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Approach to evaluating pregnant patients with elevated liver biochemical and function tests

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INTRODUCTION

Elevated liver biochemical and function tests in pregnant patients may pose a challenge for the consulting clinician. Liver abnormalities detected during pregnancy require diagnostic evaluation similar to the evaluation of the nonpregnant patient but is also informed by gestational age and expected physiologic changes of pregnancy.

Liver disease during pregnancy can be categorized by the following characteristics:

- Diseases that are unique to pregnancy: Some are primary liver diseases (eg, intrahepatic cholestasis of pregnancy, acute fatty liver of pregnancy), and others are systemic diseases with hepatic manifestations (eg, preeclampsia with severe features [including eclampsia; hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome]; hyperemesis):
  - (See "Intrahepatic cholestasis of pregnancy".)
  - (See "Acute fatty liver of pregnancy".)
  - (See "HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets)".)
  - (See "Preeclampsia: Clinical features and diagnosis".)
  - (See "Nausea and vomiting of pregnancy: Clinical findings and evaluation".)
- Diseases that are exacerbated by pregnancy: Pregnancy-related physiologic changes may increase the risk of liver-related diseases that may also occur in nonpregnant patients. Examples of such diseases include gallstones and vascular diseases (eg, Budd-

Chiari syndrome). (See "Gallstone diseases in pregnancy" and "Budd-Chiari syndrome: Epidemiology, clinical manifestations, and diagnosis".)

- Diseases that are not related but are coincidental to pregnancy (eg, acute viral hepatitis). (See "Overview of coincident acute hepatobiliary disease in pregnant women".)

This topic will provide an overview of the evaluation of patients who do not have pre-existing liver disease but develop elevated liver biochemical and/or function tests during pregnancy. Our approach is largely consistent with society guidelines on liver disease during pregnancy [1,2].

Issues related to pregnant patients with pre-existing liver disease are discussed separately. (See "Pregnancy in women with pre-existing chronic liver disease".)

GENERAL PRINCIPLES

Liver adaptation to normal pregnancy — Normal changes associated with pregnancy impact the patient's liver when assessed with physical examination, laboratory studies, and imaging [3] (see "Maternal adaptations to pregnancy: Gastrointestinal tract"):

- Physical examination findings:
  - Skin: Spider angiomas and palmar erythema, which are classically associated with chronic liver disease, are common during pregnancy and usually disappear after delivery. It is presumed that the high estrogen level induced by pregnancy is responsible for these changes, as in nonpregnant patients with cirrhosis. The precise mechanism is unknown as the effects of estrogen on the cutaneous microvasculature are unclear [4,5]. (See "Maternal adaptations to pregnancy: Skin and related structures", section on 'Vascular changes' and "Cirrhosis in adults: Etiologies, clinical manifestations, and diagnosis", section on 'Skin findings'.)
  - Abdomen: The liver may be displaced upward as the gravid uterus enlarges, and the liver is not typically palpable [2].
- Blood biochemistries: Some blood biochemistries change as a result of normal pregnancy (table 1). For example, lower serum albumin (due to hemodilution) and elevated serum alkaline phosphatase (typically <2 times the upper limit of normal and due to placental synthesis) are normal findings during pregnancy and do not require further evaluation [6]. However, the following laboratory values should remain within the normal range during pregnancy, and thus, elevated levels prompt further evaluation:

- Serum aminotransferases: Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are biochemical markers of liver injury. Elevations of aminotransferases often reflect hepatocellular damage or biliary obstruction.
- Bilirubin: Bilirubin measures the liver's ability to detoxify metabolites and transport organic anions into bile.
- Prothrombin time/international normalized ratio (INR): Prolonged prothrombin time may be seen in the setting of impaired liver synthetic function.

Liver biochemical and function tests are discussed in more detail separately. (See "Approach to the patient with abnormal liver biochemical and function tests", section on 'Common liver biochemical and function tests'.)

- Ultrasound examination: During normal pregnancy, the appearance of the liver and biliary tract on transabdominal ultrasound is typically normal.

Indications for baseline liver tests — We obtain baseline liver biochemical and function tests in pregnant patients with any of the following (see "Prenatal care: Initial assessment"):

- History of pregnancy-related liver disease in prior pregnancy (eg, intrahepatic cholestasis of pregnancy, preeclampsia; hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome; acute fatty liver)
- History of chronic hypertension or gestational hypertension
- Risk factors for liver disease (eg, metabolic syndrome, alcohol use disorder)
- Viral hepatitis identified on prenatal screening (eg, hepatitis B surface antigen-positive or anti-hepatitis C virus antibody positive)

Liver tests that are commonly measured include:

- Serum aminotransferases: ALT and aspartate aminotransferase AST
- Alkaline phosphatase
- Total bilirubin
- Prothrombin time/international normalized ratio
- Serum albumin

PREVALENCE OF LIVER DISEASE IN PREGNANCY

Approximately 3 percent of all pregnancies are complicated by liver biochemical test abnormalities [7,8]. Hospital discharge data from the Nationwide Inpatient Sample (a United States inpatient database) were used to evaluate the prevalence of liver disease in pregnant

patients hospitalized for any reason. This database included over 40 million pregnancy hospitalizations from 2002 to 2010 and found the following liver disease diagnoses (the denominator for the frequency of each liver disease diagnosis is 1000 pregnancy hospitalizations) [7]:

- Diseases bundled together as liver disorders of pregnancy (eg, acute fatty liver of pregnancy, intrahepatic cholestasis of pregnancy, and postpartum hepatorenal syndrome): 7.18
- Gallbladder disease/cholelithiasis: 4.65
- Hepatitis C virus infection: 1.70
- Biliary tract disease (biliary obstruction, cholangitis): 1.67
- Hepatitis B virus infection: 0.96
- Hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome: 0.95
- Alcohol-related liver disease: 0.30

Prevalence data for liver disease in pregnant patients who do not require hospitalization are lacking.

EVALUATION OF ACUTE LIVER FAILURE

Pregnant patients with acute severe liver injury (ie, serum aminotransferases typically more than 10 times the upper limit of normal, hepatic encephalopathy, and coagulopathy) have acute liver failure. Such patients require urgent consultation with maternal-fetal medicine and hepatology specialists and referral to a liver transplantation center.

Causes of acute liver failure during pregnancy may be classified as:

- Pregnancy-related: Acute liver failure due to pregnancy-related causes generally occurs at ≥20 weeks of gestation. These obstetric emergencies include acute fatty liver of pregnancy or preeclampsia with severe features/eclampsia/hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome. (See "Acute fatty liver of pregnancy" and "Preeclampsia: Antepartum management and timing of delivery".)
- Nonpregnancy-related: Acute liver failure in pregnant patients may be due to nonpregnancy-related causes during any stage of pregnancy. Common causes of acute liver failure include acute viral hepatitis, drug-induced liver injury (eg, acetaminophen), and ischemic hepatitis. The evaluation and management of acute liver failure due to nonpregnancy-related causes are discussed separately. (See "Acute liver failure in

adults: Etiology, clinical manifestations, and diagnosis" and "Acute liver failure in adults: Management and prognosis".)

PATIENTS WITHOUT ACUTE LIVER FAILURE

Initial evaluation — The initial evaluation for a pregnant patient with elevated liver biochemistries but without acute liver failure is similar to the evaluation of a nonpregnant patient and includes history, physical examination, laboratory studies, and a liver ultrasound. (See "Approach to the patient with abnormal liver biochemical and function tests".)

For pregnant patients, assessing clinical features and interpreting the liver biochemistries must also take into account the timing of symptom onset and gestational age because these factors inform the differential diagnosis for diseases that are unique to pregnancy.

Patient history and presentation — The patient's clinical presentation and history may suggest a possible cause(s) for elevated liver biochemistries:

- Timing of symptom onset: The timing of symptom onset (gestational age) can help guide the evaluation (table 2):
  - Gestational age <20 weeks: Severe nausea and emesis with onset in the first trimester suggests hyperemesis gravidarum. (See "Nausea and vomiting of pregnancy: Clinical findings and evaluation".)
  - Gestational age ≥20 weeks: New onset hypertension at ≥20 weeks gestation is concerning for Hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome or preeclampsia with severe features. Diagnostic criteria for hypertensive disorders during pregnancy are discussed separately. (See "Hypertensive disorders in pregnancy: Approach to differential diagnosis".)

    Symptoms of nausea, vomiting, headache, and abdominal pain in the third trimester are concerning for acute fatty liver of pregnancy. (See "Acute fatty liver of pregnancy".)
- Risk factors for exposure to potential hepatotoxins (medications, dietary and herbal supplements, alcohol use, illicit substance use) (see "Drug-induced liver injury").
- Risk factors for nonalcohol-associated fatty liver disease (metabolic syndrome, dyslipidemia) (see "Obesity in adults: Prevalence, screening, and evaluation").
- Symptoms and signs of hepatobiliary disease (pruritus, jaundice).

- History of liver disease with prior pregnancy: Some pregnancy-related diseases (eg, intrahepatic cholestasis of pregnancy) commonly recur in subsequent pregnancies (see "Intrahepatic cholestasis of pregnancy").

Physical examination — Findings on physical examination that suggest liver disease during pregnancy (but not necessarily acute liver failure) include ascites and jaundice. A palpable liver raises concern for hepatomegaly but may be difficult to detect when the uterus is enlarged near term. (See "Overview of the evaluation of hepatomegaly in adults".)

Laboratory studies — For pregnant patients with elevated liver biochemistries, laboratory tests that are measured during the initial evaluation include (see 'General principles' above):

- Complete blood count with platelets
- Serum creatinine, electrolytes, glucose
- Prothrombin time/international normalized ratio (INR)

Additional laboratory testing is determined based on symptoms and pattern of liver injury. (See 'Subsequent testing' below.)

Imaging — For pregnant patients with elevated liver biochemical and/or function tests, transabdominal ultrasound of the liver is performed initially because ultrasound is widely available and has not been associated with adverse fetal effects [1,2,9]. For patients with suspected vascular disorders (eg, right upper quadrant pain, ascites), we also obtain Doppler ultrasound study to exclude thrombosis of the hepatic or portal vein.

For patients in whom biliary obstruction or cholangiopathy is suspected but ultrasound is nondiagnostic, or for some patients with abnormal ultrasonography (eg, liver mass), additional imaging with noncontrast magnetic resonance imaging (eg, magnetic resonance cholangiopancreatography) is preferred rather than computed tomography (CT) to minimize radiation exposure to the fetus. We do not use gadolinium-containing contrast agents because gadolinium crosses the placenta and may have harmful effects. If CT is necessary, the cumulative ionizing radiation exposure should be minimized, preferably less than 0.05 Gy (50 mGy, 5 rads). (See "Diagnostic imaging in pregnant and lactating patients", section on 'Use of gadolinium' and "Diagnostic imaging in pregnant and lactating patients", section on 'Techniques for minimizing fetal exposure'.)

The evaluation of an incidental solid liver lesion is discussed separately. (See "Approach to the adult patient with an incidental solid liver lesion".)

Differential diagnosis based on initial evaluation — For some pregnant patients, the cause for elevated liver biochemistries can be suspected based on patient history, gestational age, initial laboratory studies, and liver ultrasound (algorithm 1):

- Liver ultrasound with or without Doppler study: Liver ultrasound may show biliary obstruction (see "Gallstone diseases in pregnancy") or vascular thrombosis or ascites. (See "Budd-Chiari syndrome: Epidemiology, clinical manifestations, and diagnosis".)

- Details of the patient's history (symptoms, medication use, comorbidities) may suggest a possible etiology:

  - Severe nausea and vomiting during early pregnancy suggest hyperemesis. (See "Nausea and vomiting of pregnancy: Clinical findings and evaluation".)

  - New onset hypertension and/or thrombocytopenia suggest preeclampsia with severe features or HELLP syndrome (table 3). (See "Preeclampsia: Clinical features and diagnosis" and "HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets)".)

  - Abdominal pain, headache, nausea, and vomiting in the third trimester is concerning for acute fatty liver of pregnancy or HELLP syndrome. (See "Acute fatty liver of pregnancy" and "HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets)".)

  - Pruritus (with or without increased total bilirubin) suggests intrahepatic cholestasis of pregnancy. (See "Intrahepatic cholestasis of pregnancy".)

  - History of potentially hepatotoxic medication and/or supplement use suggests drug-induced liver injury. (See "Drug-induced liver injury".)

  - History of insulin resistance, polycystic ovarian syndrome, or dyslipidemia suggests increased risk for nonalcohol-associated fatty liver disease. (See "Epidemiology, clinical features, and diagnosis of nonalcoholic fatty liver disease in adults".)

  - History of recent alcohol use raises concern for alcohol-related liver disease. (See "Alcoholic hepatitis: Clinical manifestations and diagnosis".)

Subsequent testing

Determining liver injury pattern — For pregnant patients without a suspected etiology of abnormal liver biochemistries based on initial evaluation, subsequent testing is guided by the predominant pattern of liver injury (algorithm 1):

- **Hepatocellular pattern**: Hepatocellular injury consists of a disproportionate elevation in serum aminotransferases compared with alkaline phosphatase. Other characteristics of liver enzymes (ie, magnitude of aminotransferase elevations) are interpreted similarly to patterns in nonpregnant patients. (See "Approach to the patient with

abnormal liver biochemical and function tests", section on 'Laboratory tests' and 'Evaluation of acute liver failure' above.)

Most liver disorders that are unique to pregnancy present with a hepatocellular pattern (table 2). Common causes of non-pregnancy related hepatocellular injury include drug-induced liver injury, viral hepatitis, nonalcohol-associated fatty liver disease, alcohol-associated liver disease, and autoimmune hepatitis (table 4).

- **Cholestatic pattern**: A cholestatic pattern of injury consists of a disproportionate elevation in the alkaline phosphatase compared with the serum aminotransferases. However, alkaline phosphatase will be normally elevated during pregnancy due to placental production (ie, typically <2 times the upper limit of normal). In nonpregnant patients, calculating the R value can help determine the pattern of liver injury, whereas in pregnant patients, the R value will not be accurate and cannot be used to determine the pattern of liver injury. Calculation and interpretation of the R value is discussed separately. (See "Approach to the patient with abnormal liver biochemical and function tests", section on 'Patterns of liver test abnormalities'.)

  Nonpregnancy-related causes of cholestatic injury include choledocholithiasis, drug-induced liver injury, primary biliary cholangitis and primary sclerosing cholangitis (table 5).

Of note, serum bilirubin can be elevated in both hepatocellular and cholestatic conditions. Thus, bilirubin is not usually helpful in differentiating between the two patterns. However, jaundice is uncommon in pregnancy-related liver diseases.

Patients with hepatocellular injury — Further testing for causes of hepatocellular injury includes (table 4):

- Acute viral hepatitis:
  - Immunoglobulin M (IgM) anti-hepatitis A virus
  - Hepatitis B surface antigen (HBsAg), IgM antibody to hepatitis B core antigen, antibody to HBsAg
  - Anti-hepatitis C virus antibody with reflex to hepatitis C viral RNA
  - IgM anti-hepatitis E virus (in regions where HEV infection is endemic) (see "Hepatitis E virus infection")
  - Herpes simplex virus DNA by polymerase chain reaction

- Cytomegalovirus DNA assay (see "Overview of diagnostic tests for cytomegalovirus infection")
- Epstein-Barr virus serologies (see "Infectious mononucleosis", section on 'Diagnosis')

- Autoimmune hepatitis: Antinuclear antibodies, anti-smooth muscle antibodies, immunoglobulin G
- Intrahepatic cholestasis of pregnancy (ICP): Total bile acid concentration. Patients with ICP typically present with itching during the late second or third trimester (see "Intrahepatic cholestasis of pregnancy", section on 'Clinical findings')
- Wilson disease: Ceruloplasmin (see "Wilson disease: Clinical manifestations, diagnosis, and natural history")

Patients with cholestasis — Further evaluation for causes of a cholestatic pattern of liver injury in a patient with normal liver ultrasound includes (table 5):

- Primary biliary cholangitis: Antimitochondrial antibody
- Primary sclerosing cholangitis: Noncontrast magnetic resonance cholangiopancreatography
- Drug induced liver injury (DILI) with cholestatic features: DILI is suspected based on history of use of potentially hepatoxic drugs or supplements

During normal pregnancy, alkaline phosphatase is elevated from placental production (typically up to twice the nonpregnant level, but sometimes markedly higher [10,11]); thus, a mildly elevated alkaline phosphatase does not suggest cholestatic liver injury. (See 'Liver adaptation to normal pregnancy' above.)

Other tests — A liver biopsy is rarely necessary for the diagnosis of liver diseases that are unique to pregnancy, such as hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome, and acute fatty liver of pregnancy. Because it is invasive, a liver biopsy should be performed only when a diagnosis cannot be established based clinical presentation, laboratory studies, and imaging and when the results are needed to inform therapy or the timing of delivery. The diagnosis of HELLP syndrome and acute fatty liver of pregnancy are discussed in more detail separately. (See "HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets)" and "Acute fatty liver of pregnancy".)

Percutaneous liver biopsy with ultrasound guidance is discussed separately. (See "Approach to liver biopsy".)

For patients with coagulopathy, transjugular liver biopsy is an alternative approach. (See "Transjugular liver biopsy".)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Abnormal liver biochemical tests".)

SUMMARY AND RECOMMENDATIONS

- Normal changes associated with pregnancy impact findings on physical examination and laboratory studies and include (see 'Liver adaptation to normal pregnancy' above):
  - Spider angiomas and palmar erythema
  - Upward displacement of the liver as the gravid uterus enlarges
  - Lower serum albumin level (due to hemodilution) and elevated serum alkaline phosphatase (typically <2 times the upper limit of normal and due to placental synthesis)
- Baseline liver biochemical and function tests are obtained in pregnant patients with any of the following (see 'Indications for baseline liver tests' above):
  - History of liver disease with prior pregnancy (eg, intrahepatic cholestasis of pregnancy, preeclampsia; hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome; acute fatty liver)
  - History of chronic hypertension or gestational hypertension
  - Risk factors for liver disease (eg, metabolic syndrome, alcohol use disorder)
  - Viral hepatitis identified on prenatal screening
- Pregnant patients with acute severe liver injury (ie, aminotransferases typically more than 10 times the upper limit of normal, encephalopathy, and coagulopathy) have acute liver failure. Such patients require urgent consultation with maternal-fetal medicine and hepatology specialists and referral to a liver transplantation center. (See 'Evaluation of acute liver failure' above.)
- For pregnant patients with elevated liver biochemistries but without acute liver failure, initial evaluation includes (see 'Initial evaluation' above):

- History: Assess patient's risk factors for liver disease, symptoms, and gestational age
- Physical examination: Assess for findings that suggest liver disease (eg, ascites, jaundice)
- Laboratory studies: Complete blood count with platelets, serum creatinine, electrolytes, glucose, prothrombin time/international normalized ratio (INR)
- Imaging – Liver ultrasound (with Doppler study if vascular thrombosis is suspected [eg, patients with ascites or abdominal pain])

- For pregnant patients without a suspected etiology of abnormal liver biochemistries based on history, physical examination and initial testing, subsequent testing is guided by the predominant pattern of liver injury (hepatocellular or cholestatic) (algorithm 1).

- Issues related to pregnancy in patients with pre-existing liver disease are discussed separately (see "Pregnancy in women with pre-existing chronic liver disease").

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Topic 3563 Version 29.0

GRAPHICS

Blood chemical constituent changes during pregnancy

	Nonpregnant adult	First trimester	Second trimester	Third trimester
Alanine aminotransferase (unit/L)	7 to 41	3 to 30	2 to 33	2 to 25
Albumin (g/dL)	4.1 to 5.3	3.1 to 5.1	2.6 to 4.5	2.3 to 4.2
Alkaline phosphatase (unit/L)	33 to 96	17 to 88	25 to 126	38 to 229
Alpha-1 antitrypsin (mg/dL)	100 to 200	225 to 323	273 to 391	327 to 487
Alpha-fetoprotein (ng/mL)	–	–	Approximately 130 to 400	Approximately 130 to 590
Ammonia (micrometer)	31.0±3.2	–	–	27.3±1.6
Amylase (unit/L)	20 to 96	24 to 83	16 to 73	15 to 81
Anion gap (mmol/L)	7 to 16	13 to 17	12 to 16	12 to 16
Aspartate aminotransferase (unit/L)	12 to 38	3 to 23	3 to 33	4 to 32

Bicarbonate (mmol/L)	22 to 30	20 to 24	20 to 24	20 to 24
Bilirubin, total (mg/dL)	0.3 to 1.3	0.1 to 0.4	0.1 to 0.8	0.1 to 1.1
Bilirubin, unconjugated (mg/dL)	0.2 to 0.9	0.1 to 0.5	0.1 to 0.4	0.1 to 0.5
Bilirubin, conjugated (mg/dL)	0.1 to 0.4	0.0 to 0.1	0.0 to 0.1	0.0 to 0.1
Bile acids (micromol/L)	0.3 to 4.8	0.0 to 4.9	0.0 to 9.1	0.0 to 11.3
CA-125 (microgram/mL)	7.2 to 27.0	2.2 to 268.0	12.0 to 25.1	16.8 to 43.8
Calcium, ionized (mg/dL)	4.5 to 5.3	4.5 to 5.1	4.4 to 5.0	4.4 to 5.3
Calcium, total (mg/dL)	8.7 to 10.2	8.8 to 10.6	8.2 to 9.0	8.2 to 9.7
Ceruloplasmin (mg/dL)	25 to 63	30 to 49	40 to 53	43 to 78
Chloride (mEq/L)	102 to 109	101 to 105	97 to 109	97 to 109
Creatinine (mg/dL)	0.5 to 0.9	0.4 to 0.7	0.4 to 0.8	0.4 to 0.9
Gamma-glutamyl transpeptidase (unit/L)	9 to 58	2 to 23	4 to 22	3 to 26
Lactate dehydrogenase (unit/L)	115 to 221	78 to 433	80 to 447	82 to 524
Lipase (unit/L)	3 to 43	21 to 76	26 to 100	41 to 112
Magnesium (mg/dL)	1.5 to 2.3	1.6 to 2.2	1.5 to 2.2	1.1 to 2.2
Osmolality (mOsm/kg H_2O)	275 to 295	275 to 280	276 to 289	278 to 280
Phosphate (mg/dL)	2.5 to 4.3	3.1 to 4.6	2.5 to 4.6	2.8 to 4.6
Potassium (mEq/L)	3.5 to 5.0	3.6 to 5.0	3.3 to 5.0	3.3 to 5.1
Prealbumin (mg/dL)	17 to 34	15 to 27	20 to 27	14 to 23
Protein, total (g/dL)	6.7 to 8.6	6.2 to 7.6	5.7 to 6.9	5.6 to 6.7
Sodium (mEq/L)	136 to 146	133 to 148	129 to 148	130 to 148
Urea nitrogen (mg/dL)	7 to 20	7 to 12	3 to 13	3 to 11
Uric acid (mg/dL)	2.5 to 5.6	2.0 to 4.2	2.4 to 4.9	3.1 to 6.3

CA-125: cancer antigen 125.

Graphic 114668 Version 2.0

Clinical characteristics of liver diseases in pregnancy

Disease	Symptoms	New onset hypertension	Gestational age at diagnosis	Laboratory fin	
				Aminotransferase levels	Ot
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.	▪ B n e
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.	▪ P < ▪ L ir u ▪ T ≥ (2 m ▪ R p ra p cr c ▪ E a
Preeclampsia with severe features	New-onset cerebral or visual disturbance (eg,	Yes, in 100% of cases	Onset in the second half of pregnancy, usually in the	Transaminase levels ≥2 times upper limit of normal for a specific laboratory.	▪ P <

	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.		third trimester. Can also present postpartum, usually within 48 hours of delivery.		▪ S > m tv b ▪ R p ra p cl c ▪ E a
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.	▪ E b ▪ T b c a 2 o c b ra m
Acute fatty liver of pregnancy	Initial symptoms may be nonspecific (eg nausea, vomiting, abdominal pain, malaise, and/or anorexia), but	Yes, on occasion	Onset usually in third trimester, but the diagnosis has been made as early as 22 weeks of gestation and as	Modest elevations, up to 500 international units/L.	▪ E c ▪ E cl ▪ E le ▪ E a

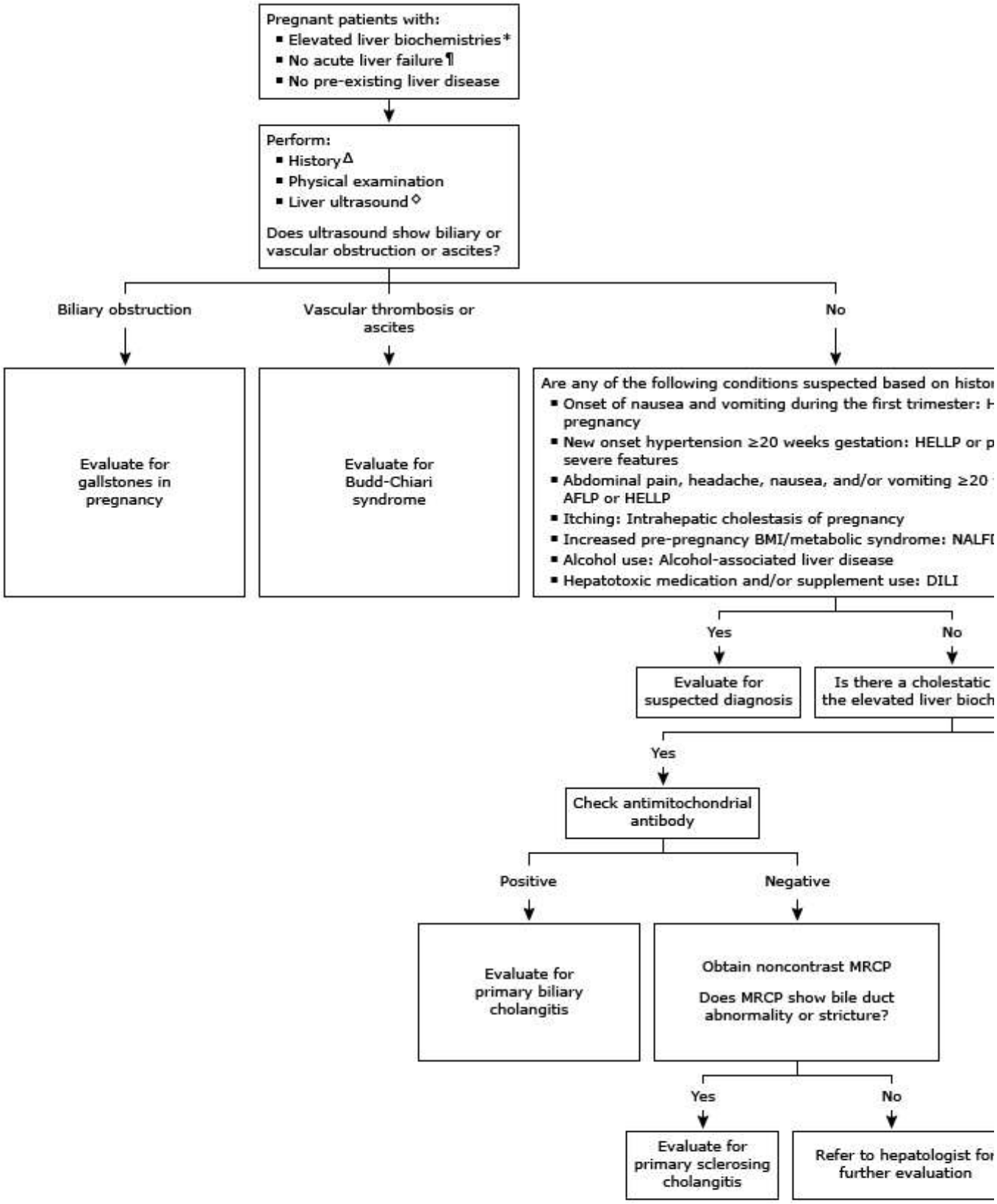
	patients may develop manifestations of acute liver failure including jaundice, encephalopathy, coagulopathy and/or hypoglycemia.		late as four days after delivery.		▪ P P ▪ D p ▪ D g ▪ D a le ▪ D fi

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

Approach to evaluating elevated liver tests in pregnant patients without acu



Refer to content on the evaluation of pregnant patients with elevated liver biochemical and function test

AFLP: acute fatty liver of pregnancy; HELLP: hemolysis, elevated liver enzymes, low platelet count; BMI: b
associated fatty liver disease; DILI: drug-induced liver injury; CMV: cytomegalovirus; EBV: Epstein-Barr vi
virus; HBsAg: hepatitis B surface antigen; anti-HBc: antibody to hepatitis B core antigen; anti-HBs: antibc
hepatitis C virus; HEV: hepatitis E virus; HSV: herpes simplex virus; ANA: antinuclear antibody; MRCP: ma
ALT: alanine aminotransferase; AST: aspartate aminotransferase; IgM: immunoglobulin M; IgG: immuno

* Liver biochemical and function tests that are commonly measured include:
- Serum aminotransferases: ALT and AST
- Alkaline phosphatase
- Total bilirubin
- Prothrombin time/international normalized ratio

¶ Acute liver failure is characterized by severe liver injury (ie, serum aminotransferases typically more th
encephalopathy, and coagulopathy). Pregnant patients with acute liver failure require urgent consultatic
hepatology specialists and referral to a liver transplantation center.

Δ History includes risk factors for liver disease (eg, medications, alcohol), symptoms of liver disease (eg,

◇ For patients with suspected vascular disorders (eg, right upper quadrant pain, ascites), we also obtain
thrombosis.

§ A cholestatic pattern is a disproportionate elevation in the alkaline phosphatase compared with ALT an
is a disproportionate elevation in ALT and AST compared with alkaline phosphatase.

¥ In regions where HEV is endemic, testing for IgM anti-hepatitis E virus is performed.

Graphic 131501 Version 1.0

Diagnostic criteria for preeclampsia

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 patient AND the new onset of 1 or more of the following*:
▪ Proteinuria ≥0.3 g in a 24-hour urine specimen or protein/creatinine ratio ≥0.3 (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 kidney disease
▪ Liver transaminases at least twice the upper limit of the normal concentrations for the local laboratory
▪ Pulmonary edema
▪ New-onset and persistent headache not accounted for by alternative diagnoses and not responding to usual doses of analgesics¶
▪ Visual symptoms (eg, blurred vision, flashing lights or sparks, scotomata)

Preeclampsia is considered superimposed when it occurs in a patient with chronic hypertension. Superimposed preeclampsia is characterized by worsening or resistant hypertension (especially acutely), the new onset of proteinuria or a sudden increase in proteinuria, and/or significant new end-organ dysfunction in a patient with chronic hypertension. It typically occurs after 20 weeks of gestation or postpartum.

Definitions/diagnostic criteria for preeclampsia are generally similar worldwide except the International Society for the Study of Hypertension in Pregnancy definition also includes signs of uteroplacental dysfunction (eg, fetal growth restriction, abnormal angiogenic markers, abnormal umbilical artery Doppler, abruption, fetal demise).

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* If systolic blood pressure is ≥160 mmHg and/or diastolic blood pressure is ≥110 mmHg, confirmation within minutes is sufficient.

¶ Response to analgesia does not exclude the possibility of preeclampsia.

Adapted from:

1. *American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin No. 222: Gestational Hypertension and Preeclampsia. Obstet Gynecol 2020; 135:e237.*
2. *Magee LA, Brown MA, Hall DR, et al. The 2021 International Society for the Study of Hypertension in Pregnancy classification, diagnosis & management recommendations for international practice. Pregnancy Hypertens 2022; 27:148.*

Graphic 79977 Version 39.0

Differential diagnosis of mildly and moderately elevated serum aminotransferases (<15 times upper limit of normal)

Hepatic disease		Nonhepatic disease
ALT predominant (AST/ALT <1)	**AST predominant (AST/ALT ≥1)**	
Drug-induced liver injury	Alcohol-associated hepatitis	Muscle injury (strenuous exercise, myopathy)
Chronic viral hepatitis (HBV, HCV)	Cirrhosis due to viral hepatitis or NAFLD	Adrenal insufficiency
Occupational, toxin-related hepatocellular damage	Wilson disease	Myocardial infarction, heart failure
Autoimmune hepatitis		Anorexia nervosa
NAFLD		Thyroid disease
Genetic disorders ▪ Wilson disease ▪ Hemochromatosis ▪ Alpha-1 antitrypsin deficiency		Celiac disease
Congestive hepatopathy		Macro-AST
Malignant infiltration of the liver		

ALT: alanine aminotransferase; AST: aspartate aminotransferase; HBV: hepatitis B virus; HCV: hepatitis C virus; NAFLD: nonalcoholic fatty liver disease.

Graphic 97018 Version 7.0

Causes of an elevated alkaline phosphatase

Marked elevation (≥4 times the upper limit of normal)*	**Extrahepatic biliary obstruction¶**
	Choledocholithiasis (most common) ▪ Uncomplicated ▪ Complicated (biliary pancreatitis, acute cholangitis)
	Malignant obstruction ▪ Pancreas ▪ Gallbladder ▪ Ampulla of Vater ▪ Bile duct ▪ Metastasis to perihilar lymph nodes
	Biliary strictures ▪ Primary sclerosing cholangitis with extrahepatic bile duct stricture ▪ Complications after invasive procedures ▪ Chronic pancreatitis with stricturing of distal bile duct ▪ Biliary anastomotic stricture following liver transplantation
	Infections ▪ AIDS cholangiopathy ▪ *Ascaris lumbricoides* ▪ Liver flukes
	Intrahepatic cholestasis
	Drug and toxins associated with cholestasis[Δ]
	Primary biliary cholangitis[Δ]
	Primary sclerosing cholangitis[Δ]
	Intrahepatic cholestasis of pregnancy
	Benign postoperative cholestasis
	Total parenteral nutrition
	Infiltrative diseases[Δ] ▪ Amyloidosis ▪ Lymphoma ▪ Sarcoidosis ▪ Tuberculosis ▪ Hepatic abscess
	Metastatic carcinoma to the liver[Δ]
	Liver allograft rejection
	Other cholangiopathies (eg, IgG4 cholangiopathy, ischemic cholangiopathy, COVID-19)

	Alcohol-associated hepatitis
	Sickle cell disease (hepatic crisis)
	Nonhepatic causes[◇]
	Transient hyperphosphatemia of infancy and childhood
Moderate elevation (<4 times upper limit normal)	**Hepatic causes**
	Nonspecific, seen with all types of liver disease including: ▪ Hepatitis: viral, chronic, alcoholic ▪ Cirrhosis ▪ Infiltrative diseases of the liver ▪ Hypoperfusion states: sepsis, heart failure
	Nonhepatic causes[◇]
	Physiologic (children and adolescents)
	Third trimester of pregnancy
	Influx of intestinal alkaline phosphatase after eating a fatty meal (individuals with blood type O or B)
	High bone turnover ▪ Growth ▪ Healing fractures ▪ Osteomalacia ▪ Paget disease of bone ▪ Osteogenic sarcoma, bone metastasis ▪ Hyperparathyroidism ▪ Hyperthyroidism
	Extrahepatic disease ▪ Myeloid metaplasia ▪ Peritonitis ▪ Diabetes mellitus ▪ Subacute thyroiditis ▪ Gastric ulcer (uncomplicated) ▪ Extrahepatic tumors • Osteosarcoma • Lung • Gastric • Head and neck • Renal cell • Ovarian • Uterine • Hodgkin lymphoma

* The alkaline phosphatase value may vary and be <4 times the upper limit of normal at times (eg, early in the disease process).

¶ May cause an isolated elevation in hepatic alkaline phosphatase if partial obstruction.

Δ May cause an isolated elevation in hepatic alkaline phosphatase.

◇ Alkaline phosphatase may be derived from several sites including the liver, bone, third trimester placenta, intestine, and kidneys. An elevation in alkaline phosphatase with a normal gamma-glutamyl transpeptidase or 5'-nucleotidase suggests a nonhepatic source of alkaline phosphatase.

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