
Dehydroepiandrosterone sulfate (mmol/L)	1.3 to 6.8[†]	2.0 to 16.5	0.9 to 7.8	0.8 to 6.5	56
Estradiol (pg/mL)	<20 to 443[Δ,¶¶]	188 to 2497	1278 to 7192	614 to 3460	56, 57
Progesterone (ng/mL)	<1 to 20[Δ]	8 to 48		99 to 342	56, 57
Prolactin (ng/mL)	0 to 20	36 to 213	110 to 330	137 to 372	30, 47, 57, 58
Sex hormone binding globulin (nmol/L)	18 to 114[Δ]	39 to 131	214 to 717	216 to 724	56, 59
Testosterone (ng/dL)	6 to 86[Δ]	25.7 to 211.4	34.3 to 242.9	62.9 to 308.6	56
17-hydroxyprogesterone (nmol/L)	0.6 to 10.6[Δ,†]	5.2 to 28.5	5.2 to 28.5	15.5 to 84	56
Lipids					
Cholesterol, total (mg/dL)	<200	141 to 210	176 to 299	219 to 349	5, 60-62
High-density lipoprotein cholesterol (mg/dL)	40 to 60	40 to 78	52 to 87	48 to 87	5, 60-63
Low-density lipoprotein cholesterol (mg/dL)	<100	60 to 153	77 to 184	101 to 224	5, 60-63
Very-low-density lipoprotein cholesterol (mg/dL)	6 to 40[†]	10 to 18	13 to 23	21 to 36	62
Triglycerides (mg/dL)	<150	40 to 159	75 to 382	131 to 453	4, 5, 60-63
Apolipoprotein A-I (mg/dL)	119 to 240	111 to 150	142 to 253	145 to 262	4, 47, 61
Apolipoprotein B (mg/dL)	52 to 163	58 to 81	66 to 188	85 to 238	4, 47, 61
Cardiac function					
Cardiac output (L/minute)	4.8 to 6.8	5.6 to 9.7	5.5 to 9.9	4.8 to 8.7	64, 65, 66, 67, 68
Cardiac index ($L/min/m^2$)	2.6 to 4.2	3.2 to 4.6	3.1 to 4.7	2.5 to 4.4	65, 68
Stroke volume (mL)	79 to 90	77.5 to 107.6	70.3 to 107.6	54 to 99	65, 68, 69
Stroke index (mL/m^2)		46 to 62	39 to 62	30 to 42	65
Systemic vascular resistance ($dyns/cm^5$)	700 to 1600	747 to 1485	692 to 1201	1034 to 1201	65, 67, 70
Echocardiography					

Intraventricular septal dimension (cm)	0.7 to 0.9	0.63 to 0.83	0.65 to 0.85	0.66 to 0.9	68, 69, 70, 91, 92
Posterior ventricular wall dimension (cm)	0.75 to 0.9	0.56 to 0.8	0.59 to 0.9	0.59 to 0.9	68, 69, 70, 91, 92
Left ventricular mass (g)	116 to 143	108 to 167	115 to 150	128 to 162	68, 70, 91, 92
Left ventricular mass index	40 to 78	53 to 79	58 to 82	60 to 88	68, 70, 91, 92
E/A ratio	1.4 to 1.75	1.6	1.4	1.3	68, 70
Left ventricular diastolic diameter (cm)	4.3 to 4.8	4.3 to 4.6	4.4 to 4.9	5.1	69, 70
Left ventricular systolic diameter (cm)	2.8 to 3.1	2.8 to 2.9	2.8 to 3.4	2.8 to 3.3	69, 70
Left vent, fractional shortening (percent)	35 to 36	35 to 37	3.5	35 to 36	69, 70
Left vent ejection fraction (percent)	60 to 73	61 to 75	61 to 63	60 to 73	69, 70
Diastolic function					
Mitral E wave (m/second)	0.77 ± 0.11	0.85 ± 0.13	0.84 ± 0.16	0.77 ± 0.15	91, 92
Mitral A wave (m/second)	0.46 ± 0.1	0.5 ± 0.09	0.5 ± 0.1	0.55 ± 0.1	91, 92
Isovolumic relaxation time (m/second)	69 ± 10	50 ± 10	79 ± 18	72 ± 16	91, 92
Cardiac function (blood tests)					
Atrial natriuretic peptide (pg/mL)	Not reported	Not reported	28.1 to 70.1	Not reported	73
B-type natriuretic peptide (pg/mL)	<167 (age- and gender-specific)	18.4	13.5 to 29.5	15.5 to 46	71, 72, 73
Creatine kinase (units/L)	39 to 238$^{\Delta}$	27 to 83	25 to 75	13 to 101	5, 74
Creatine kinase-MB (units/L)	<6$^{\Delta\Delta}$	—	—	1.8 to 2.4	74
N-terminal pro-brain natriuretic peptide (pg/mL)	50 ± 26	60 ± 45	60 ± 40	43 ± 34	96
Troponin I (ng/mL)	0 to 0.08	Not reported	Not reported	0 to 0.064 (intrapartum)	75, 76
Blood gas					
pH	7.38 to 7.42 (arterial)	7.36 to 7.52 (venous)	7.40 to 7.52 (venous)	7.41 to 7.53 (venous) 7.39 to 7.45 (arterial)	31, 77
PO_2 (mmHg)	90 to 100	93 to 100	90 to 98	92 to 107	77, 78
PCO_2 (mmHg)	38 to 42	Not reported	Not reported	25 to 33	77
Bicarbonate (HCO_3^-) (mEq/L)	22 to 26	Not reported	Not reported	16 to 22	77
Renal function tests					

Effective renal plasma flow (mL/minute)	492 to 696[Δ,†]	696 to 985	612 to 1170	595 to 945	79, 80
Glomerular filtration rate (GFR) (mL/minute)	106 to 132[Δ]	131 to 166	135 to 170	117 to 182	79, 80, 81
Filtration fraction (percent)	16.9 to 24.7[◇◇]	14.7 to 21.6	14.3 to 21.9	17.1 to 25.1	79, 80, 81
Osmolarity, urine (mOsm/kg)	500 to 800	326 to 975	278 to 1066	238 to 1034	82
2-4h albumin excretion (mg/24 hours)	<30	5 to 15	4 to 18	3 to 22	82, 83
24-h calcium excretion (mmol/24 hours)	<7.5[†]	1.6 to 5.2	0.3 to 6.9	0.8 to 4.2	15
24-h creatinine clearance (mL/minute)	91 to 130	69 to 140	55 to 136	50 to 166	15, 80
24-h creatinine excretion (mmol/24 hours)	8.8 to 14[†]	10.6 to 11.6	10.3 to 11.5	10.2 to 11.4	82
24-h potassium excretion (mmol/24 hours)	25 to 100[†]	17 to 33	10 to 38	11 to 35	15
24-h protein excretion (mg/24 hours)	<150	19 to 141	47 to 186	46 to 185	83
24-h sodium excretion (mmol/24 hours)	100 to 260[†]	53 to 215	34 to 213	37 to 149	15, 41

* Unless otherwise specified, all normal reference values are from the seventeenth edition of *Harrison's Principles of Internal Medicine*[84].

¶ Range includes references with and without iron supplementation.

Δ Normal reference range is specific range for females.

◇ Reference values are from Cerneca et al: Coagulation and fibrinolysis changes in normal pregnancy increased levels of procoagulants and reduced levels of inhibitors during pregnancy induce a hypercoagulable state, combined with a reactive fibrinolysis[19].

§ References values are from Cerneca et al and Choi et al: Tissue plasminogen activator levels change with plasma fibrinogen concentrations during pregnancy[17,19].

¥ Reference values are from Mannuci et al: Changes in health and disease of the metalloprotease that cleaves von Willebrand factor[28].

‡ Reference values are from Bacq Y et al: Liver function tests in normal pregnancy: a prospective study of 102 pregnant women and 102 matched controls[29].

† Reference values are from the fifteenth edition of *Harrison's Principles of Internal Medicine*[85].

** The American Thyroid Association recommends these TSH ranges if individual laboratories do not determine their own trimester-specific reference ranges.

¶¶ Range is for premenopausal females and varies by menstrual cycle phase.

ΔΔ Reference values are from Leiserowitz GS et al: Creatine kinase and its MB isoenzyme in the third trimester and the peripartum period[74].

◇◇ Reference values are from Dunlop W: Serial changes in renal haemodynamics during normal human pregnancy[79].

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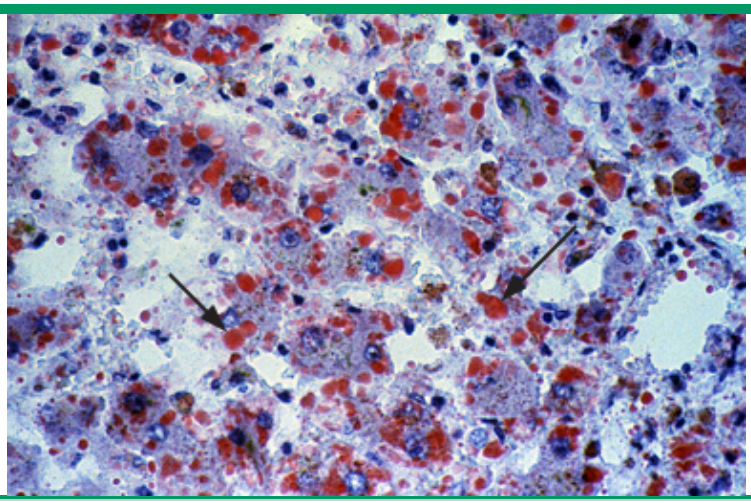
Graphic 81137 Version 45.0

Acute fatty liver of pregnancy



High power view of an oil red O stain of a liver biopsy from a patient with acute fatty liver of pregnancy. There are vacuolated hepatocytes containing microvesicular fat which stain red (arrows). This stain should be routinely used for the diagnosis of acute fatty liver of pregnancy and must be performed on a biopsy specimen that has not been fixed.

Courtesy of Caroline A Riely, MD.

Graphic 68144 Version 2.0

Criteria for the diagnosis of preeclampsia

Systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg on at least two occasions at least four hours apart after 20 weeks of gestation in a previously normotensive patient AND the new onset of one or more of the following*:
▪ Proteinuria ≥0.3 g in a 24-hour urine specimen or protein/creatinine ratio ≥0.3 (mg/mg) (30 mg/mmol) in a random urine specimen or dipstick ≥2+ if a quantitative measurement is unavailable
▪ Platelet count <100,000/microL
▪ Serum creatinine >1.1 mg/dL (97.2 micromol/L) or doubling of the creatinine concentration in the absence of other renal disease
▪ Liver transaminases at least twice the upper limit of the normal concentrations for the local laboratory
▪ Pulmonary edema
▪ Cerebral or visual symptoms (eg, new-onset and persistent headaches not accounted for by alternative diagnoses and not responding to usual doses of analgesics¶; blurred vision, flashing lights or sparks, scotomata)

In a woman with chronic/preexisting hypertension, criteria for superimposed preeclampsia are new onset of proteinuria, significant end-organ dysfunction, or both after 20 weeks of gestation. For women with chronic/preexisting hypertension who have proteinuria prior to or in early pregnancy, superimposed preeclampsia is defined by worsening or resistant hypertension (especially acutely) in the last half of pregnancy or development of signs/symptoms of the severe end of the disease spectrum.

* If systolic blood pressure is ≥160 mmHg or diastolic blood pressure is ≥110 mmHg, confirmation within minutes is sufficient.
¶ Response to analgesia does not exclude the possibility of preeclampsia.

Adapted from: American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin No. 202: Gestational Hypertension and Preeclampsia. Obstet Gynecol 2019; 133:e1-e25.

Graphic 79977 Version 33.0

In a patient with preeclampsia, the presence of one or more of the following indicates a diagnosis of "preeclampsia with severe features"

Severe blood pressure elevation:
Systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥110 mmHg on two occasions at least four hours apart while the patient is on bedrest (antihypertensive therapy may be initiated upon confirmation of severe hypertension, in which case criteria for severe blood pressure elevation can be satisfied without waiting until four hours have elapsed)
Symptoms of central nervous system dysfunction:
New-onset cerebral or visual disturbance, such as: ▪ Photopsia, scotomata, cortical blindness, retinal vasospasm ▪ Severe headache (ie, incapacitating, "the worst headache I've ever had") or headache that persists and progresses despite analgesic therapy and not accounted for by alternative diagnoses
Hepatic abnormality:
Severe persistent right upper quadrant or epigastric pain unresponsive to medication and not accounted for by an alternative diagnosis or serum transaminase concentration ≥2 times the upper limit of the normal range, or both
Thrombocytopenia:
<100,000 platelets/microL
Renal abnormality:
Renal insufficiency (serum creatinine >1.1 mg/dL [97.2 micromol/L] or a doubling of the serum creatinine concentration in the absence of other renal disease)
Pulmonary edema

In contrast to older criteria, the 2013 criteria do not include proteinuria >5 g/24 hours and fetal growth restriction as features of severe disease.

Adapted from: American College of Obstetricians and Gynecologists (ACOG Practice Bulletin No. 202: Gestational Hypertension and Preeclampsia. Obstet Gynecol 2019; 133:e1-e25.

Graphic 76975 Version 20.0

Summary of fatty acid oxidation disorders

	Enzyme	Gene	Prevalence	Symptoms	Other complications	Plasma acylcarnitines
VLCADD	Very long-chain acyl-CoA dehydrogenase deficiency	*ACADVL*	1 in 42,500 to 120,000	G, L, C, M, R		Elevated C14:1–, C14–, C16:1–, C16–
LCHADD	Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency	*HADHA*	1 in 110,000	G, L, C, M, R	Retinopathy, peripheral neuropathy	Elevated C16:1–OH–, C16–OH–, C18:1–OH–, C18–OH–
TFPD	Trifunctional protein deficiency	*HADHA, HADHB*	Rare	G, L, C, M, R	Retinopathy, peripheral neuropathy	Elevated C16:1–OH–, C16–OH–, C18:1–OH–, C18–OH–
CTD	Carnitine transporter deficiency	*SLC22A5*	1 in 20,000 to 120,000	G, L, C, M, R	NBS maternal CTD	Low total and free carnitine levels
CACTD	Carnitine-acylcarnitine translocase deficiency	*SLC25A20*		G, L, C		Elevated C16–, C16:1–, C18, C18:1–
CPT1D	Carnitine palmitoyltransferase 1A deficiency	*CPT1A*	1 in 500,000	G, L	Renal tubular acidosis, Arctic variant	Elevated total and free plasma carnitine levels
CPT2D	Carnitine palmitoyltransferase 2 deficiency	*CPT2*		G, L, C, M, R	Renal cysts, facial dysmorphism	Elevated C16–, C16:1–, C18, C18:1–
MCADD	Medium-chain acyl-CoA dehydrogenase deficiency	*ACADM*	1 in 20,000	G, L		Elevated C6–, C8–, C10–, C10:1–
MADD	Multiple acyl-CoA dehydrogenase deficiency	*ETFA, ETFB, ETFDH*		G, L, C, M	Renal cysts, congenital malformations, facial dysmorphism, sweaty foot odor	Elevated C4–, C5–, C5DC–, C6–, C8–, C10:1–, C12–, C14–, C14:1–, C16–, C16:1–, C18–, C18:1–, C16–OH–, C16:1–OH–, C18–OH–, C18:1–OH–
SCADD	Short-chain acyl-CoA dehydrogenase deficiency	*ACADS*	1 in 35,000 to 50,000		Asymptomatic	Elevated C4–
M/SCHAD	Short-chain L-3-hydroxyacyl-CoA dehydrogenase deficiency	*HADH*			Hyperinsulinism	Elevated C4–OH–

ACADVL: acyl-CoA dehydrogenase, very long-chain gene; G: hypoglycemia; L: liver dysfunction; C: cardiomyopathy; M: skeletal myopathy; R: rhabdomyolysis; *HADHA:* hydroxyacyl-CoA dehydrogenase/3-ketoacyl-CoA thiolase/enoyl-CoA hydratase (trifunctional protein), alpha subunit; *HADHB*: hydroxyacyl-CoA dehydrogenase/3-ketoacyl-CoA thiolase/enoyl-CoA hydratase (trifunctional protein), beta subunit; *SLC22A5*: solute carrier family 22 member 5 gene; NBS: newborn screening; *SLC25A20*: solute carrier family 25 member 20

gene; *CPT1A*: carnitine palmitoyltransferase 1A; *CPT2*: carnitine palmitoyltransferase 2; *ACADM*: acyl-CoA dehydrogenase, C-4 to C-12 straight chain; *ETFA*: electron transfer flavoprotein, alpha subunit; *ETFB*: electron transfer flavoprotein, beta subunit; *ETFDH*: electron transfer flavoprotein dehydrogenase; *ACADS*: acyl-CoA dehydrogenase, C-2 to C-3 short-chain; *HADH*: 3-hydroxyacyl-CoA dehydrogenase.

Adapted from: Sun A, Merritt JW II. Orphan drugs in development for long-chain fatty acid oxidation disorders: Challenges and progress. Orph Drug Res Rev 2015; 5:33.

Graphic 114663 Version 3.0

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Richard H Lee, MD Nothing to disclose **Tram T Tran, MD** Employment: Gilead [Tenofovir]. Equity Ownership/Stock Options: Gilead [Tenofovir]. **Keith D Lindor, MD** Nothing to disclose **Charles J Lockwood, MD, MHCM** Nothing to disclose **Kristen M Robson, MD, MBA, FACG** Nothing to disclose **Vanessa A Barss, MD, FACOG** Nothing to disclose

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