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CASE REPORT | LIVER

Severe Elevated Bile Acids in Early Pregnancy

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ABSTRACT

Intrahepatic cholestasis of pregnancy (ICP) typically presents in the second half of pregnancy. Severe ICP is associated with increased risk of stillbirth. Little is known regarding elevated bile acids in the first trimester. We present a case of severely elevated bile acids in the first trimester, resistant to conservative management, in a patient with pre-existing cholestatic liver disease and aortic valve disease requiring anticoagulation. Therapeutic plasma exchange was used. In those with pre-existing cholestatic disease, early bile acid elevation is likely distinct from ICP, and conservative strategies may not be useful. In addition, therapeutic enoxaparin appears safe in therapeutic plasma exchange.

KEYWORDS: Pregnancy; Bile acids; ductopenia; vanishing bile duct syndrome; ntrahepatic cholestasis of pregnancy

INTRODUCTION

Severe intrahepatic cholestasis of pregnancy (ICP) is defined as bile acids >40 μmol/L and is associated with increased risk of stillbirth.[1,2] More than 80% of cases are present in late pregnancy in patients without liver disease, but little is known about patients presenting with pre-existing liver disease. In severe ICP, medical management and therapeutic plasma exchange (TPE) must be considered to minimize risk. However, TPE may influence anticoagulation. We present a case of sustained bile acid elevations in early pregnancy in a patient with pre-existing liver disease and congenital heart disease requiring TPE while on anticoagulation.

CASE REPORT

A 29-year-old G1P0 with congenital subaortic stenosis requiring aortic valve replacement and aortic grafting and chronically elevated serum aminotransferases presented at 9-week and 1-day gestation with pruritis. One decade earlier, the patient had asymptomatic elevations in liver enzymes (Aspartate aminotransferase (AST 66), Alanine aminotransferase (ALT) 104, and Alk phos 260 U/L). Hepatitis serologies, liver ultrasound, and computed tomography scan were unrevealing, as were Antimitochondrial antibody (AMA), Anti-smooth muscle antibody (ASMA), anti-liver kidney, alpha-1-antitrypsin, ceruloplasmin, and Cytomegalovirus (CMV). Topiramate for migraines, and potential hepatotoxin, was discontinued. Genetic testing showed heterozygosity of H63D gene but normal iron panels. JAG1 and NOTCH2 mutations were negative (Alagille syndrome), and positive VPS33B was of uncertain significance. A liver biopsy was normal. She was subsequently observed by primary care for several years.

Fatigue and pruritis worsened again 4 years before gestation. Liver enzymes increased to AST 95 IU/mL, ALT 188 IU/mL, and alkaline phosphatase 454 U/L. Repeat serologies were unrevealing. Sertraline, another potential hepatotoxin, was stopped without improvement. magnetic resonance cholangiopancreatography (MRCP) was noncontributory. Repeat liver biopsy demonstrated bile duct loss in >50% of portal tracts (Figure 1). The etiology of her ductopenia was presumed genetic, perhaps in conjunction with her congenital heart disease. One sibling had similar cardiac anomalies. Ursodiol 300 mg twice daily was used for pruritis.

At preconception counseling, that patient transitioned from warfarin to enoxaparin because of teratogenicity. At 9-week and 1-day gestation, pruritis worsened, and bile acids were 84 μmol/L. Despite doubling ursodiol, bile acids increased to 340 μmol/L (Figure 2). Cholestyramine was added. However, symptoms persisted. TPE was considered. Multidisciplinary consultation determined

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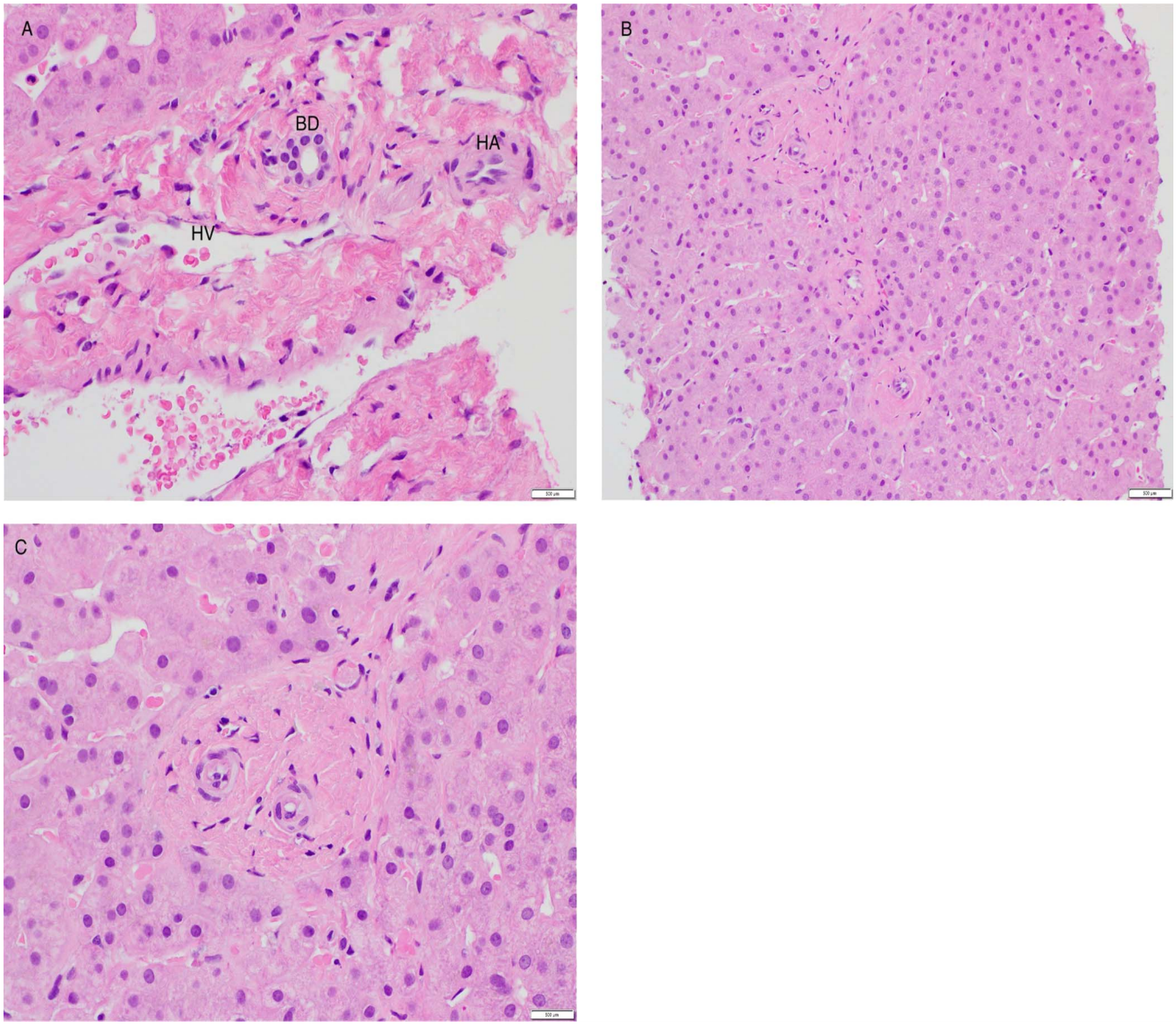

Figure 1. Histology of patients severe ductopenia. (A) A normal portal triad (40×). (B) Several portal triads with ductopenia (20×). (C) Magnified triad with no bile duct visualized (40×). BD, bile duct; HA, hepatic artery; HV, hepatic vein.

bleeding and thrombotic risk with enoxaparin may be less than warfarin when pursuing TPE. Therapeutic enoxaparin was continued until delivery.

The patient's pruritis correlated with bile acids >100 μmol/L. TPE was performed at 18 and 26 weeks. Delay in bile acid laboratory reporting of up to 48 hours caused difficulty monitoring levels immediately surrounding TPE. Despite exchange, bile acids remained severely elevated and fluctuated (Figure 2). At 29 weeks, the patient had worsening pruritus with bile acids measuring 171 μmol/L, resolving spontaneously. Bile acid recheck was 38 μmol/L. Near delivery, pruritus remained tolerable, despite levels >100 μmol/L. TPE was offered but deferred, given her stability and concern for anticoagulation effects. Induction of labor at 33 weeks 6 days led to delivery of a healthy newborn. Bile acids 1.5 months postpartum were 21 μmol/L.

DISCUSSION

Early presentation, underlying liver disease, and comorbid cardiac disease requiring anticoagulation distinguish our case. Her bile duct injury and the cholestatic effects of pregnancy appeared to drive her severe bile acid elevations, separating her pathophysiology from traditional ICP. However, the interference of bile acids with fetal cardiomyocytes, causing sudden fetal death, presents unacceptable risk, and therefore, ICP standards must be considered.[2] TPE was initiated, which demonstrated a beneficial safety profile, but was not clearly beneficial in lowering bile acids.

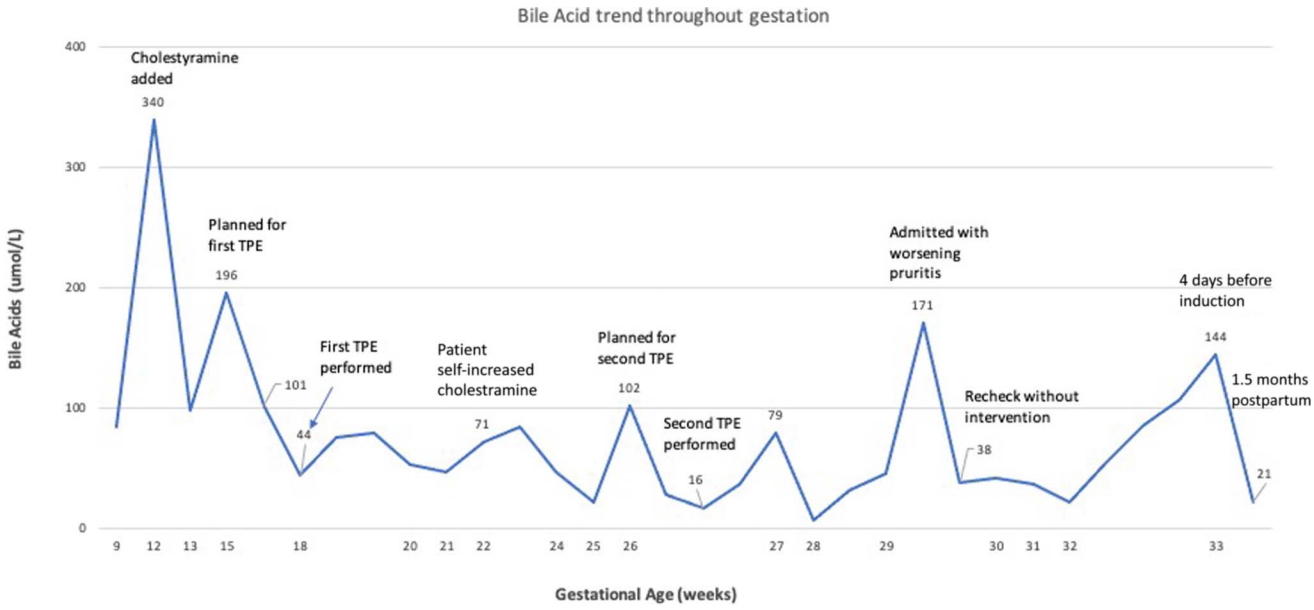

Figure 2. Bile acid trend throughout gestation. TPE, therapeutic plasma exchange.

Intensive bile acid monitoring aided management. This presented its own challenge, with a lag time of 48–72 hours on laboratory analysis. Consequently, management choices were made based on symptoms and the most recent, albeit delayed, bile acid results.

TPE for bile acids is a treatment of last resort. TPE is an extracorporeal technique for removing large molecular weight substances. Necessary criteria include size over 15,000 Da, a long half-life allowing effective periods of decreased serum concentration, and a toxic substance.[3] To the best of our knowledge, only 3 previous cases exist using TPE during pregnancy in patients with previous liver disease. Primary biliary cholangitis existed in 2 cases.[4] These patients presented with pruritus and hyperbilirubinemia at 12 weeks; bile acid levels were not reported. TPE was adopted at weeks 22 and 31, respectively.[4] A third case with known familial cholestatic disorder presented at 23 weeks of gestation with pruritis and bile acids of 130 μmol/L.[5] Four TPE sessions relieved pruritus with mild bile acid reduction. TPE has been used in patients without pre-existing liver disease and ICP with various successes and fluctuating bile acids.[6–8] Provider discretion led to repeat TPE in all cases.

TPE complications include coagulation changes.[9] Our patient transitioned from warfarin to therapeutic enoxaparin at preconception counseling and continued this throughout gestation. Enoxaparin is ideal in pregnancy as its large size precludes placental transmission and short half-life allows FOR discontinuation before delivery, minimizing bleeding risk. However, with significant valvular disease, warfarin is recommended to minimize thrombotic risk, despite the teratogenic risk.[9–11] There are no clear data on anticoagulation levels during TPE. One case series of 8 patients on warfarin undergoing 123 TPE sessions demonstrated doubling of international normalized ratio (INR) from 2 to 4 after TPE.[12] Alternatively, one report of TPE with therapeutic enoxaparin showed unchanged anti-Xa levels.[13] None were pregnant. Our patient maintained an anti-Xa level between 1.0 and 1.2 throughout TPE.

In our case, pruritis became a surrogate for bile acids given lab delays. Before her most significant pruritis, bile acids exceeded 100, and TPE was planned (Figure 2). Two TPE sessions improved pruritus, yet bile acids spontaneously fluctuated. It is unclear whether TPE significantly impacted bile acids, unlike previous reports showing reductions after TPE in patients with liver disease.[3,4] This reinforces our belief that her presentation remains separated from ICP, in which traditional measures consistently reduce bile acids. Furthermore, we cannot declare whether serial TPE sessions at set intervals would lower bile acid levels consistently, nor the best method in practical terms to determine the effect of TPE on bile acids. A specific regimen with repeated TPE remains unknown and unsupported by data. However, TPE appears safe in pregnant patients on anticoagulation. In this case, fortunately, induction of labor at 34 weeks led to delivery of a healthy newborn.

DISCLOSURES

Author contributions: L. Fass and C. Sibbald authored and edited aspects of the manuscript; L. Fass, C. Sibbald, E. Bailey, and M. Lucey cared for the patient in the hospital and clinics; E. Bailey and M. Lucey edited the manuscript; W. Zhang contributed to pathology images and processing. L. Fass is the article guarantor.

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Wisconsin and as a poster at American College of Gastroenterology Annual Scientific Meeting; October 22, 2023; Vancouver, Canada.

Informed consent was obtained for this case report.

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REFERENCES

1. Ovadia C, Seed PT, Sklavounos A, et al. Association of adverse perinatal outcomes of intrahepatic cholestasis of pregnancy with biochemical markers: Results of aggregate and individual patient data meta-analyses. *Lancet*. 2019; 393(10174):899–909. Erratum in: *Lancet*. 2019;393(10176):1100.
2. Vasavan T, Williamson C, Chapter 65–sex and cardiac electrophysiology: Fetal arrhythmia in intrahepatic cholestasis of pregnancy In: Malik M (eds). *Sex and Cardiac Electrophysiology*, Academic Press, Elsevier USA, Philidelphia PA, USA 2020, 727–35, ISBN 9780128177280.
3. Kaplan AA. Therapeutic plasma exchange: Core curriculum 2008. *Am J Kidney Dis.* 2008;52(6):1180–96.
4. Alallam A, Barth D, Heathcote EJ. Role of plasmapheresis in the treatment of severe pruritus in pregnant patients with primary biliary cirrhosis: Case reports. *Can J Gastroenterol.* 2008;22(5):505–7.
5. Mathias A, Wax JR, Pinette MG, Cartin A, Blackstone J. Progressive familial intrahepatic cholestasis complicating pregnancy. *J Matern Fetal Neonatal Med.* 2009;22(9):816–8.
6. Warren JE, Blaylock RC, Silver RM. Plasmapheresis for the treatment of intrahepatic cholestasis of pregnancy refractory to medical treatment. *Am J Obstet Gynecol.* 2005;192(6):2088–9.
7. Covach AJ, Rose WN. Intrahepatic cholestasis of pregnancy refractory to multiple medical therapies and plasmapheresis. *AJP Rep.* 2017;7(4): e223–225.
8. Ovadia C, Lövgren-Sandblom A, Edwards LA, et al. Therapeutic plasma exchange as a novel treatment for severe intrahepatic cholestasis of pregnancy: Case series and mechanism of action. *J Clin Apher.* 2018;33(6): 638–44.
9. Shunkwiler SM, Pham HP, Wool G, et al, Therapeutic Apheresis Subsection of the AABB. The management of anticoagulation in patients undergoing therapeutic plasma exchange: A concise review. *J Clin Apher.* 2018;33(3):371–9.
10. McLintock C. Anticoagulant therapy in pregnant women with mechanical prosthetic heart valves: No easy option. *Thromb Res.* 2011;127(Suppl 3): S56–60.
11. Oran B, Lee-Parritz A, Ansell J. Low molecular weight heparin for the prophylaxis of thromboembolism in women with prosthetic mechanical heart valves during pregnancy. *Thromb Haemost.* 2004;92(4):747–51.
12. Zantek ND, Morgan S, Zantek PF, Mair DC, Bowman RJ, Aysola A. Effect of therapeutic plasma exchange on coagulation parameters in patients on Warfarin. *J Clin Apher.* 2014;29(2):75–82.
13. Rahawi KW, Higgins KL, Noda C, Stultz JS. Effect of plasmapheresis on the anti-factor Xa activity of enoxaparin in an obese adolescent patient. *Pharmacotherapy.* 2017;37(4):e16–20.