Acute fatty liver of pregnancy

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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 evaluating pregnant patients with elevated liver biochemical and function tests".)

EPIDEMIOLOGY AND RISK FACTORS

Acute fatty liver of pregnancy (AFLP) is rare, with an approximate incidence of 1 in 7000 to 20,000 pregnancies [2-6]. Given the association with inherited defects, the incidence may vary based on ethnicity, but epidemiology studies are lacking. (See 'Pathogenesis' below.)

Potential risk factors for AFLP include [1,3,4,7,8]:

- Fetal long-chain 3-hydroxyacyl CoA dehydrogenase deficiency
- Prior episode of AFLP

- Multiple gestation
- Preeclampsia or hemolysis, elevated liver enzymes, and a low platelet count syndrome
- Male fetal sex
- Low body mass index (BMI <20 kg/m^2)
- Nulliparity

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 [9,10].

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 [11-13]. Because the mother is heterozygous for LCHAD deficiency, she has decreased ability to accomplish fatty acid oxidation, thus contributing to long-chain metabolites accumulating in maternal blood and hepatocytes, resulting in toxic effects.

However, not all mutations that lead to LCHAD deficiency result in AFLP [14,15]. 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 [9,11]. The heterozygous and wild-type fetal genotype are not associated AFLP [16].

The G1528C mutation has also been associated with development of hemolysis, elevated liver enzymes, and a low platelet count syndrome [9,11,16] and preeclampsia [16], which share several phenotypic features with AFLP [17].

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 [10] (see "Specific fatty acid oxidation disorders", section on 'Medium- and short-chain fatty acid oxidation disorders'):

- Short-chain acyl-CoA dehydrogenase deficiency [18].
- Medium-chain acyl-CoA dehydrogenase deficiency [19].
- Carnitine palmitoyltransferase deficiency [20].
- Mitochondrial trifunctional protein deficiency [21,22].

It is important to recognize that genetic testing may not demonstrate an abnormality. As an example, a whole-exome genetic sequencing analysis of East Asian patients with AFLP found no gene mutation in enzymes involved in fatty acid metabolism [23].

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 18 weeks [24] and as late as four days after delivery [3,25].

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. Coexisting hemolysis, elevated liver enzymes, and low platelet count syndrome occurs in 20 percent, and 20 to 40 percent of patients are also diagnosed with preeclampsia [26]. (See "HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets)" and "Preeclampsia: Clinical features and diagnosis".)

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].

Arginine vasopressin deficiency (AVP-D, previously called 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 [27]. Acute pancreatitis, which can be severe, is rare and generally occurs in the setting of hepatic and renal dysfunction [28].

In cases of maternal hypovolemia combined with metabolic acidosis from liver injury, uteroplacental perfusion is diminished and, in turn, tests of fetal well-being are frequently nonreassuring [29].

LABORATORY, IMAGING, AND HISTOLOGIC FINDINGS

Laboratory findings — All patients 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 (table 1) [26]. 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 urate 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
- Low cholesterol

Note: In normal pregnancy, the mean platelet count is slightly lower than in nonpregnant females, 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 but this is not diagnostic [26,30]. Other imaging modalities maybe more specific. For example, 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 [31]. 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 [32]. (See 'Diagnostic evaluation' below.)

Histologic findings — Biopsy is rarely needed for diagnosis or management. If performed, microvesicular fatty infiltration of swollen hepatocytes is strongly suggestive of AFLP [33,34]. 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 [35]. 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) [36,37].

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of acute fatty liver of pregnancy (AFLP) primarily involves the syndrome of hemolysis, elevated liver enzymes, and a low platelet count (HELLP) and preeclampsia with severe features (table 3 and table 1) [38]. There is a large clinical overlap between AFLP, HELLP syndrome, and severe preeclampsia [39]. Adding to the complexity, a patient may have both AFLP and HELLP or preeclampsia with severe features.

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 hypoglycemia, encephalopathy, ascites and coagulopathy are more consistent with AFLP than HELLP or severe preeclampsia. AFLP is the most common cause of acute liver failure in pregnancy [40]. Multi-organ involvement, especially concurrent renal failure, is more common with AFLP than HELLP or severe preeclampsia, while hypertension and proteinuria are often more severe in HELLP and severe preeclampsia.

In addition, non-pregnancy-related causes of abnormal liver chemistries need to be assessed, such as hepatitis (ie, hepatitis B virus, herpes simplex virus, hepatitis E virus, autoimmune), gallstone disease, Budd-Chiari syndrome and acetaminophen or other drug-induced liver injury.

Differential diagnosis is discussed in more detail separately. (See "Hypertensive disorders in pregnancy: Approach to differential diagnosis".)

DIAGNOSTIC EVALUATION

Pregnant patients 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 (HELLP) 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, cognitive assessment for encephalopathy, and:

- Complete blood count
- Creatinine
- Glucose
- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST)
- Lactate dehydrogenase
- Bilirubin
- Urate
- Urine protein (protein:creatinine ratio or 24-hour urine protein)
- Prothrombin time, international normalized ratio

For patients with signs of liver failure (eg, encephalopathy, jaundice, coagulopathy) or ALT ≥5 times the upper limit of normal, additional laboratory study is performed urgently, including ammonia.

The role of imaging for patients with suspected AFLP is uncertain. While some imaging modalities may be more specific than noncontrast ultrasound, MRI and computed tomography (CT) should be used judiciously because the safety of MRI in pregnancy is not as well established as for ultrasound and CT exposes the mother and fetus to ionizing radiation [1,41]. (See 'Imaging' above and "Diagnostic imaging in pregnant and lactating patients".)

For pregnant patients with suspected biliary tract disease (eg, cholestatic pattern of liver biochemical tests), abdominal imaging with noncontrast ultrasound is typically performed [1]. (See "Approach to the patient with abnormal liver biochemical and function tests", section on 'Evaluation of elevated alkaline phosphatase'.)

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 [25]. 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 [26]. (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 [42-44]. (See 'Laboratory findings' above and 'Differential diagnosis' above.)

In addition, diagnosis of AFLP does not exclude another diagnosis of pregnancy-induced liver disease.

Small studies have identified biomarkers that could potentially contribute to diagnostic evaluation [45,46]; however, biomarkers are not routinely used in clinical practice.

Findings on imaging may support the diagnosis, but imaging is not required in all patients with suspected AFLP. (See 'Diagnostic evaluation' 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 [3,47].

The Swansea criteria are listed below [3,26,48]. 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 patients without hemolysis, elevated liver enzymes, and a low platelet count (HELLP) syndrome or preeclampsia, which limits their clinical utility [26,49].

- Signs and symptoms
    - Vomiting
    - Abdominal pain
    - Polydipsia/polyuria
    - Encephalopathy

- Laboratory findings
  - Elevated bilirubin (>0.8 mg/dL or >14 micromol/L)
  - Hypoglycemia (glucose <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 urate (5.7 mg/dL or >340 micromol/L)
  - Acute kidney injury, or creatinine >1.7 mg/dL (150 micromol/L)
  - Coagulopathy or prothrombin time >14 seconds
- Imaging: Ascites or bright liver on ultrasound scan
- Histology: Microvesicular steatosis on liver biopsy

When the Swansea criteria were applied to a cohort of 24 patients 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 [47].

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.

Patients with signs of acute liver failure (eg, coagulopathy, encephalopathy) are transferred to a referral center for liver transplantation evaluation. Although most patients improve after delivery, transfer is required to avoid delay in liver transplantation evaluation and listing and to reduce risk of adverse outcomes. Management of patients with acute liver failure is discussed separately. (See "Acute liver failure in adults: Management and prognosis" and "Liver transplantation in adults: Patient selection and pretransplantation evaluation".)

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 in addition to acute liver failure [50]:

  - 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

  In addition to monitoring laboratory studies, we follow the Model for End-stage Liver Disease (MELD) score because high MELD score (particularly MELD ≥30) was associated with increased risk of maternal complications [51]. (See "Model for End-stage Liver Disease (MELD)".)

- **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 often 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 [4]. Patients are monitored by following physical examination with mental status assessment, pulse oximetry, and fluid balance, including urinary output. The use of invasive hemodynamic monitoring is balanced against 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 "Central venous access in adults: General principles".)

  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** – Plasma glucose concentration assessment should be done at six to eight hour intervals if the initial serum glucose is normal. If the glucose concentration is trending downward, more frequent monitoring is needed, in addition to evaluation for liver transplantation [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). Hypoglycemia is a common manifestation of

acute liver failure. (See "Acute liver failure in adults: Management and prognosis", section on 'Metabolic abnormalities'.)

- **Monitoring for and treatment of coagulopathy** – Coagulopathy is one of the most sensitive assessments of hepatic function. Platelet count, international normalized ratio, partial thromboplastin time, and fibrinogen levels are obtained every four to six hours until the patient beings to stabilize and improve. Worsening coagulopathy is an indication for expedited liver transplant evaluation. Management of disseminated intravascular coagulation in pregnancy is described in detail separately. (See "Disseminated intravascular coagulation (DIC) during pregnancy: Management and prognosis", section on 'Blood products'.)

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

- 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 patients 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: Intrapartum and postpartum management and long-term prognosis", section on 'Dosing'.)

- **Other therapies** – Data from case series suggested that therapeutic plasma exchange (TPE) may be an option for patients with progressive disease despite delivery [52]. TPE should not delay liver transplantation in patients with acute liver failure.

DELIVERY

Once a patient is diagnosed with acute fatty liver of pregnancy, plans should be made to proceed with prompt 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 standard tests for fetal well-being are reassuring, 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 "Induction of labor: Techniques for preinduction cervical ripening".)

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. In one review, the cesarean delivery rate was 66.7 percent (298/447) [29]. However, the mother should be stabilized before surgery, with special attention given towards correcting any coagulopathy [6]. (See "Disseminated intravascular coagulation (DIC) during pregnancy: Clinical findings, etiology, and diagnosis".)

Neuraxial anesthesia for labor and/or delivery may not be possible in patients with coagulopathy. The threshold platelet count for performing neuraxial techniques varies among clinicians, and is individualized based on patient factors. (See "Adverse effects of neuraxial analgesia and anesthesia for obstetrics", section on 'Neuraxial analgesia and low platelets'.)

POSTPARTUM MANAGEMENT

Maternal monitoring and course — The three major causes of maternal morbidity and mortality are hemorrhage, liver failure, and acute kidney injury [29]. Over the past several decades, maternal mortality rates have decreased from >75 percent to <5 percent [3,4,37,53,54]. This improvement has been attributed to multiple factors: earlier diagnosis of acute fatty liver of pregnancy (AFLP), prompt delivery, and advances in critical care [26].

In most patients, AFLP usually resolves completely after delivery, with return of normal liver function within 7 to 10 days [4]. Liver function and coagulopathy typically begin to improve within days after delivery. A transient worsening of liver and renal functions and coagulopathy peripartum have been reported, reinforcing the need for continued monitoring following delivery [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, dialysis for acute renal failure, nutritional support because of associated pancreatitis, or transfusion of blood products for ongoing hemolysis or postpartum hemorrhage from atony or incisional bleeding [1]. 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, supportive care, and prompt

delivery of the fetus [25,55,56]. 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 [57].

Long-term maternal consequences of AFLP are uncertain as most studies have not followed patients beyond the immediate postpartum phase of the illness, and the disease is rare [26]. Limited data suggest that there are no sequelae of the liver disease itself [4,26,58].

Genetic testing — Given the association between LCHAD deficiency in the fetus and AFLP in the mother, children born to mothers with AFLP should be monitored for manifestations of LCHAD deficiency, especially hypoglycemia. Molecular testing for long-chain 3-hydroxyacyl CoA dehydrogenase (LCHAD) in infants is performed because early diagnosis of LCHAD deficiency in the newborn can be life-saving [59,60]. 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, family screening may be indicated.

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) [10,18]. (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 4) [10,26,61]. 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 [14,49,62-66].

Affected patients 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.

Patients 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

- **Epidemiology and risk factors** – 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.)

- **Patient presentation** – AFLP 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.)

- **Diagnostic evaluation** – 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 urate level
- Elevated ammonia level
- Elevated creatinine
- Elevated white blood cell count
- Low serum glucose
- Low fibrinogen

- **Initial management** – For patients 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.)

- **Pathogenesis** – 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.)

- **Postpartum management** – We suggest that all patients 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.)

  AFLP can recur in subsequent pregnancies, even if testing for LCHAD mutation is negative. Patients 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 39.0

GRAPHICS

Clinical characteristics of liver diseases in pregnancy

Disease	Symptoms	New onset hypertension	Gestational age at diagnosis	Laboratory findin	
				Aminotransferase levels	Othe
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.	▪ Biliru norm exce
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.	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.	▪ Plate <100 ▪ LDH inter units ▪ Total ≥1.2 (20.5 micr ▪ Rand prote ratio prote creat comr ▪ Eleva acid.

	Liver rupture is rare.				
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], altered mental status) and severe, persistent right upper quadrant or epigastric pain are most common symptoms. Pulmonary edema may occur.	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.	▪ Plate <100 ▪ Seru >1.1 micr twice base ▪ Rand prote ratio prote creat comr ▪ Eleva 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	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.	▪ Eleva bile a ▪ Total biliru conc are e 25% over cases biliru rarel mg/d

	steatorrhea may occur.				
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.	▪ Eleva coun ▪ Eleva creat ▪ Eleva level. ▪ Eleva amm ▪ Prolc PT/P ▪ Decr plate ▪ Decr gluc ▪ Decr antit level. ▪ Decr fibrir

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

Reference intervals in pregnancy

	Nonpregnant females*	First trimester	Second trimester	Third trimester	Refer
Hematology					
Erythropoietin¶ (units/L)	4 to 27	12 to 25	8 to 67	14 to 222	1-3, 10
Ferritin¶ (ng/mL)	10 to 150Δ	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, 1(
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-
Haptoglobin (mg/mL)	25 to 250	130±43	115±50	135±65	91
Hemoglobin¶ (g/dL)	12 to 15.8Δ	11.6 to 13.9	9.7 to 14.8	9.5 to 15.0	2, 3, 6,
Hematocrit¶ (%)	35.4 to 44.4	31.0 to 41.0	30.0 to 39.0	28.0 to 40.0	1, 2, 5, 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 ($\times m^3$)	79 to 93	81 to 96	82 to 97	81 to 99	103
Platelet ($\times 10^9$/L)	165 to 415	174 to 391	155 to 409	146 to 429	5, 6, 14 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 ($\times 10^6/mm^3$)	4.00 to 5.20Δ	3.42 to 4.55	2.81 to 4.49	2.71 to 4.43	5, 6, 13
Red cell distribution width (%)	<14.5	12.5 to 14.1	13.4 to 13.6	12.7 to 15.3	5
White blood cell count ($\times 10^3/mm^3$)	3.5 to 9.1	5.7 to 13.6	5.6 to 14.8	5.9 to 16.9	5, 6, 13 18
Neutrophils ($\times 10^3/mm^3$)	1.4 to 4.6	3.6 to 10.1	3.8 to 12.3	3.9 to 13.1	5, 14,
Lymphocytes ($\times 10^3/mm^3$)	0.7 to 4.6	1.1 to 3.6	0.9 to 3.9	1.0 to 3.6	5, 14,

Monocytes ($\times 10^3/mm^3$)	0.1 to 0.7	0.1 to 1.1	0.1 to 1.1	0.1 to 1.4	5, 14,
Eosinophils ($\times 10^3/mm^3$)	0 to 0.6	0 to 0.6	0 to 0.6	0 to 0.6	14, 18
Basophils ($\times 10^3/mm^3$)	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 (%)	22 to 46¶	Not reported	10 to 44	5 to 37	3
Transferrin, saturation with iron (%)	22 to 46¶	Not reported	18 to 92	9 to 98	3
Hepcidin (ng/mL)	Not reported	4 to 97	6 to 36	1 to 43	98, 10
Coagulation					
Antithrombin, functional (%)	70 to 130	89 to 114	78 to 126	82 to 116	17, 19,
Factor V (%)	50 to 150	75 to 95	72 to 96	60 to 88	25
Factor VII (%)	50 to 150	100 to 146	95 to 153	149 to 211	17
Factor VIII (%)	50 to 150	90 to 210	97 to 312	143 to 353	17, 25
Factor IX (%)	50 to 150	103 to 172	154 to 217	164 to 235	17
Factor XI (%)	50 to 150	80 to 127	82 to 144	65 to 123	17
Factor XII (%)	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, 2 23, 24,
Homocysteine (mmol/L)	4.4 to 10.8	3.34 to 11	2.0 to 26.9	3.2 to 21.4	6, 9, 1
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,
Plasminogen activator inhibitor-1 (PAI-1) antigen (pg/mL)	17.3±5.7	17.7±1.9	Not reported	66.4±4.9	85
Plasminogen activator inhibitor-1 (PAI-1) activity (arbitrary units)	9.3±1.9	9.0±0.8	Not reported	31.4±3.0	85
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, 2

Protein C, functional (%)	70 to 130	78 to 121	83 to 133	67 to 135	19, 25,
Protein S, total (%)	70 to 140	39 to 105	27 to 101	33 to 101	17, 25,
Protein S, free (%)	70 to 140	34 to 133	19 to 113	20 to 65	25, 26
Protein S, functional activity (%)	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,
Tissue plasminogen activator inhibitor-1 (ng/mL)	4 to 43	16 to 33	36 to 55	67 to 92	17
Activated protein C resistance (APC-r)	2.12 to 5.00	1.79 to 4.75	1.00 to 2.83	1.61 to 5.00	104, 1(
D-Dimer (DDU) (ng/mL)	<500	200 to 900	200 to 1600	400 to 500	21-23,
von Willebrand measurements					
von Willebrand factor antigen (%)	75 to 125	62 to 318	90 to 247	84 to 422	20, 27,
ADAMTS-13, von Willebrand cleaving protease	40 to 170[¥]	40 to 160	22 to 135	38 to 105	20, 28
Blood chemical constituents					
Alanine aminotransferase (units/L)	7 to 41	3 to 30	2 to 33	2 to 25	4, 5, 8, 108
Albumin (g/dL)	4.1 to 5.3[Δ]	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,
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	93
Ammonia (microM)	31±3.2	—	—	27.3±1.6	92
Amylase (units/L)	20 to 96	24 to 83	16 to 73	15 to 81	4, 5, 33
Anion gap (mmol/L)	7 to 16	13 to 17	12 to 16	12 to 16	5
Aspartate aminotransferase (units/L)	12 to 38	3 to 23	3 to 33	4 to 32	4, 5, 8, 108

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, 9
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	86, 87,
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, 3
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 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,
Lactate dehydrogenase (units/L)	115 to 221	78 to 433	80 to 447	82 to 524	4, 5, 32
Lead (microg/dL)	Not reported	6.8 to 7.7	5.8 to 6.6	6.8 to 7.8	110
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 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 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 32, 38,
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, 3
Sodium (mEq/L)	136 to 146	133 to 148	129 to 148	130 to 148	4, 5, 15 32, 38,
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					
Adiponectin (ng/dL)	Not reported	1141 to 13,499	1205 to 16,035	1428 to 13,857	111
Aldosterone (ng/dL)	2 to 9	6 to 104	9 to 104	15 to 101	43, 44,
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	82, 84
Cortisol (mcg/dL)	0 to 25	7 to 19	10 to 42	12 to 50	5, 45
Hemoglobin A_{1C} (%)	4 to 6	4 to 6	4 to 6	4 to 7	36, 47,
Iodine (urine, microg/dL)	Not reported	75 to 291	89 to 316	Not reported	112
Leptin (pg/mL)	Not reported	5594 to 166,097	1401 to 96,912	3997 to 189,930	111
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	83
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,
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, 5
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 (mm/hour)	0 to 20[Δ]	4 to 57	7 to 47	13 to 70	55
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
Procalcitonin (ng/mL)	Not reported	0.03	0.04	0.05	113
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,

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, 60-6
High-density lipoprotein cholesterol (mg/dL)	40 to 60	40 to 78	52 to 87	48 to 87	5, 60-6
Low-density lipoprotein cholesterol (mg/dL)	<100	60 to 153	77 to 184	101 to 224	5, 60-6
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
Apolipoprotein A-I (mg/dL)	119 to 240	111 to 150	142 to 253	145 to 262	4, 47, 6
Apolipoprotein B (mg/dL)	52 to 163	58 to 81	66 to 188	85 to 238	4, 47, 6
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, 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,
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,
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, 90
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, 90

Left ventricular mass (g)	116 to 143	108 to 167	115 to 150	128 to 162	68, 70,
Left ventricular mass index	40 to 78	53 to 79	58 to 82	60 to 88	68, 70,
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 (%)	35 to 36	35 to 37	3.5	35 to 36	69, 70
Left vent ejection fraction (%)	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	89, 90
Mitral A wave (m/second)	0.46±0.1	0.5±0.09	0.5±0.1	0.55±0.1	89, 90
Isovolumic relaxation time (m/second)	69±10	50±10	79±18	72±16	89, 90
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,
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	94, 11
Troponin I (hs-TnI)	0 to 1.0	0 to 1.0	0 to 1.0	0 to 1.0	102
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, 75
PO_2 (mmHg)	90 to 100	93 to 100	90 to 98	92 to 107	75, 76

PCO_2 (mmHg)	38 to 42	Not reported	Not reported	25 to 33	75
Bicarbonate (HCO_3^-) (mEq/L)	22 to 26	Not reported	Not reported	16 to 22	75
Renal function tests					
Effective renal plasma flow (mL/minute)	492 to 696[Δ,†]	696 to 985	612 to 1170	595 to 945	77, 78
Glomerular filtration rate (GFR) (mL/minute)	106 to 132[Δ]	131 to 166	135 to 170	117 to 182	77, 78,
Filtration fraction (%)	16.9 to 24.7[◇◇]	14.7 to 21.6	14.3 to 21.9	17.1 to 25.1	77, 78,
Osmolarity, urine (mOsm/kg)	500 to 800	326 to 975	278 to 1066	238 to 1034	80
24-h albumin excretion (mg/24 hours)	<30	5 to 15	4 to 18	3 to 22	80, 81
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, 78
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	80
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	81
24-h sodium excretion (mmol/24 hours)	100 to 260[†]	53 to 215	34 to 213	37 to 149	15, 41
Pulmonary function tests					
Forced vital capacity (FVC) (L)	4.00±0.51	3.89±0.48	3.92±0.48	4.00±0.53	96
Forced expiratory volume in one second (FEV1) (L)	3.20±0.41	3.18±0.44	3.16±0.39	3.20±0.43	96
Peak expiratory flow (PEF) (L/second)	7.18±1.05	6.71±1.19	6.92±1.13	7.19±1.10	96
Tidal volume (L)	0.21 to 0.48	0.52±0.15	0.54±0.15	0.57±0.14	101
Minute ventilation (L)	2.27 to 10.35	12.63±3.89	13.05±3.55	14.08±4.07	101

A pregnancy laboratory reference interval is an approximation of what can be expected in the overall healthy pregnant population. A value inside or outside of the interval does not necessarily indicate the presence or absence of a disorder in an individual patient.

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* Unless otherwise specified, all normal reference values are from the seventeenth edition of *Harrison's Principles of Internal Medicine*[82].

¶ 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*[83].

** 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[77].

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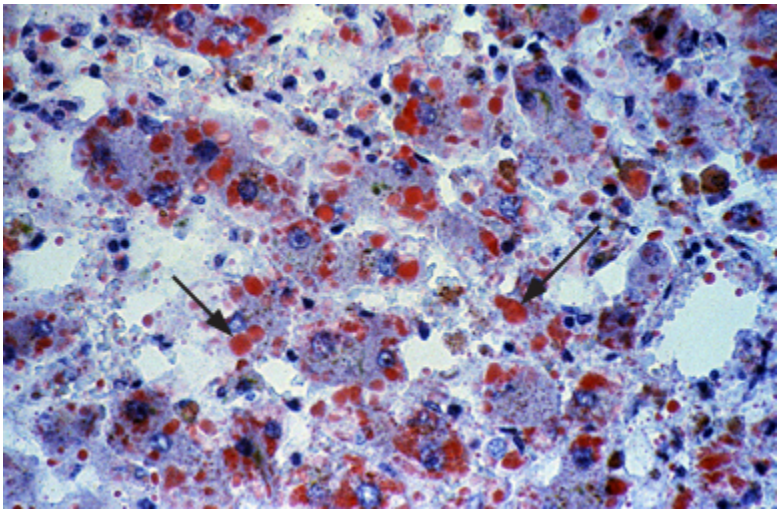
Graphic 81137 Version 51.0

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

Definitions/diagnostic criteria for the hypertensive disorders in pregnancy

Gestational hypertension	▪ New onset of systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg on at least 2 occasions 4 hours apart after 20 weeks of gestation in a previously normotensive individual **And:** ▪ No proteinuria ▪ No signs/symptoms of preeclampsia-related end-organ dysfunction (eg, thrombocytopenia, renal insufficiency, elevated liver transaminases, pulmonary edema, cerebral or visual symptoms)
Preeclampsia	▪ New onset of systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg on at least 2 occasions at least 4 hours apart after 20 weeks of gestation in a previously normotensive individual. Patients with systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥110 mmHg should have blood pressure confirmed within a short interval (minutes) to facilitate timely administration of antihypertensive therapy. **And:** ▪ Proteinuria (≥300 mg per 24-hour urine collection [or this amount extrapolated from a timed collection], or protein:creatinine ratio ≥0.3, or urine dipstick reading ≥2+ [if other quantitative methods are not available]). **In a patient with new-onset hypertension without proteinuria, the diagnosis of preeclampsia can still be made if any features of severe disease are present.**
Preeclampsia with severe features	**In a patient with preeclampsia, presence of any of the following findings are features of severe disease:** ▪ Systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥110 mmHg on 2 occasions at least 4 hours apart (unless antihypertensive therapy is initiated before this time) ▪ Thrombocytopenia (platelet count <100,000/microL) ▪ Impaired liver function as indicated by liver transaminase levels at least twice the normal concentration or severe persistent right upper quadrant or epigastric pain unresponsive to medication and not accounted for by alternative diagnoses, or both ▪ Progressive renal insufficiency (serum creatinine concentration >1.1 mg/dL [97 micromol/L] or doubling of the serum creatinine concentration in the absence of other renal disease) ▪ Pulmonary edema ▪ Persistent cerebral or visual disturbances
Eclampsia	▪ A generalized seizure in a patient with preeclampsia that cannot be attributed to other causes

HELLP syndrome	▪ **H**emolysis, **E**levated **L**iver enzymes, and **L**ow **P**latelets. Hypertension may be present (HELLP in such cases is often considered a variant of preeclampsia).
Chronic (preexisting) hypertension	**Hypertension diagnosed or present before pregnancy or on at least two occasions before 20 weeks of gestation. Hypertension that is first diagnosed during pregnancy and persists for at least 12 weeks postpartum is also considered chronic hypertension.** ▪ Blood pressure criteria during pregnancy are: • Systolic ≥140 mmHg and/or diastolic ≥90 mmHg ▪ Prepregnancy and 12 weeks postpartum blood pressure criteria are: • Stage 1 – Systolic 130 to 139 mmHg or diastolic 80 to 89 mmHg • Stage 2 – Systolic ≥140 mmHg or diastolic ≥90 mmHg
Chronic hypertension with superimposed preeclampsia*	**Any of these findings in a patient with chronic hypertension:** ▪ A sudden increase in blood pressure that was previously well-controlled or an escalation of antihypertensive therapy to control blood pressure ▪ New onset of proteinuria or a sudden increase in proteinuria in a patient with known proteinuria before or early in pregnancy ▪ Significant new end-organ dysfunction consistent with preeclampsia after 20 weeks of gestation or postpartum
Chronic hypertension with superimposed preeclampsia with severe features	**Any of these findings in a patient with chronic hypertension and superimposed preeclampsia:** ▪ Systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥110 mmHg despite escalation of antihypertensive therapy ▪ Thrombocytopenia (platelet count <100,000/microL) ▪ Impaired liver function as indicated by liver transaminase levels at least twice the normal concentration or severe persistent right upper quadrant or epigastric pain unresponsive to medication and not accounted for by alternative diagnoses, or both ▪ New-onset or worsening renal insufficiency ▪ Pulmonary edema ▪ Persistent cerebral or visual disturbances

* Precise diagnosis is often challenging. High clinical suspicion is warranted given the increase in maternal and fetal-neonatal risks associated with superimposed preeclampsia.

Adapted from:

1. *Gestational hypertension and preeclampsia: ACOG Practice Bulletin, Number 222. Obstet Gynecol 2020; 135:e237.*
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Graphic 127246 Version 7.0

Summary of fatty acid oxidation disorders

	Enzyme	Gene	Prevalence	Symptoms	Other complications	P acylc
VLCADD	Very long-chain acyl-CoA dehydrogenase deficiency	*ACADVL*	1 in 42,500 to 120,000	G, L, C, M, R		Elevat C14–, C16–
LCHADD	Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency	*HADHA*	1 in 110,000	G, L, C, M, R	Retinopathy, peripheral neuropathy	Elevat OH–, C C18:1- OH–
TFPD	Trifunctional protein deficiency	*HADHA, HADHB*	Rare	G, L, C, M, R	Retinopathy, peripheral neuropathy	Elevat OH–, C C18:1- OH–
CTD	Carnitine transporter deficiency	*SLC22A5*	1 in 20,000 to 120,000	G, L, C, M, R	NBS maternal CTD	Low to free ca levels
CACTD	Carnitine-acylcarnitine translocase deficiency	*SLC25A20*	Rare	G, L, C		Elevat C16:1- C18:1-
CPT1D	Carnitine palmitoyltransferase 1A deficiency	*CPT1A*	1 in 500,000	G, L	Renal tubular acidosis, Arctic variant	Elevat and fr carnit
CPT2D	Carnitine palmitoyltransferase 2 deficiency	*CPT2*	Rare	G, L, C, M, R	Renal cysts, facial dysmorphism	Elevat C16:1- C18:1-
MCADD	Medium-chain acyl-CoA dehydrogenase deficiency	*ACADM*	1 in 20,000 1 in 51,000 to 263,000[1]	G, L		Elevat C8–, C
MADD	Multiple acyl-CoA dehydrogenase deficiency	*ETFA, ETFB, ETFDH*	1 in 15,000 to 2,000,000[2]	G, L, C, M	Renal cysts, congenital malformations, facial dysmorphism, sweaty foot odor	Elevat C5–, C C8–, C C12–, C14:1- C16:1- C18:1- OH–, C

						C18–C OH–
SCADD	Short-chain acyl-CoA dehydrogenase deficiency	*ACADS*	1 in 35,000 to 50,000		Asymptomatic	Elevat
M/SCHAD	Short-chain L-3-hydroxyacyl-CoA dehydrogenase deficiency	*HADH*	Rare		Hyperinsulinism	Elevat

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.

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