



What caused elevated liver enzymes in this postpartum patient?

This patient had epigastric pain, chills, and nausea, but no fever, vomiting, or pruritus. How would you proceed?

CASE ▶ A 38-year-old, previously healthy G2 P2 woman arrives at your office with sudden-onset epigastric pain, chills, and nausea, but no vomiting. She has had no fever, shortness of breath, or pruritus. Her appetite is good and her weight is stable. Three days earlier, she gave birth to a healthy baby. The course of pregnancy had been uncomplicated, and delivery was vaginal at 35 weeks gestation without any complications. Her blood pressure (BP) was normal throughout pregnancy, and she had no signs of preeclampsia.

She does not smoke. Although she usually drinks 1 beer daily, she avoided alcohol during her pregnancy. She does not use illicit drugs. She has received no blood transfusions and has no history of viral hepatitis.

On examination she is alert and oriented. She is afebrile and anicteric. Her vital signs are normal with a BP of 116/80 mm Hg and a pulse rate of 86/min. Respiratory rate is 20/min, and oxygen saturation is 98% while breathing ambient air. On palpation, her abdomen is soft and nontender without organomegaly. There is no ascites and bowel sounds are audible.

Initial laboratory investigation yields the following results:

- alkaline phosphatase 436 U/L (normal, 40-135)
- alanine aminotransferase 685 U/L (4-55)
- total bilirubin 27 mcmol/L (2-20)
- serum albumin 25 g/L (35-55)
- international normalized ratio 0.9 (0.9-1.3)

- amylase 47 U/L (20-110)
- hemoglobin 146 g/L (140-180)
- platelets $296 \times 10^9/L$ (150-400)
- white blood cell count $9.7 \times 10^9/L$ (4.0-10.0)
- urinalysis reveals no proteins
- transferrin 4.58 g/L (1.32-3.02)
- iron saturation 29% (15-50)
- ferritin 70 mcg/L (10-200)
- serum copper 43.9 mcmol/L (9.0-27.0)
- ceruloplasmin 594 mg/L (200-600)
- Alpha-1-antitrypsin levels 2.05 g/L (1.06-1.58).

Q What is the differential diagnosis of abnormally elevated liver enzymes in the peripartum period?

Possible underlying causes of the patient's findings include pregnancy-related liver diseases such as hyperemesis gravidarum (HG), intrahepatic cholestasis of pregnancy, preeclampsia, eclampsia, HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets), and acute fatty liver of pregnancy (AFLP); or liver diseases unrelated to pregnancy such as viral hepatitis, autoimmune liver disease, Wilson's disease, Budd-Chiari syndrome, cholecystitis, and drug-induced hepatotoxicity.

■ **Narrowing the field.** HG usually presents between 4 to 13 weeks of the start of pregnancy and is characterized by severe nausea, vomiting, weight loss, and electrolyte

Habib U. Rehman, FRCPC, FRCPI, FRCP (Glas), FACP
Department of Medicine,
Regina General Hospital,
Saskatchewan, Canada

✉ habib31@sasktel.net

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> Absence of jaundice, ascites, and hepatic vein thrombosis on ultrasound excludes Budd-Chiari syndrome.

disturbances, none of which are present in this patient. The patient does not have neuropsychiatric symptoms and signs typical of Wilson's disease, and the high-normal ceruloplasmin level despite above-normal serum copper also weighs against this diagnosis.

Our patient was not taking any hepatotoxic drugs or over-the-counter medications that cause liver damage.

With intrahepatic cholestasis of pregnancy, aminotransferase levels can be as high as 20 times the upper limit of normal. However, with this disorder, elevated serum bile acids during the second half of pregnancy cause pruritis. Absence of pruritis, jaundice, and features of obstructive jaundice, including pale stools and dark urine, makes intrahepatic cholestasis of pregnancy unlikely. Moreover, patients with this disorder do not have constitutional symptoms.¹

Preeclampsia is characterized by hypertension and proteinuria after 20 weeks of gestation or within 48 hours of delivery. Absence of seizures differentiates it from eclampsia. Right upper quadrant pain, nausea, and vomiting may be the presenting features. Aminotransferase levels can be up to 10 times the upper limit of normal. Bilirubin concentrations are usually normal. These abnormalities typically resolve within 2 weeks of delivery. Though atypical clinical presentations have been known with preeclampsia—particularly as extremes of maternal childbearing age have been associated with preeclampsia²—the patient's normal BP and an absence of proteinuria make both preeclampsia and eclampsia unlikely.

HELLP syndrome usually arises in the second or third trimester of pregnancy but also can develop after delivery. Right upper quadrant and epigastric pain, nausea, and vomiting are usual presenting symptoms. Hypertension and proteinuria are found in 85% of cases.³ Absence of hypertension and proteinuria and normal microangiopathic blood smear and platelet count make HELLP syndrome unlikely in the patient.

AFLP usually presents in the third trimester of pregnancy with nausea, abdominal pain, jaundice, and hepatic encephalopathy. Hypoglycemia, lactic acidosis, hyperammonemia, and disseminated intravascular

coagulation may complicate the clinical picture. Leukocytosis occurs in 98% of patients.⁴ Elevated concentrations of bilirubin, aminotransferases, and uric acid are commonly found. The biochemical picture in our patient does not match that of AFLP and makes this diagnosis unlikely.

■ Remaining potential diagnoses. Hepatitis B and C are possibilities and must be excluded by appropriate serologic tests. Hepatitis E viral infection usually follows a more severe course in pregnancy. Pregnant women are more likely to acquire hepatitis E in the second or third trimester. Also, though it is rare for autoimmune hepatitis to first appear during pregnancy, it too, must be ruled out.

Pregnancy is a prothrombotic state, so you must exclude Budd-Chiari syndrome. Up to 20% of cases of Budd-Chiari syndrome occur in women who are on oral contraceptives or are pregnant or 2 months postpartum.⁵ Right upper quadrant pain, jaundice, and ascites are the common clinical features.

Gallstones are strongly associated with higher parity in women. Pre-pregnancy obesity and high serum leptin levels are strong risk factors for pregnancy-associated gallbladder disease. Gallbladder sludge and stones are common in pregnancy and the postpartum period, and cholecystectomy is frequently done within the first year postpartum.⁶ Serum alkaline phosphatase is less helpful in diagnosing cholecystitis in pregnancy because of elevated levels from the placenta.

Q With hepatitis, Budd-Chiari syndrome, and gallstones remaining in the differential, what other investigations would you pursue to narrow the differential?

A test for hepatitis A virus immunoglobulin M (IgM) proves negative. Hepatitis B surface antigen is negative, and hepatitis B surface antibody is 11.5 mIU/L, suggesting borderline protective level of antibody. Hepatitis C virus antibody also is negative. Hepatitis E occurs in the Indian subcontinent, Africa, and the Middle East, and is therefore unlikely in this patient. Serologies for cytomegalovirus IgG

and Epstein-Barr virus IgM are negative. Herpes simplex type-1 specific IgG antibody is present. These serologic results exclude viral causes of hepatitis.

Antinuclear (ANA) and antimitochondrial antibodies are negative. Antismooth muscle antibody (ASMA) is positive at a titer of 1:20. Quantitative IgG is 7.23 g/L (normal, 5.52-17.24), IgA is 1.36 g/L (0.87-3.94), and IgM is 1.19 g/L (0.44-2.47). Negative ANA, weakly positive ASMA, and normal levels of immunoglobulins in our patient do not support a diagnosis of autoimmune liver disease.

Imaging is the next step for this patient. Even during pregnancy, ultrasound and magnetic resonance imaging are safe and readily available. The diagnostic accuracy of ultrasound for detecting gallstones is 95%. When ultrasound findings are equivocal in a pregnant patient, magnetic resonance cholangiopancreatography provides an accurate evaluation of the biliary system and can substitute for endoscopic retrograde cholangiopancreatography (ERCP).⁷

An ultrasound examination of the patient shows a normal liver with no significant fatty infiltration. The gallbladder, however, is packed with calculi. The common hepatic duct measures 4.6 mm and the common bile duct measures 8.5 mm. The intrahepatic ducts are not dilated. Doppler ultrasound of the hepatic and portal veins demonstrates normal flow without evidence of thromboses. Absence of jaundice, ascites, and hepatic vein

thrombosis on ultrasound excludes Budd-Chiari syndrome.

The diagnosis

History of sudden-onset epigastric pain, chills, and nausea in the postpartum period, no history of liver disease, and an uneventful pregnancy makes cholecystitis the most likely diagnosis for the patient.

Gallstones are common in pregnancy and more than 4% of pregnant women have incident gallbladder sludge or stones persisting to the early postpartum. Cholesterol secretion is increased in the second and third trimester of pregnancy, thus increasing the lithogenicity of the bile.⁸

The outcome

ERCP showed several stones in the common bile duct. We performed a papillotomy and removed 15 pale, almost white-faced, stones. Subsequent laparoscopic cholecystectomy removed a large gallbladder with multiple remaining stones. Microscopic examination of the gallbladder wall showed thickened muscularis propria and fibrosis of the subserosa, findings consistent with chronic cholecystitis.

JFP

CORRESPONDENCE

H.U. Rehman, MBBS, Clinical Associate Professor, Department of Medicine, Regina General Hospital, 1440 14th Avenue, Regina, SK, S4P 0W5, Canada; habib31@sasktel.net



We performed a papillotomy and removed 15 pale, almost white-faced, stones.

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