A case of atypical presentation of intrahepatic cholestasis of pregnancy

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SUMMARY

Intrahepatic cholestasis of pregnancy (ICP) is the most common liver disease that occurs during pregnancy. Typically, patients with ICP present with pruritus and an elevation in transaminases and serum bile acid concentration. A critical aspect of managing the aforementioned disease includes recognising and ruling out other insidious conditions. Here, we present a case of ICP with an atypical presentation of markedly raised total bilirubin, normal transaminases, and prolonged course of jaundice postpartum.

INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP) typically presents with pruritus as the first symptom, with an 80% onset after 30 weeks of gestation.[1] In laboratory findings of ICP, alanine transaminase (ALT) can be increased by 1.5 to 8-fold from the upper limit of normal, with a critical finding of an increase in serum total bile acid concentration. Total bilirubin can be elevated in 25% of cases but seldom exceeds 100μmol/L.[2] ICP can result in maternal complications and debilitating foetal complications such as preterm birth, meconium-stained amniotic fluid, neonatal respiratory depression, asphyxia, and intrauterine foetal death.[3] The foetal risk is highest in patients with total serum bile acid levels of more than 100 μmol/L. The etiology of ICP is not fully understood but it is postulated a combination of genetic, hormonal, and environmental factors contribute to the development of this condition. The incidence of ICP is not clear in Malaysian population and may be under-diagnosed. Hence, this case report aims to increase the awareness of ICP among physician, and we also aim to showcase an atypical presentation of ICP and how we confirm the diagnosis.

CASE REPORT

A 34-year-old woman, gravida 4 para 2+1 with a history of hyperthyroidism on carbimazole, presented with yellowish discolouration of the sclera, which started at 30 weeks of gestation. At 32 weeks of gestation, she was referred to our gastroenterology clinic for further evaluation. On further inquiry, she developed pruritus and tea-coloured urine with the onset of jaundice. She denied any hyperthyroidism symptoms, vomiting, headache, abdominal pain, and pale stool. There was no consumption of traditional or over-the-counter medication throughout the pregnancy. Of note, she has had a past medical history of jaundice at 35 and 33 weeks of gestation in her first and second pregnancies, respectively. She delivered at 37 weeks of gestation in her previous two pregnancies. However, these episodes were not thoroughly investigated.

On physical examination, she was jaundiced. Otherwise, there was no other elicited finding on physical examination, and she was euthyroid clinically. Her blood pressure was normal. The slit-lamp examination by an experienced ophthalmologist did not reveal any Kayser-Fleischer ring.

Laboratory investigations revealed an increase in serum total bilirubin (257.1 μmol/L) with predominantly direct hyperbilirubinemia (196.7 μmol/L) and elevated serum bile acid (252.1 μmol/L). She had a normal level of ALT, aspartate aminotransferase, and gamma-glutamyl transferase. Her urine biochemistry did not show proteinuria, and there was no evidence of hemolysis and thrombocytopenia. The viral hepatitis A, B, and C screening were non-reactive. The autoimmune hepatitis autoantibodies, including anti-nuclear, anti-mitochondrial, anti-LKM, and anti-smooth muscle antibodies, were all negative. The blood investigation results during her first presentation are shown in Table I. Ultrasonography of the abdomen and magnetic resonance cholangiopancreatography revealed cholelithiasis with no evidence of biliary obstruction.

Based on the clinical and laboratory results, she was diagnosed with severe ICP and started on ursodeoxycholic acid (UDCA) 1000 mg daily (15 mg/kg/day) at 32 gestational weeks. She reported an improvement in pruritus after 2 days of treatment. Unfortunately, she went into spontaneous labour at 32 weeks and 5 days of gestational age. Her baby was delivered via emergency lower segment Caesarean section due to meconium-stained liquor and a non-reassuring foetal heart rate from the cardiotocography tracing. The Apgar score of her baby was 9 at the first and fifth minute. However, the baby was admitted to the neonatal intensive care unit for apnea of prematurity, neonatal sepsis, and neonatal jaundice. The baby was discharged well on day 10 of life after intensive phototherapy sessions and antibiotic therapy.

The patient was closely monitored postpartum on her symptoms and liver function test. There was a slow resolution

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Table I: Investigations done at the point of diagnosis at gestation weeks 32

Hb	10.4 g/L	Prothrombin time	9.7 s (9.4-11.0)
Wbc	11.4 × 10^9/L	Creatinine	56 µmol/L
Platelet	259 × 10^9/L	Urea	2.4 µmol/L
Bilirubin	257.1 µmol/L (5.1–17 µmol/L)	Total Serum bile acid	252.1µmol/l
		TSH	<0.008mIU/L (0.55–4.78)
Direct	196.7 µmol/L	T4	18.1 pmol/L (11.5–22.7)
Indirect	60.4 µmol/L	Ammonia	<10 umol/L (11.2–35.4)
Albumin	28 g/L	Uric Acid	212 umol/L (184–464)
Globulin	27 g/L		
Alanine transaminase	34 U/L		
Aspartate transaminase	34 U/L		
Alkaline phosphatase	276 U/L		
Gamma-glutamyl Transferase	5.8 U/L		
Activated partial thromboplastin clotting time	28.3 Sec (22.2–31.0)		

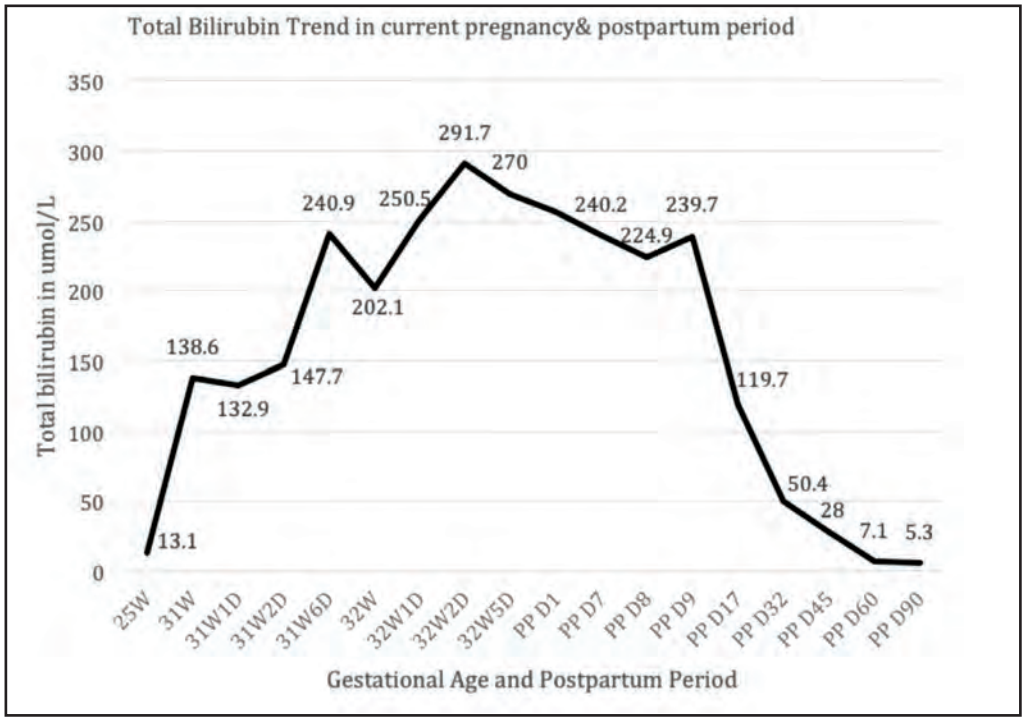

Fig. 1: Line graph showing the total bilirubin in µmol/L monitored from the point of diagnosis during pregnancy to the postpartum (PP) period.

of her total serum bilirubin (Figure 1). The UDCA was continued postpartum and stopped after the serum bilirubin was normalised at 2 months postpartum. Total bilirubin in µmol/L

DISCUSSION

Any liver pathology that can occur in the general population can affect the pregnant population besides other liver diseases that are unique to pregnancy. They include hyperemesis gravidarum, acute fatty liver of pregnancy (AFLP), HELLP (hemolysis, elevated liver enzymes), low platelets syndrome, pre-eclampsia, and ICP. We adopted a systemic approach to diagnose and recognise the patient's liver pathology, categorising the disease based on trimester, clinical symptoms, and laboratory parameters.

As the patient's onset of symptoms (jaundice and pruritus) was in the third trimester, the diseases we were actively trying to establish or rule out included ICP, pre-eclampsia, HELLP syndrome, and AFLP. The absence of hypertension, proteinuria, and hemolysis, coupled with normal platelet levels and liver enzymes, points away from pre-eclampsia and HELLP syndrome. The patient did not fulfil Swansea criteria for the diagnosis of AFLP. Based on Swansea criteria, patient has a score of 1 attributable to hyperbilirubinemia with lack of other features such as hyperuremia, elevated serum ammonia, hypoglycemia, and others.

Differential diagnosis of liver disease which can occur outside of pregnancy is explored as well.The investigations for Wilson's disease, hemochromatosis, autoimmune liver disease, primary biliary cholangitis, viral hepatitis, and biliary obstruction were unremarkable. Carbimazole toxicity

is dismissed as there are no symptoms to suggest so and no other accompanying feature like agranulocytosis. Given the patient's serial monitoring of well-controlled thyroid hormone level and history of consuming carbimazole for more than 1 year, this made the diagnosis of hyperthyroidism-related liver condition highly unlikely. A thorough history taking and examination also points away from traditional medication-induced hepatotoxicity.

The clinical presentation and the history of jaundice and pruritus in previous pregnancies in this patient fit well with ICP.[4,5] However, the markedly raised total bilirubin and normal transaminase levels are not the typical findings of ICP. Serum bile acid for this patient was markedly elevated at 252.1 µmol/l. Serum bile acid is a crucial marker for the diagnosis of ICP. A level of more than 10µmol/l confirms the diagnosis of ICP, and a value of more than 40 µmol/l carries a higher risk for disease-related complications.[4] Therefore, the patient was diagnosed with severe ICP as her total serum bile acid was more than 100 µmol/l. Since the diagnosis was confirmed on clinical judgment and biochemical parameters, invasive procedure like liver biopsy was not done at this point as the risks out weight the benefits. However, we recognize there may be role of biopsy and we reserve it for event when treatment given do not improve patient's symptoms and biochemical findings.

High serum bile acid causes little complication to the mother. However, maternal bile acids can cross the placenta, which can be detrimental to the fetus. The main complications include increased risks of intrauterine death, meconium-stained amniotic fluid, preterm delivery, and neonatal respiratory syndrome. The incidence of intrauterine stillbirth is significantly higher in pregnant women with serum bile acid more than 100µmol/l compared to those with serum bile acid less than 100 µmol/l.[6] Our patient went into spontaneous preterm delivery at 32 weeks of gestation, and her baby suffered from sepsis and complications of preterm delivery. Hence, close monitoring and anticipation of foetal complications are warranted due to high levels of bile acid concentration.

Initiating UDCA in ICP patients is postulated to have an effect on increased membrane transport protein expression in human liver ABCB11, MDR3, and MRP4 expression, which is speculated to have facilitated bile acid export via the bile salt export pump.[7] In accordance with the current recommendation, she was started on treatment with UDCA. In the PITCHES trial,[8] UDCA seems to carry a maternal benefit in improving pruritus, but no foetal or neonatal outcome was observed in patients on UDCA treatment compared with placebo. Therefore, it is essential to know that UDCA is not the definitive treatment for ICP. The recommended definitive treatment of ICP is early delivery, with its timing dependent on the serum bile acid level.

Following the initiation of UDCA, she reported improvement in pruritus symptoms within days. However, the total bilirubin level remained elevated persistently for 2 weeks postpartum before normalising at two months postpartum. As a result, UDCA was continued until 2 months postpartum. Her liver function test remained normal after stopping the UDCA during the subsequent follow-ups. The persistent and prolonged jaundice postpartum is yet another atypical presentation of ICP in this patient, as the symptoms of ICP usually disappear in the first few days following delivery, accompanied by normalisation of liver function test.[9]

CONCLUSION

Pregnancy with associated intrahepatic cholestasis may present with the main complaints of jaundice, markedly raised total bilirubin and transaminase levels, as well as prolonged jaundice that extends into the postpartum period. It is imperative that close monitoring of the foetus is provided to patients with severe ICP to prevent complications. Lastly, the authors hope to increase the awareness of diagnosing liver disease in pregnancy with atypical findings through this case report.

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REFERENCES

1. Brady CW. Liver disease in pregnancy: What's new. Hepatol Commun 2020; 4(2): 145–56.
2. Walker I, Chappell LC, Williamson C. Abnormal liver function tests in pregnancy. BMJ 2013; 347: f6055.
3. Šimják P, Pařízek A, Vítek L, Černý A, Adamcová K, Koucký M, et al. Fetal complications due to intrahepatic cholestasis of pregnancy. J Perinat Med 2015; 43(2): 133–9.
4. Singh G, Sidhu K. Cholestasis of pregnancy : A prospective study. Med J Armed Forces India 2008; 64(4): 343–5.
5. Glantz A, Reilly S-J, Benthin L, Lammert F, Mattsson L-A, Marschall H-U. Intrahepatic cholestasis of pregnancy: Amelioration of pruritus by UDCA is associated with decreased progesterone disulphates in urine. Hepatology 2008; 47(2): 544–51.
6. Ovadia C, Seed PT, Sklavounos A, Geenes B, Di Ilio C, Chambers J, et al. Association of adverse perinatal outcomes of intrahepatic cholestasis of pregnancy with biochemical markers: Results of aggregate and individual patient data meta-analyses: Results of aggregate and individual patient data meta-analyses. Obstet Anesth Dig 2020; 40(1):5.
7. Abu-Hayyeh S, Papacleovoulou G, Lövgren-Sandblom A, Tahir M, Oduwole O, Jamaludin NA, et al. Intrahepatic cholestasis of pregnancy levels of sulfated progesterone metabolites inhibit farnesoid X receptor resulting in a cholestatic phenotype. Hepatology 2013; 57(2): 716–26.
8. Chappell LC, Bell JL, Smith A, Linsell L, Juszczak E, Dixon PH, et al. Ursodeoxycholic acid versus placebo in women with intrahepatic cholestasis of pregnancy (PITCHES): a randomised controlled trial. Lancet 2019; 394(10201): 849–60.
9. Bacq Y, Sapey T, Brechot MC, Pierre F, Fignon A, Dubois F.Intrahepatic cholestasis of pregnancy: A French prospective study. Hepatology 1997; 26(2): 358–64.