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Elevated international normalized ratio (INR) and new diagnosis of hepatitis C associated with severe intrahepatic cholestasis of pregnancy (ICP): A case report

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ABSTRACT

Background: Severe intrahepatic cholestasis of pregnancy (ICP), defined as a serum bile acid (SBA) level > 100 μmol/l, remains poorly understood in its mechanism and implications.
Case: A patient with a missed diagnosis of mild ICP went on to develop clinical jaundice and liver function abnormalities in the setting of newly diagnosed hepatitis C and severe ICP on repeat SBA testing.
Conclusion: This case highlights and adds to the growing body of evidence supporting the need for universal screening for hepatitis C in ICP patients and the potential role for repeat SBA testing, which would be a notable change from the traditional care of these individuals.

1. Introduction

Intrahepatic cholestasis of pregnancy (ICP), known for its distinctive presentation of pruritus of the palms and soles in the third trimester, is a rare and poorly understood condition affecting 0.2–2% of pregnancies. The diagnosis is confirmed with a serum bile acid level and can be further supported with findings of elevated transaminases. For most women diagnosed with ICP, management is targeted towards both symptomatic relief and prevention of stillbirth [1,2].

Severe ICP, classified by serum bile acid levels >100 μmol/l, (normal ≤10 μmol/l) is an exceedingly uncommon finding during pregnancy and can present with more severe hepatobiliary symptoms and complications, including clinical jaundice, elevated serum bilirubin and coagulopathy [1,3].

Hepatitis C is another uncommon comorbidity of pregnancy, estimated to affect between 0.1 and 3.6% of pregnancies [4]. We describe the case of a patient who presented with clinical jaundice, emesis and decreased fetal movement and was ultimately diagnosed with severe ICP and previously unknown hepatitis C infection.

Abbreviations: ICP, Intrahepatic cholestasis of pregnancy; SBA, Serum bile acid; INR, International normalized ratio; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase.

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2. Case

A 31-year-old woman (G6 P 3023) presented at 31 weeks and 5 days of gestation for evaluation of new-onset scleral icterus, nausea/emesis and decreased fetal movement. Her medical history was notable for intravenous heroin abuse, for which she was enrolled in a local methadone clinic for maintenance.

The patient initially presented early in her pregnancy and her routine prenatal laboratory results were within normal limits. This evaluation included HIV and hepatitis B but notably not a hepatitis C assay. However, she did have negative hepatitis C testing documented as recently as two years before this presentation. At approximately 27 weeks of gestation she noted itching on her palms and soles. She had mild elevation of serum bile acid level, to 12 μmol/l (normal ≤10 μmol/l). Her aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were within normal limits at that time. Unfortunately, these results and the diagnosis of cholestasis were not communicated to the patient.

She continued with her routine prenatal care and had an elevated one-hour glucose tolerance test, ar 202 mg/dL (normal <130 mg/dl), leading to a diagnosis of gestational diabetes. She then presented to clinic at 31 weeks and 5 days of gestation with complaints of new-onset "yellowing" of her skin and eyes over the last week, as well as decreased fetal movement. Given these new findings she was transferred to labor and delivery for further assessment.

On presentation she had reassuring electronic fetal monitoring. Upon review of her chart she was noted to have had elevated bile

acids four weeks prior and was counseled on her diagnosis of cholestasis of pregnancy.

Initial laboratory testing revealed an elevated bilirubin level of 6.6 mg/dl (normal 0.0–1.2 mg/dl) as well as elevated AST level, to 46 units/l (normal 0–32 units/l), and ALT level, to 56 units/l (normal 0–33 units/l). The patient was evaluated for viral hepatitis and had a positive hepatitis C screen; she had a positive viral load of 118,000 I·U./ml (normal <0 I.U/ml). The patient had no knowledge of her hepatitis C status prior to admission. An abdominal ultrasound scan was negative for acute pathology. Repeat tests of serum bile acids were also ordered.

Given her marked abnormalities on initial evaluation, further workup was done to evaluate synthetic function of the liver. She was noted to have a mildly low albumin level and an elevated international normalized ratio (INR) of 2.3 (normal 0.9–1.1), for which she was treated with vitamin K.

The patient remained in hospital and had daily monitoring of her transaminase levels and coagulation panels. Her INR returned to normal with the addition of vitamin K and her AST/ALT trended down to normal. She was treated with ursodeoxycholic acid for symptomatic relief of ICP.

Fetal status was monitored daily with non-stress tests followed by biophysical profiles if non-reactive. The patient developed moderate polyhydramnios. She was also treated for preterm labor during her inpatient stay and received a course of betamethasone.

On day 7 of her admission her serum bile acid level was 104 μmol/l (normal ≤10 μmol/l). The patient was counseled extensively about this finding. In addition to her bile acids, the severity of her disease was discussed, as were the new diagnosis of polyhydramnios and her recent betamethasone course. Together with the patient and the Maternal Fetal Medicine and the Neonatal Intensive Care Unit, the decision was made to move forward with induction of labor at 32 weeks 6 days of gestation. She had a spontaneous vaginal delivery of a male infant with APGAR scores of 8 and 9 at 1 and 5 min respectively. The infant required NICU admission for respiratory support.

The patient's post-partum course in hospital was uncomplicated. She was counseled that her risk of recurrence of ICP in subsequent pregnancies was 60–70%. For her new diagnosis of hepatitis C she was recommended hepatology follow-up as an outpatient. She was discharged home with a plan for repeat laboratory evaluation at her 6-week post-partum visit.

3. Discussion

Patients with ICP typically present late in pregnancy, with 80% of women diagnosed after 30 weeks of gestation. By far the most common symptom is the characteristic pruritus of the palms and soles; however, other, rare manifestations include pigmented skin lesions, blisters, and jaundice [1].

Elevated serum bile acid levels are the confirmatory test of choice in patients with suspected ICP and are further used to categorize severity of disease as mild (SBA < 40 μmol/l), moderate (SBA > 40 μmol/l < 100 μmol/l) or severe (SBA > 100 μmol/l) [1,5]. Other common laboratory abnormalities include elevated transaminase levels. Less common laboratory abnormalities include elevated serum bilirubin, derangements in glucose metabolism and coagulopathy, all of which were seen in the case reported [1,3].

Once the diagnosis of ICP has been established, treatment is often initiated for symptomatic management of maternal pruritus. Ursodeoxycholic acid, the most commonly recommended medication for women with ICP, has been well studied and is known to reduce pruritus and decrease transaminase and serum bile acids levels. In the past, studies suggested that this decrease in SBA can lead to decreased risk of complications, including preterm delivery and improve neonatal outcomes. However, a recent large multi-center randomized control trial largely refuted these claims. [6,7]

The fetal risks of ICP include increased rates of spontaneous and iatrogenic preterm birth, non-reassuring fetal status, meconium stained amniotic fluid, NICU admissions, and stillbirth [1,5]. Due to the increased risk of these complications, most clinicians recommend twice-weekly antenatal testing following diagnosis, including non-stress tests and ultrasound scans to assess fetal status. Despite these recommendations, there is a lack of evidence to show that this increased fetal surveillance predicts or prevents the above-mentioned complications [1,2]. The current recommendation is for delivery at 36 weeks of gestation, as the increased risk of stillbirth rises with each week of gestation after this time. [8]

Traditionally, ICP patients have been treated the same regardless of their serum bile acid levels due to a lack of evidence strongly supporting repeat laboratory evaluation. However, the results of one recent meta-analysis contradict this tendency. Ovadia *et al* found in their meta-analysis that women with SBA levels in the severe range were at a significantly increased risk of stillbirth. They proposed that repeat SBA testing could be important in distinguishing women who develop severe ICP, as their management could vary significantly from those with only mild to moderate disease [5]. This point is highlighted in the case reported, where the initial SBA level was mild, but with subsequent testing, encouraged by her worsening clinical condition, the findings of SBA levels in the severe range significantly influenced her counseling and ultimately the timing of her delivery. The authors do not specifically mention an ideal interval for re-testing SBAs; however, some experts suggest it could be beneficial as frequently as once a week. [2,9]

A second key point worth discussing in the context of the case presented is the relationship between ICP and hepatitis C [10–12]. ICP has been linked to several hepatobiliary conditions, including hepatitis C, liver cirrhosis, chronic hepatitis, cholangitis and cholelithiasis. Hepatitis C specifically has been noted to worsen symptoms of ICP, including pruritus. Although no direct cause for this association has been found, one suggestion is that a common genetic predisposition may play a role [13]. Given these findings, it becomes important to test for co-existing hepatobiliary disease in this patient population. For the patient described here, the diagnosis of hepatitis C was important as it allowed precautions to be taken for the fetus and the staff during her labor course and also directed her care in the post-partum period. Given the important clinical implications of a hepatitis C diagnosis and that it is now a treatable condition, it is suggested that testing be considered in all patients with ICP [13].

Care for and treatment of women diagnosed with ICP is an evolving field of study. The present case highlights several key points in the care of ICP patients. Most importantly, we see the importance and necessity of following up on laboratory evaluations in the outpatient setting, as missing the initial diagnosis can lead to deficient care and follow-up. Additionally, this case illuminates the role of laboratory evaluation for uncommon but clinically significant sequelae, and the roles of universal hepatitis C screening and repeat SBA testing in patients with ICP.

Contributors

Courtney Birchall drafted and reviewed and revised the manuscript.
Danielle Prentice reviewed and revised the manuscript.
Jaimey Pauli reviewed and revised the manuscript.

Conflict of interest

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

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Obtained.

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