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Chronic Drug Induced Liver Injury from Labetalol During the Postpartum Period: A Case Report

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Conflict of Interest: The authors declare that they have no conflict of interest.

Abstract:

Background

Drug induced liver injury (DILI) is a common cause of transaminitis in pregnancy and postpartum period.

Case

A 34 year-old G3P2012 presented 3 weeks postpartum for preeclampsia with severe features. After receiving acute anti-hypertensive 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 work up. 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 written consent was obtained for this case report.

Conclusion

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.

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Chronic Drug Induced Liver Injury from Labetalol During the Postpartum period: A Case Report

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Abstract

Background
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A 34 year-old G3P2012 presented 3 weeks postpartum for preeclampsia with severe features. After receiving acute anti-hypertensive 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 work up. 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 written consent was obtained for this case report.

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Introduction
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. Drug-induced liver injury (DILI) is one important cause that is a challenging diagnosis due to lack of objective testing, incomplete knowledge of mechanism, and variety of offending agents. The most common causes of DILI in pregnancy include analgesics, antihypertensive medications (methyldopa and hydralazine), antimicrobials (nitrofurantoin and minocycline), antiretroviral agents, anticholinergics, and propylthiouracil. A combination of genetic predisposition and environmental factors related to drug metabolism causes a complex cascade of cellular events leading to liver injury. Withdrawal of the offending agent is the primary management leading to spontaneous resolution.

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

We present a rare case of pregnancy related DILI from labetalol resulting in chronic hepatitis.
A 34 year-old gravida 3 para 2012 presented 3 weeks postpartum for preeclampsia with severe features. She previously underwent an uncomplicated primary cesarean section for persistent category two tracings after an induction of labor for oligohydramnios at 39w5d. Intrapartum she developed gestational hypertension with normal liver enzymes. She was discharged on postpartum day 2. Her past medical history included an Anti-Nuclear Antibody (ANA) titer 1:640 and skin biopsy of rash on her back for lupus work up 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 one week postpartum visit with blood pressure (BP) of 140/80 and repeat labs was 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 (ER) on post-partum day (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 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 labs 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 hypertension 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 labs 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 labs were remarkable for a normal CBC, AST/ALT 1294/1589 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 (Figure 1). Direct bilirubin was 7.7 mg/dL (normal, 0-0.3 mg/dL) 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 work up was unremarkable: Rheumatoid Factor (RF), Anti-cardiolipin antibody (AB) IgG and IgM, anti-double stranded DNA, anti-smooth muscle A IgG, anti-mitochondrial M2 AB, F-Actin AB IgG, Beta-2-Glycoprotein IgG and IgM, C3 87 mg/dL (normal, 90-180 mg/dL) and normal C4. She previously had an elevated Anti-Nuclear Antibody (ANA) titer 1:640. Cytomegalovirus (CMV), Epstein-Barr Virus (EBV), COVID-19, and T-Spot were negative. Negative alpha-1 Antitrypsin and ceruloplasmin. Iron studies showed iron 125 ug/dL (normal, 40-170 ug/dL), Total Iron Binding Capacity (TIBC) 324 ug/dL (normal 250-450 ug/dL), iron saturations 39% (normal, 15-55%), and ferritin 439 ng/mL (normal, 10-291 ng/mL).
Coagulation studies showed mildly elevated prothrombin time (PT) 15 sec (normal, 10.2-12.9 sec), international normalized ratio (INR) 1.3 (normal, 0.9-1.1) and partial thromboplastin time (APTT) 37.2 sec (normal, 25.1-36.5 sec). Abdominal US demonstrated a normal liver with two small hemangiomas. Doppler US showed hypoechoic liver parenchyma, slightly elevated resistive index of the hepatic artery, and normal major vessels of the liver and spleen.

Labetalol dosage was reduced from 400 mg twice daily to 100 mg twice daily due to suspicion of DILI, though patient did not take this. Due to patient childcare needs, she was discharged home with outpatient follow up. Primary team suspected possible auto-immune etiology due to previous positive ANA screen. She was discharged on labetalol 200 mg twice daily and declined other anti-HTN medications, though patient reports not taking labetalol.

An outpatient liver biopsy was performed. Biopsy showed portal inflammation with neutrophils, lymphocytes, and scattered eosinophils. There was no significant cholestasis or steatosis. A trichrome stain demonstrated portal and perisinusoidal fibrosis and reticulin stain showed normal hepatocyte architecture. There was evidence of both acute and chronic inflammation. CMV and EBV stain were negative. A CD 128 immunohistochemical stain showed scattered plasma cells in portal areas. Given the lack of autoimmune and infectious etiologies, and presence of eosinophils, this was most consistent with labetalol-induced hepatotoxicity.

One-and-a-half weeks later, her liver enzymes decreased to AST/ALT 695/744 U/L and then 2 weeks later AST/ALT 69/87 associated with self-discontinuing labetalol. Her liver enzymes significantly improved, but never normalized over the next 7 months. Subsequently, she became
pregnant and resulted in worsening liver enzymes ALT 341 U/L. Fortunately, her liver enzymes decreased at 21 weeks gestation AST/ALT 68/79 U/L and ultimately normalized at 34 weeks gestation. She presented at 35 weeks for preterm labor and underwent a repeat cesarean section for category 2 tracing. She developed postpartum severe preeclampsia and received nifedipine with adequate blood pressure control.

**Discussion**

Labetalol is one of the first-line antihypertensive medications to treat hypertension 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), acute Budd-Chiari Syndrome, Wilson’s Disease, biliary obstruction, and DILI. Imaging such as an abdominal US is useful to evaluate for infiltrative process and to exclude biliary tract pathology. The Roussel
Uclaf Causality Assessment Method (RUCAM) 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 on-line 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 methyldopa resulted in acute liver failure (ALF) and liver cirrhosis at 27 weeks gestation. The most recent case involved a 37 year old 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 > 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 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 shows scattered lymphocytes with variable degrees of necrosis and apoptosis.\textsuperscript{11} Patients with an infectious or auto-immune etiology shows more significant lymphocytic infiltration with positive viral stains. A normal liver biopsy is shown in Figure 2. Our patient’s pathology showed a mix of acute and chronic inflammation with interface hepatitis and subsequent portal tract fibrosis (Figure 3). There was no evidence of cholestasis or steatohepatitis on pathology. Interestingly, the presence of eosinophils does provide some evidence of a component of immunoallergic etiology in addition to idiosyncratic predisposition. Overall, the lack of necrosis, significant fibrosis, ductular reaction and presence of eosinophils are 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 acute liver failure, liver cirrhosis, and emergency liver transplantation have been reported in pregnancy. This is the first reported case of chronic DILI from labetalol use.

\textbf{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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Figure 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.

Figure 2: Normal liver biopsy with trichrome stain at 100x.

Figure 3: A) Trichome stain at 40x magnification. Inflamed liver parenchyma with perisinusoidal fibrosis and portal tract fibrosis. B) Hematoxylin and Eosin (H&E) stain at 100x 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 400x magnification. Inflamed portal tract consists of lymphocytes, neutrophils and eosinophils. These inflammatory cells spills out of the portal tract to the surrounding liver parenchyma. Some necrotic hepatocytes are seen. D) H&E stain at 600x magnification. Eosinophils and neutrophils are more clearly seen. Lipofuscin pigmentation accumulates over time in aging cells.
Clinical Laboratory Value Trends

Liver Function Tests (U/L)

Days Since Onset of Labetalol

- Day 1: Started Labetalol
- Day 143: Self-discontinued Labetalol
- New subsequent pregnancy 5 weeks 2 days
- LFT's normalized 34 weeks gestation

- AST (normal, 7-37 U/L)
- ALT (normal, 10-49 U/L)
- T.Bili (normal, 0.3-1.2 mg/dL)