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Hepatic encephalopathy precipitated by preeclampsia in the setting of cirrhosis: A case report

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ABSTRACT

Preeclampsia and decompensated chronic liver disease are known triggers of acute hepatic dysfunction in pregnancy, rarely including hepatic encephalopathy. Differentiating the driver of acute hepatic dysfunction in patients with concomitant preeclampsia and preexisting liver disease presents a diagnostic challenge with important management implications.

A 42-year-old woman, gravida 3 para 0201, at 24 1/7 weeks of gestation presented with hepatic encephalopathy, transaminitis, and hyperbilirubinemia in the setting of cirrhosis and severe new-onset preeclampsia. The preeclampsia was thought to be the leading etiology of hepatic encephalopathy, prompting emergent Cesarean delivery at 24 2/7 weeks. Hepatic encephalopathy, blood pressure, and laboratory derangements improved promptly post-delivery.

Preeclampsia can trigger acute hepatic dysfunction, including hepatic encephalopathy, in the setting of previously compensated preexisting liver disease. Recognizing this association has important implications for management and treatment.

1. Introduction

Liver dysfunction complicates up to 3% of pregnancies, ranging from asymptomatic laboratory abnormalities to liver failure with significant maternal-fetal morbidity [1,2]. Liver disease in pregnancy can be categorized as pregnancy-related and/or coincidental to pregnancy (coincidental meaning either de novo during pregnancy or as an exacerbation of preexisting liver disease) [1–3]. The majority of liver dysfunction in pregnancy is pregnancy-related and includes: hyperemesis gravidarum, cholestasis of pregnancy, preeclampsia with severe features (PESF), hemolysis elevated liver enzymes low platelet (HELLP) syndrome, and acute fatty liver of pregnancy (AFLP) [1,2,4,22,23]. The latter three are preeclampsia-associated liver dysfunction.

Acute hepatic dysfunction can manifest as acute liver function test (LFT) derangements, impaired synthetic function, and/or hepatic encephalopathy [5]. Overlapping features exist between acute hepatic dysfunction and decompensation of preexisting liver disease, namely cirrhosis. Decompensation is marked by the transition from asymptomatic, compensated cirrhosis to development of complications, including hepatic encephalopathy, ascites, variceal hemorrhage, and/or jaundice [6]. For patients with cirrhosis who develop preeclampsia and acute hepatic dysfunction, cirrhotic decompensation with coincidental preeclampsia must be differentiated from preeclampsia-associated liver dysfunction complicating cirrhosis.

Accurate diagnosis dictates timely management, including maternal and fetal risk assessment, delivery timing, approach to complications, and liver transplant considerations [4]. We describe a pregnant woman with concomitant secondary biliary cirrhosis and PESF who presented with hepatic encephalopathy, transaminitis, and hyperbilirubinemia. We attributed acute hepatic dysfunction to preeclampsia complicating cirrhosis, prompting emergent delivery.

2. Case Presentation

A 42-year-old woman, gravida 3 para 0201, present at 24 1/7 weeks of gestation with loss of consciousness and altered mental status. She had secondary biliary cirrhosis, heart failure with preserved ejection fraction, pulmonary hypertension, chronic thrombocytopenia, and preeclampsia without severe features.

Secondary biliary cirrhosis was diagnosed at age 31 years after presenting with acute cholangitis. Exploratory laparotomy and choledochoduodenostomy revealed common bile duct stricture from an open

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Table 1
Evaluation of etiology of liver disease and baseline labs. Baseline labs obtained at 13 5/7 weeks. *Autoimmune serologies tested: anti-mitochondrial antibody, anti-double stranded DNA, anti-smooth muscle antibody, myeloperoxidase-anti cystoplasmic antibody not listed were negative.

Test	Reference range	Results
Aspartate aminotransferase (AST)	13–39 U/L	58
Alanine aminotransferase (ALT)	7–52 U/L	36
Alkaline phosphatase (ALP)	34–104 U/L	140
Bilirubin	0.2–1.2 mg/dL	1.2
Albumin	3.7–5.3 g/dL	3.1
Prothrombin time (PT)	11.7–14.5 s	16.2
International normalized ratio (INR)		1.3
Hepatitis A, B, C, D, E serologies	Negative	
Metabolic (ferritin, ceruloplasmin, alpha-1-antitrypsin)	Negative	Negative
Anti-nuclear antibody	Not detected	1:320 to 1:640
Exploratory laparotomy	- Iatrogenic stricture of common bile duct in setting of previous open cholecystectomy and stent placement	
Liver biopsy (age 31-years)	- Grade 4 cirrhosis, accentuated on trichrome stain - Bile duct proliferation, mild portal tract inflammation, no interface hepatitis - No evidence of steatosis - No ballooning degeneration, Mallory hyaline, lobular inflammation, or cholestasis - No evidence of malignancy	
Abdominal ultrasound	Cirrhotic hepatic morphology with no focal masses. 13.2 cm liver. Main portal vein measures 0.9 cm, normal size with hepatofugal flow. Spleen 18.2 cm in length.	
Esophagogastroduodenoscopy (15 0/7 weeks)	- Upper, middle, and lower esophagus appeared normal. No esophageal varices. - Gastroesophageal junction was normal. - Gastric body with mild portal gastropathy (stable). Otherwise gastric fundus, cardia, body, and antrum were normal. No gastric varices. - Duodenal bulb with normal post-surgical anatomy (choledochoduodenostomy)	

cholecystectomy at age 20 years. Liver biopsy revealed grade 4 cirrhosis and bile duct proliferation. Evaluation for viral, metabolic, and autoimmune etiologies was nondiagnostic (Table 1). At age 32 years, she underwent endoscopic band ligation for grade 2 esophageal varices on routine esophagogastroduodenoscopy (EGD). Cirrhosis remained compensated during the index pregnancy, supported by absence of esophageal or gastric varices on EGD at 15 0/7 weeks and stable laboratory testing (Table 1). Preconception Model for End-Stage Liver Disease (MELD) score was not available; first-trimester MELD score was 10 (range 6 to 40). She was on ursodiol 500 mg twice daily and beta-blocker therapy during the index pregnancy.

The patient had initially presented to care after experiencing a few weeks of volume overload, and was subsequently found to be pregnant, at 9 0/7 weeks of gestation. She did not have a preconception consult with maternal-fetal medicine. During this index pregnancy, due to acute exacerbation of congestive heart failure, she had a total of three hospitalizations, during which termination was offered. Echocardiogram and right heart catheterization at 14 5/7 weeks revealed impaired left ventricular relaxation, dilation of all chambers, and pulmonary artery pressure of 40 mmHg. Her third admission was notable for 18.5 kg removed from diuresis and development of preeclampsia without severe features at 23 3/7 weeks (by new mildly elevated blood pressure and proteinuria [197 mg/24 h at baseline to 420 mg/24 h]). She received a course of betamethasone at 23 weeks, per institutional policy of offering this in well-dated pregnancies as early as 23 weeks, regardless of estimated fetal weight (EFW). She was discharged at 24 0/7 weeks with close outpatient follow-up plans.

One day after discharge, at 24 1/7 weeks, she represented via emergency medical services for loss of consciousness. Her son noticed waxing-waning mental status before she was found unconscious at home with no witnessed tonic-clonic activity or loss of bowel or bladder function.

On admission, she presented with asterixis, disorientation to time, blood pressure of 150/74, temperature of 97.9 °F (36.6 °C), and physical examination negative for focal neurologic deficits, abdominal ascites, epigastric/right upper quadrant pain, nausea/vomiting, and signs of volume overload. The results of liver function tests (LFTs) were elevated from one day prior (AST 134 from 60 U/L, ALT 94 from 40 U/L), ammonia 111.0 umol/L, total bilirubin 3.8 (from 2.4 mg/dL), glucose 102 mg/dL, platelets 112,000 uL, and negative viral serologies (Table 2).

Maternal-fetal medicine coordinated care with cardiology, gastroenterology, neurology, neonatology, and anesthesiology. A head CT scan without contrast was negative for acute intracranial abnormalities. Abdominal ultrasound revealed stable cirrhotic hepatic morphology and portal systemic hepatofugal flow with normal main portal vein diameter. Chest x-ray revealed stable pulmonary edema and cardiomegaly. Criteria for PESF were met by acute elevation of LFTs. The leading diagnosis of altered mental status was hepatic encephalopathy precipitated by PESF, more likely than true decompensation of historically stable, compensated cirrhosis. Given worsening PESF, the multidisciplinary team and surrogate decision-maker opted for emergent Cesarean delivery at 24 2/7 weeks. Prior to delivery, she received lactulose 20 mg, a rescue dose of betamethasone, and magnesium sulfate (continued through delivery and 24-h postpartum).

The patient underwent a primary low-transverse Cesarean delivery under regional anesthesia after pulmonary artery catheter placement for close hemodynamic monitoring. Surgery was uncomplicated. She delivered a viable premature male infant weighing 560 g with Apgar

Table 2
Lab values and trends at baseline, pre-delivery, and post-delivery.

Lab value	Reference range	Baseline 13 5/7 to 14 3/7	24 0/7	24 1/7	24 2/7	POD1	3 months postpartum
AST	13–39 U/L	58	60	134	115 126 104 94	93 94 102	21
ALT	7–52 U/L	36	40	94	83 89 80 75	73 71 77	24
Platelets	150–400 10*3/uL	81	85	112	95	91	87
INR		1.3	1.1	1.0	1.2	1.4	

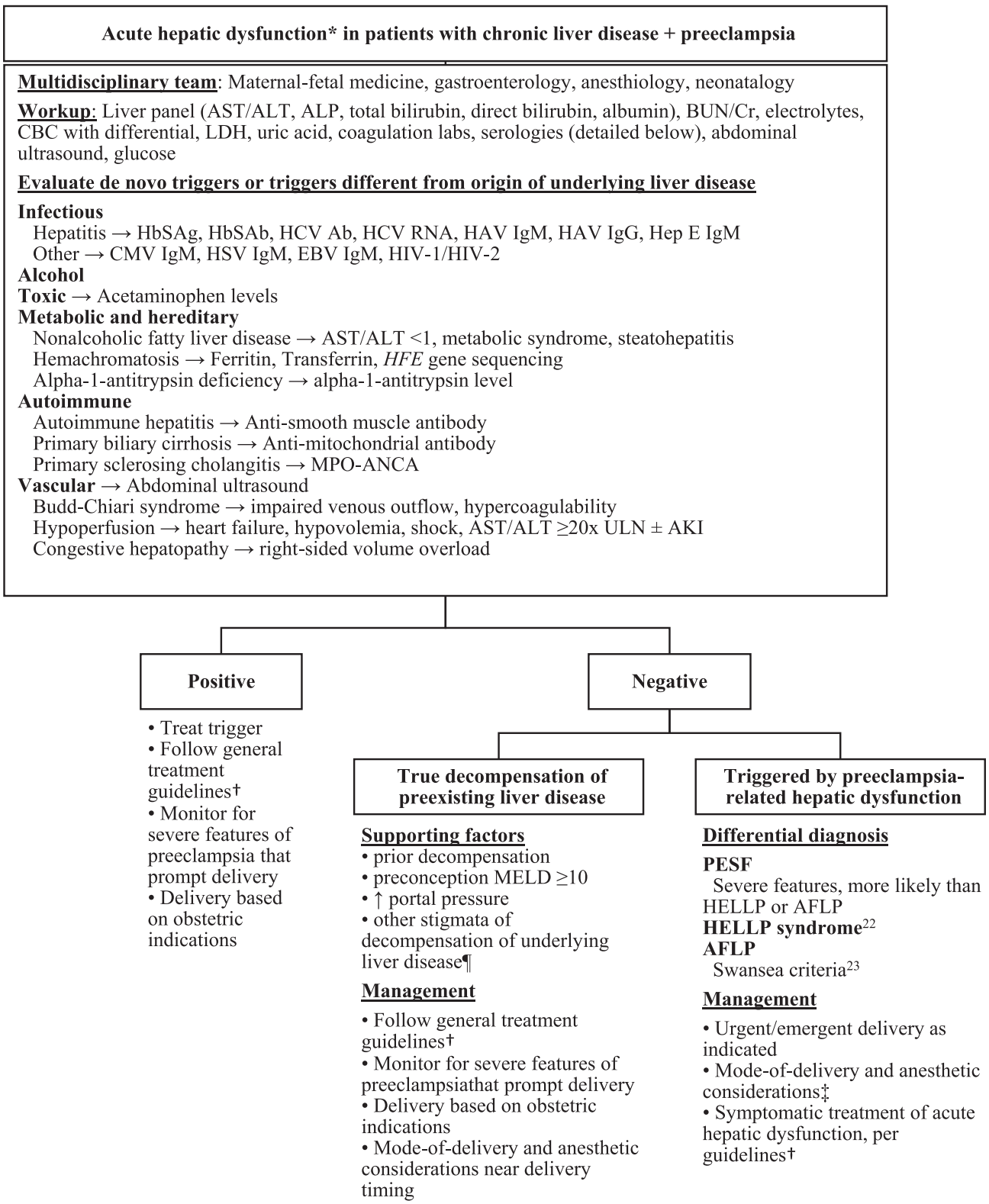

Fig. 1. Framework for acute hepatic dysfunction in gravidae with chronic liver disease and preeclampsia.
*transaminitis, jaundice, coagulopathy, synthetic dysfunction, hepatic encephalopathy.
¶ variceal bleeding, hepatic encephalopathy, ascites ± spontaneous bacterial peritonitis, hepatorenal syndrome, liver failure.
† variceal hemorrhage- band ligation + non-selective betablocker; ascites- loop diuretics + spironolactone, paracentesis; spontaneous bacterial peritonitis- albumin, antibiotics; hepatic encephalopathy- investigate precipitant, lactulose.

scores of 3, 3, and 6 at 1, 5, and 10 min, transferred to the neonatal intensive care unit (NICU) on mechanical ventilation. Postpartum, mental status rapidly improved with return to baseline within 24 h. She was discharged on post-operative day four at her baseline mental status, with improved bilirubin, LFTs, and ammonia levels on lactulose 10 mg every 8 h (Table 2). She was discharged with lactulose 10 mg every 8 h, carvedilol 3.125 mg twice daily, and furosemide 40 mg daily, and multidisciplinary follow-up.

At 3 months postpartum, hepatocellular liver enzymes had improved and returned to baseline pre-pregnancy levels; however, cholestatic liver enzymes had increased from discharge (Table 2). The neonatal course was marked by prolonged NICU admission for management of extreme prematurity-related complications (bronchopulmonary dysplasia and nutrition), with multidisciplinary follow-up post-discharge.

3. Discussion

Etiologies of acute hepatic dysfunction in pregnancy include pregnancy-associated liver conditions, most commonly preeclampsia-associated liver dysfunction, and liver disease unrelated or coincidental to pregnancy, such as decompensated cirrhosis [1,2,4,5,7]. Deciphering the etiology of acute hepatic dysfunction in patients with concomitant cirrhosis and preeclampsia is critical for prioritizing management considerations.

The shared manifestations of acute hepatic dysfunction and decompensated cirrhosis contribute to the diagnostic challenge of this scenario [8–11]. In pregnant patients with cirrhosis, the rate of decompensation ranges from 1.6% to 25% [8–10], and decompensation is higher among those with versus without pre-pregnancy decompensation (13% versus 1%, respectively) [9]. Decompensation and disease activity during pregnancy are associated with increased risk of maternal and fetal/neonatal morbidity and mortality [8,9,11,12]. Gestational age at onset of cirrhotic decompensation varies by manifestation, though, as variceal hemorrhage is the most common manifestation, decompensation often occurs in the second and third trimesters [8–11,13]. The incidence of hepatic encephalopathy varies between 1% and 13% of pregnant patients with cirrhosis [8]. Known precipitants of acute hepatic dysfunction and true decompensation of chronic liver disease include variceal bleeding, electrolyte disturbance, infection, hypoperfusion, and drugs [10]. Elucidating triggers for AHD in the setting of preexisting liver disease is critical for surveillance, prevention, and management. This case demonstrates that preeclampsia-associated liver dysfunction may trigger acute hepatic dysfunction in the setting of previously compensated cirrhosis, highlighting the potential bidirectional relationship between chronic liver disease and preeclampsia. Evidence supports chronic liver disease as a risk factor for preeclampsia; we propose that liver involvement in preeclampsia may trigger acute hepatic dysfunction in the setting of chronic liver disease [14].

We highlight the challenges of the diagnosis of acute hepatic dysfunction in patients with concomitant pregnancy-unrelated and pregnancy-related liver disease. Our approach for determining the leading diagnosis required exclusion of other causes (Fig. 1). For the patient reported, true decompensation was considered unlikely, especially considering her decade history of stable, compensated cirrhosis. The prompt resolution of hepatic encephalopathy and improvement of LFTs and bilirubin after delivery further favors placenta-driven pathology with preeclampsia as the etiology [4,14]. Among the preeclampsia-associated etiologies, PESF was the leading diagnosis, although hepatic encephalopathy as a manifestation of acute hepatic dysfunction in PESF is the rarest among preeclampsia-associated liver dysfunction compared to HELLP and AFLP [7,14]. Given absence of hemolysis and thrombocytopenia characteristic of HELLP, and lack of coagulopathy and hypoglycemia typical of AFLP, these were lower on the differential [1,4,15,22,23]. Hepatic hypoperfusion in the setting of recent aggressive diuresis was less likely, given the milder degree of liver function derangements and lack of frequently co-occurring acute kidney injury [16].

Secondary biliary cirrhosis is exceptionally rare in pregnancy and the typical course is unknown. The only other case, reported in 1999, describes a 33-year-old woman, gravida 5 para 4, with secondary biliary cirrhosis from recurrent pyogenic cholangitis who delivered a healthy 2800 g baby at 37 weeks [17]. Two years prior to this pregnancy, she was diagnosed with secondary biliary cirrhosis, complicated by portal hypertension, bleeding esophageal varices, and splenomegaly. Transplant was planned but deferred given unexpected pregnancy. During the pregnancy, there were no signs of hepatic decompensation, and she underwent induction of labor at 37 weeks given the unpredictable risk of recurrent esophageal variceal bleeding. Although this patient had a history of pre-pregnancy hepatic decompensation, cirrhosis was well compensated during pregnancy. With the limited information from this case, it is possible that the typical course of secondary biliary cirrhosis during pregnancy is decreased disease activity [18]. If true, this further supports our argument for preeclampsia-associated liver dysfunction versus true hepatic decompensation as the etiology of acute hepatic dysfunction in the present case. While the postpartum course of secondary biliary cirrhosis is unknown, there is a higher risk of biochemical disease flare for primary biliary cholangitis and other cholestatic liver diseases in the postpartum period compared with pregnancy [19,20]. Meanwhile, liver damage in preeclampsia is characterized by hepatocellular damage [21]. In the present case, the pattern of liver function tests at 3 months postpartum (return of hepatocellular liver enzymes to baseline and increase in cholestatic liver enzymes) further favor PESF over decompensated secondary biliary cirrhosis as the etiology of acute hepatic dysfunction prior to delivery.

In summary, we describe a pregnant patient who presented with hepatic encephalopathy, transaminitis, and hyperbilirubinemia in the setting of cirrhosis and PESF. This scenario presents diagnostic challenges that may lead to a missed/incorrect diagnosis, drastically altering management. While acute hepatic dysfunction in pregnant patients with preexisting liver disease should follow similar guidelines as the general population [3,4,10–12], the present case highlights the importance of considering hepatic dysfunction related to PESF, which prompted delivery (rather than expectant management), with rapid postpartum improvement. We provide a practical approach for differentiating the driver of acute hepatic dysfunction in patients with preeclampsia and cirrhosis.

Contributors

Mary E. Fang contributed to conception of the case report, acquiring and interpreting data, drafting manuscript, undertaking literature review and revising the article critically for important intellectual content.

Nicholas A. Peoples contributed to conception of the case report, and undertaking the literature review and minor revisions.

Alison N. Goulding contributed to conception of the case report, major revisions, and patient care.

Mary C. Tolcher contributed to conception of the case report, major revisions, and patient care.

All authors approved the final submission.

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Patient consent

Obtained.

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This article was not commissioned and was peer reviewed.

Conflict of interest statement

The authors declare that they have no conflict of interest regarding the publication of this case report.

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