Liver disease during pregnancy and the postpartum period is a diagnostic conundrum for clinicians due to an extensive broad differential diagnosis. Approximately 3% of women are affected by some form of liver disease during pregnancy.1 Drug-induced liver injury (DILI) is one important cause that is a challenging diagnosis due to the lack of objective testing, incomplete knowledge of mechanism, and variety of offending agents.1,2 The most common causes of DILI in pregnancy include analgesics, antihypertensive medications (methyl-dopa and hydralazine), antimicrobials (nitrofurantoin and minocycline), antiretroviral agents, anticholinergics, and propylthiouracil.2,3 A combination of genetic predisposition and environmental factors related to drug metabolism causes a complex cascade of cellular events leading to liver injury.4 Withdrawal of the offending agent is the primary management leading to spontaneous resolution.2,4

Labetalol is a selective α- and nonselective β-adrenergic antagonist and is one of the first-line treatments for preeclampsia.5 It has an excellent safety profile and efficacy compared with hydralazine and calcium channel blockers in the treatment of hypertension (HTN) in pregnancy.5 Common side effects include orthostatic hypotension, dizziness, bradycardia, nausea, and diarrhea.5 In the literature, the majority of DILI from labetalol are in nonpregnant individuals that resulted in mild–moderate transaminitis (up to 8%).6 Rarely DILI has been reported in pregnancy. Chronic liver

Drug-induced liver injury (DILI) is a common cause of transaminitis in pregnancy. A 34-year-old G3P2012 presented 3 weeks postpartum for preeclampsia with severe features. After receiving acute antihypertensive medications, she was discharged home with labetalol. She presented 5 months later with general malaise, scleral icterus, nausea, and mild right upper quadrant pain and found to have significantly elevated transaminitis. She had a negative infectious, autoimmune, biliary, and steatohepatitis workup. A liver biopsy was performed supporting the diagnosis of DILI. After patient self-discontinued labetalol, her hepatitis significantly improved. However, she developed chronic DILI and liver enzymes normalized during her subsequent pregnancy at 34 weeks. Patient’s written consent was obtained for this case report. Chronic DILI secondary to labetalol use is a rare and potentially fatal condition that should be considered on the differential for transaminitis during pregnancy and postpartum period.
injury occurs in approximately 17% of individuals experiencing DILI; however, according to LiverTox, no cases of chronic DILI have ever been reported related to labetalol use.2,6,7

We present a rare case of pregnancy-related DILI from labetalol resulting in chronic hepatitis.

Case
A 34-year-old G3P2012 presented 3 weeks postpartum for preeclampsia with severe features. She previously underwent an uncomplicated primary cesarean section for persistent category 2 tracings after an induction of labor for oligohydramnios at 395/7 weeks. Intrapartum she developed gestational HTN with normal liver enzymes. She was discharged on postpartum day (PPD) 2. Her medical history included an antinuclear antibody (ANA) titer 1:640 and skin biopsy of rash on her back for lupus workup that was negative. No prior history of liver disease. There was no alcohol or tobacco use. Allergies included shellfish (nausea and vomiting).

She presented to her 1-week postpartum visit with blood pressure (BP) of 140/80 and repeat laboratory tests were significant for an aspartate transaminase/alanine transaminase (AST/ALT) 45/33 U/L (normal, 7–37 U/L and 10–49 U/L, respectively). She then presented to the emergency room on PPD 19 after home nursing visit reported an elevated BP of 160/100. She reported headache and dizziness and was found to have severe range BPs requiring a total of 140 mg of intravenous (IV) labetalol and 20 mg of IV hydralazine. She was diagnosed with preeclampsia with severe features, received 24 hours of magnesium sulfate, and achieved adequate BP control. Her laboratory tests were significant for: normal complete blood count (CBC), AST/ALT 42/28 U/L, and normal protein/creatinine 162.9 mg/g (0–100 mg/g). She was discharged home after a 3-day hospital stay with labetalol 300 mg twice daily.

She developed chronic HTN postpartum and her primary care provider (PCP) increased her labetalol to 400 mg twice daily 3 months postpartum. She returned to her PCP after another 1 month and was prescribed hydralazine 50 mg twice daily due to persistent elevated BPs. However, the patient reported never taking this medication and was only on her prescribed labetalol at this time. She had not previously traveled, had sick contacts, or took any herbal supplements. Outpatient laboratory tests showed persistent elevated AST/ALT 38/47 and normal total bilirubin (TB) 0.3 mg/dL (normal, 0.3–1.2 mg/dL). A nephrology consult and renal ultrasound (US) were ordered, but patient did not follow-up.

She presented to the urgent care 6 months postpartum for general malaise, scleral icterus, and nausea and mild right upper quadrant pain. She attributed this to her labetalol medication and self-discontinued. Outpatient laboratory tests were remarkable for a normal CBC, AST/ALT 1,294/1,589 U/L, alkaline phosphatase (Alk Phos) 229 U/L (normal, 42–98 U/L), TB 8.4 mg/dL, amylase 145 U/L (normal, 28–100 U/L), lipase 33 U/L (normal, 6–51 U/L), and negative hepatitis (A, B, C) panel (►Fig. 1). Direct bilirubin was 7.7 mg/dL (normal, 0–0.3 mg/dL).

Fig. 1 LFTs and total bilirubin laboratory trends associated with labetalol use. LFTs normalized approximately 15 months after self-discontinuation of labetalol at her subsequent pregnancy at 34 weeks’ gestation. ALT, alanine transaminase; AST, aspartate transaminase; LFTs, liver function tests.
and indirect was 2.8 mg/dL (0.1–1.0 mg/dL). She was subsequently admitted for further evaluation with medicine, gastroenterology, and nutrition. She had a negative urine toxicology and salicylates screen.

Autoimmune workup was unremarkable: rheumatoid factor, antinuclear factor (ANF), anticyclic citrullinated peptide antibody, antithyroid peroxidase antibody, and antithyroglobulin antibody were negative. She was positive for lupus anticoagulant, anti-cardiolipin antibody (ACL), antiphospholipid antibody (aPL), ANA, anti-glomerular basement membrane (anti-GBM), anti-neutrophil cytoplasmic antibody (ANCA), antineutrophil cytoplasmic antibody (cANCA), and antineutrophil cytoplasmic antibody (pANCA) were all negative. She was positive for anti-native DNA (anti-dsDNA), antithyroid peroxidase antibody (anti-TPO), and antithyroglobulin antibody (anti-TG) were negative. She was positive for anti-smooth muscle antibody (aSM) and antimitochondrial antibody (AMA) were negative. She was positive for anti-nuclear antibody (ANA) and anti-Smith (anti-Sm) were positive. She was negative for anti-neutrophil cytoplasmic antibody (ANCA), anti-glomerular basement membrane (anti-GBM), antineutrophil cytoplasmic antibody (cANCA), and antineutrophil cytoplasmic antibody (pANCA) were all negative.

Discussion

Labetalol is one of the first-line antihypertensive medications to treat HTN in pregnancy and overall has an excellent safety profile. However, labetalol also has the highest risk of DILI among beta-antagonists causing mild–moderate transaminitis in up to 8% of patients. The specific mechanism remains unknown; however, it is thought to be due to a metabolic idiosyncratic disposition that follows a hepatocellular pattern of injury with a latency period of 3 months (time of initiating drug to DILI) and resolves after 1 month. Idiosyncratic reactions occur less commonly, have a varied presentation and less consistent dosage relationship, and only affects susceptible individuals. Obstetricians should be aware of the potential for hepatotoxicity as it is one of the most commonly used antihypertensive medications.

The American College of Gastroenterology (ACG) provides diagnosis and treatment guidelines for DILI. The most important evaluation is a complete and thorough medical history as well as ruling out other etiologies as DILI is a diagnosis of exclusion. The differential diagnosis is broad and includes acute viral hepatitis, autoimmune hepatitis (AIH), chronic active hepatitis, Wilson’s disease, biliary obstruction, and DILI. Imaging such as an abdominal US is useful for evaluating for infiltrative process and to exclude biliary tract pathology. The Roussel-UCLAF Causality Assessment Method is a useful clinical diagnostic tool in evaluation of DILI. Our patient had an R factor of 15.7 (indicating hepatocellular injury) and scored 9 indicating a highly probable cause. In addition, the National Institute of Diabetes and Digestive and Kidney Diseases and the National Library of Medicine developed LiverTox, a free and helpful online DILI resource that provides an up-to-date and unbiased medical database for clinicians and patients.

A review of the literature revealed few case reports of DILI from labetalol occurring during pregnancy. In two of these cases, withdrawal of labetalol led to the resolution of transaminitis over several weeks. In more severe cases, combination of labetalol and methylprednisolone resulted in acute liver failure (ALF) and liver cirrhosis at 27 weeks gestation. The most recent case involved a 37-year-old patient at 13 weeks who presented with ALF and required emergency liver transplantation. Similarly, our patient had a significant decline in liver enzymes approximately one-and-a-half weeks after self-discontinuing labetalol. However, she developed chronic DILI that persisted for more than 12 months and resolved at 34 weeks’ gestation in her subsequent pregnancy. To the best of our knowledge, this is the first reported case of chronic DILI due to labetalol.

The role of liver biopsy remains controversial as it is not necessary for the diagnosis of DILI. Per the ACG guidelines, a liver biopsy is indicated in our patient case as AIH remained a possible etiology due to a prior history of a positive ANA screen. It is possible that she may have an underlying autoimmune condition that has yet to be identified, but the significant decline of her liver enzymes associated with stopping labetalol argues for a DILI etiology. A trial of corticosteroids could have also been considered as recent...
Fig. 2 Normal liver biopsy with trichrome stain at ×100.

Fig. 3 (A) Trichrome stain at ×40 magnification. Inflamed liver parenchyma with perisinusoidal fibrosis and portal tract fibrosis. (B) Hematoxylin and eosin (H&E) stain at ×100 magnification showing inflamed liver core. There is significant inflammation of the portal tract and interface hepatitis in the liver parenchyma. (C) H&E stain at ×400 magnification. Inflamed portal tract consists of lymphocytes, neutrophils, and eosinophils. These inflammatory cells spill out of the portal tract to the surrounding liver parenchyma. Some necrotic hepatocytes are seen. (D) H&E stain at ×600 magnification. Eosinophils and neutrophils are more clearly seen. Lipofuscin pigmentation accumulates over time in aging cells.
literature have shown that early ALT response to corticosteroids may help distinguish idiosyncratic DILI from AIH.\textsuperscript{13} In addition, chronic DILI could have also persisted due to the hyperestrogenic state in her subsequent pregnancy.

Liver biopsies from labetalol hepatotoxicity generally show scattered lymphocytes with variable degrees of necrosis and apoptosis.\textsuperscript{11} Patients with an infectious or autoimmune etiology show more significant lymphocytic infiltration with positive viral stains. A normal liver biopsy is shown in \textsuperscript{–} Fig. 2. Our patient’s pathology showed a mix of acute and chronic inflammation with interface hepatitis and subsequent portal tract fibrosis (\textsuperscript{–} Fig. 3 ). There was no evidence of cholestasis or steatohepatitis on pathology. Interestingly, the presence of eosinophils does provide some evidence of a component of immunologic etiology in addition to idiosyncratic predisposition. Overall, the lack of necrosis, significant fibrosis, ductular reaction, and presence of eosinophils is associated with a better outcome.\textsuperscript{14} A collaborative effort between the pathologist and medical team is critical.

This case highlights the importance and need for increased awareness of DILI from labetalol use in pregnancy. A comprehensive metabolic panel should be obtained for baseline evaluation prior to starting labetalol. A high index of suspicion is necessary as cases of ALF, liver cirrhosis, and emergency liver transplantation have been reported in pregnancy. This is the first reported case of chronic DILI from labetalol use.

Conclusion

DILI secondary to labetalol is a rare cause of liver disease in pregnancy and can lead to chronic DILI. DILI should be included on the differential diagnoses in the evaluation of liver injury in pregnancy.

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Conflict of Interest

None declared.

References